

SUPPLEMENT ARTICLE

ABSTRACT

1 | Applied sensitivity analyses in pharmacoepidemiology database studies

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Background: It is widely recognized that sensitivity analyses of design choices and analytic assumptions help to interpret the robustness of pharmacoepidemiology studies. To encourage increased use of well-described techniques, this workshop will provide an introduction and demonstrations of a range of sensitivity analyses typically applied in pharmacoepidemiology with hands-on exercises.

Objectives: To discuss sensitivity analyses of study design choices and understand the impact of varying study design assumptions in practical examples. To explain quantitative confounding bias analysis and understand their interpretation in specific examples

Description: This hands-on workshop assembles academia, industry, and regulatory perspectives and consists of two parts. Part 1: Sensitivity analyses of study design choices will introduce typical variations in design choices, including variations in exposure risk window length, variations in covariate assessment period length, duration of minimum induction period, and variations in follow-up model (fix time vs as treated). Using brief lectures followed by live exercises, participants will make choices about sensitivity analysis assumptions and observe the consequences of their choices regarding changing parameter estimates and 95% confidence intervals. An example case study using claims data will illustrate the concepts. During the case study, the audience will suggest variations in design choices and predict the impact to the results. Course faculty will implement these assumptions in real time to discuss changes to findings. Part 2: Quantitative confounding bias analysis will focus on testing the influence of external assumptions or outside data on residual confounding. Using an Excel spreadsheet, participants will be guided through a “rule-out approach” and an “array approach” to residual confounding based on external assumptions. We will also illustrate a simple algebraic approach to assessing the impact of residual confounding if more detailed information from electronic health records or registry data becomes available in a subset of the larger claims-based cohort. The workshop will focus on principles and concepts, not on mathematical details.

Sebastian Schneeweiss: Moderator

Jeremy A. Rassen: Implementing design variations

Nicole Gatto: Implementing design variations

Sebastian Schneeweiss: Quantitative confounding bias analysis

Olaf Klungel: Quantitative confounding bias analysis

Xavier Kurz: Discussant

2 | Employing longitudinal trajectories to model exposure in perinatal pharmacoepidemiology research

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Background: Often, studies of the reproductive safety of pharmacologic exposures during pregnancy classify exposure dichotomously (as any use in pregnancy or by trimester), as categories of initial or highest dose, or as a count variable of days of use. Reducing exposure information in this manner removes information on changes in dose, intensity of use, and medication coverage gaps that are important for understanding temporal relations with perinatal outcomes. Recent studies have used group trajectory methods to summarize complex patterns of individuals' medication use during pregnancy.

Objectives: To describe the use of longitudinal trajectory modeling recently employed in perinatal pharmacoepidemiology studies and to provide a balanced review on the importance of this methodology, standard statistical packages available, and strengths/limitations of the approach. Researchers interested in the study of medication use during pregnancy would benefit from attending the symposium, as would researchers interested in using trajectories to model exposures in other areas.

Description: Through the use of didactic examples and analyses by the presenters, we will present the following: (1) discussion of exposure misclassification, sensitive periods of development, and the need to reconsider medication exposure modeling during pregnancy; (2) overview of trajectory modeling programs (Proc Traj (SAS), kml/kml3d (R)); (3) examples from recent medication trajectory analyses linking

prednisone, antidepressants, psychotropics, and anxiolytics/hypnotics with perinatal outcomes; (4) incorporation of other repeated measures (symptomatology and polypharmacy) for joint trajectories; (5) potential implications of the methodology from a regulatory perspective; (6) an interactive panel and audience discussion focused on the question, "Are longitudinal trajectory methods useful for studying medications in pregnancy? If so, what are the barriers to use?" The discussion will touch on strengths, limitations, and future directions of longitudinal trajectories in perinatal pharmacoepidemiology.

3 | Methodologic considerations for non-interventional studies evaluating outcomes of originator-to-biosimilar switching

Rishi J. Desai¹; Seoyoung Kim¹; Joshua Gagne¹; Jeffrey Curtis²; Jaclyn Bosco³; Brian Bradbury⁴

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Background: A biosimilar is a biologic product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference biologic product. Market entry of biosimilars may substantially impact treatment patterns as many patients may switch from the originator products to biosimilars for a variety of reasons, including provider preference, patient request, and formulary or contracting changes. Ensuring sound methodology in observational studies evaluating outcomes of biosimilar switching is critical for generation of robust real-world evidence.

Objectives: To provide an overview of the challenges in designing and conducting non-interventional studies of biosimilar switching patterns and outcomes and to offer methodological recommendations to mitigate these challenges, specifically regarding study design, variable measurements, bias, and analytic approaches. This session will be of benefit researchers interested in conducting observational studies of biosimilars and biologics.

Description: This symposium includes perspectives from academia, industry, and practicing clinicians. The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) has convened a workgroup to establish best practice recommendations for the conduct of observational studies of biosimilar and reference biologic switching. Members of the BBCIC Workgroup will share learnings as they relate to (1) challenges and gaps in observational studies of biosimilars (Dr Bosco); (2) implementation of epidemiologic designs including cohort, case-control, and case-crossover in biosimilar switching studies (Dr Desai); (3) the range of outcomes in biosimilar switching studies, including utilization endpoints such as switchback to the originator product, indication-specific effectiveness endpoints, and other endpoints of interest, such as immunogenicity and associated infusion/hypersensitivity reactions (Dr Curtis); (4) bias and confounding in biosimilar switching studies (Dr Kim); (5) application of

analytic approaches, including propensity scores, disease risk scores, and instrumental variables (Dr Gagne); and (6) discussion of importance of well-conducted observational studies of biosimilar switching from a standpoint of various stakeholders (Dr Bradbury). The symposium will conclude with a session dedicated to address questions and comments from the attendees to facilitate discussion of all pertinent issues.

4 | Long live the "medical data janitors": International data quality assurance practices in distributed data networks

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Background: Ensuring data quality for distributed data networks is challenging.

Objectives: We will examine international practices in five distributed data networks that house a mixture of administrative claims data and electronic health record data including: the US Food and Drug Administration's (FDA's) Sentinel Initiative (Sentinel), the FDA's Biologics Effectiveness and Safety (BEST) Initiative, the US National Patient Centered-Clinical Research Network (PCORnet), Japan's Medical Information Database Network (MID-NET), and the Canadian Network for Observational Drug Effect Studies (CNODES).

Description: Each network will describe its data quality processes.

1. Sentinel: (a) "always ready" paradigm to quickly support many studies, (b) adherence to FDA best practices, and (c) continuous improvement of the data network. Sentinel is primarily a claims-based data network of public and private databases that accrue data on 70 million individuals continuously. (Maro, 15 min)
2. BEST Initiative/OHDSI (Observational Health Data Sciences and Informatics) data quality assurance practices include collaborative platforms for validation of (a) data—does it confirm complete data capture to agreed structure and conventions, (b) software—does it perform as expected, (c) clinical—does analysis match clinical intention, and (d) methods—do estimates measure what they purport to. (Reich, 15 min)
3. PCORnet: (a) foundational data curation establishes baseline level readiness for prep-to-research queries, (b) study-specific data curation assesses data for the cohort under study, and (c) findings from study-specific data curation inform development of foundational curation. PCORnet relies primarily on electronic health record data housed in dozens individual health systems. (Marsolo, 15 min)

4. MID-NET: (a) checking consistency between stored data and the original data in the hospital and implementing standardized data coding process, (b) adherence to government issued Good Post-Marketing Study Practice, and (c) continuous monitoring. MID-NET currently includes data on approximately 4 million individuals of 23 hospitals. (Uyama, 15 min)
5. CNODES: (a) routine QA processes conducted at the individual sites, (b) phased study implication including QA checks at each study phase, (c) processes for post-study data queries. (Filion, 15 min)
6. Moderator-Led Discussion (Sturkenboom, 15 min)

5 | Rare disease development programs: An update

Jasmanda Wu¹; Cunlin Wang²; Daniel B. Horton³; Irene Petersen⁴; Susan Oliveria⁵; Stella Blackburn⁶; Jieying Jiang⁷; Robert LoCasale¹

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Background: Many rare disorders are serious conditions with no approved treatments, leaving substantial unmet medical needs for patients with these conditions. The FDA Orphan Drug Act provides incentives associated with the orphan-drug designation to make it more financially viable for companies to develop drugs for small numbers of patients. The EMA also provides a number of incentives for medicines that have been granted an orphan designation by the European Commission. Over the past decades, several drugs, biologics, and devices have been approved and are available to patients with rare conditions. However, effective and safe treatments are still lacking for many rare disorders. Regulators worldwide recognize that rare diseases are highly diverse and are committed to helping sponsors create successful drug development programs that address the particular challenges posed by the disease.

In recent years, several strategies have been developed to improve the orphan drug development process, including incorporating novel epidemiology approaches into clinical programs, using patients' perspectives for improving trial design, and selection of meaningful endpoints and measurements. This forum is intended to highlight new developments in the regulatory landscape and various areas to enhance drug development programs for rare diseases.

Objectives: The objective of the symposium is to provide an in-depth review of new developments in the regulatory landscape, use of off-label drugs, epidemiology approaches, patient advocacy, and risk mitigation strategies for rare diseases drug development and research.

Description:

1. Overview of current regulatory environment for rare disease drug development (Cunlin Wang, Genentech, San Francisco,

CA/ Former FDA employee, USA; Stella Blackburn, IQVIA, London/Former EMA employee, UK, 20 min)

2. Off-label drug use to treat rare pediatric diseases (Daniel B. Horton, Rutgers University, USA, 15 min)
3. Epidemiologic approaches and the use of real-world data for rare disease research (Susan Oliveria, IQVIA, USA, 15 min)
4. Incorporating the patients' perspective in drug development programs for rare diseases (Irene Petersen, University of College London, UK, 15 min)
5. Risk minimization strategies and post-marketing requirements for rare diseases therapeutic products (Jieying Jiang, Icahn School of Medicine at Mount Sinai, USA, 10 min)
6. Panel Discussion: Audience is invited to interact with all speakers (Moderator: Robert LoCasale and Jasmanda Wu, Sanofi, USA, 15 min)

6 | Validation of the reverse parametric waiting time distribution and standard methods to estimate prescription durations for warfarin

Julie M. Petersen¹; Henrik Støvring²; Maja Hellfritsch¹; Jesper Hallas¹; Anton Pottegård¹

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Background: A common challenge in registry-based pharmacoepidemiology is the lack of valid information on the duration of drug exposure that should be assigned to a single prescription record, potentially affecting study validity due to exposure misclassification.

Objectives: To validate two different approaches for estimating prescription durations, using the oral anticoagulant warfarin as a case. The approaches covered assumptions of a fixed daily intake of either 0.5 or 1.0 defined daily dose (DDD), as well as estimates based on the reverse parametric waiting time distribution (rWTD) without covariates and with three different sets of covariates.

Methods: Estimates of prescription durations were calculated using data from the regional prescription database Odense Pharmacoepidemiological Database (OPED). We converted estimates of prescription durations to estimates of daily dose (total amount of drug obtained divided by estimated duration) and compared them on the individual level (using Bland-Altman plots) to actual prescribed daily doses of warfarin as recorded in a clinical anticoagulation database. Methods were evaluated based on their average prediction error (logarithmic scale) and their limit of agreement ratio (ratio of mean error $\pm$ 1.96 SD after transformation to original scale).

Results: Prescription durations were underestimated by 19% or overestimated by 62% when assumptions of 0.5 or 1.0 DDD, respectively, were applied, and the limit of agreement ratio was 6.721 for both assumptions. The rWTD-based approaches performed better when using the estimated mean value of the inter-arrival density,

yielding negligible bias (relative difference of 0% to 2%) and with limit of agreement ratios decreasing upon additional covariate adjustment from 6.867 with no adjustment to 4.036 with the fully adjusted model. **Conclusions:** Comparing the different methods, the rWTD algorithm performed best and lead to unbiased estimates of prescription durations and reduced misclassification on the individual level upon inclusion of covariates.

7 | Correcting for differential depletion of susceptibles in time-to-event data using time-specific propensity scores

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Background: In drug safety data with differential dropout of susceptible patients, conditional (covariate adjusted) and marginal (population averaged) hazard ratios will diverge from each other, and widely used baseline propensity score-based estimators will be biased. Methods involving inverse probability censoring weights or time-varying marginal structural models could retrieve unbiased estimates of marginal hazard ratios, but application of these tools in the data environments common to drug safety surveillance can be challenging.

Objectives: We propose and evaluate novel strategies that condition on time-specific propensity scores to correct for covariate imbalances over time due to differential dropout of susceptible patients. The proposed methods estimate a conditional effect that targets the treated population at risk at specific time points, which we consider a more accurate estimate than the marginal hazard ratio when there is differential depletion of susceptibles—a situation that is common in drug safety surveillance.

Methods: Plasmode simulations were based on an empirical cohort comparing dabigatran versus warfarin with an outcome of major bleeding events. We considered a range of scenarios where we varied five parameters that have been shown in previous work to impact estimation of marginal hazard ratios due to differential depletion of susceptibles: (1) strength of the treatment effect, (2) outcome incidence, (3) correlation between the propensity score and disease risk score, (4) amount of treatment effect heterogeneity, and (5) amount of censoring.

Results: The impact of differential depletion of susceptibles was minimal when the treatment effect was weak, or the outcome incidence low (<10% when correlation between the propensity and risk score was moderate, or <5% when the correlation between the propensity and risk score was weak), but could be substantial otherwise. Rematching or conditioning on time-specific propensity scores successfully adjusted for imbalances in baseline characteristics over time, providing unbiased estimates of the conditional hazard ratio.

Conclusions: Conditioning on time-specific propensity scores provides a simple approach to correct for covariate imbalances caused by differential dropout of susceptible patients. In some post-market drug safety situations where outcome events are rare, however, differential depletion of susceptibles may have minimal impact on estimation of marginal and conditional hazard ratios.

8 | Analysis of registry-based case-control studies with a joint exposure and outcome model based on the reverse waiting time distribution

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Background: Traditional pharmacoepidemiologic studies based on case-control designs first determine treatment status and then estimates the association between treatment and case status. This may bias the association estimate and its uncertainty estimate.

Objectives: To extend the reverse waiting time distribution (rWTD) to allow direct estimation of the association in case-control studies where treatment status is not observed, but prescription redemptions are.

Methods: We built a joint model for the rWTD and case-control status. We defined the rWTD as the distribution of time from last prescription of each patient within a time window before the index date. The reverse WTD consists of two components: one for prevalent users at the index date and one for patients stopping treatment before the index date. Patients without a prescription within the time window were defined as untreated at the index date. We let case-control status depend on the latent treatment status to allow maximum likelihood estimation of the odds ratio for being exposed for cases relative to controls. We applied the method to a study on hospitalization with upper-gastrointestinal bleeding (case status) and NSAID use (exposure), comparing estimates with defining treatment status by a fixed window of 90 days before the index date. We conducted a simulation study where we assessed relative bias and coverage probability of confidence intervals and compared the precision to the setting where treatment status was observed.

Results: Using a 90-day interval to define treatment status, we estimated an odds ratio of 4.60 (4.25-4.98), whereas the new method gave 5.02 (4.62-5.47). In the simulation study, we found that the new model had low relative bias (-0.1%) and retained nominal coverage probability (95.4% of nominal 95% confidence intervals contained the true value). The standard error was 15.1% larger than if exposure status had been directly observed. The 90-day method had a relative bias of -11.6% and a coverage probability of 2.48%.

Conclusions: The algorithm allows valid estimation of the odds ratio in case-control studies without explicitly defining treatment status at index date. Statistical precision was high though lower than if actual treatment status had been observed.

9 | Amiodarone use and the risk of acute pancreatitis: Influence of different exposure definitions on risk estimation

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Background: The antiarrhythmic drug amiodarone has an extremely long half-life of approximately 60 days, yet this is hardly considered in observational studies of adverse effects of amiodarone, such as acute pancreatitis.

Objectives: To investigate the robustness of the association between amiodarone and the risk of acute pancreatitis against different exposure definitions.

Methods: All incident amiodarone users in the Dutch PHARMO database between 2005 and 2015 and two comparison groups were included: (1) incident users of a different type of antiarrhythmic drug and (2) age- and sex-matched subjects starting a non-antiarrhythmic drug. Different definitions were applied to amiodarone exposure, including dichotomized, continuous, and categorized cumulative definitions with lagged effects to account for the long half-life of amiodarone. For each exposure definition, Cox proportional hazards regression analysis was used to estimate the risk of acute pancreatitis associated with amiodarone use, while adjusting for confounding.

Results: This study included 15 378 starters of amiodarone, 21 394 starters of other antiarrhythmic drugs, and 61 579 starters of non-antiarrhythmic drugs. Compared with starters of other antiarrhythmic drugs, the adjusted hazard ratios (HRs) for the dichotomized definitions of exposure ranged between 1.21 and 1.43, for the continuous definitions of exposure between HR 1.13 and 1.22, and for the categorized cumulative definitions between HR 0.52 and 1.72. The HRs observed in the comparison with non-antiarrhythmic drugs users were generally higher: For the dichotomized exposure definitions, they ranged between 1.67 and 1.82, for the continuous exposure definitions between 1.39 and 1.70, and for the categorized cumulative exposure definitions between 0.68 and 2.55. Accounting for lagged effects had little impact on estimated HRs estimates.

Conclusions: This study demonstrates the relative insensitivity to of the association between amiodarone and the risk of acute pancreatitis against a broad range of different exposure definitions. Accounting for lagged effects had little impact, possibly because treatment switching was uncommon in this population.

10 | Estimating cumulative risk in the presence of competing events and dependent censoring in pharmacoepidemiology studies

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Background: The occurrence of an outcome of interest may be unobserved due to competing events or censoring that is differential by exposure group. Studies have traditionally not addressed these problems.

Objectives: To demonstrate a straightforward approach for estimating cumulative risk of an outcome in the presence of competing events and dependent censoring.

Methods: We used a generalization of the risk function that is equivalent to a weighted Aalen-Johansen estimator to estimate the cumulative risk of an outcome prior to competing events, accounting for dependent censoring and confounding using inverse probability (IP) weights. We show an example using data from the Women's Interagency HIV Study (WIHS) and replicate a prior analysis (Lau, Cole, & Gange, 2009) of the association between patient history of injection drug use (IDU, exposure) and time to initiation of antiretroviral therapy (ART, outcome), with clinical disease progression (AIDS diagnosis or death) as a competing event.

Results: We estimated the 10-year cumulative risk of ART initiation among 1164 women who were HIV-positive, free of clinical AIDS, and enrolled at 6 clinical sites in the United States on December 6, 1995 (when the first protease inhibitor was approved by the FDA). Over 10 years of follow-up, 671 of the women initiated ART (57.6%). The prevalence of competing events prior to ART initiation was 30.6%; therefore, censoring participants experiencing competing events would inflate the estimate of ART initiation to 76.8%. Loss to follow-up was differential by exposure (13.9% unexposed vs 5.9% exposed). Using the cumulative incidence estimator that accounts for competing events, dependent censoring, and confounding, we found that 47.2% of patients with a history of IDU and 72.7% of patients without history of IDU initiated ART over 10 years prior to AIDS or death. The cumulative risk difference was -25.5% (95% CI: -33.1, -18.0) and corresponds to a hazard ratio of 0.56 (95% CI: 0.50, 0.62), consistent with previous work.

Conclusions: Ignoring competing events and dependent censoring can produce misleading estimates. Estimating the incidence of an outcome in the presence of competing events is straightforward using a cumulative incidence estimator and can easily incorporate IP weights for dependent censoring and confounding. Applying this estimator to the WIHS data, we found that initiation of ART was markedly lower among patients with a history of IDU.

11 | Diagnostics for informative censoring: Application to antipsychotic trials with high dropout rates

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Background: In clinical trials and observational studies, follow-up is often censored when patients are lost to follow up or when they switch treatment in a per-protocol analysis. Such censoring is informative of effectiveness/safety when patients leave a study or switch treatment for lack of efficacy/tolerability. This selection bias can be

detected by data visualizations for covariate balance that compare the mean of time-varying covariates among the censored vs uncensored over time.

Objectives: To use these data visualizations to describe potential selection-bias in the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study before and after using cumulative inverse probability of censoring weights (IPCW) to remove the measured selection bias from study dropout.

Methods: 1432 patients with schizophrenia randomly assigned to one of five antipsychotics were followed for 18 months. Time-varying covariates symptom change and severity, extrapyramidal symptoms, weight gain, quality of life, and drug use were measured at months 0, 1, 3, 6, 9, 12, and 15 along with demographics. Using a person-time data structure, fully conditional specification was used to impute up to 2% missingness due to non-response. Generalized additive models were used to model the probability of study dropout given the most recent values of covariates. The predicted values were used to obtain IPCW. For each arm, standardized mean differences comparing each covariate's mean among the censored vs uncensored were computed at each measurement time, before and after applying IPCW and plotted.

Results: Dropout was high and ranged from 43% to 57% across the treatment arms. For each arm, dropout peaked in the first month and declined sharply. For many arms, those who were censored were more likely to show worsening symptoms, poorer quality of life, higher drug use, and less extrapyramidal symptoms and weight gain. The weights largely resolved mean differences down to a quarter of a standard deviation through month 12, but were ineffective for differences at later times.

Conclusions: Covariate-balance across censoring can describe potential (measured) selection bias.

12 | Risk of major and clinically relevant non-major (CRNM) bleeding in patients prescribed rivaroxaban for stroke prevention in non-valvular AF (SPAF) and the prevention and/or treatment of deep vein thrombosis and/or pulmonary embolism (DVT/PE) in primary care in England

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Background: Clinical trials and observational studies have reported bleeding risk in patients (pts) taking rivaroxaban. A PASS was carried out as part of the RMP to monitor the safety and use of rivaroxaban using real-world primary (1°) care data in England.

Objectives: To estimate the risk of major and CRNM bleeding in pts prescribed rivaroxaban for SPAF and DVT/PE in 1° care.

Methods: Pts identified from dispensed prescriptions in England (2012-2016). Detailed questionnaires sent to general practitioners (GPs) at ≥ 3 and ≥ 12 months of observation collected information on

risk factors for bleeding (HAS-BLED) and bleeding outcomes. Summary descriptive statistics and 12-month risk estimates were calculated.

Results: Cohort = 17546 pts: 10 225 pts with AF (58.3% of cohort, median age 78 years (yrs) [IQR 70-84], 5253 (51.4%) male); 5959 pts with DVT/PE (34.0% of cohort, median age 66 yrs [IQR 50-78]; 3197 (53.6%) female). In both groups, the median HAS-BLED score was 1 (IQR 1-2, 0-1, respectively) reflecting a low risk of major bleeding. AF group: Risk Major + CRNM bleeding 8.3% ([95% CI 7.8, 8.9]; n = 825). Risk Major bleed (MB) 2.4% ([95% CI 2.1, 2.7]; n = 239), CRNM bleeding 6.0% ([95% CI 5.5, 6.4]; n = 592). MB further stratified by site: gastrointestinal (GI) (1.2%; n = 117), urogenital (UG) (0.1%; n = 13), intracranial (IC) (0.4%; n = 42), all other critical organ (excluding IC) (0.3%; n = 26) and all non-critical organ sites (0.4%; n = 44). DVT/PE group: Risk Major + CRNM bleeding 4.2% ([95% CI 3.7, 4.7]; n = 240). Risk MB 1.4% ([95% CI 1.1, 1.7]; n = 82), CRNM bleeding 2.8% ([95% CI 2.4, 3.3]; n = 162). MB further stratified by site: GI (0.7%; n = 38), UG (0.3%; n = 18), IC (0.2%; n = 12), all other critical organ (excluding IC) (0.1%; n = 4) and all non-critical organ sites (0.2%; n = 10).

Conclusions: For the primary outcome of major bleeding, the estimates of risk in the AF and DVT/PE rivaroxaban user populations were overall low and consistent with those estimated from clinical trial data. Differences in methodologies and analysed study populations prevent meaningful comparisons with other studies. This study design has unique strengths, including the collection of timely, granular data directly from prescribing GPs; however, selective reporting of outcomes and selection bias might be present and should be considered when interpreting results.

13 | Association between proton pump inhibitor use and gastrointestinal bleeds in NOAC-treated AF patients

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Background: Clinical trials demonstrated an increased risk of gastrointestinal bleeds (GIB) in atrial fibrillation (AF) patients taking non-vitamin K oral anticoagulants (NOACs) compared with warfarin. It is unknown to what extent proton pump inhibitors (PPI's) can prevent GIB.

Objectives: To assess if concomitant PPI use in AF patients taking NOACs is associated with decreased risk of GIBs.

Methods: All AF patients in the Stockholm Healthcare database (VAL-database) who claimed a NOAC from July 2010 until October 2017 were included. VAL contains information on diagnoses (ICD-10) and pharmacy claims (ATC) emanating from both primary and secondary care. Patients with a GIB within 2 years prior to inclusion were

excluded to reduce confounding by indication. Follow-up was from the claim of a NOAC until the occurrence of a GIB, death or migration, or discontinuation of the drug. Patients were defined as exposed after claiming a PPI, and exposure time ended with similar definitions as the follow-up time. We used a Cox-proportional hazards model to calculate the hazard ratio (HR) and 95% confidence intervals (CI) of GIB associated with PPI use and to adjust for baseline confounders (ie, demographics, comorbidities, and co-medication that are considered risk factors for GIB).

Results: PPI users ($n = 8105$; total follow-up time, 5210 person-years) were slightly older and had more comorbidities on average than non-users ($n = 16\,420$; 36 834 person-years). Among PPI users, the incidence of GIB was 14.8 per 1000 person-years vs 14.9 per 1000 person-years for non-users. The most common recorded GIB was an unspecified GI haemorrhage (ICD-10, K92.2), accounting for 73% of outcomes among PPI users and 71% among non-users. After full adjustment, PPI use was not associated with a reduced risk of GIB overall (HR: 0.86 [CI: 0.67-1.10]). However, in the elderly (≥ 85 years of age), a protective effect was found: HR: 0.48 (CI: 0.26-0.87). No differences were observed for different NOACs or for different types of GIB.

Conclusions: Overall, PPI use was not associated with a lower GIB risk in AF patients using NOACs, but potential beneficial effects were observed in elderly AF patients.

14 | Frailty and benefit of dabigatran versus warfarin in older adults with atrial fibrillation

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Background: A large clinical trial showed that dabigatran was more effective in preventing stroke than warfarin with similar rates of major bleeding. Whether the benefit of dabigatran relative to warfarin is similar in frail and non-frail older patients is of great practical relevance but unknown.

Objectives: To evaluate the effectiveness and safety of dabigatran compared with warfarin in older patients with atrial fibrillation and different levels of frailty.

Methods: A retrospective cohort study included 1 046 237 Medicare beneficiaries 65 years and older with atrial fibrillation who initiated dabigatran or warfarin between October 2010 and December 2014. The outcome was a composite endpoint of death, ischemic stroke, acute myocardial infarction, and major bleeding. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and their 95% confidence intervals (CIs) comparing dabigatran and warfarin across different levels of a validated claims-based frailty index (mild < 0.15 , moderate 0.15-0.24, severe ≥ 0.25) in a 1:1 propensity score (PS)-matched population.

Results: The analysis included 153 421 patients initiating dabigatran and 153 421 warfarin initiators matched by PS. Compared with warfarin, dabigatran-treated patients had lower rates, per 1000

person-years, of the composite endpoint (88.7 vs 103.8 events; HR, 0.89; 95% CI, 0.86-0.93), acute myocardial infarction (18.9 vs 23.5 events; HR, 0.85; 95% CI, 0.78-0.92), and major bleeding (55.7 vs 65.0 events; HR, 0.89; 95% CI, 0.85-0.94), but similar rates of death (14.2 vs 15.0 events; HR, 0.98; 95% CI, 0.88-1.09) and ischemic stroke (9.2 vs 9.9 events; HR, 0.95; 95% CI, 0.83-1.08). This lower rate of the composite endpoint for dabigatran compared with warfarin was observed in patients with mild frailty (HR, 0.71; 95% CI, 0.63-0.79) and with moderate frailty (HR, 0.85; 95% CI, 0.81-0.90), but not in patients with severe frailty (HR, 1.02; 95% CI, 0.94-1.10). This treatment effect heterogeneity seemed to be driven by the greater benefit of dabigatran relative to warfarin for major bleeding in patients with less frailty: mild frailty (HR, 0.65; 95% CI, 0.56-0.74) and moderate frailty (HR, 0.83; 95% CI, 0.78-0.89), vs severe frailty (HR, 1.05; 95% CI, 0.96-1.16).

Conclusions: In an older population with atrial fibrillation, dabigatran was superior to warfarin, but this advantage diminished with increasing levels of frailty. In severely frail patients, dabigatran was not more effective or safer than warfarin.

15 | Benefit-risk profile of dabigatran compared with vitamin-K antagonists in elderly patients with non-valvular atrial fibrillation: A cohort study in the French Nationwide Claims Database

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Background: The real-life benefits and risks of the direct oral anticoagulants (DOAC) for non-valvular atrial fibrillation (NVAf) in the elderly are still uncertain.

Objectives: To compare in a whole country database, in daily practice, the 1-year risk of major events in new elderly users of dabigatran or VKA for NVAf.

Methods: Cohorts of new users of dabigatran or VKA for NVAf aged ≥ 80 years in 2013 were identified and followed-up for 1 year in the SNDS 66 million persons nationwide French claims database. NVAf was defined from long-term disease registration, hospitalisation, or procedure for atrial fibrillation without valvular disease (3-year database history). Dabigatran and VKA patients were 1:1 matched on gender, age, date of the first drug dispensing, and high-dimensional propensity (hdPS) including CHA₂DS₂-VASc and HAS-BLED risk factors. Hazard ratios (HR) [95% confidence interval] were estimated over 1 year during first prescribed anticoagulant exposure, using Cox proportional hazard risk or Fine and Gray models.

Results: Of 103 101 new anticoagulant users for NVAf identified in 2013, 53 910 were aged 80 years or more and were included in this

analysis (9257 with dabigatran and 44 653 with VKA), and 8569 were matched per arm (93% of dabigatran patients). Mean age was 85 years, 41% male, 100% with CHA₂DS₂-VAsC score ≥ 2 and about 10% with HAS-BLED score > 3 . One-year cumulative incidence of clinically relevant bleeding was, respectively, 3.7% and 5.2% in matched dabigatran and VKA patients (HR: 0.76 [95% CI: 0.64-0.89]), 2.1% and 2.6% for arterial thrombotic events (0.76 [0.60-0.96]), 1.6% and 1.5% for acute coronary syndromes (1.01 [0.76-1.34]), 8.7% and 10.6% for death (0.84 [0.75-0.94]), 14.3% and 17.1% for the composite criterion of all events above (0.84 [0.77-0.92]). Results were similar for all patients when hdPS-adjusted analyses were used.

Conclusions: This nationwide cohort study of more than 50 000 new anticoagulant users for NVAf aged ≥ 80 years shows a significantly better benefit-risk profile for dabigatran versus VKA in elderly patients with 16% fewer major outcomes of clinically relevant bleedings, arterial thrombotic events, acute coronary syndromes, or death.

16 | Drug interactions with oral anticoagulants in German nursing home residents—A comparison between vitamin K antagonists (VKA) and non-VKA oral anticoagulants

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Background: Vitamin K antagonists (VKA) are susceptible to drug-drug interactions. Non-VKA oral anticoagulants (NOAC) have a decreased sensitivity to pharmacokinetic interactions and might be therefore considered superior to VKA in patients treated with multiple drugs. Nursing homes residents comprise a population with a high prevalence of polypharmacy in addition to indications for anticoagulation but also an elevated risk for bleeding.

Objectives: To compare the risk of serious bleeding associated with the use of interacting drugs in German nursing home residents treated with VKA or NOAC.

Methods: Using claims data of new nursing home residents aged ≥ 65 years (2010-2014), we identified two cohorts of patients treated with VKA or NOAC, respectively. During the patients' first continuous treatment episode with the respective oral anticoagulant (OAC) class, we conducted two nested case-control analyses. Cases were defined as patients hospitalized for bleeding. Up to 20 controls were matched to each case by age, sex, and OAC treatment status at the time of the first prescription during nursing home stay (incident OAC user vs prevalent user of the same OAC class). Conditional logistic regression was used to obtain confounder-adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the risk of bleeding associated with OAC use and interacting drugs compared with the use of the respective OAC alone.

Results: Among 127 227 new nursing home residents, 15 877 OAC users were identified. Bleeding rates per 100 person-years were

higher in patients treated with VKA (9.68; 95% CI: 8.73-10.72) than in those receiving NOAC (7.85; 6.89-8.90). Based on 372 cases and 7281 matched controls, the highest risk of bleeding in VKA users was observed for the concomitant use of antibiotics (aOR: 3.08; 2.17-4.38) vs VKA use alone followed by non-steroidal anti-inflammatory drugs (1.83; 1.25-2.68) and heparins (1.51; 1.12-2.04). Among 243 NOAC cases and 4776 matched controls, elevated risks for bleeding were observed for the use of heparins (2.06; 1.26-3.37), platelet inhibitors (1.89; 1.34-2.67), and antibiotics (1.80; 1.07-3.05).

Conclusions: Known interacting drugs increased the risk of bleeding in VKA users. Also in NOAC-treated patients, the use of interacting drugs was associated with an elevated risk of bleeding. Comedication needs to be initiated cautiously and monitored closely in nursing home residents treated with OAC.

17 | Dabigatran versus rivaroxaban for secondary stroke prevention in patients with atrial fibrillation rehabilitated in skilled nursing facilities

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Background: Thromboembolic and bleeding risk are elevated in older patients with atrial fibrillation and prior stroke.

Objectives: To compare outcomes of dabigatran versus rivaroxaban use for secondary prevention in a national population after skilled nursing facility (SNF) discharge.

Methods: Medicare fee-for-service beneficiaries aged ≥ 65 years with atrial fibrillation hospitalized (Part A) for ischemic stroke (11/2011-10/2013) and subsequently admitted to an SNF (minimum data set) were studied. Dabigatran ($n = 332$) and rivaroxaban users ($n = 378$) were identified (Part D) and compared in a retrospective, active comparator, new-user cohort. The index medication claim was identified in 120 days after hospital discharge and exposure continued until a 14-day treatment gap ("as treated"). The primary net clinical benefit outcome was the time to recurrent stroke, transient ischemic attack, intracranial hemorrhage, extracranial bleed, myocardial infarction, venous thromboembolism, or death. Multivariable-adjusted Cox models stratified by dosage-estimated hazard ratios (aHR) for the composite outcome and for all-cause mortality among dabigatran versus rivaroxaban users.

Results: The median age of the cohort was 84 years. Functional impairment was common at SNF admission (median Barthel Index: 40), as were stroke risk factors (87% with CHADS₂ score ≥ 4). The crude composite event rates were 40.4/100 person-years and 19.5/100 person-years among low and standard dose dabigatran users, respectively. Crude composite event rates were 33.7/100 person-years and 37.1/100 person-years among low and standard dose rivaroxaban users. The incidence of ischemic stroke and bleeding

(intracranial and extracranial) among low dose dabigatran users was 1.4 and 11.5 events per 100 person-years, respectively, and was 10.1 and 3.4 events per 100 person-years among low dose rivaroxaban users, respectively.

The composite outcome (aHR: 1.48; 95% confidence interval (CI): 0.87-2.51) and all-cause mortality (aHR: 1.67; 95% CI: 0.84-3.31) rates tended to be higher among low dose dabigatran users. Among standard dose dabigatran users, rates of death were similar (aHR: 1.05; 95% CI: 0.45-2.47) while composite outcome rates were lower (aHR: 0.65; 95% CI: 0.36-1.15).

Conclusions: Evidence was inconclusive regarding the net clinical benefit of dabigatran versus rivaroxaban for older adults post-stroke. Ischemic stroke and bleeding rates varied by anticoagulant and dosage.

18 | National impact of Prevnar 13[®] vaccine on ambulatory care visits for otitis media in children under 5 years in the United States

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Background: In the United States (US), otitis media (OM) is among the most common cause of sick visits in children under 5 years of age. The 7- and 13-valent pneumococcal conjugate vaccines (PCV7 and PCV13) were approved in the US in 2000 and 2010, respectively, for active immunization against invasive disease and OM caused by 7 serotypes common to both vaccines starting at ≥ 6 weeks of age.

Objectives: This study assessed the impact of PCV13 on OM by evaluating changes in US ambulatory care visit rates between the period before (pre-) PCV7 (1997-1999), during PCV7 (2001-2009), and after the introduction of PCV13 (2011-2013) among US children <5 years, stratified by <2 years and 2 to <5 years.

Methods: This ecologic study used data from the US National Ambulatory Medical Care and National Hospital Ambulatory Medical Care Surveys. Trends using weighted least-squares regression, mean visit rates, rate ratios (RR), rate differences (RD), and percentage change $((1-\text{RR}) * 100)$ over comparison periods were analyzed for OM and control endpoints unrelated to vaccinations, skin rash, and trauma. Outcomes were defined by ICD-9-CM codes.

Results: Among children <2, 2 to <5, and <5 years, statistically significant downward trends of OM visits during pre-PCV7, PCV 7, and PCV13 periods were observed ($p < 0.0001$, $p < 0.002$, $p < 0.0001$). Statistically significant reductions in OM visits per 100 children among children <2, 2 to <5, and <5 years were 24% (95% CI: 13%, 35%) and 21 visits (95% CI: 9.98, 31.04), 16% (95% CI: 2%, 29%) and 6 visits (95% CI: 0.57, 12.36), and 22% (95% CI: 12%, 32%) and 13 visits (95% CI: 6.26, 19.69) comparing PCV13 with PCV7 periods; and 48% (95% CI: 37%, 59%) and 59 visits (36.86, 80.60), 29% (95% CI: 13%, 45%) and 14 visits (95% CI: 3.88, 24.25), and 41% (95% CI:

30%, 52%) and 32 visits (95% CI: 19.19, 45.35) comparing PCV13 with pre-PCV7 periods. Visit rates for skin rash and trauma remained stable during PCV13 and PCV7 periods across each age group ($p > 0.05$, 95% CI for RRs include 1 and RDs include 0).

Conclusions: Significant reductions of OM visit rates were observed among children aged <5 years after introduction of PCV13 compared to before and during PCV7 periods, suggesting a significant and positive national impact of 13vPnC vaccination program for children <5 years with OM in the US ambulatory care setting. The observed reductions were most marked among children <2 years who bear the highest OM burden and are the target for PCV13. The additional reductions beyond PCV7 period are likely due to the 6 additional serotypes in PCV13.

19 | Safety of newly adjuvanted vaccines among older adults, a systematic literature review and meta-analysis

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Background: New adjuvants have been developed to improve the efficacy of vaccines and for dose-sparing and may overcome immunosenescence in the elderly.

Objectives: We reviewed the safety of newly adjuvanted vaccines in older adults (≥ 50 years).

Methods: We searched Medline for clinical trials (CTs) including new adjuvant systems (AS01, AS02, AS03, or MF59), used in older adults, published between 01/1995 and 09/2017. Safety outcomes were serious adverse events (SAEs), solicited local and general AEs (reactogenicity), unsolicited AEs, and potentially immune-mediated diseases (pIMDs). Standard random effects meta-analyses were conducted by type of safety event and adjuvant type, reporting relative risks (RR) with 95% confidence intervals (95% CI).

Results: We identified 1040 publications, from which we selected 7, 7, and 12 CTs on AS01/AS02, AS03, and MF59, respectively. Among a total of 92 123 study participants, 47 602 received adjuvanted vaccine and 44 521 control vaccine, or placebo. The majority of subjects (99%) were enrolled in influenza and Zoster vaccine trials. Rates of SAEs (RR = 0.99, 95% CI = 0.96-1.02), deaths (0.99, 0.92-1.06), and pIMDs (0.94, 0.79-1.1) were comparable in adjuvanted and control groups. Vaccine-related SAEs occurred in <1% of the subjects in both groups. The reactogenicity of AS01/AS02 and AS03 adjuvanted vaccines was higher compared with control vaccines, whereas MF59-adjuvanted vaccines resulted only in more pain. Grade 3 reactogenicity was reported infrequently, with fatigue (RR = 2.48, 95% CI = 1.69-3.64), headache (2.94, 1.24-6.95), and myalgia (2.68, 1.86-3.80) occurring more frequently in adjuvanted groups. Unsolicited AEs occurred slightly more frequently in adjuvanted groups (RR = 1.04, 95% CI = 1.00-1.08).

Conclusions: Our meta-analyses showed no increase in SAEs or fatalities following newly adjuvanted vaccines. Higher rates for local

or general solicited AEs were observed for all newly adjuvanted vaccines, especially those adjuvanted with AS01/AS02 or AS03, but AEs were mostly mild and transient. Our review suggests that the use of new adjuvants in older adults has not led to any safety concerns thus far. Potential limitations are the restriction to CTs performed in healthy older adults, and numbers too small to detect rare events.

20 | Hospital-diagnosed adverse events after HPV vaccination: A self-controlled case series analysis

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Background: Conventional methods for examining exposure-outcome associations usually rely on establishing an exposed and an unexposed cohort. In vaccine studies with very high uptake and few unexposed persons, this may not be an ideal method, as non-vaccinated persons may differ greatly from vaccinated persons in terms of unmeasured or unknown confounding factors.

Objectives: To use self-controlled case series (SCCS) analysis to examine whether hospital-based diagnoses of non-specific conditions happened more frequently within 30 days after an HPV vaccination than during a baseline period.

Methods: The HPV vaccine has been suspected to cause several non-specific conditions, including pain, non-specific malaise/fatigue, and chronic fatigue syndrome. We used Danish health registries to establish a cohort of all girls aged 11 to 17 years in Denmark during 2000–2014. For each outcome, we created a cohort of girls who had at least one hospital-based diagnosis of the outcome. We then conducted a SCCS analysis. This is a case-only method in which individuals experiencing an outcome act as their own control. As SCCS is a self-controlled method, it eliminates all confounding that is stable over time. As the SCCS method does not control for increasing age, we included age in the model. We estimated the relative incidence of selected outcomes in the exposure period compared with the baseline period.

Results: In total, 303 163 girls aged 11 to 17 years were eligible for our study. Preliminary results showed no association between HPV vaccination and subsequent hospital-based (inpatient or outpatient) discharge diagnoses of pain (relative incidence 0.71; 95% confidence interval (CI) 0.48–1.04, n with an outcome = 1397), no association with diagnoses of non-specific malaise/fatigue (relative incidence 0.79; 95% CI 0.43–1.14, n = 824), and no association with chronic fatigue syndrome (relative incidence 0.79; 95% CI 0.11–5.88, n = 24).

Conclusions: The SCCS method reduces confounding that is stable over time. It thus may be a suitable approach to control for confounding in settings where the non-exposed group is small and very distinct from the exposed group. Our preliminary SCCS results showed no association between HPV vaccine and several suspected adverse

outcomes. However, further refinement of the analysis is needed, as it is unclear if our results reflect a true null association or is due to an inaccurate definition of the etiological window, combined with defining outcomes based on hospitalizations rather than GP visits.

21 | Advance system testing: Benefit-risk analysis of a marketed vaccine using cohort modelling and MCDA swing weighting

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Background: Recently, more formal approaches for benefit-risk (BR) assessments have emerged. The effects table is even introduced in the European Public Assessment Reports (EPARs). As previous work is mostly related to pharmaceuticals, there is a need to explore BR methods for use with vaccines.

Objectives: To test BR methods for vaccines, using the comparison of the BR profiles of whole-cell (wP) and acellular pertussis (aP) formulations in children (<6 years) as test case.

Methods: We used cohort modelling to build the effects table, simulating number of events within 2 hypothetical cohorts of 10⁶ children from birth to age 6 yrs: one cohort received wP, the other aP. The benefit events were pertussis and its complications. The risk events were febrile convulsions, fever, hypotonic-hyporesponsive episodes, injection site reactions, and persistent crying. The model parameters (age-specific baseline incidences, coverage, and relative risks) were informed by multi-database studies with real-world data from Denmark (AUH -SSI), Spain (BIFAP-SIDIAP), Italy (Pedianet), and the UK (RCGP-THIN). Preferences were elicited from medical experts using MCDA swing weighting and combined with the cohort modelling results to obtain BR scores. Sensitivity analyses were performed assessing the impact of data uncertainty and variability in preference weights.

Results: We demonstrated how modelling can be used to build the effects table based on real-world evidence and how these results can be combined with preference weights to obtain BR scores. Conditional on our model assumptions and preference weights, we found

higher BR scores for wP (BR = 84.3; 95% UI: 64.6-99.1) compared with aP (BR = 58.4%, 95% UI 24.5-97.5), though with strongly overlapping distributions of aP and wP BR scores.

Conclusions: Our experience with the cohort modelling was positive as it allowed accounting for many vaccine specificities (eg, differences in age at vaccination/baseline risks, differences in number of doses, and differences in outcome-specific length of risk windows), which would otherwise be difficult to account for. The modelling results were easy to combine with preference weights to obtain BR scores. This study was for system testing and not to inform regulatory/clinical decisions on pertussis vaccination.

22 | Evidence from a quasi-experimental study for the effectiveness of the influenza vaccination against myocardial infarction in UK adults aged at least 65 y

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Background: A recent investigation using routinely collected health records found the influenza vaccine to be effective against heart failure. However, treatment of overt myocardial infarction (MI) events is important in preventing progression to heart failure, especially in older adults, yet evidence for the association between respiratory disease and subsequent MI is from observational data and subject to confounding bias.

Objectives: Using linked electronic health records, this study aimed to adjust for unmeasured confounding in the estimation of the effectiveness of the influenza vaccine against MI in adults aged 65 y and older in the UK.

Methods: Design: Cohorts of patients in the UK from general practices registered to the Clinical Practice Research Datalink with linkage to Hospital Episode Statistics.

Setting: Adults aged 65 y and older recruited from September in annual cohorts from 1997 to 2012 with no record of influenza vaccination in the preceding five years.

Exposure: Influenza vaccination

Outcome: Hospitalisation for MI as set out in the protocol for the study.

Statistical analysis: Survival times until MI in new beneficiaries of the influenza vaccine versus patients without vaccination were analysed for each annual cohort using a novel pairwise method to adjust for confounding bias. This alternative formulation of the prior event rate ratio method utilised data on each annual cohort from the preceding vaccine-free year. The results from both methods were compared.

Results: Cohort sizes ranged from 56 151 patients in 2002 to 144 566 in 2012. The hazard ratios (HR) for influenza vaccination from a Cox regression adjusting for age and gender were either greater than, or not significantly different from unity. After adjustment using the PERR method, the HRs were significantly less than unity (at 5% level), varying between 0.43 and 0.74, except in 2001 (HR = 0.89). The same

annual trend was closely mirrored in the pairwise-adjusted results, which were significantly below unity, varying between 0.37 and 0.66, except for 2001 (HR = 0.81).

Conclusions: After adjustment for unmeasured confounding bias, there was real-world evidence of the influenza vaccine conferring a protective effect against MI in patients aged 65 y and older in every year from 1997 to 2012, except 2001.

23 | Real-world effectiveness of influenza vaccination in older adults in the UK from 1997-2012: A quasi-experimental cohort study

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Background: Ageing is associated with a decline in the normal function of the immune system which may limit the effectiveness of the influenza vaccine. However, the absence of strong evidence from randomised controlled trials and conflicting results from observational studies has led to ongoing debate about the effectiveness of influenza vaccination in the elderly.

Objectives: To determine the real-world effectiveness of the influenza vaccine in UK adults aged 65 y and older and its relationship with age and receipt of the pneumococcal vaccination.

Methods: Design: Quasi-experimental cohort study of patients in the UK from general practices registered to the Clinical Practice Research Datalink with linkage to Hospital Episode Statistics and the Office of National Statistics databases. Setting: Adults aged 65 y and over, recruited, starting in September, in annual cohorts from 1997 to 2012, with no record of influenza vaccination in the preceding five years. Exposure: Influenza vaccination. Outcome measure: Hospitalisation for influenza, and prescriptions for antibiotics for symptoms consistent with lower respiratory tract infections. Statistical analysis: Application of the prior event rate ratio (PERR) method to estimate vaccine effectiveness in each annual cohort after removing the effect of time-invariant unmeasured confounding using outcomes from the year before vaccination. Vaccination effectiveness was also studied by age and pneumococcal (PPV) vaccination subgroups.

Results: The rates of influenza in the year before vaccination were higher for patients that proceeded to be vaccinated than for patients who remained unvaccinated, indicating the presence of confounding bias. Adjustment for this bias using the pairwise PERR method showed that influenza vaccination was moderately effective in all cohorts (HR ranging from 0.59 in 2012 to 0.89 in 2001, all significant at the 5% level except 2001). There was no discernible difference in influenza effectiveness between the PPV subgroups, although accuracy was affected by fewer patients in the PPV group. There was no significant age interaction except for the 2009 cohort, for which effectiveness of vaccination increased with age.

Conclusions: The UK policy of vaccinating older adults is effective at reducing risk of influenza infection. There was no clear evidence to

suggest influenza vaccine effectiveness was attenuated by the pneumococcal vaccine and no consistent moderation of effectiveness with increasing age.

24 | Gabapentin use in pregnancy and the risk of maternal and neonatal outcomes

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Background: Gabapentin is an anticonvulsant drug increasingly used for pain in many settings of care including pregnancy. Results based on small human studies suggest that its use during pregnancy is associated with an increased risk of small for gestational age (SGA), preterm birth (PTB), and neonatal intensive care unit admission (NICUa), but with a similar risk of preeclampsia (PE), compared with the general population.

Objectives: To assess the risk of PE, SGA, PTB, and NICUa associated with maternal use of gabapentin in a large US cohort.

Methods: We included 1 745 722 women with a liveborn infant during 2000-2013 and enrolled in Medicaid from 3 months before the last menstrual period (LMP) to 1 month after delivery. To conservatively address the etiologically relevant window for exposure occurrence, we examined the risk of PE, SGA, PTB, and NICUa among women with ≥ 1 pharmacy dispensing of gabapentin in both early (LMP to LMP + 140 days) and late (LMP + 141 to LMP+245) pregnancy, vs unexposed women. Fine stratification on the propensity score (PS) controlled for over 80 potential baseline confounders including indications and maternal use of opioids. We estimated relative risks (RR) and 95% confidence intervals (CI) in generalized linear models.

Results: In the cohort, 1275 women filled ≥ 1 prescription for gabapentin in both early and late pregnancy. Overall, 4.1% vs 6.3%, 4.9% vs 7.6%, 10.5% vs 20.2%, and 5.8% vs 17.6% of unexposed vs gabapentin-exposed pregnancies experienced PE, SGA, PB, and NICUa, respectively. The PS-adjusted RR associated with gabapentin exposure was 0.92 (95% CI 0.74-1.13) for PE, 1.32 (1.08-1.60) for SGA, 1.22 (1.09-1.36) for PTB, and 1.35 (1.20-1.52) for NICUa. Results were consistent in sensitivity analyses using high-dimensional PS adjustment or that re-defined exposure based on gabapentin use in late but not early pregnancy; however, gabapentin use in early but not late pregnancy was only associated with an increased risk of SGA. Bias analyses suggested that potential residual confounding by smoking was unlikely to fully explain the observed increase in SGA and PTB risk.

Conclusions: Results from this large cohort study suggest that maternal use of gabapentin, particularly late in pregnancy, may be associated with an increased risk of SGA, PTB, and NICUa. The careful adjustment for potential confounders, including maternal use of opioids,

may explain the large attenuation from crude to PS-adjusted results, in particular for NICUa, and the reduced magnitude of the associations compared with previous studies.

25 | Infections in children after prenatal exposure to methadone and buprenorphine: Nordic registry study

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Background: Little is known about long-term consequences of in utero exposure to methadone and buprenorphine, drug used for opioid maintenance treatment (OMT). Opioids modulate the immune system by binding to opioid mu receptors; prenatal exposure to OMT drugs may increase children's susceptibility to infections later in life.

Objectives: To examine susceptibility to infections measured as the number of antibiotic prescriptions dispensed in pharmacies to children prenatally exposed to OMT drugs.

Methods: Our study population included all children born 2005-2015 in Norway and 2006-2013 in Sweden. Maternal treatment with OMT drugs during pregnancy was identified from linkage between the nationwide Birth Registries and Prescription Databases. Prenatally OMT exposed children were compared with children born to mothers who had discontinued OMT drugs before pregnancy. Incidence rate ratios (IRR)s for antibiotic prescriptions during the first 3 years of life were calculated using Poisson regression with robust standard errors for 95% confidence intervals (CI)s. Inverse-probability-of-treatment weights (IPTW) were applied to adjust for confounding. Dose-response effect of opioids on the infections in children was tested within a population of women in Norway who were not in OMT but were dispensed analgesic opioids during pregnancy, by grouping the number of dispensed prescriptions into 3 groups (1, 2-10, and 10+).

Results: During the study period, 255 and 140 OMT exposed infants in Norway and Sweden, respectively, were followed until age of 3. In Norway, the incidence of infections was 481 per 1000 person-years in OMT-exposed children, compared with 328 per 1000 person-years in the reference group (adjusted IRR 1.45; 95% CI 0.79-2.69). In Sweden, the incidence of infections was 655 per 1000 person-years in exposed and 667 per 1000 person-years in the reference group (adjusted IRR 1.18; 95% CI 0.66-2.11). The rate of antibiotics prescriptions in the infants increased with the number of analgesic opioid prescriptions to the mother during pregnancy. Compared with children of mothers dispensed only one prescription, the IRR was 1.09 (95% CI 1.04-1.14) for group dispensed between 2 and 10 prescriptions and 1.29 (95% CI 1.13-1.47) for more than 10 prescriptions.

Conclusions: Our study suggests that children exposed to OMT in utero don't have higher susceptibility to infections in early childhood.

However, more studies are needed to clarify the effect of in-utero opioid exposure on the immune system.

26 | Ondansetron and the risk of congenital malformations

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Background: Available evidence on the fetal safety of ondansetron—a 5-HT₃ receptor antagonist that is commonly prescribed for treatment of nausea and vomiting in pregnancy—is limited and conflicting. Some recent studies reported a 1.5-fold to twofold increase in the risk of cardiac defects and oral clefts (in particular cleft palate) in newborns exposed to ondansetron during pregnancy, but residual confounding and chance have both been posited as alternative explanations.

Objectives: To examine the risk of major cardiac malformations and oral clefts associated with ondansetron use in a large national cohort of publicly insured pregnant women in the United States.

Methods: We conducted a cohort study nested in the Medicaid Analytic eXtract for 2000–2013. We examined the risk of major cardiac malformations and oral clefts in women who filled ≥ 1 prescription for ondansetron during the first trimester versus unexposed women. We adjusted for confounding through fine stratification on the propensity score (PS), estimated in a logistic regression model including treatment indication, demographics, maternal comorbidities, co-medications, and health care use. Relative risks (RR) were estimated in generalized linear models. A negative control analysis assessed the risk of malformations in women who filled their first ondansetron prescription in gestational months 5–8, which is after the etiologically relevant window. As a secondary approach, high-dimensional (hd)-PS analyses were used to account for proxies of unmeasured confounding.

Results: The cohort consisted of 1 816 414 pregnancies, of which 88 467 (4.9%) were exposed to ondansetron during the first trimester. Use increased from $<1\%$ in 2000 to 12% in 2013. The unadjusted RR was 1.12 (95% CI, 1.04–1.20) for cardiac malformations (835 exposed and 14 577 unexposed cases) and 1.26 (1.05–1.51) for oral clefts (124 exposed and 1921 unexposed cases). The RR attenuated in PS-adjusted analyses for cardiac malformations (0.99, 0.93–1.06), but not for oral clefts (1.24, 1.03–1.48). The PS-adjusted association for cleft palate was 1.20 (0.94–1.55) (65 exposed and 988 unexposed cases). Results were consistent with hdPS adjustment. No association was observed for exposure in months 5–8.

Conclusions: In this large pregnancy cohort with careful control for confounding, we did not confirm earlier findings of an increased risk for cardiac malformations. A small increase in the risk of oral clefts cannot be excluded, but the risk is much smaller than previously suggested, corresponding to about 3 additional cases per 10 000 women treated.

27 | Rurality and variability in opioid use among pregnant women

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Background: Opioid use has increased in the past years and remains high in the general population. Few studies have evaluated the patterns of opioid use among pregnant women or assessed opioid use by the rurality of their residence.

Objectives: To describe patterns of opioid use and discontinuation during preconception and pregnancy and explore variability by rurality.

Methods: We characterized monthly opioid use among pregnant women age 18–45 years enrolled in Tennessee Medicaid from preconception (PC: 90 days before last menstrual period) through postpartum (PP: 42 days after delivery) [2006–2014]. Proportions of prevalent opioid use (≥ 1 opioid prescription) and new opioid use (≥ 1 opioid prescription among those without prior use) were calculated per month and by pregnancy stage (PC, first trimester [1T], second trimester [2T], third trimester [3T] and PP). Discontinuation of opioid use during each pregnancy stage was assessed by calculating the proportion of subjects without opioid use in the current month among the eligible population with ≥ 1 opioid prescription in the prior month during a previous pregnancy stage. We also examined patterns of opioid use by rurality based on women's county of residence and the Waldorf's Index.

Results: The average monthly proportion of opioid use among all pregnant women was 7.7% (median eligible pregnant women per month: 11 782) with hydrocodone being the most commonly used opioid. The average monthly proportion of opioid use among pregnant women was generally highest in 2009 (PC: 12.9%, 1T: 9.7%, 2T: 8.5%, and 3T: 8.0%). Since 2009, opioid use decreased during PC to 8.3% (36% reduction), during 1T to 5.8% (40% reduction), during 2T to 4.7% (44% reduction), and during 3T to 4.7% (41% reduction). There was a similar decrease in new users across all stages. The proportion of women discontinuing opioid use upon entering the 1T increased 10% after 2010, yet discontinuation upon entering the 2T and 3T decreased in the study period (19% and 24%, respectively). Opioid use was highest in rural counties across all stages of pregnancy compared with urban counties throughout the study period. Similarly, rural counties had lower rates of discontinuation than urban counties across all pregnancy stages.

Conclusions: Opioid use during all stages of pregnancy has declined in Tennessee but remains common. The higher use of opioids in rural versus urban counties represents further opportunity to continue improving opioid prescribing.

28 | Comparative safety of ondansetron use during pregnancy

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Background: Recent data suggest ondansetron is being used off-label by ~20% of pregnant women to treat nausea and vomiting of pregnancy despite inadequate evidence of its safety.

Objectives: Evaluate the safety of ondansetron use during early pregnancy compared with alternatives for the outcomes of preterm birth, gestational hypertension, and preeclampsia.

Methods: Using the MarketScan Commercial Claims and Encounters Database, a cohort of privately insured pregnant women in the United States with live births from January 2000-September 2016 was created. Women were included if they filled a prescription for ondansetron or comparator antiemetics (metoclopramide, promethazine) during the first 20 weeks of pregnancy. Antiemetic exposure groups were defined by first prescription filled. Preterm birth was defined as birth at ≤ 252 days of gestation, determined with an algorithm for gestational age at birth using ICD-9 codes at delivery. Gestational hypertension and preeclampsia were defined using ICD-9 codes. Risk ratios and 95% confidence intervals were estimated using log-binomial regression. Confounding by age, comorbidities, and medication use was controlled using stabilized inverse probability of treatment weights.

Results: There were 305 807 pregnancies ending in live birth with at least one prescription for an antiemetic in the first 20 weeks of gestation. Defining exposure groups by first antiemetic filled, 189 874 pregnancies (62%) had ondansetron exposure, 97 195 pregnancies (32%) had comparator antiemetic exposure, and 18 738 pregnancies (6%) had exposure to both groups on the same day and were therefore excluded. After weighting, there were no meaningful differences between groups for any potential confounders. There was no clinically meaningful increase in risk of preterm birth (RR = 1.03, CI 1.00, 1.06) or preeclampsia (RR = 0.97, CI 0.94, 1.00) for ondansetron users. Risk of gestational hypertension was decreased among ondansetron users (RR = 0.91, CI 0.87, 0.94). Sensitivity analyses defining exposure by initial prescriptions in the first 10 weeks of pregnancy showed a small protective effect of ondansetron exposure for preeclampsia (RR = 0.93, CI 0.89, 0.98), and results for preterm birth and gestational hypertension were unchanged.

Conclusions: No meaningful difference in the risk of preterm birth was detected between pregnancies exposed to ondansetron or comparator antiemetics. A possible protective effect was observed for gestational hypertension and preeclampsia with ondansetron use; however, the relative differences were small.

29 | Opioid dispensing after vaginal delivery

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Background: Although pain following vaginal delivery is common, it is generally short-lived and mild to moderate in severity.

Objectives: Describe opioid dispensing after vaginal delivery among a national cohort of commercially insured women.

Methods: We used Truven MarketScan claims to identify women hospitalized for vaginal delivery 2003-2015 who were opioid-naïve for 12 weeks prior to delivery admission and report the proportion of women dispensed an oral opioid within 1 week of discharge, the initial median oral morphine milligram equivalent (MME) dose dispensed, and the frequency of opioid refill during the 6 weeks post-discharge. We also evaluated predictors of opioid dispensing using multivariable logistic regression, and separately assessed variation in MME dispensed by associated conditions and procedures.

Results: Among 1 345 244 women having a vaginal delivery, 28.5% were dispensed an opioid within 1 week of discharge, with a median (interquartile range, IQR; 10th-90th percentile) dose of 150 (113-225; 80-345) MME, equivalent to 20 tablets (IQR 15-30; 10th-90th percentile 11-46) of oxycodone 5 mg. The most commonly dispensed opioids were hydrocodone (44.7%), oxycodone (34.6%), and codeine (13.1%). Opioids were more commonly dispensed to women from the South, North Central, and West regions, compared with women from the Northeast, as well as women with a smoking-related claim, use of benzodiazepines or antidepressants, or undergoing tubal ligation, operative vaginal delivery, or third- or fourth-degree perineal lacerations. Median MME dose did not vary by additional procedures (operative vaginal delivery, tubal ligation, and third- or fourth-degree perineal laceration repair) performed at the time of delivery. At 6 weeks discharge, 8.5% filled ≥ 1 additional opioid prescription, but the frequency of refill was independent of the initial dose dispensed.

Conclusions: Opioid dispensing after vaginal delivery exceeds expectations set by recommendations, occurs in high doses, and is associated with patient and regional characteristics. The initial opioid dose was unrelated to refill frequency. As greater than 3 million vaginal deliveries occur annually in the United States, curbing unnecessary opioid prescribing could have a significant public health impact by reducing leftover opioid medication available for diversion or misuse.

30 | A real-world comparison of effectiveness and safety outcomes between clinical trial eligible and ineligible patients in the British Association of Dermatologists Biologic Interventions Register (BADBIR)

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Background: There is preliminary evidence that psoriasis patients eligible for clinical trials of biologics are not representative of real-world patients.

Objectives: To determine whether patients enrolled in BADBIR identified as eligible or ineligible for clinical trials differed in effectiveness and safety profiles.

Methods: BADBIR is a pharmacovigilance register of psoriasis patients exploring the long-term safety of biologics compared with

conventional systemic therapies. Patients with at least 6 months of follow-up who registered on Enbrel ($n = 1509$), Humira ($n = 4000$), or Stelara ($n = 1627$) were included in the analysis. Eligibility criteria were extracted from phase III trials submitted for licensing. The analyses focused on patients classified as eligible and ineligible. Effectiveness was calculated by linear regression of absolute change in Psoriasis Area and Severity Index (PASI) from baseline to 12 months. Incidence rate ratios (IRR) were calculated between the eligibility categories for the total number of serious adverse events (SAEs) reported within 12 months of initiating therapy.

Results: 838 (56%) Enbrel, 2219 (56%) Humira, and 754 (46%) Stelara registrations were classified as eligible with 367 (24%), 282 (7%), and 394 (24%) registrations classified as ineligible, respectively. Absolute changes in PASI at 12 months for ineligible Humira and Stelara patients were significantly smaller than for eligible patients (β [95% confidence interval]; 2.7, [0.5, 4.9] and 1.8 [0.1, 3.5], respectively). There was no significant difference in absolute change in PASI for Enbrel patients at 12 months. SAE rates were highest in the ineligible patients, with significantly higher IRR compared with eligible patients (IRR [95% confidence interval]; Enbrel 1.9, [1.4, 2.6]; Humira 2.0 [1.5, 2.6]; Stelara 2.8 [2.1, 3.8]).

Conclusions: Patients classified as ineligible for clinical trials for Enbrel, Humira, and Stelara have lower effectiveness and higher SAE rates than those who would be eligible. Thus, clinical trial findings are not representative of real-world patients.

31 | The risk of keratinocyte carcinoma (KC) in psoriasis patients receiving biologic therapy compared with conventional systemic therapy: Results from the British Association of Dermatologists Biologic Interventions Register (BADBIR)

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Background: Whether psoriasis patients exposed to biologic therapies have an elevated risk of KC (basal cell carcinoma [BCC] or cutaneous squamous cell carcinoma [cSCC]) remains uncertain.

Objectives: To determine whether such patients were at higher risk of developing a KC compared with those on conventional therapy.

Methods: BADBIR, a pharmacovigilance register of psoriasis patients, explores the long-term safety of systemic therapies. Patients with chronic plaque psoriasis registering to BADBIR on their first biologic or a conventional therapy, who had at least one follow-up completed, were included in analyses if they were of white ethnicity, Fitzpatrick skin types 1–4, and reported no previous cancers. Confounding factors included age; sex; smoking; and previous exposure to acitretin, psoralen ultraviolet-A (PUVA), ciclosporin, and/or PUVA and ciclosporin. Propensity score-weighted Cox-proportional hazard models estimated the hazard ratio (HR) for developing a first KC or separately, first BCC or cSCC.

Results: In total, 5672 patients initiating biologic therapy and 3188 patients on conventional therapy who met the entry criteria were identified with 20 558 and 7829 person-years of follow-up, respectively. During follow-up, 74 (1.3%) patients initiating a biologic therapy were diagnosed with their first KC (43 BCC; 34 cSCC first) and 22 (0.7%) patients receiving conventional therapy with their first KC (15 BCC; 10 cSCC first). No significant difference in risk was observed for developing a KC (adjusted HR 1.05; 95% CI 0.64, 1.73), BCC (0.84; 95% CI 0.45, 1.54), or cSCC (1.20; 95% CI 0.57, 2.50) on biologic compared with conventional therapy.

Conclusions: Biologic therapy does not appear to confer a higher risk of developing a first KC as compared with conventional therapy in psoriasis patients. These data will help inform clinical decision making in psoriasis patients at risk of KC in whom biologic or conventional therapy is being considered.

32 | Comparative effectiveness of tumour necrosis factor inhibitor therapy vs conventional synthetic DMARDs on need for joint replacement among rheumatoid arthritis patients: A propensity score-matched analysis of UK registry data

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Background: Previous ecological data suggest the incidence of joint replacement has declined among rheumatoid arthritis (RA) patients following approval of tumour necrosis factor inhibitors (TNFi). However, patient-level data on TNFi use and need for total hip (THR) or knee (TKR) replacement are lacking.

Objectives: To estimate the comparative effectiveness of TNFi compared with conventional synthetic disease modifying anti-rheumatic drug (csDMARD) use on subsequent need for THR or TKR (primary outcomes) or other joint replacement (OJR) in RA.

Methods: A propensity score (PS)-matched cohort was analysed using the British Society for Rheumatology Biologics Registry for RA (BSRBR/RA) data (2001–2016). Multiple imputation was used to deal with missing data. The PS (ie, probability of receiving TNFi conditional on observed characteristics) was estimated using logistic regression. This included age, gender, ethnicity, index of multiple deprivation, BMI, smoking, year of registration, duration of RA, DAS-28, HAQ, SF36, ACR criteria, comorbidities, and comedications. A PS caliper of 0.2 was used to match all incident TNFi users to csDMARD users (with replacement) with a 1:1 ratio. Weighted Cox regression was used to estimate the impact of TNFi use on study outcomes, adjusted for any remaining unbalanced confounders (SMD > 0.1).

Results: Our 1:1 matched cohort contained a total of 19 116 patient records. THR rate was 6.30/1000 PYs (95% CI: 4.24-9.76) and 5.22/1000 PYs [CI: 4.66-5.88] in the csDMARD and TNFi cohorts, respectively. TKR rate was 8.09/1000 PYs (CI: 5.32-12.89) and 8.89/1000 PYs (CI: 8.13-9.72), respectively. There was no significant association between TNFi use and THR or TKR (HRs = 0.86 (CI: 0.60-1.22) and 1.11 (CI: 0.84-1.47), respectively), although when analyses were restricted to patients with DAS > 5.1 (as per NICE guidance), these HRs were 0.74 (CI: 0.51-1.05) and 0.95 (CI: 0.71-1.26), respectively. Among those over 60 years old, TNFi was associated with a significant reduction in THR (HR = 0.60 [CI: 0.41-0.87]) but not TKR (HR = 1.31 [CI: 0.87-1.99]). THR but not TKR rates were also reduced among those with above average HAQ score. No significant associations were found for OJR.

Conclusions: Our findings suggest TNFi use may reduce the need for THR in older and more severe RA patients, although no reduction was seen for TKR or OJR. Further work is needed to confirm these results.

33 | The association of biologic drug-levels with infection risk: Results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

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Background: High-dose biologic drugs are associated with an increased serious infection (SI) risk [1]. It is feasible that high biologic levels predict dose-dependent adverse events such as SI. No registries have systematically evaluated the effect of drug levels on infection risk.

Objectives: To assess the effect of biologic drug levels in rheumatoid arthritis (RA) patients on (i) all infections (AI) and (ii) SI (infections requiring hospitalization, IV antibiotics or lead to death).

Methods: Patients were selected if they were recruited to both large UK national prospective RA cohorts: the British Society for Rheumatology Biologics Register-RA (BSRBR-RA) and the Biologics in RA Genetics and Genomics Syndicate (BRAGGSS) to allow serum sample measurement, exposure, and systematic adverse event capture. Biologic drug levels were measured at 3/6/12 months after biologic initiation and stratified as low/normal or high drug levels as per thresholds defined using concentration-effect curves generated for each drug. The risk of first and total infections within the first year was analysed. Events occurring on drug or within 90 days of last dose were included. The risk of an event was compared between low/normal vs high drug level groups using Cox proportional-hazard models. Factors affecting both drug levels and infection risk were adjusted for in the models.

Results: 703 patients (286 etanercept, 179 adalimumab, 120 certolizumab, 104 tocilizumab, and 14 infliximab) had clinical data and serological samples. 74% were women, mean (SD) age 58 (12) years, on a first biologic (89%). The crude rate/1000 pyrs was 314 and 464 for AI; 54 and 76 for SI in the low/normal and high drug level groups, respectively. The adjusted hazard ratio (HR) for AI within the first year differed significantly between the two groups with the high drug level group having 50% higher risk of AI (HR: 1.51; 95% CI: 1.14, 2.01). For SI, the the adjusted hazard ratio was 1.26 (95% CI: 0.50, 3.16). The most common types of AI in the high drug level group were lower (34%) and upper (16%) respiratory tract infections, urinary tract infections (15%), and skin infections including shingles (8%).

Conclusions: RA patients with high biologic drug levels have a higher risk of infection. Monitoring drug levels may be helpful in prediction of infection. In disease remission patients with high drug levels, biologic dose tapering may lower infection risk.

Reference: [1] Singh JA, Cameron C et al. Lancet 2015;368:258-265

34 | Tumor necrosis factor-alpha inhibitors and risk of non-Hodgkin lymphoma in a cohort of adults with rheumatologic conditions

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Background: Based on limited evidence, the US Food and Drug Administration (FDA) issued a black box warning for the use of tumor necrosis factor-alpha inhibitors (TNFIs) and risk of non-Hodgkin lymphoma (NHL) and earlier initiation of these medications for the treatment of rheumatologic conditions is increasing.

Objectives: Our purpose was to determine the risk of NHL associated with TNFIs, their duration of use, and by types of anti-TNF agents.

Methods: We conducted a nested case-control study within a retrospective cohort of adults with rheumatologic conditions in the Truven Health MarketScan® Research Database between 2009 and 2015. Patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis ages 18 years and older without prevalent cancer or HIV/AIDS were included in our study. Medical and pharmacy claims data were used to determine use of TNFIs (infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol) and conventional-synthetic disease-modifying antirheumatic drugs (csDMARDs). To estimate risks of NHL, we used conditional logistic regression models and calculated adjusted odds ratios (aOR) and 95% confidence intervals (CI) associated with TNFI use.

Results: From a retrospective cohort of 55 446 adult patients, 101 NHL cases and 984 incidence density sampled controls matched on age, gender, and rheumatologic indication were included in our analysis. Compared with controls, NHL cases had greater use of TNFIs (33%

vs 20%) but were similar with respect to use of csDMARDs (70% vs 71%). Ever use of TNFIs was associated with a nearly twofold increased risk of NHL (aOR = 1.93; 95% CI 1.16-3.20; $P = 0.011$) with only suggestion of increased risk with duration of use (P -trend = 0.053). TNF fusion protein (etanercept) was associated with increased risk of NHL (aOR = 2.73; 95% CI 1.40-5.33; $P = 0.003$), whereas risk with anti-TNF monoclonal antibodies was increased but not statistically significant (aOR = 1.77; 95% CI 0.87-3.58; $P = 0.112$). In sensitivity analyses evaluating channeling bias by unmeasured rheumatologic disease severity, three times greater prevalence of high disease severity in TNFI users and a more than fourfold increased risk of NHL with severe rheumatologic disease would be needed to entirely account for our findings.

Conclusions: Our findings support the FDA black box warning for risk of NHL. Continued surveillance and awareness of this rare but serious adverse outcome are warranted with new TNFIs and biosimilar products forthcoming.

35 | Methotrexate use and the risk for cardiovascular disease among rheumatoid patients initiating biologic disease-modifying antirheumatic drugs

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Background: Methotrexate (MTX) has been associated with reduced risk for CVD among rheumatoid arthritis (RA) patients never exposed to biologic disease-modifying antirheumatic drugs (bDMARDs). Effect of MTX use on CVD risk among RA patients initiating bDMARDs remains unknown.

Objectives: The objective of this study was to assess the CVD risk associated with MTX use among RA patients initiate bDMARDs, overall, and by each bDMARDs initiated.

Methods: A retrospective cohort study was conducted using 2006-2015 Medicare claims data for RA patients. Follow-up started at initiation and ended at earliest of (1) end of exposure of the specific bDMARDs agent (days of supply plus 90 days extension), (2) switched to other bDMARDs or tofacitinib, (3) CVD event, (4) death date, (5) loss of Medicare coverage, and (6) end of study. MTX use was defined as (1) concomitant MTX use, with prescription for MTX within 120 days after index date and (2) time-varying MTX, defined as prescription date to prescription date plus days of supply without extension. The primary outcome was composite of incident MI, incident stroke and fatal CVD. Incidence rates (IR) and 95% confidence intervals (CI) were calculated using Poisson regression. Association between MTX use and risk of CVD were assessed using Cox regression. Contrast (MTX yes vs no) was conducted to examine the association between MTX and risk for CVD for each underlying bDMARDs in one model.

Results: A total of 88 255 bDMARDs initiations were included in the study. The average age was 64.6 (12.3) years, 84.0% were female, 68.2% were non-Hispanic white. The crude IRs for CVD were 13.1

(95% CI: 12.2-14.0) and 18.7 (17.6-19.9) events per 1000 person-years for RA patients with and without concomitant MTX, respectively. The crude IRs for CVD were 12.1 (11.1-13.2) and 17.9 (16.9-18.8) for RA patients with and without time varying MTX, respectively. The overall HR was 0.77 for concomitant MTX and 0.73 for time-varying MTX. Interaction between MTX and bDMARDs was significant. The contrast HRs for concomitant MTX ranged from 0.61 (0.37, 1.01) for golimumab initiators to 0.97 (0.74, 1.26) for adalimumab initiators. The contrast HRs for time-varying MTX ranged from 0.58 (0.35, 0.96) for certolizumab initiators to 0.90 (0.68, 1.18) for adalimumab initiators. Results were robust in sensitivity and subgroup analyses.

Conclusions: Our observational study suggests an overall 23% reduction of CVD risk associated with concomitant MTX use. The effect sizes vary among background bDMARDs.

36 | Agomelatine and other antidepressants and the risk of acute liver injury (ALI), a pass in four European countries

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Background: Agomelatine is a melatonergic agonist and 5-HT_{2C} antagonist indicated for depression in adults. Hepatotoxicity is an identified risk in the risk management plan

Objectives: To evaluate the risk of ALI associated with agomelatine and other antidepressants

Methods: Nested case-control study of new users of agomelatine (main exposure), citalopram (common comparator), fluoxetine, paroxetine, sertraline, escitalopram, mirtazapine, venlafaxine, duloxetine, and amitriptyline from 2009 to 2014. Data sources included EpiChron and SIDIAP (Spain), GePaRD (Germany), and national registers in Denmark and Sweden. Three endpoints were identified using ICD codes: primary (specific codes) and secondary (all codes) endpoints used only discharge diagnosis codes for ALI; the tertiary endpoint included

both inpatient and outpatient settings (all codes). Validation was implemented in Denmark, Spain, and Germany. Combined adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for current use were estimated by meta-analysis. Preplanned and two post hoc sensitivity analyses, one applying no liver-related exclusion criteria and one with all exclusion criteria but alcohol and drug abuse, were implemented.

Results: There were 3 238 495 new users of study antidepressants (74 440 of agomelatine). The positive predictive values for specific hospitalisation codes ranged from 60% to 84%. The agomelatine OR for the primary endpoint when compared with citalopram was 0.48 (CI, 0.13-1.71). Results were similar in the two post hoc sensitivity analyses, when no exclusion criteria were applied ($n = 117\ 240$ new users of agomelatine; OR, 0.37; CI, 0.19-0.74) and when all exclusion criteria except alcohol and drug abuse were applied ($n = 84\ 210$ new users of agomelatine; OR, 0.47; CI, 0.20-1.07). Results for the other two endpoints and for preplanned sensitivity analyses were similar to the results of the primary endpoint. Regarding other study antidepressants compared with citalopram, most OR point estimates were also below one except for the tertiary endpoint, for which paroxetine and venlafaxine showed increased risk of ALI.

Conclusions: This study suggests that, among patient populations in health care systems with similar prescription patterns and risk minimisation measures, agomelatine does not seem to be associated with an increased risk of ALI. When compared with citalopram, most antidepressants evaluated had OR point estimates below 1.

37 | Risk of traumatic brain injury in elderly new users of antidepressants

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Background: In the elderly, falls are the main cause of traumatic brain injuries (TBI), a major health problem leading to short-term mortality and disability. Antidepressants (AD), frequently used in this group, have been associated with increased risk of falls and hip fracture, but the association with TBI is still unclear.

Objectives: To estimate the risk of TBI in elderly new users of AD.

Methods: Based on data from the German Pharmacoepidemiological Research Database (GePaRD), we conducted a case-control study nested in a cohort of new users of AD (ATC code N06A) ≥ 65 years, during 2005-2014. Cases were identified through ICD-10-GM main hospital discharge code for TBI. For each case, up to 100 controls were selected using incidence density sampling with matching on sex, age, and length of follow-up. Exposure to AD was ascertained at index date (ID) based on the days of supply of the last dispensing estimated as 3.5 times (sensitivity analysis: 2.5 times) the number of defined daily doses (DDD) to account for lower dosage and categorized as (a) current use (supply overlapped ID), (b) recent use (supply ended within 30 days before ID), (c) past use (supply ended 31 to

90 days before ID), and (d) remote use of any AD (supply ended ≥ 91 days before ID). Conditional logistic regression was used to estimate adjusted odds ratios (aORs), with 95% confidence intervals (CI), using remote use as reference category. The model was adjusted for co-morbidities, co-medications, Charlson co-morbidity index, polypharmacy, and nursing home residence.

Results: In the cohort of 701 309 new AD users, 18 224 cases of TBI were identified and matched to 1 820 362 controls. In both cases and controls, 70.4% were women and median age was 80 years (interquartile range 74-85). The aOR (95% CI) was 1.85 (1.77-1.93) for current use of selective serotonin reuptake inhibitors (SSRI), 1.84 (1.69-2.00) for selective serotonin noradrenalin reuptake inhibitors (SSNRI), 1.22 (1.15-1.29) for tri- and tetracyclic AD (TCA), and 1.66 (1.53-1.79) for multiple AD. The aOR in recent and past users, respectively, was 1.36 (1.14-1.64) and 1.26 (1.09-1.47) for SSRIs, 1.22 (0.82-1.81) and 0.96 (0.66-1.39) for SSNRIs, 1.11 (1.00-1.22) and 0.97 (0.88-1.07) for TCAs, and 1.60 (1.18-2.16) and 1.42 (1.07-1.88) for multiple AD.

Conclusions: Risk of TBI was increased in current users of AD and was higher for SSRIs, SSNRIs, and multiple ADs than for TCA. For all AD, risks remained elevated shortly (30 days) after end of supply and only for SSRIs beyond this time window. The results were robust in sensitivity analysis.

38 | Zolpidem use and suicide death in South Korea: A population-based case-control study

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Background: Zolpidem is one of the most commonly prescribed hypnotics, both globally and in South Korea. In general, it has been believed to be safer as a sleeping pill than benzodiazepines. However, several adverse effects of zolpidem have been reported including sleep walking, sleep-driving, involuntary self-intoxication, and sleep-related amnesic eating behavior. Recently, several reports have expressed increasing concerns about the suicide risk of zolpidem use.

Objectives: To investigate whether zolpidem use is associated with suicide death, in adults.

Methods: We conducted population-based, case-control study using the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database in South Korea. In our case-control study, the case group was determined to be those with a record of suicide (ICD-10 codes; X-60-X84 and Y87.0) between January 1, 2004, to December 31, 2013, aged over 20 years. The control group was randomly selected from patients without a record of suicide with 10 case-control ratio of 1:10, matched on age, sex, index year, region, income level, and health insurance type. We quantified zolpidem use during a period of 2 years before suicide using the defined daily dose (DDD) and duration of use in days. To compare the risk of suicide among patients who did and did not use zolpidem, adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were estimated using conditional multivariate logistic regression.

Results: The percentage of patients who used zolpidem was significantly higher in the case group (451 of 1928 [23.4%]) than in the control group (832 of 18 404 [4.5%]). After controlling for several potential confounders (benzodiazepines, antidepressants, opioid analgesics, mental disorders, substance use, insomnia, and chronic diseases), the use of zolpidem was significantly associated with suicide (aORs, 2.09; 95% CI, 1.74-2.52). Dose-response relationships between zolpidem and suicide were observed (for trend, $p < .0001$). Consistent findings were observed when analyses were limited to suicide death cases and controls (aORs, 2.08; 95% CI, 1.73-2.51) and non-medication poisoning suicide death cases and controls (aORs, 2.10; 95% CI, 1.74-2.53).

Conclusions: We found a significant and positive association between zolpidem use and suicide death. Zolpidem should be prescribed cautiously, only for a short-term use, and with a due caution of increased suicide risk.

39 | Abstract Withdrawn

40 | Degree of serotonin reuptake inhibition of antidepressants and the risk of ischemic stroke and myocardial infarction

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Background: Antidepressants inhibiting serotonin reuptake have an antiplatelet action that varies with the degree of serotonin reuptake inhibition. However, the effect of such antidepressants on arterial ischemic disease is unclear.

Objectives: To assess the risk of ischemic stroke and myocardial infarction (MI) associated with the degree of serotonin reuptake inhibition of antidepressants.

Methods: Using the UK Clinical Practice Research Datalink, we formed a cohort including new users of selective serotonin reuptake inhibitors (SSRIs) or third-generation antidepressants aged 18 years or older between 1995 and 2014. Antidepressants were classified based on the degree of serotonin reuptake inhibition. With use of a nested case-control approach, each case of a first ischemic stroke or MI identified during follow-up was matched with up to 30 control individuals on age, sex, calendar time, and duration of follow-up. We estimated incidence rate ratios (RRs) and 95% confidence intervals (CIs) of ischemic stroke or MI associated with current use of strong compared with weak inhibitors of serotonin reuptake using conditional logistic regression. In a secondary analysis, we compared the risk of ischemic stroke or MI between SSRIs strongly inhibiting serotonin reuptake and SSRIs intermediately inhibiting serotonin reuptake.

Results: The cohort included 938 388 incident users of SSRIs or third-generation antidepressants (64% female). During follow-up, 15 860 cases of ischemic stroke and 8626 cases of MI were

identified and matched to 473 712 and 258 022 controls, respectively. Current use of strong inhibitors of serotonin reuptake was associated with a decreased risk of ischemic stroke (RR, 0.88; 95% CI, 0.80-0.97) but no difference in the risk of MI (RR, 1.00; 95% CI, 0.87-1.15) relative to weak inhibitors of serotonin reuptake. Current use of SSRIs strongly inhibiting serotonin reuptake was associated with no difference in the risk of ischemic stroke (RR, 0.98; 0.92-1.04) or MI (RR, 1.09; 95% CI, 1.00-1.18) relative to SSRIs intermediately inhibiting serotonin reuptake.

Conclusions: Antidepressants strongly inhibiting serotonin reuptake could be associated with a small decrease in the risk of ischemic stroke compared with antidepressants weakly inhibiting serotonin reuptake, while no difference was observed regarding the risk of MI. The degree of serotonin reuptake inhibition does not seem to have a pivotal effect on ischemic risk.

41 | Risk of suicide with concurrent use of benzodiazepine, antidepressant, opioid analgesic, and zolpidem: A population based case-control and case-crossover study

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Background: Previous studies have reported the association between zolpidem and suicidality. However, current evidence may be the results of co-prescribed medications that are suspected to be associated with suicide, such as benzodiazepine, antidepressant, and opioid analgesic.

Objectives: To evaluate whether the concurrent use of benzodiazepine, antidepressant, and opioid analgesic with zolpidem increase or trigger the risk of suicide compared with zolpidem-only use.

Methods: We conducted a population-based case-control and case-crossover study using the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database. Cases were defined as having a suicide record (ICD-10 codes: X-60-X84, Y87.0) between January 1, 2004, to December 31, 2013, aged over 20 years. For the case-control design, 10 controls were matched to each case by age group, sex, index year, region, income level, and type of health insurance. At first, exposure categorized into 15 mutually exclusive groups according to the combination of benzodiazepine, antidepressant, opioid analgesic, and zolpidem and was assessed during 60 days prior to suicide. Finally, only the results of the eight groups, including zolpidem, were displayed for comparison. For the case-crossover analysis, we set hazard period as 60 day and corresponding 5 control periods with same length of hazard period. We conducted conditional logistic regression to estimated odds ratios and their 95% confidence interval.

Results: For case-control study, we selected 1928 cases and 18 404 matched controls. For the case-crossover analysis, we selected 1803 cases exposed in hazard period and matched 9015 control periods. In case-control study, we found the risk of suicide was 2.80-fold

higher in the triple combination of benzodiazepine, antidepressants with zolpidem compared with zolpidem-only use (aOR = 2.80; 95% CI, 1.35-5.70). However, in the case-crossover study, suicide risk decreased 1.80-fold, and statistical significance was lost (aOR = 1.80; 95% CI, 0.94-3.44).

Conclusions: The conflicts between the current traditional case-control study and case-crossover study results might mean that concurrent use of benzodiazepine and antidepressant with zolpidem is associated with increased risk of suicide but is less relevant to the trigger of suicide compared with zolpidem-only use. On the other hand, it could be due to residual confounding which not entirely be ruled out in case-control study.

42 | Sequential and SequentialDesign: Tools for prospective sequential medical product safety surveillance

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Background: Prospective sequential medical product safety surveillance provides a mechanism for continuous monitoring of particular exposure-outcome pairs for early warning of safety signals of interest.

Objectives: This workshop will teach the theory of prospective sequential observational surveillance, describe recent implementation efforts and their challenges while testing known exposure-outcome pair associations, and demonstrate how to use Sequential and SequentialDesign (R packages with a web-based interface at <https://www.sequentialanalysis.org/>) using simulated data. Investigators that seek to learn exact sequential surveillance statistics for matched, stratified, or self-controlled inferential designs will benefit from attending.

Description: The workshop agenda follows:

1. Overview of exact sequential statistics for observational data (Kulldorff, 15 min)
2. Findings from recently completed implementation activities (Eworuke, 15 min):
 - a. We will review prior work on prospective sequential surveillance of the risk of angioedema following angiotensin converting enzyme inhibitor use as compared with beta-blocker use.
 - b. Challenges of a dynamically updated database when follow-up data for individuals spans multiple monitoring periods.
3. Findings from implementing near real-time vaccine safety surveillance using data from the Clinical Practice Research Datalink (CPRD) (Leite, 15 min):
 - a. Two vaccine-outcome pairs were considered: seasonal influenza Guillain-Barré syndrome and measles-mumps-rubella vaccine (MMR)-febrile seizures using the Poisson and binomial versions of sequential statistics.

4. Interactive demonstration of sequential statistical software (<https://www.sequentialanalysis.org/>) with audience participation (Maro, 20 min). Audience members will have log in to use the software and upload data using simulated datasets and then will execute exact sequential testing on those datasets.
5. Interactive monitoring exercise (Maro, 20 min). Audience members will manipulate the set-up parameters (eg, total alpha spending function shape, maximum length of surveillance in events, and minimum monitoring values) to understand their impact on monitoring.
6. Discussion and questions from the audience (All, 5 min).

43 | Bringing patient-generated data into pharmacoepidemiology: The who, what, why, where, when, and how

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Background: Pharmacoepidemiology research is often conducted using data reported by clinical staff in health systems, including electronic health records and administrative databases. We rely on data such as prescriptions and clinical code lists as a proxy for what medication has been taken and the health outcomes following drug exposure. Yet the patient often contributes no data, despite them being the sole person who knows what medication has been taken and what has happened to their health thereafter. The huge uptake of consumer technology means we have an opportunity to change this, leading to the challenge of further developing pharmacoepidemiological methods to deal with this new data source.

Objectives: This symposium will introduce to ISPE delegates the new world of digital epidemiology and where it fits for pharmacoepidemiology. It will describe the opportunities and challenges from actively-contributed patient-generated data through a series of talks and worked examples.

The symposium will be a useful introduction and showcase of this new area for all ISPE delegates, including academics, industry representatives, and regulators, especially those interested in incorporating digital patient-generated data into their research. The panel includes representatives from all of these stakeholder groups.

Description: Presentations will introduce concepts and terminology, current best practice, and lessons learnt from real studies. Talks and discussion will cover the following topics:

- An overview of how patient-generated data might fit in a pharmacoepidemiology study
- Considerations when designing a system for collecting patient-generated data and implications for analysis

- A scan of current best practice in collecting patient-generated data about medication use, disease symptoms, and adverse events
- Learning about recruitment and ongoing collection of frequent patient-generated data
- Understanding regulatory considerations
- Analytical challenges and opportunities from frequent longitudinal patient-generated data

44 | Time series analysis; where are we now, and what will the future bring?

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Background: Time series (TS) analyses, including interrupted time series (ITS), have steadily increased in popularity over the last few years. They have been used to study the impact of interventions on prescribing behavior, drug utilization patterns, and drug-related outcomes in many areas, including effects of changes in drug pricing and reimbursement policies, new guidelines and treatment recommendations, and the dissemination of drug safety warnings. Despite the relatively simple ideas behind the TS approach, complex mechanisms are hidden in the methods. A good understanding beyond the basics of TS analysis is necessary for the optimal application of these techniques in pharmacoepidemiological studies.

Objectives: After the symposium, attendees will be able to critically assess (I)TS papers, will have a starting point for conducting their own (I)TS research, have been introduced to advanced TS modelling, and have gotten a glimpse of the application of TS principles in other areas of pharmacoepidemiology. The target audience includes academics, industry representatives, regulators, and policy makers interested in evaluating effects of, eg, health policy interventions or risk minimization efforts where it is often difficult to perform controlled studies.

Description: The first speaker will introduce the ITS method toolbox and show how data management and analysis for ITS is done in SPSS and SAS. Examples from studies of policy interventions on drug utilization are used. The second speaker will continue on how to interpret ITS results and what pitfalls there are, given experiences from recent literature reviews of safety communication by regulatory authorities across the world. The importance of TS to identify successful interventions will be illustrated based on three published systematic reviews (Dusetzina et al, *Med Care* 2012; Pienig et al, *Drug Saf* 2012; Goedecke et al, *BCJP* in press). Then the third speaker shows the technical parts of different TS techniques, including ARIMA modelling, using examples from R. Topics covered include how to account for general trends, cyclic and seasonal effects, averaging, and forecasting. The last speaker will

finalize by relating (I)TS to the underlying processes of treatment choice, initiation, switching, and discontinuation and putting it into the broader perspective of other analytical approaches used in longitudinal studies such as repeated cross-sectional or multistate models. The symposium will conclude with a moderated panel discussion with prompted input from the audience.

45 | Implementation science—The Art Nouveau of pharmacoepidemiology for improving risk mitigation in health care

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Background: To date, many risk minimization and communication programs required for medicinal products have failed to meet their goals. As these programs are complex interventions, their implementation process in real-world health care is a critical factor for success. Evaluation of program effectiveness is a regulatory requirement, and pharmacoepidemiologists have an important role in designing and conducting risk minimization evaluation studies. However, most study reports have so far provided little description and analytics regarding program implementation, including whether the program featured a dissemination strategy and how the dissemination to the patient was integrated in existing health care processes of prescribing, dispensing, and administration of medicines.

Objectives: The aims of this symposium are therefore to (1) introduce key implementation science methods and their critical importance for risk minimization and communication program success; (2) report first experiences from applying the recent RIMES Statement, which incorporates this approach and provides a checklist for the reporting quality of results from risk minimization evaluation studies in the published literature; (3) present, with the example of the recent EU teratogenic risk assessment of valproate, how implementation thinking can be applied to analysing input from patients and health care professionals for the evaluation and planning of risk minimization and communication programs; and (4) discuss how implementation science can enrich pharmacoepidemiological designs of post-authorisation safety and risk minimisation measures evaluation studies.

Description: 4 presentations and discussion with the audience: 1. Implementation science as a new methodological approach to risk mitigation; 2. The RIMES Statement—first experiences with the quality reporting checklist for risk minimization evaluation studies; 3. Implementation-based analysis of patients' and health care professionals' input to evaluating risk minimization measures—the case of valproate in the EU; 4. Implications of implementation science approaches for pharmacoepidemiology and study designs.

46 | Advances in the study of medication errors in computerized health care databases and spontaneous reporting systems in Europe and North America

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Background: Medication errors are preventable events that can lead to inappropriate medication use or cause patient harm in health care. Recent advances in large multisite electronic databases, coupled with changes in reporting requirements, and enhances to international data standards for spontaneous reporting systems, are creating new opportunities to better characterize the root causes and contributing factors of medication errors and to mitigate them.

Objectives: In this session, we share regulatory perspectives from the European Union and the United States on the evaluation and prevention of medication errors and discuss recent studies from EudraVigilance, CNODES (Canadian Network for Observational Drug Effect Studies), and FDA's Sentinel System. Researchers, industry, and regulators interested in medication error measurement and prevention would benefit, as the tools and approaches being developed can be more widely applied in other databases.

Description: The symposium will consist of five presentations (15 min each), followed by discussion (15 min). Speakers include two leads from EMA's and FDA's medication error analysis programs, and three academic investigators from CNODES and FDA's Sentinel System. Speaker 1 will discuss key concepts from the EU's 2015 Good Practice Guidance and present results from a 10-year comprehensive analysis of EudraVigilance data on medication errors. Speaker 2 will present FDA's perspective on the use of Sentinel in identifying medication errors to inform regulatory decision-making, potential future application of Sentinel in medication error surveillance, and ongoing collaborations with the International Conference on Harmonization. Speaker 3 will present a conceptual framework and safety evidence from Canada on the study of medication errors in drug claims databases. Speaker 4 will present results from an analysis of name confusion errors between Brillinta and Brintellix in the Sentinel System and how this approach could be generalizable for a wide range of medication errors. Speaker 5 will share results from a chart confirmed analysis in Kaiser Permanente Northern California characterizing the rate of wrong dose frequency error of methotrexate as a paradigm for evaluating future medication errors. Audience members should leave the symposium with new understanding of the opportunities and limitations of using electronic health care data for medication error surveillance.

47 | Propensity score matching versus propensity score fine stratification and coarsened exact matching in claims data

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Background: Criticisms of propensity score matching (PSM) have accrued in the literature. For example, it has been suggested that continuous deletion of matched sets in decreasing order of propensity score distance may lead to increased bias in the effect estimate. We present the results of a comparison of PSM with propensity score fine stratification (FS) and with coarsened exact matching (CEM). We chose these alternative techniques because of the suggestion of their superiority over PSM in the literature.

Objectives: Compare PSM with FS and CEM with respect to validity and precision of effect estimates using claims data.

Methods: We used data from the Pharmaceutical Assistance Contract for the Elderly database (PACE, n = 49 653, 19 pre-specified confounders) to assess the association between NSAIDs vs COX-2 inhibitors and gastrointestinal complications and data from the Medicaid Analytic eXtract database (MAX, n = 886 996, 20 pre-specified confounders) to assess the association between statins vs no statins and congenital malformations. PACE was analyzed with 50 and 100 additional empirical confounders selected from a high-dimensional propensity score algorithm. Three techniques were applied to each dataset: (1) 1:1 PSM using a nearest neighbor matching algorithm, (2) FS using 10, 50, and 100 strata ranked by the propensity score distribution of the exposed after deleting observations from non-overlapping propensity score regions, and (3) CEM using an auto-coarsening technique.

Our strategy generated 20 analytic datasets. For each analytic dataset, we compared the resulting relative risks (RR) and standard errors (SE) from weighted log binomial models, as well as the numbers of units remaining.

Results: For each PACE dataset, FS resulted in a larger analytic dataset (>90% of the original dataset) and a lower SE than PSM and CEM. The RRs from PSM and FS were similar (indicating a ~10% increase in risk with NSAIDs) and consistent with prior evidence from experimental studies, while CEM resulted in larger effect estimates in all cases (indicating up to a 150% increase in risk). The MAX analyses led to similar findings.

Conclusions: FS was optimal in our analyses due to the high retention of study size and low SEs. CEM appears sub-optimal for claims data, likely due to the high volume of binary confounders. As next steps, we will explore different coarsening strategies for CEM, and we will generate plasmode-simulated datasets, which allow for clearer comparisons based on known effect sizes.

48 | Propensity score diagnostics: The challenges we face when providing evidence that a propensity-based estimate is unbiased

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Background: Propensity scores aim to balance covariate distributions between treatment groups, reducing confounding bias in observational data. Despite the recent increase in their use, there is still scepticism about their trustworthiness. One concern is that a misspecified propensity score may not achieve sufficient balance, leading to biased results. There are a variety of diagnostics being used to assess covariate balance after propensity adjustment; however, no consensus on the best way to do this.

Objectives: A simulation study was conducted to compare diagnostics in terms of their ability to identify different types of propensity score misspecification.

Methods: Diagnostics included are categorised as follows: (1) mean-based, (2) distribution-based, or (3) prevalence-based. Categories 1 and 2, respectively, include diagnostics which compare covariate means and distributions between treatment groups. Category 3 diagnostics are new; they involve comparing the number of exposed subjects at each covariate value to that predicted by the propensity score. Logistic regression was used to assess how well diagnostics could predict when misspecification occurred and corresponding c-statistics were obtained. c-statistics close to 0.5 indicated that a diagnostic was unable to identify misspecification, hence is an unreliable measure of covariate balance.

Results: When a nonlinear term was incorrectly omitted from the propensity score model, mean-based diagnostics performed poorly (eg, c-statistic of 0.552 for standardised difference). When an interaction term was missing from the propensity score model, mean-based diagnostics were reliable; however, distribution-based diagnostics were unreliable when sample sizes were small (eg, at sample size 500, c-statistics for the overlapping coefficient [distribution-based] and standardised difference were 0.585 and 0.946, respectively). Prevalence-based diagnostics performed consistently well across all misspecification types, and in most cases, the regressions failed to converge due to perfect prediction.

Conclusions: To help overcome scepticism about propensity scores, being able to reliably assess covariate balance obtained after propensity-adjustment is essential. Unfortunately, our results demonstrate that some of the most widely used (category 1) or readily available (categories 1 and 2) diagnostics can be misleading. Introduction of prevalence-based diagnostics into the applied literature is recommended.

49 | Evaluation of treatment effect modification in propensity score matching: An empirical example

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Background: Propensity score matching (PSM) is a common approach to estimate treatment effects in observational studies. Of interest to in studies is whether treatment effect is modified by some covariate. This is often assessed by stratifying the PSM data by levels of the effect modifier which may break the match resulting in biased treatment effect in strata of the modifier.

Objectives: To assess the impact of stratifying on effect modifier after PSM on balance of covariates and treatment effects

Methods: We used the United Kingdom Clinical Practice Record Datalink (CPRD) data to evaluate the association between bariatric surgery (BS) on the risk of type 2 diabetes mellitus (T2DM) as an example. We followed patients from index date until the earliest of T2DM, death, loss-to follow-up, or end of study (December 31, 2014). We considered cardiovascular disease status (CVD status) as effect modifier of bariatric surgery on T2DM. We applied 1:1 PSM with caliper of 0.20 standard deviation on the logit of the PS. We evaluated covariate balance using absolute standardized mean difference (ASMD) in the full PSM data as well as PSM data stratified by CVD status. We estimated hazard ratios and 95% confidence intervals (95% CI) using Cox proportional hazard models. We also fitted traditional Cox models and compare the treatment effects.

Results: After PSM, we had 5132 patients with 406 having T2DM events during follow-up. When stratified by CVD status, the number of subjects and events in the two groups were 4946/378 and 180/28 with and without CVD, respectively. PSM improved covariate balance, ASMD all below 10%. On the other hand, stratification after PSM by CVD status broke the match resulting in imbalance in the covariates with ASMD up to 42%. Bariatric surgery reduced the risk of T2DM, HR [95% CIs], 0.65 [0.53, 0.79] in the full matched cohort. Similar risk was detected in those without CVD at baseline HR = 0.65 [0.53, 0.79] but not in patients with CVD, HR = 0.80 [0.37, 1.7]. Traditional Cox models resulted in similar effect estimates, HRs = 0.56 [0.47, 0.66], 0.51 [0.47, 0.65], and 0.80 [0.40, 1.52], in the full data, in those with and without CVD, respectively.

Conclusions: Our findings highlight consequence of stratification on levels of effect modifier on covariate balance after PSM. Covariate balance achieved on the full PS-matched data does not transfer to balance within strata of a modifier unless further matching is considered, and we recommend against using this approach for evaluating treatment effect modification in PSM.

50 | Covariate balance assessment in propensity score matching after multiple imputation with chained equations: An empirical example

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Background: Multiple imputation with chained equations (MICE) is a popular approach in observational studies to account for missing values in covariates. Although different approaches of applying propensity score matching (PSM) after MICE have been proposed, the impact of each approach on covariate balance has not been evaluated.

Objectives: To assess the impact of different PSM-MICE approaches on covariate balance and treatment effect estimate.

Methods: We used the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES) to study the association between oral bisphosphonates (OBP) and the risk of acute kidney injury (AKI). We applied PSM after MICE and assessed covariate balance using absolute standardized mean difference (ASMD) in three ways: (I) Estimate the PS in *m* imputed datasets, PSM the *m* imputed datasets, calculate ASMD and estimate treatment effect in each of *m* datasets and average the *m* ASMDs and treatment effect estimates using Rubin's rules. (II) Similar to the previous one but PS from *m* imputed datasets are first averaged. Patients are then PSM using the average PS, from which the ASMD and treatment effect were estimated in one dataset. (III) Estimate PS using one PS model, average PS for each patient across *m* datasets, PSM on the average PS, and calculate ASMD and treatment effect on the PSM dataset. We PSM-matched 1:5 with caliper 0.20 standard deviations on the logit of the PS, estimated hazard ratios, and 95% confidence intervals (95% CI) using Cox proportional hazard models and compared covariate balance and HRs from the three approaches.

Results: The three approaches retained similar number of outcome events treated/controls, *n* = 253/1597, 253/1604, and 256/1668 for I, II, and III, respectively. They also resulted in similar ASMD and treatment effect estimates, HR [95% CIs]: 0.93 [0.80, 1.07], 0.91 [0.80, 1.04], and 0.90 [0.79, 1.03] for approaches I, II, and III, respectively. Covariate balance was slightly better with the first approach (I) particularly for covariates with missing values in the original data. Approaches I and II were similar with respect to covariate balance.

Conclusions: In general, the different approaches were similar with respect to covariate balance and treatment effect estimate in our example. This could be due to the confounding structure of the dataset we used; hence, generalisation requires a simulation study. We recommend balance assessment should be conducted in line with treatment effect estimation.

51 | Extension of disease risk score based confounding adjustments for multiple outcomes of interest: An empirical evaluation

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Background: Disease risk scores (DRS), which can summarize multiple outcome risk factors into a single scalar score, are commonly considered for confounding control as an alternative to propensity scores in observational studies with infrequent exposures, such as safety studies of newly marketed medications. However, one of the often-cited advantages of PS-based adjustment over DRS-based adjustment is that, after PS-matching, multiple outcomes can be compared between two treatments in a single cohort.

Objectives: To evaluate approaches of extending DRS-based confounding adjustment to scenarios of multiple outcomes of interest.

Methods: We compared dabigatran versus warfarin initiators for ischemic stroke and major bleeding risk among atrial fibrillation patients in a sequential monitoring framework for 12 periods of 90 days each after dabigatran market entry (Oct, 2010) using a commercial insurance claims database from the United States. DRS models were developed using an out-of-sample strategy in a cohort of patients initiating warfarin prior to dabigatran entry (Jan, 2009-Sep, 2010). We compared two approaches for combining DRS for multiple outcomes: (1) 1:1 matching on prognostic propensity scores (PPS), created using DRS for bleeding and stroke as the only independent variables in a propensity score (PS) model, and (2) simultaneous 1:1 matching on DRS for bleeding and stroke using Mahalanobis (M) distance, against traditional PS matching.

Results: A total of 56 456 warfarin initiators and 22 809 dabigatran initiators were included. M-distance matching appeared to produce more stable results in the early marketing period compared with both PPS and traditional PS-matching; hazard ratios (95% confidence intervals) for unadjusted, traditional PS-matching, PPS-matching, and M-distance matching after 4 periods were 0.72 (0.51-1.03), 0.61 (0.31-1.09), 0.55 (0.33-0.91), and 0.78 (0.45-1.34) for stroke, and 0.65 (0.53-0.80), 0.78 (0.60-1.01), 0.75 (0.59-0.96), and 0.78 (0.64-0.95) for bleeding. In later periods, estimates were similar for traditional PS-matching and M-distance matching, but suggested potential residual confounding with PPS-matching.

Conclusions: Simultaneous M-distance matching using multiple DRS led to similar confounding adjustment as a traditional PS-based approach in the analysis of multiple outcomes. These findings provide support for a novel strategy to address one of the most commonly noted limitations of DRS-based confounding adjustment.

52 | A joint application of disease risk score and propensity score to control for confounding: A clinical example

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Background: Propensity scores (PS) and disease risk scores (DRS, also called prognostic scores) are two commonly used methods to deal with observed confounding in observation studies of treatment effects. Although clinical disease risk scores such as CHA₂DS₂-VASc score are often included in the PS modelling, combined empirical applications of DRS and PS have been limited to simulations which showed better performance compared with individual DRS or PS applications in terms of bias and precision.

Objectives: To illustrate a joint application of DRS and PS to control for confounding using clinical example.

Methods: We used the United Kingdom Clinical Practice Record Datalink (CPRD) data to evaluate the association between bariatric surgery (BS) on the risk of type 2 diabetes mellitus (T2DM) as an example. We followed patients from index date until T2DM, death, loss to follow-up, or end of study (December 31, 2014), whichever came first. We fitted DRS in the patient groups without the exposure (bariatric surgery) and predicted the baseline risk for T2DM for the entire cohort using logistic regression. We then applied 1:1 PSM with caliper width of 0.20 standard deviation on the logit of the PS including the DRS as quintiles in the PS model. We also used only the PSM without the DRS included as a reference. We evaluated covariate balance using absolute standardized mean difference (ASMD) in the combined PS_DRS matched dataset as well as PSM dataset. We estimated hazard ratios and 95% confidence intervals (95% CI) using Cox proportional hazard models.

Results: After PSM, we had 5132 patients with 406 having T2DM events during follow-up. Both PS_DRS combined matching and PSM improved covariate balance, ASMD all below 10%. Bariatric surgery reduced the risk of T2DM, HRs [95% CI], 0.57 [0.47, 0.70] in the full matched cohort. The risk was similar when we use PSM without the DRS HR [95% CI], 0.65 [0.53, 0.79].

Conclusions: Joint application of DRS and PS has improved covariate balance and could be a preferred application of covariate summary score in high dimensional data. Further studies are needed to evaluate in the performance of this approach in the presence of effect modification and multiple exposures.

53 | Performance of a distributed regression analysis software and workflow

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Background: Distributed regression analysis (DRA) is a privacy-protecting analytic method that performs multivariable-adjusted regression analysis using only summary information from participating data sources. However, DRA of models common to clinical research (eg, logistic and Cox) requires multiple iterations of data sources computing summary-level information from participating data partners and transferring them to an analysis center for regression parameter estimate and model convergence assessment. These iterations of data exchange require extensive coordination. The inability to automate and organize these exchanges has impeded the use of DRA.

Objectives: To develop a DRA software and workflow for iterative, automatable DRA and evaluate its performance.

Methods: We developed a SAS macro to perform DRA computations in three regression model types (linear, logistic, and Cox) using a secure summation protocol. We enhanced the functionalities of PopMedNet, an open-source query distribution application that supports numerous distributed data networks (DDNs), to create an iterative, automatable file transfer process for DRA. We integrated the SAS macro into the workflow. We evaluated the statistical and operational performance of the DRA software and workflow with a real-world test case ($n = 5766$, 14 covariates) with three data partners in the Sentinel System. We considered the integration successful if the results were statistically equivalent between DRA and the pooled patient-level data analysis. We extracted the start and end time stamps of each workflow step and computed the average iteration time.

Results: The SAS macro and DRA workflow produced equivalent regression estimates to the results from the pooled patient-level data analysis, with a precision of $1E-16$. For each iteration, the statistical computation could be completed within seconds, and the file transfer process could be done in minutes. Users have the ability to specify a fully manual, semi-automated, or fully automated file transfer workflow.

Conclusions: We successfully integrated a DRA SAS macro with an iterative and automatable file transfer workflow and produced equivalent results to those from the corresponding pooled patient-level analysis.

54 | Performance of fixed and all-available look-back approaches in claims database studies: A plasmode simulation

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Background: Methodologists have debated whether utilizing all available database history may outperform commonly used fixed (eg, 1-year) look-back windows.

Objectives: Assess bias and precision of estimates produced using various look-backs (1-year, 3-year, and all-available) applied within claims data.

Methods: We simulated plasmode cohorts with $N = 10\,000$ sampled with replacement from 5176 Medicare Current Beneficiary Survey (MCBS) respondents (2009–2011). We simulated statin initiation as a function of clinical variables and demographics in MCBS and outcomes as a function of these variables and a statin effect which varied by prior statin use (no prior statin: rate ratio [RR] = 0.4; prior statin: RR = 0.8). We applied 1-year, 3-year, or all-available look-backs to assess key eligibility criteria (continuous enrollment, no prior use) and measure confounders in linked Medicare claims. Thus, two sources of error biased estimates: (1) imperfect exclusion of prior statin exposures use and (2) imperfect confounder ascertainment. Covariates measured with all-available data were controlled using time-specific (0–6 mo; >6 mo) indicator variables. We adjusted estimates using inverse-probability-of-treatment weighting (IPTW). We present median RR estimates (from 1500 simulations), empirical 95% confidence intervals [CIs], and root mean squared errors.

Results: In the source (MCBS) cohort, 41.6% were statin naive. Using claims data to exclude those with prior statin use, the proportion of patients in plasmode cohorts that were actually statin naive ranged from 92% in the all-available and 3-year cohorts to 83% in the 1-year cohorts. Median Medicare enrollment history was longer among initiators (56 mo) vs non-initiators (52 mo) and those with outcomes (57 mo) vs. those without (48 mo). Compared with the truth (RR = 0.4), all-available look-backs produced the least biased estimate (RR = 0.59 [0.53, 0.67]) and the best rMSE (0.399). One-year look-backs produced the most biased estimate (RR = 0.66 [0.59, 0.73]) and worst rMSE (0.499). Three-year look-backs produced an estimate with moderate bias (RR = 0.63 [0.55, 0.71]) and rMSE (0.451). When prior statin history or confounders were classified using the true data (MCBS), the magnitude of bias decreased but relative performance was similar.

Conclusions: Based on both simulation and real-world data, our findings provide evidence that all-available look-backs outperform fixed look-backs in new user cohort studies conducted using claims data.

55 | Do gaps in enrolment matter? A study of the effect of strict enrolment criteria in US commercial and Medicaid databases on population representativeness and the prevalence of COPD and asthma

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Background: Real-world studies often use continuous enrolment criteria to maximize the completeness of information on exposure, outcomes, and potential confounders within the study period. However, this may eliminate key patient groups from the resulting cohort, thereby reducing the representativeness of results, and trading off internal and external validity.

Objectives: This work studied how different enrolment requirements change the characteristics of cohorts in US commercial and Medicaid health care claims databases. It described variation in enrolment over time and DB, identified factors associated with incomplete enrolment,

and assessed whether of COPD and asthma prevalence changed by enrolment criteria.

Methods: Data from 2011–2015 were studied in 1-, 2-, and 3-year periods. Inclusion was defined by age <64 throughout observation and presence of any enrolment in the years before and after the study period. COPD and asthma codes were defined using ICD9/10 codes (COPD assessment was restricted to >35 years). Characteristics were compared between enrollees with complete and incomplete coverage. Enrollees with incomplete enrolment were subdivided into groups by presence/absence of a 1- to 30-day gap per year. The majority of incomplete enrollees had >30-day gap.

Results: In the commercial DB, 96.0%, 85.0%, and 90.7% of enrollees had complete enrolment in 1-, 2-, and 3-year periods. Only 80.5%, 69.9%, and 63.2% of Medicaid enrollees had complete enrolment in these years. Commercial DB incomplete enrollees were more likely to have hourly jobs (39.3% vs 32.4%) and work in the services industry (34.5% vs 30.0%) than complete enrollees. Medicaid DB incomplete enrollees were more likely to be female (63.0% vs 54.5%), have eligibility status of “adult” (23.1% vs 13.8%), have an HMO plan (10.4 vs 3.9%), and less likely to have drug benefits (11.2% vs 20.2%) than complete enrollees. The 2012 period prevalence of asthma per 1000 in the commercial DB was 67.7 in enrollees with a gap of 1–30 days ($n = 0.13M$) compared with 45.9 for complete enrollees ($n = 23.4M$), despite having less person-time available. Similar patterns were seen in the Medicaid DB and for COPD.

Conclusions: The application of strict enrolment criteria may remove the sickest and poorest patients from studies. This could be quantified through sensitivity analyses to understand the impact of varying length of gaps in enrolment on risk estimation and potential inference limitations. GSK funded study.

56 | Assessment of misclassification bias due to short look-back periods in epidemiological studies of chronic disease incidence

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Background: Estimating disease incidence based on secondary data typically requires a look-back period to exclude those with pre-existing disease from the incidence risk set. While the length of the look-back period may impact the incidence estimation, this is often chosen arbitrarily based on data availability/data type, patient retention/turnover rate, and sample size considerations. We used population-based registers with longitudinal data since 2005 and minimal loss to follow-up to investigate the impact of the look-back period on the incidence rates for various diseases.

Objectives: To assess the impact of length of look-back period on incidence rates of 24 different chronic/long-term diseases (such as types 1 and 2 diabetes, rheumatoid arthritis, and narcolepsy) using linked Swedish registers.

Methods: All adults, 18 years and older, in Sweden, were identified from national registries and followed for a maximum of 2 years, from January 1, 2014 (index date), until end of study period on December 31, 2015. Outcome events were obtained from inpatient and outpatient hospital visits, and incidence rates were calculated for each chronic disease. The length of the look-back period to exclude patients with prevalent disease was varied with 6-month increments. Nine years was the maximum look-back and considered “gold standard.”

Results: Approximately 5.9 million persons were included in the analysis, mean (standard deviation) age of 46 (16) years (51% females). Incidence rates were higher across all diseases when applying a look-back period of 1 year compared with 9 years, indicating presence of misclassification bias. The magnitude of bias varied between diseases and incidence rates were overestimated from 13% (temporal arteritis) to 174% (type 1 diabetes) when applying a look-back period of 1 year compared with 9 years. In general, the marginal effect of extending the look-back period beyond 3-5 years was comparably small.

Conclusions: This nationwide analysis showed that using short look-back periods for incidence estimates of chronic/long-term diseases introduce misclassification bias in epidemiological studies. The magnitude of bias varies greatly between different diseases. The results suggest that sensitivity analyses with respect to look-back period should be conducted, especially if using data sources with limited information on past medical history (look-back).

57 | Privacy-protecting analytic methods using only aggregate-level data for multivariable-adjusted analysis in distributed data networks

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Background: Distributed data networks enable large-scale comparative safety and effectiveness studies, but protecting privacy while sharing minimum necessary data continues to pose methodologic challenges. Questions remain as to how to share only aggregated data and yet appropriately adjust for a large number of patient-level covariates. **Objectives:** To assess the performance of analytic methods for multivariable-adjusted analysis in distributed data networks pooling only aggregate-level data.

Methods: Using 2 empirical examples within a 3-site distributed data network (Kaiser Permanente: Colorado, Northern California, and

Washington), we tested combinations of (1) 3 aggregate-level data-sharing approaches (risk-set, summary-table, and effect-estimate), (2) 4 confounding adjustment methods (matching, stratification, inverse probability, and match weighting), and (3) 2 summary scores (propensity score and disease risk score) for binary and survival outcomes. We assessed the performance of various combinations of methods by comparing their results against pooled individual-level data analysis results (reference) and calculated %bias and ratio in standard errors (SE). The empirical examples were comparative effectiveness and safety of (1) bariatric procedures in patients with obesity and (2) biologic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis.

Results: For both outcome types, the data-sharing and adjustment method combinations examined yielded identical or highly comparable results with the reference in most scenarios. Within each data-sharing approach, comparability between aggregate- and individual-level data analysis depended on adjustment method; eg, risk-set with matched or stratified analysis of summary scores produced identical results (%bias = 0, ratio in SE = 1), while weighted analysis showed discrepancies (%bias range = 0-6%, ratio in SE = 0.7-2.4). Results from summary-table and effect-estimate data-sharing were sensitive to outcome incidence and sample size across adjustment methods examined.

Conclusions: We can validly perform multivariable-adjusted analysis in distributed data networks pooling only aggregated data. Choice of the optimal privacy-protecting methods depends on exposure prevalence, outcome incidence, and outcome type; eg, summary-table sharing is unsuitable for survival outcomes with time-varying hazards, and effect-estimate sharing is less suitable for rare outcomes.

58 | Multi-database multiple imputation within a distributed data drug safety network: A simulation study and real-world data example

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Background: In distributed data drug safety networks such as the Canadian Network for Observational Drug Effect Studies, some databases may be missing important confounders that are captured by other databases in the network (eg, body mass index [BMI]). To reduce confounding in these situations, we propose a unique application of multiple imputation, which we call multi-database imputation (MDI). In MDI, a validation database containing the variables of interest is used to develop predictive distributions from which missing values are imputed in the other databases.

Objectives: To explore the validity of MDI in distributed data drug safety networks.

Methods: We conducted a simulation study and a real-world analysis using the UK's Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics. Both analyses were retrospective cohort studies conducted in mock distributed networks of the effect of statins on the risk of myocardial infarction (MI) among patients with type 2 diabetes determined by meta-analysis of Cox models across sites. For the simulation study, we applied MDI to correct for missing BMI in all but one of D databases of N patients among whom statins had a true hazard ratio (HR) of MI of 0.8. For 20 study scenarios that involved changing 14 parameters (200 simulations per scenario; default: D = 7, N = 1000), we compared true and estimated HRs. In the real-world analysis, we identified all initiators of non-insulin antidiabetic agents in the CPRD from 1998 to 2016. We divided the resulting population into 5 mock distributed databases based on geographic region and determined the true meta-analyzed effect of current statin use in this mock network. We then ignored BMI, smoking history, HbA1c, and total cholesterol from all but one database and estimated the effect of statins with and without MDI.

Results: In our simulation study, MDI repaired bias from missing BMI in all scenarios, with a median bias reduction of 118% in the default scenario. In our real-world study, the multiply-imputed analysis (HR: 0.86; 95% confidence interval [CI]: 0.69-1.08) was closer to the analysis that considered the true confounder values (HR: 0.85; 95% CI: 0.66-1.10) than the one that ignored them (HR: 0.93; 95% CI: 0.73-1.20).

Conclusions: MDI may be a feasible method to reduce bias from confounders missing from some databases in a distributed data network and is robust to changes in study parameters, though further research is needed to evaluate its validity in real-world networks.

59 | Oral fluconazole in pregnancy and risk of stillbirth and neonatal death

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Background: Up to 4% of pregnant women in the United States use oral fluconazole. Reports have raised concern that fluconazole may be associated with stillbirth, particularly in doses above those commonly used for the treatment of vaginal candidiasis (single dose 150 mg, administered once or twice). The risk of neonatal death has not been studied.

Objectives: To investigate if fluconazole use during pregnancy is associated with increased risk of stillbirth and neonatal death.

Methods: We conducted a cohort study using nationwide registers in Sweden and Norway, 2005-2015. From 1 485 316 eligible pregnancies, fluconazole-exposed and unexposed pregnancies were matched (1:10 ratio) on age and propensity score. The primary outcomes were stillbirth and neonatal death associated with any fluconazole exposure during pregnancy. A secondary analysis was

conducted by fluconazole dose. Cox and Poisson regression were used to estimate hazard ratios (HRs) for stillbirth and risk ratios (RRs) for neonatal death, respectively.

Results: Among 10 669 pregnancies exposed to fluconazole, 29 (2.7 per 1000) had a stillbirth, compared with 387 (3.6 per 1000) among 106 690 unexposed pregnancies (HR, 0.76 [95% CI, 0.52-1.10]). In analyses by fluconazole dose, the HRs for stillbirth were 0.80 (95% CI, 0.50-1.28) for a dose of 300 mg and below and 0.70 (95% CI, 0.39-1.26) for a dose above 300 mg. Among 10 640 liveborn infants of mothers exposed to fluconazole during pregnancy, there were 13 (1.2 per 1000) neonatal deaths, compared with 177 (1.7 per 1000) neonatal deaths among 106 387 infants of mothers who were unexposed (RR, 0.73 [95% CI, 0.42-1.29]). In analyses by fluconazole dose, the RRs for neonatal death were 0.78 (95% CI, 0.39-1.59) for a dose of 300 mg and below and 0.66 (95% CI, 0.27-1.61) for a dose above 300 mg.

Conclusions: In this large cohort from Sweden and Norway, use of fluconazole during pregnancy was not associated with increased risk of stillbirth and neonatal death. These findings were similar for doses of fluconazole commonly used for the treatment of vaginal candidiasis and for higher doses. These findings are reassuring but need to be interpreted considering other pregnancy safety issues with fluconazole when they are used to inform clinical care.

60 | Tnf inhibitor treatment during pregnancy and risk of preterm birth

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Background: Tumor necrosis factor inhibitors (TNFi) are used increasingly to treat inflammatory bowel disease (IBD), rheumatoid arthritis (RA), psoriasis (PsO), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) in pregnant women. TNFi may be associated with an increased risk of preterm birth. Data are scarce on agent-specific risks.

Objectives: To assess the risk of preterm birth among women with IBD, RA, PsO, PsA, and AS (non-IBD) who received TNFi treatment during pregnancy.

Methods: Population-based study including all births 2006-2013 in Denmark, Finland, and Sweden from the medical birth registers. Disease diagnoses and drug exposure data were collected from the patient registers and prescribed drug registers in all countries and from disease-specific registers in Finland and Sweden. Women of the general population and women with TNFi treatment were compared with women with non-biologic systemic treatment for the same diseases, who served as the reference in all analyses. Adjustments were made for country, maternal characteristics, and underlying disease. Apart from TNFi agents as a group, adalimumab, etanercept, and infliximab were studied separately. Results from

logistic regression models are presented as odds ratios (ORs) with 95% confidence intervals (CI).

Results: Among 1 633 909 births, 1027 infants were born to women treated with TNFi and 9399 to women who received non-biologic systemic treatment during pregnancy. Compared with the reference, women in the general population had a lower risk of preterm birth, OR 0.52 (95% CI: 0.48-0.56) and women who received TNFi treatment had a higher risk of preterm birth, OR 1.59 (95% CI: 1.27-1.99). Results for women receiving TNFi treatment were similar when stratified by disease group: IBD, OR 1.55 (95% CI: 1.08-2.21) and non-IBD, OR 1.62 (95% CI: 1.22-2.16). For IBD, the OR for infliximab was 1.98 (95% CI: 1.28-3.06) and for adalimumab OR 0.89 (95% CI: 0.46-1.72). For non-IBD, the OR for infliximab was 3.31 (95% CI: 1.40-7.82), the OR for adalimumab was 2.12 (95% CI: 1.23-3.63), and the OR for etanercept was 1.45 (95% CI: 1.04-2.03).

Conclusions: Although all TNFi agents were associated with an increased risk of preterm birth, infliximab differed most from the reference group. However, the inconsistent estimates observed across disease groups may indicate an association related to the underlying disease and disease severity, rather than to agent-specific effects.

61 | Impact of maternal infection and antibiotic use in pregnancy on the risk of childhood obesity: A study of 203 999 mother-child pairs with up to 12 years of follow-up

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Background: Maternal use of antibiotics in pregnancy has been associated with risk of obesity in offspring. However, it is not clear whether the risk is due to the underlying infection, antibiotic use, or both.

Objectives: To disentangle the effect of *maternal infection* from that of *maternal antibiotic use* on the risk of childhood obesity.

Methods: A birth cohort study was conducted among 203 999 mother-child dyads, with up to 12 years of follow-up, among the members of Kaiser Permanente Northern California. We used electronic medical records (EMRs) to ascertain maternal infection diagnosis, results of screening for group B streptococcus (GBS), and antibiotic use during pregnancy. EMRs were also used to ascertain anthropometric measurements of offspring. Childhood obesity was defined as BMI $\geq$ 95th percentile, based on age- and gender-specific criteria set by the CDC. Mixed effects logistic regression for repeated measurements was used to analyze multiple BMI measurements per child during the follow-up period.

Results: After controlling for confounders, maternal infection *without* antibiotic use during pregnancy was associated with an increased risk of childhood obesity. Offspring of mothers who were GBS positive during pregnancy had a 17% higher risk of obesity; adjusted odds ratio

(aOR) = 1.17 (95% confidence interval (CI): 1.10-1.25), compared with offspring whose mothers did not use antibiotics or have an infection diagnosis during pregnancy. There was also a dose-response relationship, with increased number of infection episodes being associated with higher risk of childhood obesity. We also examined the impact of maternal antibiotic use during pregnancy on childhood obesity separately for antibiotic use with or without concurrent infection diagnoses. For antibiotic use with an underlying infection, we used the group of women who had similar infections, but did not use antibiotics, as the reference group, to remove confounding by indication. Maternal antibiotic use during pregnancy was associated with an increased risk of childhood obesity similarly among those with an infection: aOR = 1.11 (95% CI: 1.06-1.16), and without an infection, aOR = 1.12 (95% CI: 1.07-1.17).

Conclusions: Both maternal infection and antibiotic use during pregnancy were independently associated with increased risk of childhood obesity. These findings suggest a long-term impact of in utero exposure to infections and antibiotics on childhood development and growth.

62 | Disparities in asthma prevalence, severity, and control in pregnancy. Evidence from two health care databases in the United States

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Background: Asthma is among the most common pre-existing medical conditions in pregnancy. Uncontrolled asthma has been shown to increase the risk of adverse pregnancy outcomes including growth restriction and mortality.

Objectives: To describe the prevalence, severity, and control of asthma in both publicly and commercially insured pregnant women in the United States.

Methods: We conducted a cohort study within two large health care databases: the nationwide Medicaid Analytic eXtract (MAX, public health insurance) for 2000-2013 and the Truven MarketScan Commercial Claims and Encounters Database (MarketScan, private health insurance) for 2011-2015. The study population included pregnancies ending in a live birth. We identified asthma based on both diagnoses and asthma-related treatments within the 12 months preceding delivery. We classified asthma severity using as a proxy the stepwise Global Initiative for Asthma algorithm (GINA; five steps reflecting treatment intensity) and assessed asthma control based on unique asthma exacerbations (hospitalization, emergency visits, or oral corticosteroid use) and the number of prescriptions for short-acting beta-agonists (SABA) filled during pregnancy. Markers of poor control were defined as at least one exacerbation in the 12 months before delivery or >4

SABA dispensed. We assessed maternal characteristics associated with asthma and poor asthma control.

Results: Among 2 785 245 pregnancies in MAX and 604 420 in MarketScan, we identified 120 745 (5.8%) and 20 104 (3.3%) women with asthma, respectively. Asthma was classified as severe (GINA steps 4 or 5) for 18.8% of cases in MAX and 7.9% in MarketScan. The proportion of cases with poor asthma control was 35.5% in MAX and 20.7% in MarketScan. Poor control was associated with increasing GINA treatment steps; however, many women on mild treatment strategies (GINA steps 1 and 2 and no treatment) had poorly controlled asthma during pregnancy (28.1% in MAX and 18.4% in MarketScan). Within each cohort, women with poor control were more often smokers, had more comorbidities, and used more concomitant non-asthma medications.

Conclusions: We identified a higher prevalence of asthma overall and more severe and poorly controlled asthma, among publicly versus privately insured pregnancies in the United States. Factors that contribute to and the consequences of poorly controlled asthma during pregnancy should be explored further. Funding: GSK (206948).

63 | Use of multiple sclerosis drugs among live birth pregnancies in the United States

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Background: Despite the availability of many disease-modifying therapies (DMT) for multiple sclerosis (MS), there are limited safety data to inform use in women who are pregnant, trying to become pregnant, or who are breastfeeding. Also, MS is common in females of reproductive potential, and since approximately 50% of pregnancies are unintended, inadvertent exposure to DMTs in pregnancy may occur.

Objectives: To describe DMT use among pregnancies with live birth deliveries before and during pregnancy and post-delivery in the Sentinel Distributed Database (SDD).

Methods: We identified pregnancies with live birth deliveries among women aged 15-49 years using a previously validated algorithm between January 1, 2001, and August 31, 2017, in SDD. We used National Drug Codes and/or procedure codes to identify all forms of DMTs. We calculated the prevalence of DMT use by trimester, age group, and calendar year of delivery.

Results: Among the 2 205 383 pregnancies with live birth deliveries that met our enrollment criteria, 1011 (0.05%) had exposure to any DMT during pregnancy. Among DMTs dispensed any time during pregnancy, glatiramer (GA) (n = 501; 49.6%), interferon (IFN) beta-1a (n = 307; 30.4%), and INF beta-1b (n = 78; 7.7%) were most common. Exposure to DMTs declined by 21.9% (GA), 43.6% (IFN beta-1a), and

41.3% (IFN beta-1b) from 6 months pre- to first trimester of pregnancy. Recently approved oral DMTs were less commonly dispensed; use of dimethyl fumarate, fingolimod, and dalfampridine any time during pregnancy was observed among 51 (5.0%), 26 (2.6%), and 6 (0.6%) pregnancies, respectively. DMT use was most common during the 6 months pre-pregnancy, decreased during pregnancy, and increased 6 months post-delivery to near pre-pregnancy levels. Furthermore, use of DMTs was highest among women aged 45-49 years (0.16%), followed by women aged 40-44 years (0.07%) and 35-39 years (0.07%). We observed no noteworthy patterns of use by calendar year of delivery, but GA and IFN b-1a remained the most commonly dispensed DMTs across the study period.

Conclusions: In our cohort, DMT use in pregnancy was rare. First generation DMTs were the most commonly dispensed in pregnancy. There was a considerable decline in DMT use from 6 months before pregnancy through the first trimester, followed by an increase in use post-delivery. These findings suggest that women with MS are planning their pregnancies, discontinuing DMTs before pregnancy, and resuming DMTs post-delivery. Data are needed to inform the safety of these products in pregnancy and lactation.

64 | Uncontrolled maternal chronic respiratory diseases in pregnancy increase the risk of anorectal malformations in offspring

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Background: Chronic respiratory diseases and the use of anti-asthmatic medication during pregnancy may both play a role in the etiology of congenital anorectal malformations (ARM). However, it is currently unclear whether the medication use or the underlying condition would be responsible.

Objectives: To unravel the role of maternal chronic respiratory diseases from that of anti-asthmatic medication use in the etiology of ARM in offspring.

Methods: We obtained 412 patients with ARM and 2137 population-based controls from the AGORA (Aetiologic research into Genetic and Occupational/environmental Risk factors for Anomalies in children) data- and biobank in the Netherlands. We used maternal questionnaires and follow-up telephone interviews to obtain information on chronic respiratory diseases, such as asthma and chronic bronchitis, anti-asthmatic medication use, and potential confounders from 3 months before conception until 10 weeks of pregnancy. Multivariable logistic regression analyses were performed to estimate

odds ratios (ORs) with 95% confidence intervals (CIs) corrected for confounders.

Results: We observed a higher risk among women with chronic respiratory diseases without medication use (OR 2.0, 95% CI 0.8-5.0) than among women with chronic respiratory diseases with medication use (OR 1.4, 95% CI 0.8-2.7). When the latter group was studied in more detail, increased risks of ARM were found in women using rescue medication (OR 2.4, 95% CI 0.8-7.3) or a combination of maintenance and rescue medication (OR 2.6, 95% CI 1.0-7.3). In addition, increased risks were found for women having non-allergic triggers (OR 2.5, 95% CI 1.0-6.1) or experiencing exacerbations during the periconceptional period (OR 3.3, 95% CI 1.3-7.9).

Conclusions: The results of this study indicate that uncontrolled maternal chronic respiratory diseases in pregnancy, with or without the use of rescue medication to alleviate exacerbations, seem to be associated with ARM in offspring.

65 | Direct oral anticoagulants versus low-molecular-weight heparins for venous thromboembolism prevention following total hip replacement: Comparative effectiveness and medical costs from a French nationwide cohort study of around 120 000 patients

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Background: Thromboprophylaxis is recommended after major orthopaedic surgery to prevent the risk of deep vein thrombosis and pulmonary embolism. Three direct-acting oral anticoagulants (DOAC), apixaban, dabigatran, and rivaroxaban, was granted a European market authorization for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement (THR) surgery.

Objectives: To assess the benefit-risk and medical costs of DOAC vs low-molecular-weight heparin (LMWH) for VTE prophylaxis following THR in real-life setting.

Methods: Cohort of all patients with THR performed in France from Jan 2013 to Sept 2014, home return after discharge, followed-up for 3 months in the French nationwide claims and hospitalization database. Patients treated with a DOAC were 1:1 matched on gender, age, and propensity score with those receiving LMWH. Main outcomes were hospitalization with primary diagnosis of VTE or bleeding and all causes death during the follow-up or anticoagulant switch. Relative risk (RR) between DOAC and LMWH were

estimated using quasi Poisson model, with sub-analyses for each DOAC. Medical costs were calculated according to the collective perspective.

Results: Among the patients who returned home, 31 680 were treated with a DOAC (rivaroxaban 66.9%, dabigatran 22.4%, apixaban 10.7%), 65 966 with LMWH. Mean age was 65.7 (±10.8) years for DOAC patients, 69.8 (±12.0) for LMWH patients, respectively, 47.6% and 52.1% women, a mean duration of hospital stay of 7.9 days and 5.9 days, a mean IMPROVE VTE risk score = 2, and bleeding risk score = 3.5. Almost all DOAC patients (31 619) were matched to an LMWH patient. For them, the risk of VTE was significantly lower with DOAC than LMWH (0.9‰, 2.5‰ respectively, RR = 0.35 [0.23-0.54]), while the risk of bleeding was not different (1.8‰ and 2.3‰, RR = 0.88 [0.62-1.25]) and without difference for all cause death (0.7‰ and 1.1‰, RR = 0.68 [0.40-1.15]). The mean total medical costs per matched patients was €444 lower with DOAC compared with LMWH (-29%), difference been mainly from drugs, nursing, and hospitalizations.

Conclusions: This study shows a low risk of VTE, clinically relevant bleeding, and death after discharge for patients with anticoagulant for VTE prevention following THR with a better benefit-risk ratio of DOAC compared with LMWH and associated with cost savings.

66 | Serious bleeding and use of warfarin in combination with sulfonylureas or metformin

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Background: Whether sulfonylureas increase the risk of serious bleeding when used concomitantly with warfarin is clinically important, but remains unclear.

Objectives: To measure the association between serious bleeding and the concomitant use of either sulfonylureas (as precipitant drugs) or metformin (as a negative control precipitant drug) in users of warfarin (object drug).

Methods: **Design** - Self-controlled case series. **Setting** - Five large US Medicaid programs constituting ~40% of enrollees nationwide, with Medicare claims for dual enrollees, from 1999 to 2011. We included adults who experienced serious bleeding while receiving warfarin. **Exposure of interest** - Use of sulfonylureas or metformin within observation time, concomitantly exposed to warfarin. Exposed time was categorized into pre-specified risk windows based on time since the beginning of concomitancy. **Outcome measure** - (a) serious bleeding, a composite outcome of gastrointestinal bleeding (GIB) and non-traumatic intracranial hemorrhage (ICH), (b) GIB, and (c) ICH, ascertained by the ICD-9-CM discharge diagnosis codes (GIB: any position on inpatient claims, positive predictive value ~81%; ICH: any position on emergency department or inpatient claims, positive predictive value ~77-94%).

Statistical analysis - We calculated the rate ratios (RRs) for exposed time vs unexposed time using conditional Poisson regression, controlling for time-varying covariates, including drugs that can increase the bleeding risk or international normalized ratio, acute infection, etc.

Results: The RRs increased over time, mostly, and the late risk window (>120 days) had the highest RR for all outcomes and precipitant drugs. The RR with glipizide in this window for ICH was particularly high (RR: 16.57; 95% confidence interval: 7.56, 36.30).

Conclusions: Concomitant use of warfarin with glimepiride, glipizide, glyburide, or metformin may increase the risk of bleeding. Physicians and patients need to be carefully monitoring potential bleeding throughout the concomitant use period, especially in the late risk window, and with glipizide for ICH.

67 | Sodium-glucose co-transporter-2 inhibitors and the risk of cardiovascular outcomes and adverse events

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Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2-i) are used as second-line treatment of type 2 diabetes mellitus. The first large SGLT2-i placebo-controlled trials demonstrated cardiovascular risk reduction, but were underpowered to explore important adverse effects, such as ketoacidosis, amputations, and serious urogenital infections. Large observational studies of the comparative effectiveness and safety of SGLT2-i in a real-world setting are urgently needed.

Objectives: To investigate the risk of hospitalization for heart failure or in-hospital death among patients who initiated SGLT2-i compared with dipeptidyl peptidase-4 inhibitors (DDP4s) and sulfonylureas in patients with diabetes previously managed on metformin.

Methods: Using a large database of US employer and government insurance claims (MarketScan), we conducted a retrospective cohort study of adults treated with metformin who added or switched to a new non-insulin glycemic medication between the date SGLT2-i entered the market (March 2013) and December 2015. Outcomes were assessed using Cox proportional hazards regression with propensity score adjustment. The primary analysis used a 365-day maximum follow-up, censoring on treatment discontinuation. The primary outcome was a composite of hospitalization for heart failure or in-hospital death. Secondary outcomes included hospitalization for cardiovascular events (heart failure, myocardial infarction, and stroke were evaluated separately), ketoacidosis, and amputation.

Results: The study included 292 907 metformin users who added or switched to either an SGLT2-i (14 612), DPP4 (82 981), or sulfonylurea (175 314). At baseline, the SGLT2-i users were younger and had a lower proportion of cardiovascular disease compared with DPP4 and SU users. SGLT2-i were associated with a lower risk of heart failure hospitalization or in-hospital death compared with DPP4s (HR = 0.33, 95% CI [0.13-0.83]) and SUs (HR = 0.25, 95% CI [0.10-0.61]). No significant differences were observed in the secondary outcomes.

Conclusions: SGLT2-i were associated with a lower risk of hospitalized heart failure or in-hospital death compared with DPP4s or sulfonylureas among patients with diabetes previously managed on metformin.

68 | Benefit-risk of rivaroxaban 20 or 15 mg compared with vitamin-K antagonists in patients with non-valvular atrial fibrillation: A cohort study in the French Nationwide Claims Database

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Background: Real-life benefits and risks of direct-acting oral anticoagulants for non-valvular atrial fibrillation (NVAf) remain uncertain. Rivaroxaban 20 mg (R20) is the standard dose, and rivaroxaban 15 mg (R15) is recommended for patients with moderate or severe renal failure but not if renal clearance is below 15 ml/min.

Objectives: To compare the 1-year risk of major events in new users of R20 and R15 versus vitamin K antagonists (VKA) in patients with NVAf in real-life setting.

Methods: Cohorts of new users of R20, R15, or VKA for NVAf in 2013-2014 were identified in the SNDS (Système National des Données de Santé) 66 million persons nationwide French claims database and followed for 1 year. NVAf was defined from full coverage, hospitalization, or procedure for atrial fibrillation without rheumatic valve disease or valve replacement (3-year database history). Rivaroxaban and VKA patients were 1:1 matched on gender, age, date of the first drug dispensing, and high-dimensional propensity score including major arterial thrombosis and bleeding risk factors. Hazard ratios (HR) [95% confidence interval (CI)] were estimated over the 1-year follow-up during first prescribed anticoagulant exposure, using Cox proportional hazards risk or Fine and Gray models.

Results: Of 220 011 new anticoagulant users for NVAf in 2013-2014, 42 531 were treated with R20, 24 585 with R15, and 108 666 with VKA with several large standardized differences between groups.

From them, 31 171 R20 patients and 23 314 R15 patients were matched to VKA patients with good overlap of hdPS distributions with weak or no standardized differences between groups. For R20 versus VKA, the risk was significantly lower with R20 for hospitalization for stroke and systemic embolism (HR: 0.79 [95% CI: 0.69-0.90]), for major bleeding (0.67 [0.59-0.77]), for death (0.67 [0.61-0.73]), and for composite of the 3 above (0.70 [0.65-0.74]). The risk was significantly lower with R15 than VKA for major bleeding (0.84 [0.74-0.96]), for death (0.85 [0.79-0.90]), for composite (0.89 [0.84-0.94]), but with no difference for stroke and systemic embolism (1.05 [0.92-1.21]).

Conclusions: This nationwide cohort study of new anticoagulant users for NVAf shows a significantly overall better benefit-risk in real life of rivaroxaban 20 mg or 15 mg compared with matched VKA.

69 | Comparative effectiveness of apixaban versus rivaroxaban for the prevention of cardiovascular diseases and recurrent venous thromboembolism

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Background: The effectiveness of apixaban, a novel oral anticoagulant, for the long-term prevention of venous thromboembolism (VTE) was observed in randomized clinical trials, but there is an absence of head-to-head comparison between apixaban and rivaroxaban in patients with VTE.

Objectives: To assess the effectiveness of apixaban in preventing cardiovascular diseases (CVD) and recurrent VTE compared with rivaroxaban in patients with VTE.

Methods: A retrospective cohort analysis of Truven Commercial and Medicare supplemental database (2014-2015) was conducted for patients who had a diagnosis of first VTE (ICD-9 CM: 451.1, 451.2, 453.40, 453.41, 453.42, 453.8, 453.9) or pulmonary embolism (ICD-9: 415.1x). Patients who newly initiated apixaban or rivaroxaban who had no prior use for at least 12 months (baseline period) were included. The study outcomes including CVD (non-fatal myocardial-infarction [ICD-9: 410.x] and non-fatal stroke [ICD-9: 433.x1, 434 (excluding 434.x0), 436]) and recurrent-VTE were compared between apixaban and rivaroxaban. Follow-up continued until the occurrence of the first event, switch to the comparator, end of study period, or end of enrollment. Propensity score matching (PSM) was employed to balance differences in baseline characteristics (eg, age, gender, CVD and VTE risk factors, and use of other medications) between the two groups. Cox-proportional hazard model after PSM was used to obtain the hazard ratio (HR) and 95% confidence interval (CI).

Results: Before PSM adjustment, 3546 new users of apixaban (47% male, 34.5% CVD, 17.4% chronic kidney disease [CKD]), and 29 746 new users of rivaroxaban (51% male, 27% CVD, 11% CKD) were identified. The incidence rates of CVD were 35 and 47 per 1000 person-years in the apixaban and the rivaroxaban groups, respectively. After PSM, the use of apixaban was associated with a lower risk of recurrent-VTE compared with rivaroxaban (HR: 0.73, 95% CI [0.64, 0.82]). However, there

was no statistically significant difference in the risk of CVD between apixaban and rivaroxaban groups (HR: 0.85, 95% CI [0.67, 1.08]).

Conclusions: Compared with rivaroxaban, apixaban was associated with a decreased risk of recurrent-VTE although no difference in the risk of CVD was found in patients with VTE.

70 | Comparative effectiveness and safety of low-dose non-vitamin K oral anticoagulants and acenocoumarol in patients with atrial fibrillation in Valencia, Spain

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Background: Low dose non-vitamin K oral anticoagulants (NOAC) in non-valvular atrial fibrillation (AF) are recommended mainly in elderly patients and those with kidney disease. However, there is a lack of evidence on the effectiveness and safety of low-dose NOAC and vitamin K antagonists in "real-world" clinical practice.

Objectives: To compare the effectiveness and safety of low-dose NOACs and acenocoumarol in patients with AF, overall, and in patients with a potential indication for low dose.

Methods: Population-based retrospective cohort study using electronic health records from Valencia Region, Spain. We included all new users of acenocoumarol and low-dose NOACs (apixaban 2.5 mg, dabigatran 110 mg, and rivaroxaban 15 mg) from Nov 2011 to Dec 2015 with AF diagnosis. The outcomes assessed were death, hospitalization for gastrointestinal (GI) bleeding, intracranial hemorrhage, and ischemic stroke. We used inverse probability of treatment weights to correct for biases across different treatments. We did a sub-analysis including only the group of patients with potential indication for low-dose use.

Results: Among 36 851 NVAf patients, 89.3% were treated with acenocoumarol, 2.2% with apixaban, 5.2% with dabigatran, and 3.3% with rivaroxaban. For the whole cohort, the weighted incidence of mortality was 72.8 per 1000 person-years for acenocoumarol, 138.1 for apixaban, 83.8 for dabigatran, and 115.4 for rivaroxaban; while that of ischemic stroke was 10.3 for acenocoumarol, 27.3 for apixaban, and 11.3 for both dabigatran and rivaroxaban. The incidence of GI bleeding was 8.1 for acenocoumarol, 5.7 for apixaban, 8.3 for dabigatran, and 7.7 for rivaroxaban; and that of intracranial hemorrhage was 7.2 for acenocoumarol, 3.0 for dabigatran, and 4.9 for rivaroxaban. Compared with acenocoumarol, we found an increased risk of ischemic stroke for apixaban (HR: 1.69, 95% CI: 1.06-2.68), increased risk of GI bleeding for dabigatran (HR: 1.38, 95% CI: 1.02-1.87), and a decreased risk of intracranial hemorrhage for dabigatran (HR: 0.38, 95% CI: 0.22-0.66). These results were consistent in the sub-analysis for patients with indication for low dose.

Conclusions: In real-world clinical practice, low-dose apixaban was associated with higher risk of ischemic stroke, while dabigatran was associated with a lower risk of intracranial hemorrhage, but also with higher risk of GI bleeding, overall, and among patients with indication for low-dose NOAC.

71 | Association between glycaemic control and fracture risk in diabetic patients: A nested case-control study

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Background: Diabetes mellitus type 1 (DM1) and 2 (DM2) are associated with an increased risk of low-trauma fractures. However, the impact of glycaemic control on fracture risk remains unclear.

Objectives: We aimed to evaluate the association between diabetes control and the risk of low-trauma fractures.

Methods: We conducted a nested case-control study within a cohort of patients with incident DM1 or DM2 between 1995 and 2015 based on the UK-based primary care database Clinical Practice Research Datalink. We identified all patients with a low-trauma fracture after the diabetes diagnosis and matched them to 4 diabetes patients with no recorded fracture (matching on age, sex, general practice, index date, diabetes type, and diabetes duration, which represents the follow-up time between diabetes onset and fracture date). We characterised the study population regarding comedications and comorbidities and used conditional logistic regression analysis to assess the association between diabetes control (based on HbA1c-levels) and the risk of low-trauma fractures. We calculated crude and adjusted odds ratios (aOR), adjusting for BMI and smoking, as well as for specific diabetes complications and medications.

Results: We identified 566 DM1 cases and 2225 DM1-matched controls, as well as 8859 DM2 cases and 35 416 DM2-matched controls. DM1 and DM2 patients had a mean of 8.5 (SD 8.4) and 11.1 (SD 9.6) recorded HbA1c-values and median disease durations of 4.2 years (Q₁ 1.9, Q₃ 7.6) and 4.5 years (Q₁ 2.0, Q₃ 7.9), respectively. In DM1 patients with a 3-year mean HbA1c > 8.0%, fracture risk was significantly increased (aOR 1.46; 95% CI, 1.09-1.97) compared with DM1 patients with HbA1c levels < 8.0%. In DM2 patients with mean HbA1c levels of 8-9% and >9%, aORs were 0.91 (95% CI, 0.84-0.99) and 0.96 (95% CI, 0.88-1.06), showing no elevated fracture risk compared with HbA1c levels < 8.0%. Comorbidities associated with microvascular and macrovascular complications of diabetes, such as diabetic retinopathy, chronic renal failure, and coronary heart failure, were all associated with an elevated fracture risk.

Conclusions: The impact of glycaemic control on low-trauma fracture risk differs in DM1 and DM2 patients. While poor glycaemic control (HbA1c levels > 8%) elevated the fracture risk in DM1 patients significantly, no such association was observed in DM2. In our study, fracture risk in DM2 is related to microvascular and macrovascular comorbidities rather than to HbA1c levels. Funding: Swiss National Science Foundation (grant 320030_169407).

72 | Sodium-glucose cotransporter-2 inhibitor use and lower-extremity amputation risk among commercially insured US Patients, 2013-2015

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Background: Results from the Canagliflozin Cardiovascular Assessment Study Program suggest an increased risk of lower-extremity amputation (LEA) in patients with type 2 diabetes using sodium-glucose cotransporter-2 inhibitors (SGLT-2i) compared with placebo.

Objectives: To evaluate the incidence and risk of LEA among new users of SGLT-2i compared with new users of two similar, second-line active comparators, dipeptidyl peptidase-4 inhibitors (DPP-4i) and sulfonylureas (SU).

Methods: In a retrospective cohort study using the Truven Health Analytics' MarketScan® Commercial Claims and Encounters Database, we identified new users of SGLT-2i, DPP-4i, or SU between March 1, 2013, and September 30, 2015. Eligible patients were required to have at least two same-drug class prescription claims, be under 65 years old, and have at least 1 year of continuous enrollment prior to index date with no claims for any study drug. LEA was defined using ICD-9 and CPT procedure codes. We estimated crude incidence rates (IR), as well as adjusted hazard ratios (aHR) and 95% confidence intervals (CI) using propensity score (PS) weighted Cox proportional hazard models censoring for treatment changes. Multivariable analyses adjusted for baseline demographics and any comorbidity, medication use, and health care utilization factors that remained unbalanced after PS weighting.

Results: We compared 48 934 new users of SGLT-2i to 118 266 new users of DPP-4i and 47 154 new users of SGLT-2i to 152 073 new users of SU. Median follow-up time ranged from 0.46 to 0.51 years. We observed 127 LEA events in SGLT-2i vs DPP-4i cohorts and 159 events in SGLT-2i vs SU cohorts. Crude IRs of LEA were 1.3 (95% CI, 1.0-1.8) and 1.0 (0.8-1.2) events per 1000 person-years (PYs), respectively, in SGLT-2i vs DPP-4i cohorts, and 1.0 (0.7-1.5) and 1.2 (1.0-1.4) events per 1000 PYs, respectively, in SGLT-2i vs SU cohorts. New use of SGLT-2i was associated with increased risk of LEA compared with new use of DPP-4i (aHR, 1.34 [95% CI, 0.89-2.02]) but with decreased risk compared with new use of SU (aHR, 0.85 [0.55-1.30]).

Conclusions: Among commercially insured patients under 65, new use of SGLT-2i was associated with differential LEA risk compared with other second-line diabetes drugs. However, the low absolute risks of LEA were reflected in a small number of observed events and contributed to statistically non-significant effect estimates. Moreover, the direction of relative risk was dependent on choice of active comparator drug.

73 | Delays in anti-hyperglycemic treatment intensification impacts risk of diabetes complications

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Background: Longer delays in anti-hyperglycemic treatment intensification (TI) are associated with poorer glycemic control, but whether these delays increase the risk of poor outcomes is unclear.

Objectives: To determine the risk of cardiovascular (CV) events, heart failure (HF) hospitalizations, and all-cause mortality associated with delays in anti-hyperglycemic treatment intensification (TI).

Methods: We combined 2005-2016 data from the Northwest and Mid-Atlantic regions of Kaiser Permanente to identify 3 cohorts of patients who intensified therapy by (1) initiating metformin (MET) as their first diabetes drug (n = 18,762); (2) adding a sulfonylurea (SU) to existing MET (n = 10 076); (3) initiating insulin after MET and/or SU therapy (n = 9778). We used the TI date to calculate delay in TI (time between A1C $\geq$ 7% and TI) and pre-TI A1C in a 6-month look-back period, and A1C approximately 12 months later to determine achievement of A1C < 7% on the cohort therapy. We followed patients through December 2016 until they experienced an MI, stroke, or other CV event, a HF hospitalization, or all-cause mortality, censoring follow-up when the cohort therapy changed. Multivariable cox regression controlled for CV risk factors including age, sex, race/ethnicity, smoking, blood pressure, statin and ACE/ARB use, and prior history of CV or HF.

Results: In the metformin cohort, each percentage point of pre-TI A1C was associated with a 10% increase in CV events (HR 1.10, 95% CI 1.03-1.16) and a 7% increase in HF hospitalization and all-cause mortality (1.07, 1.01-1.14 for each) after adjustment for CV risk factors. Each month of delay in TI was associated with a 6% increased risk of HF hospitalization and all-cause mortality (1.06, 1.00-1.13 for each). In the SU cohort, each month of delay in TI was associated with a 5% increase in CV events (1.05, 1.00-1.11) and a 6% increased risk of all-cause mortality (1.06, 1.00-1.12). In the insulin cohort, each percentage point of pre-TI A1C was associated with a 9% increase in CV events (1.09, 1.04-1.13) and each month of delay in TI was associated with a 4% increase in CV events (1.04, 1.00-1.08). Achievement of A1C < 7% was not associated with any of the cohorts or outcomes.

Conclusions: Delays in treatment intensification independently increase CV, HF, and mortality risk at all stages of diabetes therapy; intensifying therapy at the first sign of deteriorating glycemic control may be critically important.

74 | Risk of amputations associated with SGLT2 inhibitors: A propensity-matched cohort study

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Background: A large clinical trial program recently reported a twofold increase in risk for amputations in patients with type 2 diabetes randomized to canagliflozin, a sodium-glucose co-transporter 2 inhibitor (SGLT2i), prompting the US FDA to issue a safety alert. Risk for amputations was not observed in other clinical trials involving canagliflozin or other SGLT2is. Recent real-world studies report conflicting results.

Objectives: To determine the risk of amputations associated with SGLT2i relative to dipeptidyl peptidase-4 inhibitors (DPP4i).

Methods: We conducted a retrospective cohort study with an active comparator, new user design using data from Truven Health MarketScan[®] (2009-2015). Patients aged $\geq$ 18 years newly initiating SGLT2i or DPP4i between April 1, 2013, and March 31, 2015, were included. New use was defined as no use of index or comparator drugs in the prior 12 months. Patients were excluded on the basis of lack of continuous enrollment, use of insulin, prolonged hospitalizations, or having contraindications for SGLT2i use during baseline. Patients were followed until the earliest of any amputation, treatment discontinuation, disenrollment, or end of follow-up. Patients were matched 1:1 on high dimensional propensity scores (hdPS). Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for amputation risk.

Results: Of 137 012 patients in the study cohort, 34 999 were new users of SGLT2i. The majority were treated with canagliflozin (69% of all SGLT2i) or sitagliptin (71% of all DPP4i). Patients treated with DPP4is were older (58.7 vs 54.7 years, standardized difference [SD] 0.35) and with more diabetes complications (39.3% vs 33% with >1 complications, SD 0.13) than those treated with SGLT2i. After matching, there were 30 216 comparable patients in each arm. Over a median follow-up of 8.5 months, there were 60 amputations (SGLT2i: 36; DPP4i: 24). The majority of amputations were at the level of partial foot (75%) and due to diabetes-related vascular disease (66.7%). The incidence of amputations was higher among SGLT2i patients (1.62 vs 1.15 per 1000 person-years) with an HR of 1.38 (CI: 0.82-2.32). In stratified analyses, effect estimates differed by type of SGLT2i (canagliflozin vs DPP4i, HR 1.15 [CI: 0.63-2.09]; dapag- or empagliflozin vs DPP4i, HR 2.25 [CI: 0.78-6.47]).

Conclusions: Our findings suggest an elevated, though not statistically significant, risk of amputations associated with SGLT2is and warrant further research.

75 | A safety signal of venous thromboembolic events with the use of DPP-4 inhibitors: A pharmacovigilance disproportionality analysis

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Background: The use of dipeptidylpeptidase-4 inhibitors (DPP-4i) has rapidly increased for treating type 2 diabetes; knowledge regarding their safety profile in real-life setting remains incomplete.

Objectives: This study aimed at investigating the risk of venous thromboembolic (VTE) adverse events associated to their use.

Methods: Individual case safety reports (ICSRs) collected in VigiBase[®], and related to DPP-4i (sitagliptin, saxagliptin, and vildagliptin) and VTE were analyzed. VTE cases were identified using the standardised MedDRA Queries (SMQ) "Embolic and thrombotic events, venous." A descriptive analysis was performed according to median age, gender, seriousness, drug, and dose used. Disproportionality analyses were performed using information component (IC) in a subset of VigiBase[®] in which only related non-insulin glucose lowering drugs were considered. This was done using the SMQ and also by classifying the correspondent terms as follows: (i) related to pulmonary embolism and (ii) related to VTE at gastrointestinal level. A signal was considered if the lower limit of 95% credibility interval (LL 95% CI) was positive.

Results: A total of 268 ICSR of VTE events were identified; median age of patients was 63 years (interquartile range: 59-72), and 60% were men. Sitagliptin was involved in 92% of ICSR; DPP-4i were used at usual dosage in 62% of ICSR. Almost all cases were serious (97%), and 68% were fatal. Seventy-four cases (28%) were VTE at gastrointestinal level, while 97 (36%) concerned pulmonary embolism. Gastrointestinal VTE mainly concerned portal vein thrombosis (n = 28), splenic vein thrombosis (n = 27), and splenic vein occlusion (n = 16). Signals of disproportionate reporting were found for DPP-4i for all the studied events: the overall SMQ for VTE events (IC 1.09, LL 95% CI 0.91), pulmonary embolism (IC 0.54, LL 95% CI 0.24), and gastrointestinal VTE (IC 2.49, LL 95% CI 2.14).

Conclusions: This study found signals of disproportionate reporting of VTE for DPP-4i. Owing to the potential high public health impact of this signal, issued from the high prevalence of use of DPP-4i and the seriousness of VTE, these findings deserve to be further investigated through ad hoc and more robust studies.

76 | Frailty and risk of adverse events associated with dipeptidyl peptidase-4 inhibitors versus sulfonylureas in older adults with type 2 diabetes

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Background: Dipeptidyl peptidase-4 inhibitors (DPP4i) have a lower risk of hypoglycemia than sulfonylureas (SU). Older patients with type 2 diabetes and frailty may benefit more from DPP4i relative to SU than non-frail patients.

Objectives: To evaluate the risk of cardiovascular events, fractures, and severe hypoglycemia associated with DPP4i vs SU in older adults with type 2 diabetes and different levels of frailty.

Methods: A retrospective cohort study was conducted using a US commercial database that included 128 289 adults 60 years and older who had type 2 diabetes and initiated a DPP4i or a SU in 2006-2015. Outcomes were a composite endpoint of major cardiovascular events, fractures, and severe hypoglycemia, and individual components. Cox proportional hazards models were used to estimate the hazard ratio (HRs) and their 95% confidence intervals (CIs) comparing DPP4i and SU across different levels of a validated claims-based frailty index (mild < 0.15, moderate 0.15-0.24, severe ≥ 0.25) in the 1:1 propensity score (PS)-matched population.

Results: The analysis included 60 596 patients treated with either DPP4i or SU matched by PS. Compared with SU-treated patients, patients initiating DPP4i had lower rates, per 1000 person-years, of the composite endpoint (24.9 vs 40.4 events; HR, 0.60; 95% CI, 0.54-0.67), cardiovascular events (10.1 vs 13.9 events; HR, 0.71; 95% CI, 0.60-0.84), and hypoglycemia (10.8 vs 22.7 events; HR, 0.46; 95% CI, 0.40-0.53), but a similar rate of fractures (4.6 vs 5.2 events; HR, 0.86; 95% CI, 0.67-1.10). DPP4i therapy was associated with reduced cardiovascular events in patients with mild frailty (5.7 vs 9.1 events; HR, 0.62; 95% CI, 0.46-0.83), but not in those with severe frailty (27.5 vs 29.9 events; HR, 0.91; 95% CI, 0.56-1.45). In contrast, DPP4i therapy was associated with a greater reduction in fractures in patients with severe frailty (14.1 vs 21.4 events; HR, 0.67; 95% CI, 0.36-1.24) compared with in those with mild frailty (3.1 vs 3.0 events; HR, 1.05; 95% CI, 0.68-1.63). The lower rate of hypoglycemia with DPP4i therapy was consistent across the frailty levels.

Conclusions: In older adults with type 2 diabetes, DPP4i therapy was associated with a lower risk of adverse events than SU. The association with cardiovascular events and fractures seems to vary by the severity of frailty, whereas the association with hypoglycemia was consistent across the frailty levels.

77 | Real-world persistence for newly prescribed HIV-1 treatment: Single versus multiple tablet regimen comparison

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Background: Once-daily, single-tablet regimens (STRs) have been associated with improved patient outcomes compared with multi-tablet regimens (MTRs).

Objectives: Evaluate real-world persistence for HIV-1 treatment comparing STRs versus MTRs, backbones, and third agents using the Truven Medicaid database.

Methods: Adults (≥ 18 years) newly starting antiretroviral therapy (ART) with ≥ 2 claims for ART during the index period (01JAN2015–31DEC2016) were included. For STRs, the index date was defined as the first ART claim date; for MTRs, it was the claim date of the last filled drug in the regimen. All MTR regimen fills occurred within a 5-day window. Patients had continuous enrollment for a 12-month baseline period and were followed until disenrollment or the end of the study, whichever occurred earlier. Persistence was defined as the time from the index regimen start date to the start of the first 90-day gap between fills or the end of study period. Kaplan-Meier and Cox proportional hazard models evaluated persistence and discontinuation (gap of ≥ 90 days between fills) across treatments, controlling for age, gender, race, insurance type, pre-index medication use, number of unique medications on index except ART, Deyo-modified Charlson comorbidity index, and baseline comorbidities.

Results: A total of 1782 and 627 patients on STR and MTR, respectively, were identified, with a mean (standard deviation) age of 39.7 (13.5) years for STR patients (57.6% male) and 41.4 (12.0) years for MTR patients (52.2% male). In unadjusted analyses, 36.3% of STR patients discontinued first line therapy compared with 48.8% for MTR patients. Controlling for baseline differences, MTR patients had a higher risk of treatment discontinuation (hazard ratio [HR]: 1.6, $p < 0.0001$). Among STR patients, EVG/COBI/FTC/TAF had greater persistence than EFV/FTC/TDF (HR: 3.6, $p < 0.0001$), EVG/COBI/FTC/TDF (HR: 2.8, $p < 0.0001$), and ABC/3TC/DTG (HR: 1.8, $p = 0.004$). Among backbones, FTC/TAF had greater persistence than FTC/TDF (HR: 4.4, $p < 0.0001$) and ABC/3TC (HR: 2.2, $p < 0.0001$).

Conclusions: Among patients newly treated with ART, STR patients were found to have greater persistence as compared with MTR patients. Regimens containing FTC/TAF were found to have higher persistence than other backbones. As new regimens with improved safety and tolerability profiles become available, continued research of persistence with HIV patients is needed to inform patient therapeutic management.

78 | Abstract Withdrawn

79 | Predictors of persistent prescription opioid analgesic use among people without cancer in Australia: A retrospective cohort study

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Background: Long-term opioid analgesic use for chronic non-cancer pain is associated with uncertain clinical benefits but clear harms.

Objectives: To identify patterns of opioid analgesic use and determine predictors of persistent opioid use among people without cancer.

Methods: A population-based cohort study of Australians initiating prescription opioids from July 2013 to December 2015 was conducted using data from a random 10% sample of people who accessed medicines through Australia's Pharmaceutical Benefits Scheme. A 12-month look-back period was used to define opioid initiation, exclude people with cancer, and determine comorbidities. Persistent use over 12 months since initiation was identified through group-based trajectory modelling. Odds ratios (OR) and 95% confidence intervals (CIs) for predictors of opioid persistence were estimated using logistic regression.

Results: The cohort consisted of 431 963 people without cancer who initiated opioids. A total of 11 323 (2.6%) persistent opioid users were identified. Predictors of persistence included initiation with transdermal formulations (OR 4.2, 95% CI 3.9–4.5), or initiation with total oral morphine equivalents (OME) ≥ 750 mg (OR 3.7, 95% CI 3.3–4.1), having depression (OR 1.6, 95% CI 1.5–1.7), or psychotic illness (OR 2.0, 95% CI 1.9–2.2). Previous dispensing of paracetamol (OR 2.0, 95% CI 1.9–2.1), pregabalin (OR 2.0, 95% CI 1.8–2.1), and benzodiazepines (OR 1.53, 95% CI 1.4–1.6) predicted persistence. Compared with people aged 18–44 years, those ≥ 75 years were 2.5 (95% CI 2.3–2.6) times more likely to be persistent users.

Conclusions: Patient-specific characteristics (older age, prior history of mental health comorbidities, and use of non-opioid analgesics) and choice of initial opioid (transdermal formulation and higher total OMEs) were found to strongly predict persistent use. This information may help prescribers target monitoring and early intervention efforts in order to prevent harms associated with the long-term use of opioids.

80 | Time-varying measures of adherence to other medications to predict persistence to statin treatment

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Background: Many studies have examined claims-based predictors of medication persistence. Few have considered whether time-varying variables, such as whether patients persist with other drugs, improve prediction.

Objectives: To assess the added value of time-varying variables, including time-varying measures of adherence to other drugs, in predicting statin treatment persistence.

Methods: We identified a cohort of statin initiators in a large US claims database. Patients were followed for up to 12 prescription dispensings. At each statin dispensing, we used logistic regression to predict whether patients fill at least one subsequent prescription. Baseline predictors included demographics, clinical characteristics, and measures of adherence to other chronic medications. At each statin dispensing during follow-up, we also assessed changes in clinical characteristics and adherence to other medications and to the statin up to that point. The c-statistic was used to compare discrimination between various models with and without time-varying variables.

Results: Of 695 253 eligible statin initiators, 54% filled a second prescription and <8% filled 12 prescriptions. The probability of a subsequent dispensing ranged from 74% among those filling a second prescription to 83% among those filling at least 11 prescriptions. The model with only baseline patient characteristics yielded a c-statistic of 0.624 for predicting the second dispensings. Adding measures of prior adherence to the baseline patient characteristics increase the c-statistic to 0.645. The discriminative ability of these baseline variables declined with each subsequent dispensing, with a c-statistic of 0.598 for predicting the 12th dispensings. Adding time-varying patient characteristics and adherence measures during follow-up modestly improved the c-statistic to 0.624.

Conclusions: In a cohort of statin initiators, filling a second prescription was a key indicator of whether patients would persist with treatment. The predictive performance of baseline predictors decreased over time. Incorporating time-varying variables modestly enhanced model discrimination.

81 | The impact of the duration of bisphosphonate drug holidays on hip fracture rates

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Background: Given FDA warnings, drug holidays (temporary or permanent discontinuation) of bisphosphonates (BPs) after long-term (3-5 years) continuous therapy is becoming increasingly common in the United States (US). However, the benefits and risks of stopping BPs, and the optimal timing to restart, remain unclear.

Objectives: We conducted a population-based cohort study of women on long-term BP therapy to evaluate the rate of hip fracture following a drug holiday.

Methods: We used Medicare data (2006-2014) to identify all women with medical and pharmacy coverage who initiated a BP and were at least 80% adherent for ≥ 3 years ("baseline"), at which follow-up time began. Patients using other bone therapies (eg, denosumab, estrogen, teriparatide, and calcitonin) were excluded or censored if they started after follow-up began. We calculated crude rates of hip fracture for continuing BP therapy and among those who discontinued, for categories of time since discontinuing (ie, length of drug holiday), extending up to 3 years. We used Cox proportional hazards models to evaluate the risk of discontinuing per the length of the drug holiday, using age as the time axis and controlling for potentially confounding factors, with and without adjusting for death as a competing risk.

Results: We identified 156 236 women who were highly adherent, long-term BP users. The mean (SD) age was 78.5 (7.5) years. The most commonly used BPs were alendronate (71.7% ever use, 52% exclusive use) and zoledronic acid (16.2% ever use, 8.9% exclusive use). During a median (IQR) follow-up of 2.1 (1.0, 3.3) years, 62 676 (40.1%) of women stopped BP therapy for at least 6 months or more. Among these women, 7947 (12.7%) subsequently restarted any BP. Overall, 16 904 (10.8 %) died. A total of 3745 hip fractures occurred during follow-up. Hip fracture rates were lowest among women who were current users (9.6/1000py) and gradually increased as the length of the drug holiday increased, achieving their maximum with a drug holiday >2 years (15.7/1000py). The adjusted hazard ratio for hip fracture for drug holiday >2 years was 1.39, referent to current BP use.

Conclusions: In a large cohort of US women, a BP drug holiday greater than 2 years was associated with a significantly increased risk for hip fracture of up to 39% compared with continued BP use.

82 | Adherence trajectories to essential medications after acute coronary syndrome and their impact on clinical outcomes. A population-based cohort study

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Background: Treatment with antiplatelet, statins, beta-blockers, and ACEI/ARBs after an acute coronary syndrome (ACS) has improved greatly in the last decade. However, adherence is still suboptimal.

Objectives: To identify adherence patterns to the recommended medications after an ACS in the Valencia region and to assess their impact on clinical outcomes.

Methods: Population-based retrospective cohort of all patients discharged after hospitalization for ACS in the Valencia region (Spain) during 2009-2011. We created a sub-cohort of patients with prescriptions from at least three therapeutic groups within the first month after discharge. We assessed monthly medication adherence for 12 months following initiation, defined as having ≥ 24 days covered out of 30, and identified adherence patterns through group-based trajectory models. A composite clinical outcome (hospitalization for ACS, heart failure, stroke, revascularization, and mortality) during the year after adherence assessment was evaluated. A multivariable Cox proportional hazards model was used to assess the association between adherence patterns and clinical outcomes.

Results: Among 15 797 patients discharged alive, 12 057 (76.32%) initiated treatment with ≥ 3 therapeutic groups. We identified seven different adherence trajectories: (1) Adherent, 52.94% of patients in the cohort; (2) Early Gap (6.64%); (3) Middle Gap (5.67%); (4) Late decline (10.93%); (5) Occasional Users (5.45%); (6) Early Decline (8.79%) and (7) Non-Adherent (9.58%). Compared with the Adherent group, patients in the trajectories of Early Gap (HR: 1.33; 95% CI 1.09, 1.63), Late decline (HR: 1.32; 95% CI 1.11, 1.57), and Non-Adherent (HR: 1.38; 95% CI 1.15, 1.65) had a greater risk of adverse clinical outcomes.

Conclusions: Seven adherence patterns to 3 or more essential medications after ACS were identified. Moderate and non-adherence patterns were associated to a higher risk of adverse clinical outcomes as compared with adherent patients. The identification of adherence patterns associated to higher risk of adverse clinical outcomes may be useful to target interventions to improve medication adherence.

83 | Detection of fluoroquinolone use and the risk of rhegmatogenous retinal detachment: Sequence symmetry analysis using nationwide South Korea health care database between 2004 and 2015

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Background: The association between fluoroquinolone and rhegmatogenous retinal detachment (RRD) has been controversial from inconsistent findings.

Objectives: To detect a possible association of fluoroquinolone use and incidence of RRD, using sequence symmetry analysis (SSA).

Methods: We conducted a SSA, a case-only design including only those with the record of exposure and outcome, using a Korean nationwide health insurance database between 2004 and 2015. Exposure was defined as new fluoroquinolone use and outcome as an incident RRD, defined by a diagnosis of RRD (ICD-10: "H33.0") and surgery for RRD. Reference antibiotic drugs include first generation

cephalosporin, second generation cephalosporin, third generation cephalosporin, extended spectrum penicillin, and macrolides. The pairs of exposure and RRD within 1-year time-window were included. The sequence ratio (SR) was calculated by the ratio of the number of patients prescribed with exposure first and diagnosed with RRD second (causal group) divided by the number of patients diagnosed with RRD first and prescribed with exposure second (non-causal group). SR was adjusted (aSR) for trends of exposures and diagnoses of RRD to rule out null-effect, and 95% confidence intervals (CIs) were calculated. In order to observe whether the estimated ratio stabilized over time, we did a repeated time-sequential analysis with the cumulative data starting from the three year period, 2004-2006, to 2015.

Results: Our SSA study included a total of 5234 pairs of fluoroquinolone users, composed of 3143 causal group and 2091 non-causal group, were included. Fluoroquinolone use and RRD event showed a greater association as compared with comparators (fluoroquinolone: 5234 pairs; aSR = 1.45 [95% CI = 1.37-1.53], first generation cephalosporin: 4139 pairs; aSR = 1.18 [95% CI = 1.12-1.26], second generation cephalosporin: 5914 pairs; aSR = 1.14 [95% CI = 1.08-1.20], third generation cephalosporin: 3650 pairs; aSR = 0.74 [95% CI = 0.70-0.80], extended spectrum penicillin: 4823 pairs; aSR = 1.21 [95% CI = 1.14-1.28], macrolides: 4115 pairs; aSR = 1.13 [95% CI = 1.07-1.21]). Time-sequential analyses also supported the possible association between fluoroquinolone and RRD.

Conclusions: Our detection suggests a possible association between fluoroquinolone use and RRD. Further pharmacoepidemiological studies are recommended to confirm the causal association.

84 | Renin-angiotensin-aldosterone system inhibition and outcome of sepsis

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Background: Early antibiotic treatment and hemodynamic optimization remain the cornerstones of sepsis management. Despite these medical advances, the outcome of sepsis remains poor, with mortality rates of 20 to 40%. Exploration of novel therapeutic strategies is therefore warranted. Antagonists of the renin-angiotensin-aldosterone system (RAAS) might prevent organ failure and reduce mortality, especially when administered early in the course of sepsis.

Objectives: To determine whether specific RAAS inhibitors are associated with reduced all-cause mortality in patients with sepsis.

Methods: The National Health Insurance Research database, containing electronic claims records of 1 million patients, was used to conduct a cohort study using propensity score (PS) based regression to control for differences among patients using RAAS inhibitors. To directly compare ACEI users, ARB users, and nonusers, a three-way PS match was

performed to calculate the cumulative hazard of mortality for the three groups.

Results: A total of 52 727 patients were hospitalized with sepsis between 2001 and 2011, of whom 7642 were prescribed an angiotensin converting enzyme inhibitor (ACEI) and 4237 were prescribed an angiotensin II receptor blocker (ARB). In the PS-matched analysis, prior ACEI use was associated with decreased 30-day mortality (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.75-0.92) and 90-day mortality (HR, 0.85; 95% CI, 0.78-0.93) compared with non-users. Prior ARB use was associated with decreased 30-day mortality (HR, 0.85; 95% CI, 0.79-0.92) and 90-day mortality (HR, 0.87; 95% CI, 0.82-0.93). In three-way comparison, the cumulative hazards revealed ACEI users had the highest survival rate at 90 days, followed by ARB users, and then nonusers. Prior ACEI or ARB use was not associated with decreased incidence of septic shock or acute renal failure requiring emergent hemodialysis.

Conclusions: Compared with people who were not prescribed RAAS inhibitors, the short-term mortality after sepsis was significantly lower among those who were previously established on RAAS inhibitor treatment when sepsis occurred. These data may encourage the use of ACEIs or ARBs as favorable antihypertensive agents in patients with hypertension who are at particularly high risk of sepsis. Data from randomized controlled trials are required to verify this potential protective effect.

85 | The cardiovascular risk of febuxostat among patients with hyperuricemia or gout compared with allopurinol: A population-based study in Taiwan

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Background: The US FDA has issued a safety communication highlighting that febuxostat has been associated with an increased risk for cardiovascular-related death compared with allopurinol among patients with gout on 2017/11/15. However, the cardiovascular risk of febuxostat still remains unknown.

Objectives: This study was aimed to evaluate the cardiovascular risk of febuxostat and allopurinol use in patients with gout or hyperuricemia in Taiwan.

Methods: We identified the patients who newly received febuxostat and allopurinol treatment for gout or hyperuricemia from Taiwan Health Welfare Database (THWD) during 2012 to 2014 and had at least 1-year follow-up. The index date was the date who start to use febuxostat and allopurinol. The newly users were defined those who were not prescribed febuxostat or allopurinol for treatment in prior 1 year. The primary endpoint was composite of CV risk (acute

myocardial infarction, stroke, and heart failure). The secondary endpoint was the all-cause mortality. First exposure forward analyses were presented by using COX proportional hazard model. In addition, we used propensity score (PS) matching method to reduce the effects of confounders between febuxostat and allopurinol users, and estimated subdistribution hazard ratios (SHR) by using Fine-Gray model.

Results: There were 194 473 patients included in study population, and febuxostat and allopurinol groups were 37 090 and 157 383, respectively. Febuxostat users (61±15) was older than allopurinol (55±16), and male was dominate (78%) in two groups. Febuxostat had a significantly higher CV risk than allopurinol (adjusted HR: 1.13; 95% CI 1.07-1.19). The result was consistent in PS (1.12; 95% CI 1.06-1.19) and Fine-Gray model (SHR: 1.10; 95% CI 1.03-1.14). The secondary endpoint showed that there were no significant difference between febuxostat and allopurinol users (adjusted HR: 0.99; 95% CI 0.94-1.03).

Conclusions: Our study showed that the febuxostat has higher CV risk than allopurinol in patients with gout or hyperuricemia in Taiwan. Further study to development of an intervention focused on high risk in febuxostat users is needed.

86 | Mortality risk associated with haloperidol use compared with other antipsychotics: An 11-year population-based propensity score-matched cohort study

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Background: Haloperidol is a frequently prescribed antipsychotic worldwide. However, the mortality risk of all-cause, cardiovascular disease (CVD), and pneumonia associated with haloperidol compared with other antipsychotics is unknown.

Objectives: This study is to investigate the risk of mortality associated with long-term haloperidol treatment as compared with other antipsychotics.

Methods: This is a cohort study using a population-based electronic health record database. Patients on haloperidol or other antipsychotics (amisulpride, aripiprazole, chlorpromazine, olanzapine, quetiapine, risperidone, sulpiride, and trifluoperazine) from 2004 to 2014 were matched on propensity score. The outcome was mortality of all-cause, CVD, and pneumonia. Absolute rates of outcome were calculated in the number of deaths per 1000 person-year follow-ups. Relative risks of outcome were calculated in hazard ratios (HR) with 95% confidence intervals (95% CI) using the Cox proportional hazards model.

Results: A total of 136 593 incident users of antipsychotic (44.7% male) were included with a mean age of 68 years (SD 22.3). Patients on haloperidol (n = 65 510 [48.0%]) were matched to patients on other antipsychotics. During a mean follow-up of 3.2 person-years, mortality rates by drug varied from 186.8 (per 1000 person-year [haloperidol]) to 10.4 (per 1000 person-year [trifluoperazine]). Compared

with haloperidol, a lower risk of all-cause mortality was shown in all non-haloperidol antipsychotic drugs, with HRs by drug ranging from 0.68 (95% CI 0.64 to 0.72 [chlorpromazine]) to 0.43 (95% CI 0.36 to 0.53 [trifluoperazine]). Significantly lower pneumonia-related mortality risk was observed with all non-haloperidol antipsychotics except amisulpride and olanzapine, with HRs varying from 0.76 (95% CI 0.68-0.85) for risperidone to 0.38 (95% CI 0.24-0.61) for trifluoperazine. A significantly lower risk of CVD mortality was observed for risperidone (HR 0.79 [95% CI 0.66-0.93]), sulpiride (HR 0.78 [95% CI 0.64-0.96]), chlorpromazine (HR 0.76 [95% CI 0.65-0.90]), and quetiapine (HR 0.67 [95% CI 0.57-0.78]).

Conclusions: Haloperidol is associated with an increased mortality risk compared with other antipsychotics in long-term follow-up. Treatment with haloperidol, especially in the elderly and patients at risk of CVD or pneumonia, should be cautiously reassessed while other antipsychotics associated with lower risk should be considered as a preferred option.

87 | Comparative physical morbidity and mortality risk of antipsychotics in patients with Parkinson's disease

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Background: Use of antipsychotics is a common treatment for psychosis in patients with Parkinson's disease (PD). However, the decreased level of dopamine caused by antipsychotics warrants attentions on worsening movement symptoms of PD.

Objectives: To compare the risk of physical morbidities and mortality in patients with PD receiving different antipsychotics for the control of psychosis.

Methods: We conducted a retrospective cohort study using the Taiwan's National Health Insurance Research Database (NHIRD) from 2004 to 2012. Study population consists of patients aged +40 years who diagnosed with PD newly receiving antipsychotic medications. The outcome of interest was the composite of death and hospitalizations due to physical morbidities related to PD, including pneumonia and wrist, femur, and hip fractures because of accidental falls. Quetiapine was selected as reference group for comparisons because it was the most commonly used antipsychotics for patients with PD. We performed Cox proportional hazards models with adjustments of covariates such as age, sex, and baseline PD treatments to compare the physical morbidity and mortality risks between antipsychotic groups.

Results: We identified a cohort of 22 057 patients with the mean age of 76.54 years (SD 8.87) and 50.5% female. Quetiapine

(48.8%) was the most frequently used antipsychotics, followed by risperidone (16.8%), haloperidol (14.6%), sulpiride (7%), and trifluoperazine (2.6%). We found the risks were higher in risperidone (adjusted hazard ratio, 1.14; 95% CI, 1.07-1.22) and haloperidol (1.09; 1.02-1.17) compared with quetiapine. Notably, the findings indicated patients receiving trifluoperazine (0.63; 0.52-0.77) and clozapine (0.76; 0.58-0.99) had significantly lower risks compared with quetiapine users.

Conclusions: Although trifluoperazine and clozapine were not used commonly, we found they had better profiles on physical morbidity and mortality risks compared with quetiapine.

88 | Analysis on reasons for discontinuations of sodium glucose co-transporter 2 inhibitors in patients with type 2 diabetes mellitus in real-world practices in Taiwan

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Background: Adherence on glucose co-transporter 2 inhibitors (SGLT2i) is the primary issue for type 2 diabetes mellitus (T2DM) patients in real-world settings. Understanding the reasons for discontinuations is crucial for successful strategies to improve treatment outcome.

Objectives: To investigate the reasons for discontinuations of SGLT2i treatment in real-world practices in Taiwan.

Methods: We conducted a cohort study and analyzed the data of three hospitals in northern Taiwan from May 2016 to April 2017. We selected a random sample of 10% adult patients with T2DM initiating empagliflozin or dapagliflozin. We investigated the discontinuation rate of SGLT2i during one year follow-up period and the reasons, including the loss of follow-up, ineffectiveness, side-effects, and others.

Results: We sampled a total of 597 patients with mean age of 58.7 (± 11.8) years; 41.6% were female, and 55.9% received empagliflozin. The baseline HbA1c was 9.3 ± 1.8 mg/dL. Patient received 2.8 (± 1.1) diabetes agents before SGLT2i initiation. We found 167 patients (27.9%) discontinued SGLT2i during follow-up period. The most frequent reasons for discontinuations were loss of follow-up of patients ($n = 43$, 25.7%), followed by ineffectiveness ($n = 40$, 24.0%), side-effects ($n = 39$, 23.3%), and others ($n = 15$, 9.0%). There were 20.9% of unknown reasons for discontinuations.

Conclusions: The findings indicated a high discontinuation rate for SGLT2i, which raised a concern of poor adherence and possible treatment failure. The study provided foundations for development of strategy to improve treatment outcome while using SGLT2i.

89 | Beliefs about medicines and nonadherence in patients with coronary heart disease, hypertension, type 2 diabetes mellitus: A cross-sectional online survey in China

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Background: Beliefs about medicines have been proposed as a strong determinant of medication adherence. The Beliefs about Medicines Questionnaire (BMQ), a common measure to assess medication beliefs, has not been widely studied in China.

Objectives: To investigate Chinese people's beliefs about medicines and their associations with medication adherence in patients with coronary heart disease (CHD), hypertension, and type 2 diabetes mellitus (T2DM).

Methods: A cross-sectional online survey was conducted between February and October 2017 in Jiangsu province, China. 746 adult patients (191 CHD patients, 314 hypertension patients, and 241 T2DM patients) completed the survey and were included in the analysis. The main outcomes included patients' perceived needs and concerns to their medicines (Necessity and Concern) assessed by the BMQ-specific subscale (BMQ-S), general background beliefs about pharmaceutical medicines (Benefit, Harm, and Overuse) assessed by the BMQ-general subscale (BMQ-G), and patients' beliefs about how sensitive they were to the effects of medicines assessed by the Perceived Sensitivity to Medicines Scale (PSM). All questionnaires above were 5-Likert scales with average scores arranged from 1 to 5. Non-adherence was defined as <20 scores assessed by the Medication Adherence Report Scale (MARS) which has a maximum score of 25. The associations between non-adherence and each domain of beliefs about medicines were assessed using a logistic regression model.

Results: 407 (54.6%) men and 339 (45.4%) women were included in the study. The overall mean values of BMQ and PSM were 3.62 ± 0.63 (Necessity), 3.27 ± 0.68 (Concern), 3.35 ± 0.55 (Overuse), 3.63 ± 0.55 (Benefit), 3.06 ± 0.60 (Harm) and 2.24 ± 0.66 (PSM). 215 patients did not adhere their prescriptions (54 [30.5%] in the CHD group, 90 [30.7%] in the hypertension group, and 71 [31.8%] in the T2DM group). Across the whole participants, after adjusting for demographic characteristics, non-adherence was associated with higher lower necessity beliefs (OR 0.63, 95% CI 0.46 to 0.86) and higher general harm beliefs (OR 1.49, 95% CI 1.08 to 2.07).

Conclusions: BMQ collected through online appears to be a useful tool in identifying patients at risk of nonadherence.

90 | Randomized controlled trial to test the effectiveness of a patient-tailored intervention programme to enhance adherence to antihypertensive medication

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Background: Due to non-adherence, substantial numbers of patients benefit from their medication only to a limited extent. Several interventions have been developed; however, most interventions achieved only a modest positive effect.

Objectives: The patient-tailored, pharmacist-led CATI care programme was developed and evaluated to improve patients' adherence to antihypertensive medication.

Methods: A randomised controlled trial in 20 community pharmacies with a 9-month follow-up was conducted. Patients (45-75 years) using antihypertensive medication and considered non-adherent according to pharmacy dispensing data, as well according to a self-report questionnaire, were eligible to participate. The programme consisted of two visits to the pharmacy to identify patients' barriers to adherence and to counsel patients in overcoming these barriers. Primary outcome was self-reported medication adherence assessed with the MARS-5 questionnaire. Secondary outcome measures were beliefs about medicines, illness perceptions, and quality of life. Mixed-model analyses were used to assess the effect of the intervention programme.

Results: 170 patients were included. No significant differences between the intervention and control group were found for self-reported medication adherence, illness perceptions, and quality of life. Regarding the beliefs about medicines, only the BMQ Necessity score was significantly higher in the intervention group compared with the control group (B 0.71 [95% CI 0.00-1.41], P 0.05).

Conclusions: The intervention programme seems not to influence self-reported medication adherence in patients using antihypertensive medication. The lack of instruments to properly measure medication adherence might play a role. Per protocol and subgroup analyses will be performed to explore effectiveness differences in subgroups.

91 | Abstract Withdrawn

92 | Abstract Withdrawn

93 | Mediation by patient-reported outcomes of the association between film-coated or dispersible formulations of deferasirox and serum ferritin reduction: A post hoc analysis of the eclipse trial

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Background: The ECLIPSE trial demonstrated similar safety of the deferasirox (DFX) film-coated tablet (FCT) to dispersible tablet (DT), with fewer severe gastrointestinal (GI)-related adverse events (AEs), and more favorable patient-reported outcomes (PROs), including reported adherence. FCT patients (pts) showed a larger median reduction in serum ferritin (SF) from baseline (−350.0 vs −85.5 ng/mL) than DT, despite similar doses (Taher AT et al, *Am J Hematol* 2017), which may be due to better adherence. PROs may be a useful surrogate marker of actual pt adherence.

Objectives: To estimate the proportion of the association between treatment (tx) with deferasirox FCT or DT and SF reduction from baseline that is mediated through PROs, in a post hoc analysis.

Methods: Transfusion-dependent thalassemia or myelodysplastic syndrome pts were randomized to receive equivalent bioavailable doses of deferasirox FCT (N = 87) or DT (N = 86). PROs were assessed using the Palatability and modified Satisfaction with Iron Chelation Therapy questionnaires, the latter assessing adherence, satisfaction, and concerns. Frequency of GI-related AEs was assessed. Mediation analysis was used to compute proportion mediated (PM), which quantified the proportion of association between FCT or DT tx and SF reduction mediated by patient-reported adherence score, other PROs, and frequency of severe GI-related AEs. The analysis was adjusted for age, sex, race, underlying hematological disease, prior use of DT, baseline iron overload severity, average planned dose, and number of blood transfusions on tx. Subgroup analyses were conducted in: all pts with prior deferasirox DT use (DT non-naïve); all thalassemic pts; DT non-naïve thalassemics.

Results: Association between FCT or DT tx and SF reduction was substantially mediated by patient-reported adherence (PM = 66.6%, $p = 0.01$). Patient-reported adherence, along with satisfaction, concerns, palatability scores, and frequency of severe GI-related AEs together mediated 90.1% of the association ($p = 0.01$). PM by patient-reported adherence was increased in DT non-naïve pts (PM = 80.5%, $p = 0.01$).

Conclusions: PROs, particularly patient-reported adherence, are significant mediators of the association between the formulation of deferasirox treatment and SF reduction from baseline. PM was

increased in non-naïve DT pts, suggesting their enhanced appreciation for FCT over DT.

94 | Mobile health intervention increases inhaled corticosteroid adherence in adolescents with asthma

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Background: Adherence rates among asthma patients are generally low, resulting in poorly controlled asthma. Adherence decreases even more during adolescence. We developed (in co-creation with patients) an interactive mobile health (mHealth) intervention; the Adolescent Adherence Patient Tool (ADAPT) containing different elements, such as questionnaires to monitor symptoms, medication alarm, educational movies, peer chat, and health care provider chat.

Objectives: To evaluate the effect of the ADAPT intervention on inhaled corticosteroid adherence and asthma control in adolescents (12–18 years) with asthma.

Methods: We conducted a cluster randomized controlled trial in 66 community pharmacies. Self-reported adherence (Medication Adherence Report Scale [MARS]), asthma control (Control of Allergic Rhinitis and Asthma Test [CARAT]), and asthma-related quality of life were measured at start ($t = 0$) and end of follow-up ($t = 6$). We used mixed effect models to analyse the effect.

Results: In total, 234 adolescents (147 in the control and 87 in the intervention group) completed the study (mean age 15.1 ± 1.9 years; 52.6% females). Adherence rates of patients with low baseline adherence ($N = 76$; $MARS \leq 19$) increased with 1.42 points in the intervention group ($N = 26$), whereas the rates of patients in the control group ($N = 50$) decreased with 0.70 (intervention effect +2.12, $P = 0.04$). This effect was larger (+2.52, $P = 0.02$) in patients with uncontrolled asthma ($CARAT \leq 24$) having low adherence rates ($MARS \leq 20$). No effect was observed on asthma control or asthma related quality of life.

Conclusions: The ADAPT intervention increases adherence in adolescent asthma patients with poor adherence. Health care providers should consider a personalized mHealth approach to improve adherence in adolescents with asthma.

95 | The association between adherence to antihypertensive medications and subsequent health care utilisation in the ageing community dwelling adults: Results from wave one of the Irish Longitudinal Study on Ageing (TILDA)

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Background: Non-adherence to antihypertensive (AHT) medication is common. AHT non-adherence leads to an increased risk of cardiovascular related hospitalisations, but few studies have focussed on the association between AHT non-adherence and general practitioner (GP), emergency room (ER), and outpatient visits in ageing adults in Europe.

Objectives: To establish the association between adherence to AHT and subsequent health care utilisation in ageing adults.

Methods: TILDA is a nationally representative sample of the ageing population in Ireland. Wave one of the cohort (2009/2010) included a computer-aided personal interview (CAPI) with each participant recording health and social variables. A cohort study was performed using a subset of participants, aged ≥ 50 years, who had their pharmacy claims linked to responses. Participants were included in the analysis if they had at least 3 claims for one or more AHT (ATC codes "C02, C03 C07, C08, or C09") within the year preceding the time period referred to in the CAPI. Adherence was measured using proportion of days covered (PDC), with patients being classified as adherent if the average PDC > 0.8 . Non-persistence to AHT was measured as > 90 -day gap between claims. Negative binomial regression was used to analyse the association between AHT adherence and number of GP, ER, outpatient visits, and overnight hospital stays (adjusted incidence rate ratios, IRR, and 95% CI are presented). Covariates adjusted for included age, sex, polypharmacy, depression, socioeconomic status, functional disability, cognitive impairment, and social support.

Results: 1431 participants were included in the study. Average PDC was 0.85, 72.6% of ageing adults were considered adherent (PDC > 0.8) and very few had a gap > 90 days (3.9%). Adherence to AHT was associated with a decrease in GP visits reported (adjusted IRR 0.91, 95% CI 0.83-0.99, $p < 0.001$). Adherence had no significant impact on ER visits, outpatient visits, or overnight hospital stays reported, but a gap > 90 days resulted in a significant increase in ER visits (adjusted IRR 1.99, 95% CI 1.04-3.84).

Conclusions: Adults who adhere to their AHT appear to visit the GP less, suggesting improved overall health status, as each participant included can avail of free GP care. Large gaps in claims for AHT may result in increased ER visits, which could be potentially avoidable if non-persistence was addressed at a primary care level.

96 | Variation in medicines use by ethnicity: A comparison between 2006/2007 and 2012/2013

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Background: Disparities in health between Māori (indigenous people) and non-Māori populations have been a longstanding issue in New

Zealand. However, there is limited information regarding disparities in the use of publicly funded medicines.

Objectives: To assess whether there are disparities—after adjusting for age, population size, and disease severity—between Māori and non-Māori in access to and persistence with publicly funded medicines and to examine changes in access and persistence rates over time.

Methods: Data were obtained from prescription medicine dispensing claims for the financial years 2006/2007 and 2012/2013. The claims database links patient-level dispensing of medicines listed on the New Zealand Pharmaceutical Schedule with demographic data. ICD-10 codes were used to link dispensed medicines with relevant medical condition(s) described in 2013 New Zealand Burden of Disease Study. Disparities in disease burden estimates (ie, DALY counts) and medicine dispensings on an absolute scale were estimated using differences in standardised rates, being differences in age-standardised rates for DALYs or dispensed scripts between Māori and non-Māori populations, whereas disparities on a relative scale were estimated using standardised rate ratios, being the ratios of the age standardised DALY or dispensed scripts for the two groups.

Results: After adjusting for age and disease burden, Māori had lower dispensings overall than non-Māori in both time points, with net differences of 601 871 (2006/2007) and 1 126 281 (2012/2013) scripts. The overall disease burden-adjusted inequalities in medicine dispensings between Māori and non-Māori widened by 6% (0.94 ratio of rate ratios, comparing Māori vs non-Māori age-standardised rate ratio overall in 2012/2013 [0.59] against that in 2006/2007 [0.63]). The overall increase in the apparent gap seems due to a further deterioration in access, while relative persistence has improved over time. Among the largest areas of apparent under treatment are cardiovascular disease, diabetes, infectious diseases, mental health, asthma and COPD, and cancer.

Conclusions: After adjusting for age, population size, and disease severity, this research has shown that Māori have fewer prescriptions dispensed for medicines to treat many major medical conditions compared with non-Māori. The potential disparities in medicine use between Māori and non-Māori populations warrant further investigation, to better understand reasons why and design interventions that reduce these disparities.

97 | Comparison of adherence and discontinuation of hypoglycemic agents among patients with asthma and diabetes: A retrospective analysis from 2005 to 2015

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Background: Adherence and persistence to antihyperglycemic agents are key components in controlling patients' HbA1c. Growing evidence suggests a negative interaction between HbA1c and lung function; as

HbA1c is elevated, lung function decreases. Contributing mechanisms may include health behavior.

Objectives: To compare the adherence and discontinuation of different hypoglycemic agents in asthmatic-diabetic patients.

Methods: Utilizing the Truven Marketscan commercial claims database, patients aged 18–64 who were dispensed glucagon-like peptides-1 (GLP-1), dipeptidyl peptidase-4 inhibitors (Dpp-4), sodium-glucose cotransporter-2 inhibitors (SGLT-2), sulfonylureas (SU), or thiazolidinediones (TZDs) between 2005 and 2015 were included. The study index date was the first dispensing date. A 1-year baseline period was used to identify new users who have asthma and type 2 diabetes. Adherence was calculated over a 6-month follow-up period as >80% of the proportion of days covered (PDC). Discontinuation was measured as time to a ≥ 60 -day gap without drug supply. A logistic regression model was fit to compare odds of adherence across drug classes, and time to discontinuation was analyzed via proportional hazards regression, adjusted for baseline age, sex, plan type, drug filled via mail order, capitated services, region, total antihyperglycemic prescriptions, antihyperglycemic class, Charlson Comorbidity Index, year of drug initiation, and macrovascular and microvascular diseases.

Results: Cohorts included 7419, 10 478, 3150, 5906, and 14 901 asthmatic-diabetic patients who initiated GLP-1, DPP-4, SGLT-2, TZDs, and SU, respectively. Adjusted odds of being adhered for SGLT-2 was higher when compared with GLP-1 (OR: 1.85 95% CI: 1.61, 2.12), DPP-4 (OR: 1.25 95% CI: 1.07, 1.42), SU (OR: 1.29 95% CI: 1.12, 1.48), and TZDs (OR: 1.48 95% CI: 1.25, 1.74). Patients initiating DPP-4 had significantly higher odds of adherence when compared with GLP-1 (OR: 1.55 95% CI: 1.40, 1.70) and TZDs (OR: 1.14 95% CI: 1.02, 1.28). Adjusted discontinuation rates for SGLT-2 were significantly lower when compared with GLP-1 (HR: 0.62 95% CI: 0.56, 0.70), DPP-4 (HR: 0.71 95% CI: 0.64, 0.80), TZDs (HR: 0.60 95% CI: 0.53, 0.67), and SU (HR: 0.68 95% CI: 0.62, 0.76).

Conclusions: Asthmatic-diabetic patients who initiated SGLT-2 were more adhered and persistent. Reasons for these differences including effects on HbA1c and lung function should be examined.

98 | Characterization of patients with ulcerative colitis in a postauthorization safety study of golimumab based in the Spanish ENEIDA registry

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Background: Simponi[®] (golimumab) is an anti-tumour necrosis factor alpha (αTNFα) agent authorized for the treatment of moderately to severely active ulcerative colitis (UC). As part of its risk management

plan, the sponsor is conducting a postauthorization safety study (PASS) using data from ENEIDA, a large, prospectively maintained registry of patients with inflammatory bowel disease in Spain in the setting of routine clinical practice. Founded in 2006, ENEIDA has not previously been used in a PASS.

Objectives: To describe the ongoing cohort assembly, baseline characteristics of currently enrolled patients with UC, and experience with this new data source. At planned completion in 2023, the study will provide data on the risk of colectomy (due to intractable disease), advanced colonic neoplasia (ACN), and hepatosplenic T cell lymphoma among users of the study medications.

Methods: Qualitative evaluations of the registry data set were performed. On the basis of data accumulated from September 2013 through May 2017, we identified 3 cohorts of adults with UC who were newly prescribed golimumab, other αTNFα agents, or thiopurines. Patients could switch therapies and, if so, were included in all qualifying cohorts.

Results: The total number of patients in the ENEIDA registry with a diagnosis of UC was 21 253; of these, 14 297 were from sites considered to be of research quality. The number of patients in the 3 study cohorts that fulfilled study criteria was 193 for golimumab, 638 for other αTNFα agents, and 610 for thiopurines. As of May 2017, median follow-up time was 12.9 months for golimumab, 14.4 months for other αTNFα agents, and 17.3 months for thiopurines. Median age at enrolment (ie, first prescription of the corresponding study drug) in the 3 cohorts ranged from 42 to 44 years. Between 51.8% and 55.4% of patients were male. The median duration of UC was longer for the golimumab cohort (6.5 years) than for the other αTNFα agents (4.2 years) or the thiopurines (2.4 years) cohorts. Pancolitis was more common in new users of golimumab and other αTNFα agents than in thiopurines users. As of May 2017, 47 study outcomes have been identified across the 3 cohorts (45 colectomies due to intractable disease and 2 ACNs).

Conclusions: Results indicate that the ENEIDA registry is a useful data source to identify and study patients with UC in Spain who are newly exposed to αTNFα agents and to thiopurines. Results also highlight the need for extended patient follow-up.

99 | Tocilizumab and the risk for cardiovascular disease events among rheumatoid arthritis patients: A direct comparison in real-world setting

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Background: Multiple studies have observed unfavorable changes in lipid profile associated with tocilizumab (TCZ) and some other rheumatoid arthritis (RA) therapies. The real-world cardiovascular disease (CVD) risk associated with TCZ remains uncertain.

Objectives: The objective of this study was to assess the CVD risk associated with TCZ compared with individual tumor necrosis inhibitor (TNFi) therapies, as well as to other biologics used for RA.

Methods: Using 2006-2015 Medicare and MarketScan claims data, we conducted a retrospective cohort study among RA patients who initiated biologic disease-modifying antirheumatic drugs (bDMARDs) after January 1, 2010, and had at least 365 days full coverage before initiation. The primary outcome was a composite of myocardial infarction (MI), stroke, and fatal CVD assessed using a validated method. Subgroup analyses were done for RA patients experienced to other bDMARDs before initiation and by stratifying patients with respect to key CVD risk factors to identify both higher and lower CVD risk patients. Incidence rates and 95% confidence intervals were calculated using Poisson regression. COX regression was used to generate unadjusted and adjusted hazard ratio.

Results: We identified 354 486 RA patients and 463 446 initiations of bDMARDs. After applying inclusion and exclusion criteria, the final cohort contained 88 463 RA patients and 117 493 episodes. The mean (SD) age was 64.7 (12.1) in Medicare and 52.2 (12.3) in MarketScan. The majority of patients were female (83.9% in Medicare and 80.5% in MarketScan), and 68.6% were non-Hispanic White in Medicare. The crude incidence rate (IR) per 1000 patient-years for composite CVD among Medicare patients ranged from 13.3 (95% CI: 11.1-16.0) for etanercept to 19.4 (95% CI: 16.3-20.9) for rituximab users. The crude incidence rate for pooled TNFi users was 16.4 (15.2-17.7). Compared with TCZ, the adjusted hazard ratios were 1.03 (0.82-1.29) for abatacept, 1.25 (0.96-1.61) for rituximab, 1.13 (0.84-1.52) for etanercept, 1.33 (0.99-1.80) for adalimumab, and 1.57 (1.21-2.05) for infliximab. There were no significant differences in CVD risk between tocilizumab and any other biologic using in MarketScan data. Results were robust in numerous subgroup analyses.

Conclusions: Consistent with findings of a recently completed safety trial in RA, tocilizumab was associated with a comparable CVD risk compared with etanercept, as well as a number of other RA biologics, in two large data sources.

100 | Dose escalation, switching, and discontinuation of biologic disease modifying drugs in patients with rheumatoid arthritis: A comparison of concomitant versus non-concomitant users of methotrexate

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Background: Concomitant use of methotrexate (MTX) and leflunomide (LE) when starting biologic disease modifying antirheumatic drugs (bDMARDs) has been shown to decrease discontinuation of those medications. The evidence on time dependency of this effect is incomplete, and the evidence on the effect on dose changing and switching is also sparse.

Objectives: To compare time-dependent changes in dose, switching, and discontinuation of bDMARDs in rheumatoid arthritis patients who are concomitant versus non-concomitant users of MTX or LE.

Methods: This study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES) in five provinces of Canada (Alberta, Manitoba, Ontario, Quebec, and Saskatchewan) and in one US database (MarketScan). We studied adult patients with RA who were new users of a bDMARD (adalimumab, etanercept, abatacept, or infliximab) and who were receiving treatment with MTX or LE at the time they started their bDMARD. Patients entered the study cohort at the end of a 3-month loading dose period for their bDMARD. We evaluated 3 outcomes over 2 years of follow-up in patients exposed and not exposed to MTX or LE: (1) percentage change in dose of bDMARD compared with the loading dose, (2) switching to a different bDMARD than the one started, and (3) discontinuation of bDMARD therapy. Inverse probability of treatment weighting was used to adjust for confounding factors. Exposure to MTX and LE was assessed along with other time-varying covariates in 4 six-month time periods. Results from all sites were combined using likelihood ratio meta-analysis (LRMA).

Results: The study population included 19 933 adult patients who were new users of bDMARDs: adalimumab (7609), etanercept (9809), abatacept (846), or infliximab (1,669). Compared with baseline loading dose, concomitant MTX or LE use was associated with a small additional 0.56% increase in bDMARD dose compared with non-concomitant MTX or LE use (adjusted mean difference 0.56%, 95% intrinsic confidence interval [ICI] 0.14% to 0.97%). Concomitant MTX or LE patients were not significantly less likely to switch bDMARDs (hazard ratio 0.95, 95% ICI 0.80 to 1.11) or to discontinue their bDMARD (hazard ratio 0.90, 95% ICI 0.79 to 1.02).

Conclusions: A small observed increase in bDMARD dose in concomitant MTX or LE patients was clinically insignificant, contrary to expectation, and could be the consequence of unmeasured or residual confounding.

101 | Development and internal validation of a multivariate prognostic model for serious infection in patients with psoriasis on systemic therapies

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Background: There is concern over the risk of serious infection in psoriasis patients undergoing treatment with systemic therapies.

Objectives: To produce a personalised risk prediction score for serious infection that can help patients with psoriasis and clinicians identify risk-minimising modifiable behaviours and treatment strategies

Methods: We used data from a UK and Ireland psoriasis registry, the British Association of Dermatologists Biologic Interventions Register (BADBIR), to develop the serious infection risk prediction score. BADBIR registers patients with psoriasis (Psoriasis Area and Severity Index ≥ 10 and Dermatology Life Quality Index > 10) on either systemic biologic therapies (etanercept, infliximab, adalimumab, and ustekinumab) or non-biologic therapies (acitretin, psoralen-UVA

[PUVA], ciclosporin, fumaric acid esters, methotrexate, or hydroxycarbamide). Data from BADBIR were included from September 2007 to February 2017. The outcome was serious infection within the first year of therapy, defined by association with intravenous antimicrobial therapy, hospitalisation, or death. Important co-variables were selected for inclusion in the multi-variate logistic regression model a priori; other potential co-variables were assessed in a forward selection stepwise logistic regression model ($p = 0.1$). The model's performance was assessed by C-statistic in both the development and validation cohorts. Leave-one-out cross validation was performed for internal validation.

Results: 175 out of 10 033 patients suffered from serious infection within 1 year of starting therapy. Female gender (odds ratio [OR] 1.53, 95% confidence interval [CI] 1.12, 2.10); infliximab compared with non-biologics (OR 4.24, 95% CI 2.22, 8.09); alcohol (units per week; OR 1.01, 95% CI 1.00, 1.02); number of comorbidities (OR 1.10, 95% CI 1.05, 1.15), and being retired compared with working (OR 2.30, 95% CI 1.31, 4.03) were statistically significant predictors of serious infection. Crude and optimism-adjusted C-statistics were 0.69 (95% CI 0.65, 0.73) and 0.66 (95% CI 0.61, 0.70), respectively.

Conclusions: We identified covariates to develop a clinical risk prediction model for serious infections for patients on systemic therapies for psoriasis. These include treatment choice and modifiable lifestyle factors that may help patients reduce their risk of serious infection. We will perform external validation using data from the German Psoriasis Registry PsoBest.

102 | A propensity-score weighting approach to compare registry and trial populations of patients with psoriasis on biologic therapies

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Background: Previous studies using incomplete trial inclusion and exclusion criteria suggest a difference between the reported effectiveness and safety of biologic therapies between randomised clinical trials (RCT) and real-world populations of patients with psoriasis. **Objectives:** To estimate the difference in safety and effectiveness outcomes in biologic therapies for psoriasis between the trial and real-world populations using a standardisation method. **Methods:** Data from patients on etanercept, adalimumab, or ustekinumab in the British Association of Dermatologists Biologic Interventions Register (BADBIR) were appended to individual participant-level data from two RCTs assessing ustekinumab in patients with psoriasis, PHOENIX 1 and 2. Baseline patient variables were assessed for association of being in a RCT using a multivariate logistic regression model. Propensity score based standardized mortality ratio weights were derived to

reweigh the registry sample so that all variables had the distribution seen in the trial sample. The incidence rate of SAEs in the first year and the proportion of patients achieving an absolute Psoriasis Area and Severity Index (PASI) <1.5 at 6 months were calculated in the BADBIR cohort before and after weighting, with 95% confidence intervals calculated using bootstrapping. **Results:** 6790 registry and 2021 trial participants were included. There were marked differences in the baseline co-variables between the registry and trial participants, and the multivariate logistic model had a C-statistic of 0.84 (95% confidence interval 0.83, 0.84). All variables had a standardised difference between -0.1 and 0.1 after weighting. The incidence rate difference of SAEs between the registry and trial sample was 9.30 (95% CI -3.91, 22.50) per 1000 person-years; the incidence rate ratio was 1.14 (95% CI 0.91, 1.37). The difference in proportion achieving absolute PASI < 1.5 between the registry and trial sample was 1.09% (95% CI -1.98%, 4.15%); the relative risk ratio was 1.03 (95% CI 0.94, 1.11). **Conclusions:** Our results suggest that the difference between the baseline characteristics of a real-world and a trial psoriasis population leads to the underestimation of the true real-world incidence of SAEs, but not effectiveness, in psoriasis clinical trials. Real-world data are therefore needed to understand the true safety of biologic therapies in psoriasis.

103 | Impact of rheumatoid arthritis patient eligibility for tumour necrosis factor therapy (as per NICE guidance concerning disease activity) on need for joint replacement: A regression discontinuity study

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Background: Data are lacking on the comparative effectiveness of tumour necrosis factor inhibitor (TNFi) therapy compared with conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) on the need for total hip (THR) or knee replacement (TKR).

Objectives: NICE guidance restricts TNFi use to patients with a disease activity score (DAS) >5.1. We aimed to estimate the effect of meeting the DAS eligibility criteria on the incidence of THR and TKR in rheumatoid arthritis (RA).

Methods: We obtained data from the British Society for Rheumatology Biologics Registry for RA (BSRBR-RA) (2001-2016). Prior THR/TKR and prevalent TNFi users were excluded. Baseline characteristics of patients "just below" ($5.0 \leq 5.1$) the DAS treatment threshold were compared with those "just above" ($5.2 \leq 5.3$). Patients were followed from date of registration to earliest of outcome, death, loss-to-follow-up, or change of TNFi exposure status (stopping, switching, or

starting). Incidence of THR and TKR was estimated per 0.1 increment of the DAS score. A regression discontinuity design (RDD) was used to estimate the impact of the DAS 5.1 threshold for TNFi treatment eligibility (rather than treatment allocation per se). Specifically, segmented linear regression was used to estimate the difference in incidence of THR and TKR (analysed separately) at the DAS threshold, taking into account trends within different bandwidths around the cut-off: ± 0.3 , ± 0.5 , and ± 0.7 .

Results: Patients with a DAS "just below" or "just above" the DAS treatment threshold were similar in baseline characteristics, although small differences were found in age, health activity score (HAQ), and pain (SF-36). In analyses using a bandwidth of ± 0.3 around the DAS threshold for TNFi eligibility, there was a non-significant reduction in THR incidence of -6.88 (95% CI: -22.48 to 8.72 ; $p = 0.20$) per 1000 PYs associated with being above the threshold. In analyses using a bandwidth of ± 0.5 , there was a reduction in THR of -5.69 (-10.98 to -0.39 ; $p = 0.039$) per 1000 PYs, and when using a bandwidth of ± 0.7 , there was a reduction in THR of -4.37 (-7.91 to -0.84 ; $p = 0.020$) per 1000 PYs associated with being above the DAS threshold. There was no effect on TKR incidence.

Conclusions: Our findings suggest that RA patients with a DAS "just above" vs "just below" the NICE criteria for TNFi eligibility had a reduced risk of THR but not TKR. Further work is needed to confirm these findings.

104 | Exploring the association between monoclonal antibodies and depression and suicidal ideation and behaviour: A VigiBase study

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Background: Recently exposure to monoclonal antibodies has been associated with rare adverse neuropsychiatric effects, eg, depression, suicidal ideation, and behavior. Understanding these associations is difficult given the diversity of indications for use of these products. So far, also little is known about any differential risk between individual monoclonal antibodies.

Objectives: To quantify and characterize spontaneously reported adverse drug reactions (ADRs) related to depression and suicidal ideation and behavior for monoclonal antibodies.

Methods: ADRs reported until December 2017 in VigiBase, the WHO global database of Individual Case Safety Reports, were included. A MedDRA standardized search was used to identify reports related to depression and suicidal ideation and behaviour for monoclonal antibodies, as well as for all other drugs in the database. Monoclonal antibodies that had been authorised by any global regulatory authority (eg, FDA and EMA) for at least 3 years were included. Reporting odds

ratios were estimated and compared relative with bevacizumab as a reference.

Results: A total of 44 monoclonal antibodies were included in the study. For these, 9455 reports related to depression and 1770 reports related to suicidal ideation and behaviour were analysed. For both depression and suicidal ideation and behaviour, natalizumab and belimumab showed the highest relative (to bevacizumab) reporting odds ratio, ie, for depression 5.7 (95% CI: 5.0-6.4) and 5.1 (95% CI 4.2-6.2), for suicidal ideation and behaviour 12.0 (95% CI: 7.9-18.3) and 20.2 (95% CI: 12.4-33.0), respectively. These two products show little to no mechanistic commonalities. Moreover, we found several compounds with mechanistic commonalities with comparable reporting odds ratios (TNF-alpha inhibitors, alpha-4 integrin antibodies, checkpointinhibitors, and HER-2 antibodies).

Conclusions: Adverse neuropsychiatric effects are seen in patients exposed to monoclonal antibodies. Two antibodies peaked (ie, natalizumab and belimumab) regarding reporting of depression and suicidal ideation and behaviour. For the interpretation of these data, the indications for use and other population characteristics need further consideration.

105 | Timing of the last dose of biologic therapy and risk of post-surgical infections in patients with psoriasis

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Background: There is limited evidence to guide clinical decisions on whether biologic therapies should be suspended prior to surgical procedures.

Objectives: We investigated the impact of the timing of the last dose of biologic therapy on the risk of post-surgical infections using the British Association of Dermatologists Biologic Interventions Register (BADBIR).

Methods: BADBIR is a registry of UK and Eire psoriasis patients treated with either biologic or conventional systemic therapies. Dates of all given doses were collected for patients on ustekinumab and infliximab. Data on surgical procedures, entered either as an event of special interest (ESI) or as an adverse event under MedDRA SOC code of "Surgical and medical procedures" from patients on biologic therapies (etanercept, infliximab, adalimumab, and ustekinumab), were extracted from September 2007 to February 2017. The outcome was extracted from adverse events flagged as a serious infection ESI or under the MedDRA SOC code of "Infections and infestations." Entries with a present last biologic dose date prior to the surgical procedure were included. A post-surgical infection was defined by any infection occurring within 30 days of the surgical procedure.

Results: 709 surgical procedures from 577 patients were included. 41 procedures were performed after etanercept; 90, infliximab; 92, adalimumab; and 486, ustekinumab. The median time between last

biologic dose and surgical procedure was 46 days (interquartile range 63 days). The most common sites for MedDRA HLGT-coded surgical procedures were bone and joint ($n = 175$), skin and subcutaneous tissue ($n = 104$), and head and neck ($n = 81$). There were 33 post-surgical infections; 15 of which were wound infections. Adherence to the recommended stopping time from the BAD Guidelines for Biologic Therapy for Psoriasis 2017 (stopping more than time of $3 \times$ half-life or length of the treatment cycle) compared with surgeries that were non-adherent had a crude odds ratio for post-surgical infection of 0.40 (95% confidence interval 0.15, 1.06) and post-surgical wound infection of 0.58 (95% C.I. 0.16, 2.06). Adjusting by age, gender, and comorbidities made no difference.

Conclusions: We found a non-statistically significant decrease in the risk of post-surgical infection with adherence to the recommended stopping time prior to surgery. Further work should be performed in large multi-national datasets to understand the association between the time of the last biologic dose and the risk of post-surgical infection.

106 | Three-group extension of propensity score trimming rules: A simulation study

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Background: Propensity score (PS) trimming has been used to improve validity and/or statistical efficiency in comparative effectiveness research (CER). Trimming options for binary exposures include the Crump (*Biometrika* 2009; 96:187), Stürmer (*Am J Epidemiol* 2010; 172:843), and Walker (*Comp Eff Res* 2013; 3:11) methods. However, their extensions to the multinomial exposure setting are unavailable.

Objectives: To propose PS trimming strategies for CER with 3 treatment groups and to examine their performance in simulation.

Methods: Each individual i was given a PS vector $\mathbf{e}_i = (e_{0i}, e_{1i}, e_{2i})^T$ having one probability of assignment for each treatment $j \in \{0, 1, 2\}$: $e_{ji} = P[A_i = j | \mathbf{X}_i]$ (A_i treatment; $\mathbf{X}_i$ covariates). We defined 3-group versions of the trimming rules that specified trimming threshold for each component of the PS vector. The thresholds were defined as some appropriate constant α_c for Crump trimming, α_s -th quantile in the corresponding treatment group for Stürmer trimming, and constant α_w on the 3-group version of the preference score scale for Walker trimming. We constructed new-user design simulation scenarios in which tails of PS distribution had unmeasured confounders as in Stürmer's simulation study. Six covariates were considered measured and were used in PS vector estimation, whereas three additional covariates were designed to be rare (1%) unmeasured confounders concentrated in the extremes of estimated PS. The three proposed

3-group PS trimming methods were combined with 3 PS weighting strategies: inverse probability of treatment weights (IPTW), matching weights (MW), and overlap weights (OW). We examined the trimmed cohort size, bias, variance, and mean squared error (MSE).

Results: Unmeasured confounding was reduced by all three trimming methods. However, Crump trimming had the largest bias with imbalanced treatment prevalence (10:10:80 treatment distribution). Initial benefits on variance reduction were seen for IPTW for all trimming methods, but this was not the case for MW or OW, which were stable from the start. We found MSE was optimized by Crump trimming at a threshold of 1/15, Stürmer trimming at a threshold of 1/60-1/30, and Walker trimming at a threshold 1/20-1/10.

Conclusions: Compared with Crump's, Stürmer, and Walker's PS trimming methods more reliably reduced bias in 3-group exposure settings with highly imbalanced treatment frequencies.

107 | Comparative effectiveness of two-drug therapy versus monotherapy as initial regimen in hypertension: A propensity score matched cohort study in CPRD

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Background: Clinical trials have previously shown initial combination therapy to be more effective on blood pressure control than initial monotherapy, but few studies have examined the question in a large primary care database.

Objectives: To evaluate the relative effectiveness on blood pressure of an initial two-drug therapy compared with monotherapy in hypertension.

Methods: In CPRD with hospitalisation and mortality data linkage, we identified a cohort of adults with uncontrolled hypertension and initiating one or two antihypertensive drug class(es) (among ACEIs, ARBs, CCB, BB, and thiazide-like diuretics) between 2006 and 2014, with follow-up until February 2016. New users of 2 drugs and monotherapy were matched 1:2 using a propensity score. Exposure was defined as intention-to-treat (ITT) or as treated (AT), ie, until first regimen change. Primary and secondary endpoints were, respectively, blood pressure (BP) control and serious cardiovascular event (SCE). Hazard ratios (HR) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. Analyses in planned subgroups, according to hypertension severity or most frequent classes of drugs (ACEi and CCB), used specific propensity scores.

Results: Among the 54 523 eligible hypertensive patients included in the cohort, 3256 patients were initiated on 2 drugs of which 2807 (86.2%) were matched to 5614 monotherapy new users (mean SBP/DBP 164.6/94.8 mm Hg). During a mean follow-up (ITT) of 4.6 years, the mean exposure duration (AT) was 12.7 months, with 76.5% patients changing initial regimen. In the AT analysis, use of 2 drugs

was associated with 17% increased BP control in all hypertensive patients (HR [95% CI]: 1.17 [1.09-1.26]), increasing to 28% in patients with grades 2-3 hypertension (1.28 [1.17-1.41]) and 27% in patients with ACEi + CCB (1.27 [1.08-1.49]). A positive association was also observed in the ITT analysis of all hypertensive patients (1.08 [1.03-1.13]) or those with grades 2-3 hypertension (1.10 [1.03-1.18]). For SCE, overall no significant association with 2-drug therapy was found. **Conclusions:** In line with UK guidelines, only a small fraction of hypertensive patients used two drugs in combination as initial therapy. This large population-based cohort study supports the evidence of greater effectiveness of 2-drug therapy for BP control, while further investigation with more data would be required for SCE.

108 | Comparative safety of sodium-glucose cotransporter-2 (SGLT-2) inhibitors: Risk of hospitalization and cardiovascular events in patients with type 2 diabetes

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Background: In the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), patients who received empagliflozin had a 14% reduction in the primary composite cardiovascular outcome compared with those who received placebo.

Objectives: To determine if the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors is associated with a reduction in all-cause hospitalization, myocardial infarction, or stroke compared with active comparators in a real-world cohort of type 2 diabetics.

Methods: Design and setting: Retrospective, new-user design cohort study using Truven MarketScan Commercial Claims and Encounters data from September 2012 to December 2015. Two-million commercially insured diabetes patients were considered for the analysis. Propensity score weighted Cox proportional hazards regression models were used to compute adjusted hazard ratios (aHR) to assess the association between SGLT-2 use and study outcomes. **Exposure:** New users of SGLT-2 inhibitors were compared with new users of dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 (GLP-1) agonists. **Main outcome measures:** The primary composite outcome was first occurrence of all-cause hospitalization, myocardial infarction, or stroke. Secondary outcomes were all-cause hospitalization, myocardial infarction, or stroke. We used validated ICD-9 and ICD-10 algorithms to define myocardial infarction and stroke.

Results: A total of 198 583 patients were included in the final analyses, including 44 319 (22.3%) SGLT-2 inhibitor users, 110 896 (55.8%) DPP-4 inhibitor users, and 43 368 (21.9%) GLP-1 agonist

users. There was no statistically significant difference in the primary composite outcome between SGLT-2 users and DPP-4 users (aHR: 1.05, 95% CI: [0.98, 1.13]) and SGLT-2 users and GLP-1 users (aHR: 1.00, 95% CI: [0.91, 1.09]). Similarly, there was no statistically significant differences between SGLT-2 users and DPP-4 user and SGLT-2 users and GLP-1 users in any of the study secondary outcomes.

Conclusions: In a real-world cohort, SGLT-2 use was not associated with a decreased risk of all-cause hospitalization, myocardial infarction, or stroke compared with the other oral glucose lowering agents examined.

109 | Baseline information from a post-marketing monitoring program on empagliflozin: Implications for study validity and exposure accrual

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Background: Baseline information from a post-marketing monitoring program on the effectiveness and safety of a new drug can provide early insights regarding study validity and exposure accrual over the program lifetime, which may be crucial for early decision making.

Objectives: To describe validity in terms of observed covariate balance in the first year (baseline) of EMPRISE, a post-marketing monitoring program on the comparative effectiveness and safety of empagliflozin, a new drug for type 2 diabetes (T2DM) therapy, to evaluate population risk of heart failure hospitalization (HHF), and to project exposure accrual over time and study power.

Methods: Within two US commercial claims datasets (08/2014-09/2015) included in the monitoring program, we identified a 1:1 propensity score (PS)-matched cohort of T2DM patients ≥ 18 years initiating empagliflozin or dipeptidyl peptidase-4 inhibitor, a comparator used at a similar stage of diabetes progression ($n = 6552$ pairs). We included over 120 baseline covariates in the PS model including proxies of diabetes severity and duration, produced standardized differences (SD), and check whether covariates were balanced. We measured the population incidence rate (IR) of HHF in the overall matched population. We predicted exposure numbers over subsequent years, including projections for Medicare, the third dataset included in the EMPRISE monitoring program, and calculated expected power (alpha level = 0.05, 2-sided test, no alpha spending) assuming a 35% HHF risk reduction found by the EMPA-REG OUTCOME trial.

Results: Covariates were well balanced ($SD < 0.1$) after PS-matching (post-matching c-statistic = 0.55), including laboratory test results available in a subset of the cohort but not included in the PS model. Mean age was 54 years. HHF IR was 1.7 per 1000 person-years. We assumed baseline drug use in Medicare to be equal to the one observed in commercially-insured patients ≥ 65 years. In the most

conservative accrual scenario, assuming equal number of empagliflozin initiators at baseline and in subsequent years, about 50 000 initiators would accrue in the 3 datasets by the end of the program at year 5, with projected powered (80%) analyses for HHF at year 4.

Conclusions: Baseline information from a post-marketing drug monitoring program provided early evidence of solid confounding control and adequate exposure accrual confirming the pre-specified study plan.

110 | Comparison of propensity score (PS) weighting and trimming strategies to reduce variance and bias of treatment effect estimates: A simulation study

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Background: To reduce the variance of PS-based treatment effect estimates, biostatisticians have proposed various covariate-balancing weights and trimming the tails of the PS distribution. In parallel, pharmacoepidemiologists have proposed PS trimming to reduce confounding in the tails of the PS distribution where unmeasured factors can cause patients to be treated contrary to prediction.

Objectives: To compare the performance of PS weighting and trimming methods with respect to both variance and bias.

Methods: We simulated cohort studies with a binary intended treatment T as a function of 4 measured covariates (confounders and instruments, dichotomous and continuous). We mimicked treatment withheld and last-resort treatment by adding two “unmeasured” dichotomous factors that caused treatment assignment to change for some patients in both tails of the PS distribution. The number of outcomes Y was simulated as a Poisson function of T, all confounders (including unmeasured), and 2 risk factors. We estimated the PS based on measured covariates using logistic regression and trimmed the tails of the PS distribution using 3 strategies (Crump et al., *Biometrika* 2009; Stürmer et al., *AJE* 2010; and Walker et al., *Comp Eff Res* 2013). After trimming, we re-estimated the PS and then implemented various PS weights to estimate the treatment effect (rate ratio) in the population (ATE), the treated (ATT), the untreated (ATU), the overlap (ATO), and the matched (ATM) (Li et al., *JASA* 2017).

Results: With no unmeasured confounding and 20% treatment prevalence, relative efficiency (RE) versus the untrimmed ATE ranged from 61% (ATU, Walker) to 123% (ATO, untrimmed). Crump trimming improved efficiency for ATE (RE = 112%), but not for ATO (RE = 120% vs 123%). With unmeasured confounding leading to treatment withheld, ATO and ATM were more biased than ATE, and only Stürmer and Walker trimming reduced bias for all estimates. Mean squared

error (MSE) was lowest for Stürmer trimming. With unmeasured confounding leading to last-resort treatment, ATT, ATO, and ATM were less biased than ATE, and all trimming methods reduced bias. MSE was lowest for Crump trimming.

Conclusions: ATO and Crump trimming reduce the variance of PS-weighted treatment effect estimates compared with ATE but change the causal interpretation. In settings where unmeasured confounding (eg, frailty) may lead physicians to withhold treatment, only Stürmer and Walker trimming reduce bias consistently in scenarios assessed.

111 | Comparative safety of atypical antipsychotics used in the treatment of neuropsychiatric symptoms of dementia: A mixed treatment comparison

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Background: Pairwise meta-analyses of randomized clinical trials (RCTs) suggest safety concerns from the use of atypical antipsychotics (AAPs) in the treatment of neuropsychiatric symptoms (NPS) of dementia. However, a high-level prescription of AAPs in patients with dementia is seen in some countries, despite regulatory warnings. Mixed treatment comparison (MTC) enables the estimation of relative treatment effects for all possible comparisons in the same model and synthesizes evidence from direct and indirect estimates simultaneously. To our knowledge, no MTC that simultaneously compared different AAPs for the treatment of NPS of dementia has been published.

Objectives: To assess the safety of AAPs used in the treatment of NPS of dementia.

Methods: We performed a MTC in accordance with the PRISMA guidelines. Relevant clinical trials were searched from MEDLINE/PubMed, Embase, Cochrane library, and PsychINFO databases up to September 2017. We included RCTs of patients with NPS of dementia using AAPs (aripiprazole, olanzapine, quetiapine, and risperidone) and reporting safety outcomes of death, cerebrovascular adverse events (CVAEs), injury, fracture or fall, and somnolence or sedation with a minimum follow-up period of 6 weeks. Odds ratios (OR) for this MTC were estimated using random-effects model. The AAPs were ranked according to their probability of being the safest using surface under the cumulative ranking curve (SUCRA).

Results: A total of 17 clinical trials with 5373 participants were included. The MTC suggests the following AAPs, in comparison with placebo, were associated with increased risk of CVAEs: risperidone (OR; 95% CI, 3.85; 1.55-9.55) and olanzapine (OR; 95% CI, 4.28; 1.26-4.56). In comparison with olanzapine, risperidone was found to have a reduced risk of injury, fracture, or fall (OR; 95% CI, 0.63; 0.43-0.94). Risperidone was also associated with reduced risk of somnolence or sedation in comparison with olanzapine (OR; 95% CI, 0.63; 0.41-0.96) and with quetiapine (OR; 95% CI, 0.58; 0.34-0.97). For the

risk of death, based on SUCRA, placebo was ranked as the safest treatment approach (87.3%), followed by risperidone (55.4%), then aripiprazole (37.9%), and then quetiapine (37.1%), and olanzapine (32.4%) is the least safe.

Conclusions: Off-label use of AAPs in patients with NPS of dementia is not entirely safe and risk differ by drugs. Clinicians should carefully gauge their risks against expected benefit when faced with a decision to prescribe them.

112 | SGLT2 inhibitors and mycotic infections: A prescription sequence symmetry analysis

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Background: Clinical trials of sodium-glucose co-transporter 2 inhibitors (SGLT2i) report a twofold to sixfold increase in the risk for genital mycotic infections that is modified by gender, drug, and dose. Prescription sequence symmetry analysis (PSSA) can help provide insight into the risk of the event in a non-clinical trial population.

Objectives: To determine the risk of mycotic infections treated with prescription antifungals associated with the use of SGLT2i.

Methods: We conducted a PSSA using data from Truven Health MarketScan® (2009-2015). PSSA is a case-based design studying the sequence of treatment initiation in “cases” defined as patients initiating both index (SGLT2i) and remedy (anti-fungal) drugs within a certain time period. In the absence of an association, sequence of treatment initiation is symmetrical. We selected continuously enrolled patients newly initiating an SGLT2i and an antifungal (imidazoles, triazoles, sulfanilamide, and nystatin) between April 1, 2013, and December, 31, 2015, within intervals of 30, 60, 90, 180, or 365 days of each other. Crude sequence ratios (CSR) were calculated for each interval as number of patients initiating SGLT2i first over those initiating an antifungal first. Null-effect ratios were calculated to adjust CSRs for trends in prescribing, and 95% confidence intervals (CI) were calculated using the binomial distribution. Analyses were stratified by gender and SGLT2i (canagliflozin or non-canagliflozin). Results for 90-day analysis are presented.

Results: There were 23 276 patients that newly initiated both SGLT2i and an anti-fungal agent in the study period. Of these, 7697 patients initiated SGLT2i and an anti-fungal agent within 90 days of each other. Of those that initiated SGLT2i first (ie, had an event of mycotic infection), the majority were dispensed canagliflozin followed by fluconazole. Increased risks of mycotic infections were present across all time intervals, with the strongest effect observed in the 90-day interval (adjusted sequence ratio [ASR]: 1.53 [CI 1.43-1.60]). Findings differed by gender (90-day ASR females: 1.65 [CI 1.56-1.74]; males 1.25 [CI 1.14-1.36]) and by SGLT2i (90-day ASR canagliflozin 1.57 [CI 1.49-1.66]; non-canagliflozin 1.42 [CI 1.31-1.55]).

Conclusions: There were increases in antifungal use post-SGLT2i initiation indicating increased risk of mycotic infections and latency

periods of approximately 90 days. Findings from this commercially insured population are consistent with evidence available from clinical trials.

113 | Comparative effectiveness of P2Y12 antiplatelet switching strategies

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Background: Switching P2Y12 medications may alter pharmacodynamic effects to optimize therapy. There is a lack of research quantifying the effectiveness and safety of switching P2Y12 treatment.

Objectives: Compare effectiveness and safety between P2Y12 switching strategies in patients following percutaneous coronary intervention (PCI).

Methods: We included US commercial insurance beneficiaries who underwent a PCI from Sept 2011 to Dec 2015 captured by the Optum Clinformatics database and who switched P2Y12 medications once after initiation. The primary outcome was defined as composite incident MI, ischemic stroke, or death. The secondary outcome included intracranial hemorrhage, GI-bleed, or other major hemorrhage. Subgroup studies were conducted to compare outcomes between medication switches and were stratified by presence of acute coronary syndrome (ACS) occurring between PCI and switch dates. Cox proportional hazard models with propensity score inverse weighting were used to assess hazard ratios (HR) between switches.

Results: There were 1274 patients initiated on clopidogrel (C), 3494 initiated on prasugrel (P), and 2090 initiated on ticagrelor (T) following PCI. Patients initiated on ticagrelor were older (mean age: T 68.2, C 64.5, P 61.8, $p < 0.01$), more likely to be female (T 34%, C 33.5%, P 25%, $p < 0.01$), and had dyslipidemia (T 78%, C 81%, P 79%, $p < 0.01$). Prior to stratification, there was no difference in primary or secondary outcomes for patients switching from clopidogrel to prasugrel or ticagrelor. After stratification, patients with a non-ACS related switch from clopidogrel to prasugrel showed improved event-free survival for the primary endpoint (HR 0.54, 95% CI 0.38-0.78) and no difference in the likelihood of bleeding (HR 1.2, 95% CI 0.82-1.6) when compared with patients that switched from clopidogrel to ticagrelor. There was no difference in the incidence of either endpoint for patients who switched from prasugrel to clopidogrel or ticagrelor, regardless of stratification. Likewise, there was no difference in the incidence of either endpoint when comparing patients switching from ticagrelor to either prasugrel or clopidogrel.

Conclusions: Overall, there was no significant difference in the incidence of cardiovascular or bleeding outcomes when switching between antiplatelet medications. After stratification by ACS-related switch, patients with a non-ACS switch from clopidogrel to prasugrel had improved cardiovascular outcomes when compared with those who switched from clopidogrel to ticagrelor.

114 | Assessing disease activity with PROMIS measures using smartphone technology among patients with rheumatic diseases

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Background: Current technology has enabled efficient PROs collection using computer adaptive testing (CAT) to minimize missing data and participant burden. The bridge between PROMIS (patient reported outcomes measurement information system) and traditional patient-reported PROs (eg, Routine Assessment Patient Index Data 3 [RAPID3]) is not clear, and some instruments in PROMIS might proxy for measuring more lengthy PROs.

Objectives: To compare agreement between RAPID3 (gold standard) with a predicted "CAT-PROMIS RAPID3," substituting selected PROs from PROMIS for elements of the RAPID3, collected using a smartphone/web app by patients with rheumatic diseases.

Methods: Participants in the PCORI-funded ArthritisPower registry completed four PROMIS CAT instruments: Pain Interference, Physical Function, Sleep Disturbance, Fatigue; a visual analog scale (Pain Intensity); and RAPID3 via a mobile/computer application. Multiple correlations (Pearson) between RAPID3 and PROMIS were evaluated and total variance explained using mixed models. Both the new predicted score ("CAT-PROMIS RAPID3") and score category was predicted using the selected 4 PROMIS instruments and pain intensity. Kappa statistics and Bland-Altman 95% limits of agreement (LOA) were used to measure agreement between the measured RAPID3 and the predicted CAT-PROMIS RAPID3.

Results: A total of 6154 patients answered all assessments and contributed 11 275 records. Mean $\pm$ SD age was 52.7 $\pm$ 10.5 years; 90% were women. The common rheumatic diseases represented were osteoarthritis (65%) and rheumatoid arthritis (44%). Most (81%) had high RAPID3 scores. The median assessment time for each of the PROMIS instruments ranged from a low of 29 seconds (sleep disturbance) to a high of 35 seconds (physical function), versus 116 seconds for the RAPID3. The 4 PROMIS CATs and RAPID3 were modestly correlated ($r \sim 0.4$ - 0.6) to one other. The PROMIS instruments explained a high fraction of total variance ($R^2 = 71\%$) of the RAPID3. The measured RAPID3 was highly correlated with the CAT-PROMIS predicted RAPID3 ($r = 0.97$). Overall agreement between categories of the RAPID3 vs CAT-PROMIS RAPID3 also was high (kappa = 0.81). Bland-Altman 95% limits of agreement shows minimal residual differences and no systematic biases.

Conclusions: Computer/mobile applications can capture PROs efficiently. Agreement between the measured RAPID3 and a predicted RAPID3 score estimated using PROMIS instruments is excellent and reduces participant burden.

115 | Assessment of medication use during pregnancy by web-based questionnaires, pharmacy records, and biological monitoring in blood

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Background: More research into the safety of medication use during pregnancy is urgently needed, but exposure assessment is challenging: Self-administered questionnaires often result in underreporting, whereas prescription databases suffer from both overreporting and underreporting.

Objectives: To compare assessment of medication exposure in early pregnancy using self-administered web-based questionnaires, pharmacy records, and untargeted liquid chromatography high resolution spectrometry (LC-QTOF-MS) biological monitoring in serum samples.

Methods: Serum samples were obtained from 752 women participating in the PRenancy and Infant DEvelopment (PRIDE) Study in the first trimester of pregnancy. For women exposed to selected medication at the date of blood sampling according to the web-based questionnaire or pharmacy records, we analyzed the serum samples using untargeted LC-QTOF-MS with a library that covered approximately 1300 substances.

Results: A total of 52 women used medication according to the questionnaire and/or pharmacy records. In serum samples of 18 women (35%), medication was detected with LC-QTOF-MS. Medications taken orally for chronic conditions (ie, fexofenadine, mesalazine, paroxetine, sulfasalazine, venlafaxine) detected in serum were also reported in the questionnaire and vice versa. Pharmacy records did not yield additional exposures for these medications, but misclassified 5 truly exposed women as unexposed. Pregnancy-related medication detected in 7 samples (ie, meclizine) was underreported by 2 women. We observed substantial discordance between the modes of data collection for inhaled medication, dermatological preparations, and medications for short-term use, which often could not be detected in serum samples.

Conclusions: Many potential medication exposures in early pregnancy were missed in untargeted LC-QTOF-MS analysis compared with web-based questionnaires or pharmacy records, with the exception of medications taken orally for chronic conditions. It remains challenging to determine exposure status with conflicting sources of information as no "gold standard" is currently available for assessing medication use in large-scale studies.

116 | Patients' perceptions of unmet medical need in rheumatoid arthritis

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Background: Despite many available treatments for rheumatoid arthritis (RA), a considerable proportion of patients do not achieve their treatment goals. Some RA patients continue to experience symptoms, such as pain and diminished function that may affect their psychosocial outcomes and activities of daily living.

Objectives: To identify, characterize, and quantify the unmet needs of patients with RA in the United States currently taking a disease-modifying antirheumatic drug (DMARD).

Methods: A cross-sectional, web-based survey was conducted with RA patients who were identified and recruited through CreakyJoints, an online patient support community, and ArthritisPower, an online patient research registry, from 12/2017 to 1/2018. Eligible patients were aged ≥ 21 years, reported a diagnosis of RA, and failed ≥ 1 DMARDs and were receiving their current DMARD medication(s) for ≥ 6 months. Patients answered 50 questions about treatment history, RA symptoms, disease-related impacts using the Rheumatoid Arthritis Impact of Disease (RAID), flares, and treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM). Descriptive analyses were used to summarize the responses.

Results: Of 415 patients screened, 258 (62%) were eligible and completed the survey. Patients were predominantly female (87%) and Caucasian (87%), with a mean (SD) age of 54.5 (11.4) years. In total, 232 (90%) had current or past experience with a biologic, with 67% currently on a biologic, 71% on at least one conventional synthetic DMARD, and 40% on methotrexate. While almost half (46%) of patients were satisfied-to-extremely satisfied with the way their medication relieves their symptoms, the study sample reported a mean (SD) RAID score of 5.06 (2.0) on a scale from 0 to 10, with higher scores indicating worse status. Overall, 67% of patients reported moderate-to-severe pain, 61% reported difficulty with daily physical activities, and 74% reported moderate to severe fatigue because of their RA in the prior 7 days. 43% of patients reported daily or almost daily use of prescription treatments for pain relief and 44% of patients reported a current flare in their RA.

Conclusions: Results from this real-world sample of RA patients indicate that although patients tend to report satisfaction with their treatment, many continue to experience bothersome symptoms (eg, pain and impaired physical function). Despite many available RA therapies, these results suggest that there remains significant unmet need for RA patients on current approved treatments.

117 | Using social media to collect patient perspectives on quality of life: A feasibility study

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Background: Development of innovative drugs for melanoma is occurring rapidly. These drugs are often associated with marginal prolongation of overall survival, as well as increased toxicity profiles. Therefore, HTA agencies increasingly require information on health related quality of life (HRQoL) for the assessment of such drugs.

Objectives: This study explored the potential of using social media to assess patient perspectives on HRQoL in melanoma, and whether current cancer- and melanoma-specific HRQoL questionnaires represent these patient perspectives.

Methods: A web-based survey with open-ended questions to assess melanoma patients' perspectives regarding HRQoL was distributed on social media channels of Melanoma Patient Network Europe (Facebook, Twitter, and LinkedIn). Two researchers independently assessed completed surveys and conducted content analysis to identify key themes. Themes identified were subsequently compared with questions used in three current HRQoL questionnaires (EORTC QLQ-C30, EORTC QLQ-MEL38, FACT-M).

Results: In total, 72 patients and 17 carers completed the survey. Patients indicated that family, having a normal life, and enjoying life were the three most important aspects of HRQoL. Carers indicated that being capable, having manageable adverse events, and being pain-free were the three most important aspects of HRQoL for patients. Respondents seem to find some questions from HRQoL questionnaires relevant (eg, "Have you felt able to carry on with things as normal?") and others less relevant (eg, "Have you had swelling near your melanoma site?"). Additionally, wording may differ between patients and HRQoL questionnaires, whereby patients generally use a more positive tone. For example, FACT-M states "I have a lack of energy," while patients rather focus on "having enough energy."

Conclusions: Social media may provide a valuable tool in assessing patient perspectives regarding HRQoL. However, differences emerge between patient and carer perspectives. Additionally, cancer- and melanoma-specific HRQoL questionnaires do not seem to correlate fully with patient perspectives.

118 | Designing and evaluating a web-based app as a digital risk minimization tool: Practical considerations

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Background: Digital approaches to “additional risk minimization measures” (aRMMs) offer important advantages over traditional, paper-based measures both in terms of practical implementation as well as potential increased effectiveness.

Objectives: (1) To describe the process for developing a web-based application (“app”) as an aRMM; (2) to propose methods for evaluating its effectiveness.

Methods: App development and evaluation were guided by social marketing and RE-AIM frameworks. Key steps included (1) defining the problem to be addressed; (2) identifying the value proposition; (3) clarifying project goals; (4) assembling a cross-functional team; (5) specifying technical resources and project timelines; (6) developing content and intervention features to support active learning; (7) piloting with end users in different regions globally; (8) identifying barriers and facilitators to adoption.

Results: The project goal was to develop an interactive, web-based app for refresher admixing training. App content was derived from the Prescribing Information. The app was piloted with pharmacists in different practice settings, with positive feedback. Barriers and facilitators were identified through informal interviews with key informants. Proposed metrics to evaluate the effectiveness of the app included process measures (website analytics), intermediate outcomes (user satisfaction, self-reported confidence to perform admixing), and outcome measures (volume of admixing errors reported annually).

Conclusions: Our project supports the use of a framework-based approach to the design of digital aRMMs as a recommended best practice and demonstrate feasibility and acceptability.

119 | Monitoring and managing medication adherence in community pharmacies

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Background: Community pharmacists have direct access to prescription refills information and have frequent interactions with their patients. Therefore, pharmacists are in the best position to promote optimal medication use.

Objectives: To describe the practices used by community pharmacists in Quebec to identify non-adherent patients, monitor medication use, and intervene to promote optimal medication adherence.

Methods: A cross-sectional survey was published online through different platforms including a Facebook pharmacists group, the electronic newsletter of the Quebec Order of Pharmacist (*La Dépêche*), and the forum of a networking and research infrastructure in pharmacy (*Réseau STAT*). Furthermore, emails were sent to the supervising pharmacists of pharmacy interns of two universities. The survey was separated into three sections: participants characteristics, methods to identify non-adherent patients and to monitor medication use, and interventions to promote optimal adherence. We conducted a statistical descriptive analysis on the responses collected.

Results: A total of 342 community pharmacists completed the survey. Participants were mainly women (71.6%), staff pharmacists (56.7%), aged 30 to 39 years old (34.2%), and worked in pharmacies located in urban areas (65.2%). The most common method to identify non-adherent patients was by verifying the gaps between prescription refills (98.8%), while the most common intervention was patient counselling (82.5%). The most common barriers to the identification of non-adherent patients are the lack of time (73.1%) and the lack of information on the medication prescriptions (65.8%), while the most common barriers to the intervention are the anticipation of the negative attitude of the patient (91.2%) and the lack of time (64.0%).

Conclusions: The lack of time is a frequent challenge to effectively monitor and manage patients with low level of adherence in community pharmacies. Quick and effective electronic tools that provide interpretable information based on prescription refills could help pharmacists for the monitoring of and the interventions related to medication adherence.

120 | Association between daily versus evening/bedtime statin dosing and medication adherence

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Background: The Food and Drug Administration recommends certain statins for evening/bedtime administration, whereas others are recommended for daily administration. However, little is known about how these different dosing instructions may impact statin adherence.

Objectives: To evaluate the association between daily versus evening/bedtime statin dosing and medication adherence among new initiators.

Methods: This was a retrospective analysis of electronic health records (EHR) and pharmacy claims data from a health care delivery system in northern California between 2010 and 2016. The study cohort was composed of new users of statin therapy ≥ 35 years of age at the time of first electronic prescription, with EHR activity 12–36 months before and after the index statin prescription, and at least 12 months of follow-up. Statin administration was dichotomized as daily vs evening/bedtime based on the medication order field. We excluded patients who had a change in instructions during follow-up and patients with all other dosing instructions (eg, three times per

week). The outcome was statin adherence operationalized as proportion of days covered (PDC) ≥ 0.80 over 12 months. We used a logistic regression model to assess differences in the likelihood of adherence for patients with daily vs evening/bedtime dosing. Odds ratios (OR) with 95% confidence intervals (CI) were estimated before and after statistical adjustment for patient, prescription, and provider covariates.

Results: Among 8053 statin initiators (mean age, 62.6 years; female, 48.9%), 3794 were prescribed a statin with a daily administration schedule, and 4259 were prescribed a statin with an evening/bedtime administration schedule. The mean PDC over 12 months among all statin users was 0.65 (SD, 0.32), with a mean PDC of 0.65 (SD, 0.32) among those receiving daily administration schedules and 0.66 (SD, 0.32) among those receiving evening/bedtime administration schedules. Compared with daily statin dosing, medication adherence among those receiving evening/bedtime dosing was similar in unadjusted (odds ratio, 1.03; 95% confidence interval 0.94, 1.12) and adjusted analyses (adjusted odds ratio, 1.06; 95% confidence interval 0.96, 1.17).

Conclusions: Adherence was similar between daily and evening/bedtime dosing administration schedules among new statin initiators. Future research is needed to assess the comparative effectiveness of these different dosing regimens on cholesterol fractions.

121 | Too many cooks in the kitchen: The association of medication adherence and diabetes control with number and type of prescribing physicians

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Background: Most Medicare beneficiaries with diabetes see a primary care physician and multiple specialists. It is unclear whether patient outcomes vary by the number and type of prescribers.

Objectives: We examined whether differences in refill adherence to oral hypoglycemic agents or diabetes control varied by the number and type of prescribers seen by older adults with diagnosed diabetes.

Methods: In a retrospective cohort of 51 879 elderly Medicare fee-for-service beneficiaries with diabetes living in 10 states in the Eastern United States, refill adherence was constructed from 2011 Medicare Part D pharmacy claims for oral hypoglycemic agents using proportion of days covered. A binary outcome of glycemic control (HbA1c < 7.5) was constructed from the last available HbA1c in 2011 laboratory results data from a large national vendor. We identified the most prevalent combinations of prescribers of cardiometabolic medications from 2010 Part D claims: (1) 1 primary care prescriber (PCP) only, (2) 2 PCPs, (3) 1 PCP and 1 cardiometabolic specialist, (4) one cardiometabolic specialist only, (5) 3+ PCPs, (6) 1 prescriber of other specialty, (7) 2 PCPs and 1 cardiometabolic specialist, and (8) all other combinations. The association between prescriber combinations (1 PCP as the reference) and

outcomes of refill adherence and disease control was estimated in logistic regression models, controlling for age, gender, race, Medicaid enrollment, 17 chronic conditions, and state fixed effects.

Results: The most common prescriber combination was 1 primary care prescriber alone. In adjusted analyses, refill adherence was similar across all prescriber combinations; while some differences were seen for glycemic control. Compared with having a single PCP prescriber, beneficiaries were less likely to have glycemic control if they had 1 PCP prescriber and 1 cardiometabolic prescriber (odds ratio [OR]: 0.92, 95% confidence interval [CI]: 0.86-0.98), 2 PCP prescribers and 1 cardiometabolic prescriber (OR = 0.83, 95% CI: 0.74-0.93), 3 or more PCP prescribers (OR = 0.82, 95% CI: 0.74-0.91) or multiple prescribers of other specialties (OR = 0.82, 95% CI: 0.76-0.89).

Conclusions: Several combinations of multiple prescribers were associated with worse glycemic control despite similar adherence.

122 | Variability of chronic disease medication adherence measures—A systematic review

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Background: Poor adherence to medication, especially for chronic disease management, poses a huge burden to the health system. An essential step towards consistent conceptualization of adherence and identification of successful strategies for improvement is through the use of reliable measures. The heterogeneity between different methodologies, however, introduces difficulties in interpretation of results across studies.

Objectives: To summarize tools used to measure adherence to diabetes and hypertension medication in the context of racial and socioeconomic disparities in the United States.

Methods: A comprehensive search strategy was used to identify observational studies in PubMed, Embase, and The Cochrane Library through August 2017. An additional manual search of the references of the included articles was performed. Only English articles focusing on the US population were included. Following PRISMA guideline, two independent reviewers screened, adjudicated, and extracted data. Any discrepancies were resolved through discussion and a third reviewer, if needed.

Results: Of 907 screened articles, 39 studies were deemed eligible for inclusion in the systematic review; 18 on hypertension, 15 on diabetes, and five on both conditions. Adherence measurement was assessed through using objective measures in 29 studies (74%) and subjective measures in 12 (31%) (two studies applied both measures). Among studies which used objective measures, 28 (97%) used claims data, among which medication possession ratio (MPR) was the most frequent measure used (13/29 studies). Proportion of days covered (PDC) was used in six studies to assess adherence. Same objective measures were not consistently used to measure adherence. Three different adherence definitions were used for MPR and two were for PDC. Eight-item Morisky medication adherence scale and cost-related nonadherence were the most common self-reported measures utilized: 3/12 and 2/12 studies, respectively.

Conclusions: There is substantial variation between adherence measurement tools and the definition used to assess adherence to chronic disease medication. This lack of uniformity may hinder health outcomes and reliability of cost-effectiveness analyses which incorporate measures of medication adherence. Adherence measures that utilize individual attributes along with performance measures of the health systems are needed to tackle the rising health care expenditure due to nonadherence.

123 | Influence of race/ethnicity on medication nonadherence among US adults with diabetes or hypertension—A systematic review

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Background: Medication nonadherence is a major public health issue associated with worse outcomes and increased health care expenditure. Certain racial/ethnic minority groups shoulder a greater burden of chronic diseases and are more likely to suffer from adverse outcomes. Existing evidence lacks a collective and large-scale picture of the medication adherence status among disadvantaged groups at the country level.

Objectives: To systematically review and describe evidence regarding the role of race/ethnicity on medication nonadherence among US adults with diabetes or hypertension.

Methods: We conducted a systematic search of the literature for observational studies in PubMed, Embase, and The Cochrane Library through August 2017. A manual search was conducted to identify additional references. All studies were screened, adjudicated, and extracted by two reviewers independently, and any discrepancies were resolved through discussion and a third reviewer, if needed.

Results: A total of 907 articles were screened, 101 articles were retained for full text review, and 39 were included: 27 cohort and 12 cross-sectional studies. Electronic health record data were used in 36 studies to assess adherence. 18 studies assessed medication adherence in adults with hypertension, 15 for diabetes, and five for either diabetes or hypertension. Adherence was assessed using 11 different measurement tools, among which Medication Possession Ratio was most frequent (13/39: 30%). Twenty-three studies reported adherence rates by race/ethnicity and 29 estimated the risk of adherence associated with race/ethnicity. Higher medication adherence was reported in Whites (20/23: 87%) compared with all others. Blacks and Hispanics had a significantly higher risk of nonadherence in 76% (22/29) of studies, adjusted odds ratio ranged from 1.1 to 5.6. Underuse, patient/physician race and language concordance, and socioeconomic-related factors were discussed as reasons for higher nonadherence among non-Whites.

Conclusions: Racial/ethnic disparities exist in chronic disease medication adherence. Differences in adherence are additionally attributable to socioeconomic constructs associated with disparate access to care;

low income, low education, unemployment, and lack of health insurance. Studies which characterize the value of improving adherence in racial/ethnic minorities are essential to understand how to achieve better health outcomes and effectively reduce health care costs.

124 | Oral antidiabetic drugs adherence and glycemic control among patients with type 2 diabetes mellitus

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Background: The prevalence of diabetes in Saudi Arabia is very high, and it is one of the highest in the world. It is a leading cause of morbidity and mortality. Medication adherence is an important contributor to improve diabetic patient health outcomes. Given the huge clinical and economic burden of diabetes in Saudi Arabia, understanding the rate and impacts of medication adherence for patient with type 2 Diabetes Mellitus (T2DM) is crucial.

Objectives: To determine the adherence rates among different oral antidiabetic drugs (OADs) and assess the relationship of adherence to OADs and glycemic control.

Methods: A retrospective cross-sectional study was conducted using data extracted from the Electronic Medical Records (EMR) at a large tertiary hospital in Riyadh, Saudi Arabia, from Jan 2016 through Dec 2016 to assess adherence rates using medication possession ratio (MPR) across different classes of OADs. Patients with T2DM who have at least two prescription fills for OADs during the study period were included in this study. Multivariate and univariate regression models were used to assess the factors associated with adherence and to determine the relationship between OADs medication adherence and glycemic control. Statistical analysis software (SAS® 9.2) was used to analyze the study data.

Results: A total of 5457 eligible diabetic patients were included in the study, of those 3400 (62.3%) patients were female. The average HbA1c was 7.8 (±1.59). Overall, 42% of patients were determined to have poor adherence (MPR < 80), and 48% had good adherence (MPR > 80). Poor adherence was more common with patients who were taking liraglutide 63% followed by metformin 48% and combination therapy 47%. Being female, having hypertension, dyslipidemia, ischemic heart disease, heart failure, chronic kidney disease, anxiety, and on polypharmacy were significantly have a higher rate of poor adherence compare with other groups. In multivariable adjusted analyses, change in HbA1c was more likely among individuals with good adherence (OR = 1.15, 95% CI = 1.02, 1.30) and female diabetic patients were less likely to have good adherence as compared with men (OR = 0.76, 95% CI = 0.67, 0.86).

Conclusions: Findings of this study provide insight into adherence issues with OADs among patients with T2DM. Policymakers and health care providers may consider establishing and implementing different policies and tools to improve adherence behavior especially among diabetic patients, which will have a great impact on achieving HBA1c goal.

125 | Real-world adherence to warfarin, dabigatran, rivaroxaban, and apixaban among patient with nonvalvular atrial fibrillation: 2010-2015

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Background: Oral anticoagulants (OAC) are used for patients with nonvalvular atrial fibrillation (AF) to prevent stroke. Adherence to OACs is important to improve effectiveness over the course of treatment.

Objectives: To evaluate adherence to OACs in real-world setting.

Methods: This is a retrospective cohort study using 2010-2015 Truven Health Market Scan Database. All index users of warfarin (W), dabigatran (D), rivaroxaban (R), and apixaban (A) were identified within 60 days after AF diagnosis. A 12-month continuous enrollment before the first prescription fill was required for each subject to assess baseline characteristic such as demographic, medical history, and health care utilization. Proportion of days cover (PDC) was used to measure patients' adherence to index OAC and to any OAC at 3, 6, 9, and 12 months. Gaps and switches were also evaluated during follow-up. Analysis was stratified by number of first fill's days supplied and stroke risk score. Logistic regression was used to compare adherence among OACs after adjusting for baseline characteristic.

Results: A total of 48 787 W, 14 864 D, 16 005 R, and 8078 A users were included in the study. Overall, A had higher adherence compared with other OACs, with average PDC at 3, 6, 9, and 12 months of 0.83, 0.76, 0.72, and 0.69, while D had the lowest adherence of 0.78, 0.67, 0.61, and 0.57, respectively. For the stratified analysis, adherence to OAC increased when stroke risk score increased and adherence for all OAC was higher when first days supplied was 90 days compared with 30 days. Switching to another OAC was highest among D users, with nearly 7% of the patients switching after 3 months and increased up to nearly 15% after 1 year. After adjusting for baseline covariates, we found that patients initiated with A were most likely to have high adherence ($PDC \geq 0.80$) compared with other OACs for 1 year (A vs W: OR = 1.95, 95% CI = 1.81-2.09; A vs D: OR = 1.74, CI = 1.61-1.88, A vs R: OR = 1.24, CI = 1.14-1.34); however, no difference were found between adherence to A and R at 3 months. At longer follow-up period (12 months), A showed more favorable adherence profile compared with R. Among NOACs, D users were the least likely to have high adherence. The findings were similar when evaluating adherence to any OACs.

Conclusions: In real-world setting, both A and R had high adherence compared with other OACs. These findings would be useful for

physicians and health care organization in decision-making and assessing clinical outcomes.

126 | Tree-temporal scan analyses for detecting safety signals in clinical development of vaccines: A simulation study

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Background: The analysis of safety data from clinical development of vaccines presents difficulties. There are issues of multiplicity due to many safety endpoints. Exposures may have a transient effect with unknown risk period. Medical codes need to be combined to avoid the dilution of the exposure effect in several endpoints for a same condition. These difficulties motivated the evaluation of tree-temporal scan methods for the safety signal detection in clinical trials data.

Objectives: Assess performance of methods for routine signal detection in data of clinical development of vaccines.

Methods: Three complementary tree-temporal scan methods were evaluated using Monte Carlo simulations: the self-controlled tree-temporal scan (SCTTS) analysis for the detection of transient effects of exposure, a between group tree-temporal scan (BGTTTS) for the differences between the randomized groups, and a log-rank test based tree-temporal scan (LgRTTS) for the comparison of the time-to-onset (TTO) between the randomized groups. The BGTTTS is sensitive to premature censoring of subjects while LgRTTS is not. The methods were put in perspective with (conditional) Poisson regressions and Kolmogorov-Smirnov (KS) comparison of the TTO distribution with a uniform. In each simulation scenarios, 100 true positives and 100 true negatives were simulated according to a range of baseline incidences (BI) and a range of permanent and temporary exposure effects. The evaluation of the methods was based on the positive predictive value (PPV) and the sensitivity (Se).

Results: In simulations of permanent effects of exposure, the PPV of the BGTTTS and LgRTTS was close to 100% when signals were detected, even with high alpha level (0.2). With low BI, the Se of the LgRTTS became higher than BGTTTS when the incidence rate ratio (IRR) increased, likely due to the longer follow-up considered. With a higher BI, the LgRTTS had a better Se even with low IRR. In simulations of temporary exposure effects, the SCTTS showed a PPV close to 100% when signals were detected. The Se of the SCTTS was generally lower than the KS test even with multiplicity adjustment based on the false discovery rate. KS tests with Se similar to the SCTTS had lower PPV.

Conclusions: The results of this simulation study suggest that the three tree-temporal scan methods are addressing the multiplicity issues in the analysis of safety data from clinical trials. The three methods are complementary in terms of the characteristics of the safety signals they are able to detect.

127 | Estimation of the effect of discontinuing a preventive therapy in older adults using health care databases: An exploration of the use of marginal structural models on the example of statins

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Background: Marginal structural models (MSMs) were developed for effect estimation from time-varying exposure, allowing for adjustment for time-dependent confounders affected by previous exposure. Their successful implementation in observational studies relies on the availability of information on relevant confounders and is particularly critical in settings with preventive therapies and old age, where, eg, comorbidity highly influences both adherence and outcome measures such as mortality.

Objectives: To test the use of Cox MSMs for the assessment of the effect of statin discontinuation in previously adherent older adults treated for primary prevention.

Methods: Using the French health care databases, 120 173 patients, having passed their 75th birthday in 2012-2014, without prior cardiovascular disease and with statin medication possession ratio $\geq 80\%$ in each of the two prior years, were followed for 2.4 years on average. Statin discontinuation was defined as 3 consecutive months without exposure. If statins were resumed later on, follow-up was stopped. Time-dependent covariates included cardiovascular drug use and numerous comorbidities and frailty indicators. Outcome measures were hospital admission for cardiovascular event (coronary, cerebrovascular, or other vascular event) and the composite with all-cause mortality.

Results: A total of 8639 patients (7.2%) experienced the composite outcome, of whom 37.5% had death as first event. 17 204 patients (14.3%) discontinued statins. A large discrepancy with evidence from randomized trials was observed for the composite with mortality but not for the cardiovascular event outcomes: For cardiovascular admission, the crude and MSM-adjusted hazard ratios (HRs) for statin discontinuation were 1.26 (95% CI 1.14-1.40) and 1.33 (1.18-1.50), respectively; for the composite, they were 2.25 (2.10-2.40) and 1.59 (1.46-1.73), respectively. The MSM-adjusted HRs were 1.46 (1.21-1.75), 1.26 (1.05-1.51), and 1.02 (0.74-1.40) for coronary, cerebrovascular, and other vascular events, respectively.

Conclusions: Results of this cohort study based on health care databases and assessing the effect of statin discontinuation suggest that the use of MSMs allowed correcting for a substantial amount of time-dependent confounding also in the setting of previously adherent older adults treated for primary prevention as long as all-cause mortality is not an outcome of interest.

128 | A comparison of methodological approaches on the association between de novo vitamin D supplement use post-diagnosis and breast cancer mortality

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Background: Pharmacy claims data offers a unique opportunity for non-randomized comparative effectiveness research, but studies can be inherently biased due to confounding by indication.

Objectives: This study investigates different methodological approaches to overcome inherent bias while examining the association between vitamin D supplements initiated after breast cancer incident diagnosis on survival.

Methods: Women aged 50-80 years with a record of invasive breast cancer were identified on the National Cancer Registry Ireland database ($n = 5417$). Initiation of de novo vitamin D post-diagnosis was identified from linked prescription data ($n = 2581$, 49%). We first implemented a standard multivariate Cox proportional hazards (PH) model to estimate adjusted HRs (95% CIs) for breast cancer-specific mortality. We compared these findings with a propensity score analysis approach. We subsequently sought to account for the time-varying nature of vitamin D use and time-varying confounding by bisphosphonate use using inverse probability of treatment weighted marginal structural models (MSMs), exploring the impact various weight trimming approaches have on the effect estimates.

Results: Using the standard Cox PH models, we found a 20% reduction in breast cancer-specific mortality in de novo vitamin D users compared with non-users (HR, 0.80; 95% CI, 0.64-0.99). A similar point estimate was observed, but larger CIs, for the association between vitamin D use and breast cancer-specific mortality (HR: 0.80; 95% CI: 0.60-1.06) when correcting for covariate imbalance between treatment groups at baseline using propensity score analysis (1:1 exact matching). Using truncated stabilized weights (truncation fraction=0.01) in an MSM, we obtained a similar result (HR: 0.76; 95% CI: 0.47-1.24); however, point estimates of treatment effects varied greatly depending on weight trimming.

Conclusions: Our results highlight the importance of treatment model specification and weight trimming on MSM estimates.

129 | Statistical inference in an updated network meta-analysis: A comparison of likelihood ratio meta-analysis and conventional meta-analysis

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Background: A potential problem for distributed drug safety networks is a situation where a meta-analysis is undertaken because a prior meta-analysis lacked adequate precision. Under this circumstance, the 95% confidence interval (CI) from the new meta-analysis will not have the expected 95% coverage. The method of likelihood ratio meta-analysis (LRMA) provides an alternative mechanism of inference which is immune to this phenomenon.

Objectives: To compare confidence intervals from updating a meta-analysis using both conventional meta-analysis and LRMA methods, using an example of discontinuation of biologic disease modifying (bDMARD) therapy in rheumatoid arthritis (RA) patients.

Methods: Data for this example were provided by a study from the Canadian Network for Observational Drug Effect Studies (CNODES). The study included adult RA patients from four Canadian provinces (Alberta, Manitoba, Ontario, and Quebec) and one US database (MarketScan). The outcome was discontinuation of bDMARDs in patients who were concomitant versus non-concomitant users of methotrexate (MTX) or leflunomide (LE). Comparison of confidence intervals from conventional meta-analysis and LRMA proceeded under a hypothetical scenario where an initial random effects meta-analysis was done by CNODES, but which did not include data from Quebec. Under the scenario, a non-significant result from the first meta-analysis prompted the national regulator to ask for additional data. CNODES responded by conducting a study in Quebec and adding those results to a new meta-analysis.

Results: The study population was composed of 19 933 adult patients who were new users of bDMARDs. Random-effects LRMA and conventional meta-analysis yielded the same maximum likelihood estimates of the total meta-analytic association. In the first conventional meta-analysis, concomitant MTX or LE patients were not statistically significantly less likely to discontinue their bDMARD (hazard ratio [HR] 0.90, 95% confidence interval [CI]: 0.80 to 1.01). When data from Quebec were included in a new meta-analysis, the new result was spuriously significant (HR 0.90, 95% CI: 0.81 to 0.99). By comparison, an intrinsic 95% confidence interval (95%CI) from the LRMA method remained non-significant HR 0.90, 95% CI: 0.79 to 1.02.

Conclusions: When a meta-analysis is updated with additional data, the LRMA method avoids the problem of overly narrow confidence intervals that can occur with a conventional meta-analysis.

130 | Overcoming temporal confounding in the assessment of therapeutic equivalence of brand and generic drugs

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Background: Generic drugs are required to be bioequivalent to their brand counterparts; yet the generic approval process does not require

demonstration of therapeutic equivalence. The FDA considers that if a generic meets its therapeutic equivalence criteria, it can be substituted for its brand counterpart with the full expectation that it will have the same clinical effect and safety profile. While most generics are considered to be therapeutically equivalent to their brand counterpart, this is not routinely assessed with a formal statistical evaluation. Methods are needed to assess therapeutic equivalence in situations where questions arise. A primary difficulty is that dates of initiation for brand and generic users largely do not overlap. This positivity violation makes it difficult to adjust for temporal confounding due to secular trends in health outcomes.

Objectives: We aimed to develop a method to obtain causal estimates of the effectiveness of a generic compared with a brand product that accounts for temporal confounding in the presence of a positivity violation.

Methods: Using venlafaxine as a case study, we identified new users of brand and generic products within OptumLabs Commercial Claims Data from 1994-2016. The primary outcome is treatment failure defined as a switch to a new antidepressant, use of electroconvulsive therapy, a psychiatric hospitalization or emergency department visit, a suicide-related encounter or death within the first 9 months of use. We apply regression discontinuity to survival curves with a discontinuity in the probability of initiation to generic at the date when generic becomes available. The survival curves are estimated using G-computation to adjust for time-varying confounding. We also adjust for baseline variables like age, sex, and race.

Results: The method provides a comparison between the survival curves under adherent use of brand and generic, conditional on initiating treatment on the date of generic market entry.

Conclusions: Usual methods for estimating survival curves under adherence to a treatment regime do not result in meaningful comparisons of treatment groups when there is temporal confounding. Our approach builds on these using regression discontinuity to allow for meaningful comparisons. Because brand and generic initiation times often do not overlap, this method is useful for assessing differences in the effectiveness of brand and generic drugs.

131 | Trends of insulin-like growth factor 1, growth hormone, and biochemical control of patients with acromegaly in Italy: A longitudinal retrospective chart review study

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Background: Long-term biochemical control (ie, normalization of growth hormone [GH] and insulin-like growth factor 1 [IGF1]) is the goal of treatment of acromegaly. Few studies have characterized the sustainability of GH/IGF1 levels in acromegaly.

Objectives: To identify long-term time trends of GH, IGF1 levels and biochemical control in patients with acromegaly using longitudinal real-world data.

Methods: Medical records of adult patients with confirmed acromegaly, ≥ 2 readings of GH and IGF1 and ≥ 6 months of follow-up at an endocrinology center in Italy, were reviewed. Patients were followed from first documented GH or IGF1 measurement at the study center until end of data availability, loss to follow-up, or death. Mean GH and IGF1 levels were obtained across multiple measurements per year. Biochemical control was assessed annually and defined as having $>50\%$ of IGF1 measurements $\leq$ upper limit of normal or GH measurements $\leq 2.5 \mu\text{g/L}$ (when IGF1 unavailable). Latent class growth analyses were conducted to identify different time trends of mean IGF1, mean GH, and probability of being biochemically controlled over 10 years and to estimate the proportion of patients with these time trends. Trends were based on model fit.

Results: All 150 eligible patients were Caucasian, 47% female, with mean age of 43.1 years (range: 19–70) at diagnosis and mean follow-up time of 9 years. 81 (54%), 84 (57%), and 81 (54%) patients had normal IGF1, GH, and biochemical control status, respectively, for $\geq 50\%$ of the follow-up. 4 trends were identified for IGF1 (% of population; mean levels): 1 stable (15.3%; 186.5 ng/mL) and 3 declining ([1] 39.3%; initial [year 1]: 465.8, last [year 10]: 142.9; [2] 38.0%; initial: 576.8, last: 280.1; [3] 7.3% initial: 664.1, last: 403.4). 3 declining trends were identified for GH ([1] 23.6%; initial: 1.63 $\mu\text{g/L}$, last: 0.32 $\mu\text{g/L}$; [2] 50.7%; initial: 4.57, last: 1.03; [3] 25.7% initial: 12.99, last: 3.34). Probability of achieving biochemical control followed 2 trends (% of population; probability of control): 1 stable (26.7%; 20.4%) and 1 increasing (73.3%; initial: 33.1%, last: 98.0%).

Conclusions: IGF1 and GH levels were initially elevated in the majority of patients and declined over time. Biochemical control was reached by $\geq 70\%$ of patients after 10 years. One-third of the population had low likelihood of achieving control at any time. Future research is warranted to understand the impact of long-term biochemical levels on patients' disease course.

132 | Comparison of case definitions for harmonized health outcome assessments

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Background: Standardized case definitions promote a common understanding of health outcomes and improve data comparability.

Objectives: Comparing case definitions and identifying elements of a standard performance profile of case definitions.

Methods: We conducted a systematic literature search for methods comparing case definitions. We compared Brighton Collaboration (BC) standardized case definition of neonatal infections: bloodstream

infections and the definition of neonatal sepsis developed by the European Medicine Agency (EMA). We classified 72 patients with an ICD-10 code of neonatal sepsis hospitalized 2011–2017 at the University Basel Children's Hospital, Switzerland. Performance indicators were calculated for comparison.

Results: We identified 46 publications comparing case definitions. Of these, 27 reported at least one performance indicator: Sensitivity ($N = 15$), specificity ($N = 13$), positive predictive value ($N = 7$), negative predictive values ($N = 6$), accuracy ($N = 2$), or inter rater reliability and Cohen's Kappa (Kappa) ($N = 7$). EMA and BC definitions differed in levels of diagnostic certainty, number of criteria, and cut-off for 7 numerical continuous variables. The PPVs of the EMA and BC definitions were 96.7% and 94.5% and sensitivities of the EMA and BC definitions were 95.8% and 80.6%, respectively. Of the 72 events, 57 were recognized by both definitions, one by the EMA definition and 12 by the BCF definition exclusively. Two coded events were missed by both definitions. IRR and kappa between definitions were 81.9% and 0.179 (95% CI -0.231 to 0.589), respectively.

Conclusions: The levels of diagnostic certainty could not be compared due to the lack of this dimension in the EMA definition. The difference in performance indicators emphasizes the usefulness of evaluation. Building a standard performance profile to characterize and compare case definitions could guide implementation.

133 | Performance indicators of the Brighton Collaboration case definition “neonatal infections”

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Background: Standardized case definitions can be used to identify health outcomes and allow classifying cases for further analysis. Brighton Collaboration case definitions for adverse events following immunization comprise different levels of diagnostic certainty.

Objectives: To assess the difference in performance of the three levels of diagnostic certainty of the Brighton Collaboration (BC) standardized case definition of “neonatal infections: bloodstream infections” developed within the GAIA project (<http://gaia-consortium.net/>) and to identify elements of a standard performance profile.

Methods: Neonates with sepsis hospitalized between 2011 and 2017 at the University Basel Children's Hospital, Switzerland, were identified by ICD-10 code. Data extraction and classification of events according to the Brighton Collaboration case definition was conducted by two investigators (M.Z. and J.U.) independently. Performance indicators were calculated for each level and overall.

Results: 72 patients with neonatal sepsis were identified. Of these, 69 were true positives, 3 false negatives. This leads to an overall sensitivity of 95.8%, PPV of 94.5%, IRR of 97.2%, and Cohen's kappa between

ratios of 0.65 (95% CI 0.18-1.23). Levels 1, 2, and 3 classified 37, 32, and 0 cases, respectively. Overall, 69 cases met the case definition at any level. 3 events coded as sepsis had insufficient information to meet the case definition.

Conclusions: The Brighton case definition for “neonatal infections” had a high sensitivity and PPV. Interrater reliability and Cohen's kappa demonstrate a strong standardization effect. Overall, the indicators used appear to be useful elements of a standard performance profile for multi-level case definitions. A model determining the relative contribution of each criterion to the performance of a case definition will be useful.

134 | Targeted estimation of background rates with existing data via odds-weights computed from simulated data of target referents

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Background: Probability (p) weighting methods are frequently used to address lack of internal validity. Yet, in certain applications, external validity is a priority, including observational studies that supplement randomized clinical trials (RCTs). We describe a procedure to target inferences from existing data to trial participants. We estimate the incidence of select outcomes within an electronic health record (EHR) population weighted to be comparable with a recently completed RCT of patients with type 2 diabetes (T2D).

Objectives: To describe the development of a RCT-like population using data from a large US EHR database.

Methods: We identified patients with T2D between 2008 and 2013 within Optum's EHR database (EHR-T2D). We emulated the RCT population by applying the trial's eligibility criteria to the EHR data and simulating data from reported covariate distributions of trial participants (including demographics, biometrics, laboratory values, diagnoses, and medications). The simulated RCT population was appended to the EHR-T2D database, and odds weights $[p/(1-p)]$ were derived from logistic regression procedures with the dependent variable representing membership in the simulated RCT cohort vs EHR-T2D. Patient characteristics are reported for the RCT participants, the EHR-T2D population, and the EHR-RCT-like population. Incidence rates/100 000 person-years of select outcomes are reported for the EHR cohorts.

Results: Relative to the RCT participants, before weighting, the EHR-T2D ($n = 208\ 672$) population was different regarding demographics (eg, % Male: 49.7 vs 64.3), comorbidities (eg, % Coronary artery disease: 19.2 vs 56.8), treatment (eg, % Insulin: 8.3 vs 41.8), and laboratory values (eg, % eGFR > 90: 64.0 vs 36.9), but comparable regarding BMI, smoking status, and HbA1c. Odds weighting to the simulated RCT population balanced all measured covariates between RCT participants and the EHR-RCT-like population. Compared with

the EHR-T2D population, the EHR-RCT-like population had lower rates of thyroid cancer (16.2 95% CI: 9.3-26.2 vs 28.8 95% CI: 25.5-32.4) and acute pancreatitis (131.3 95% CI: 92.0-181.7 vs 152.4 95% CI: 144.7-160.4) but were comparable for all other outcomes.

Conclusions: Odds weighting to a simulated referent successfully balanced all selected covariates relative to the external RCT population. Observed differences in outcome rates highlight the importance of external validity in studies intended to support ongoing RCTs.

135 | Dealing with time-varying confounding by marginal structural model in observational study: An application in Parkinson's disease

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Background: Istradefylline is an adenosine A2A receptor antagonist, first approved as antiparkinsonian medication in Japan 2013. The types or the dosage of Parkinson disease (PD)'s medications are often changing over time. Therefore, it's hard to evaluate the treatment effect of specified drug, especially in longitudinal observational studies with time-varying treatment and time-varying confounding. In order to estimate the treatment effect, we used the method of marginal structural model (MSM), which is widely used for adjusting time-varying issues.

Objectives: The aim was to demonstrate how to conduct the MSM in PD study. And to compare the weights for MSM between considering time-varying nature of covariates or not.

Methods: We used the data from the first-in-Japan large-scale observational study for NMSs and treatment in patients with PD (J-FIRST). Patients were enrolled between March 2014 and January 2015 in 35 sites throughout Japan and were prospectively examined for 52 weeks. And followed the next steps. Step 1: Deciding the causal directed acyclic graph of the hypothesized relationship between istradefylline and MDS-UPDRS part I score. And discussed with clinicians to select possible time-fixed and time-varying confounders. Step 2: Calculating propensity score and estimate stabilized inverse probability of treatment weight (S-IPTW) weights and model the MSM. Step 3: Using repeated measures linear regression models to test whether the confounders are predicted by prior exposures or the confounders influenced next outcome. Step 4: Repeating step 2 by using confounders selected in step 3. Step 5: Comparing the S-IPTW calculated by steps 2 and 4.

Results: 7 baseline covariates and 20 possible time-varying confounders were selected for clinical judgments. After the test, 7 time-varying covariates left. The cumulative S-IPTW were inflating over time, but the means were around 1 for all time points in both two models. Also, the standard deviations are smaller in step 4's model, which only composed with selected time-varying confounders.

Conclusions: MSM can be conducted by these steps in PD study. Time-varying nature of the confounders should be considered when conduct MSM, which may result in more stable estimates of S-IPTW.

136 | Adjusting for multiple use of patients when matching with replacement: A simulation

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Background: Treatment propensity-based matching is used frequently in observational data analysis in order to address any imbalance between groups in a real-world setting. When treatment propensity distributions for treated vs untreated are particularly dissimilar, it may be advisable to implement matching “with replacement” of controls to improve the overall matches. The resulting analysis dataset will have the same patients repeated across time, but also across match groups, which needs to be considered in the analysis.

Objectives: To explore alternative modeling approaches to adjust for multiple use of patients and to illustrate the use of a COLLECTION effect in PROC GLIMMIX

Methods: Setting: PROC MIXED can be used to adjust for patient correlations within match group but does not take account of reuse of patients across match groups. PROC GLIMMIX, through the use of the EFFECT statement with the COLLECTION specification, allows one to take account of correlations across match groups arising from reuse of patients. We simulated a dataset in which patients' outcomes were varied over time and correlated with other clinical measures at baseline and during follow-up. Two additional datasets were simulated, each with greater baseline differences between treated and untreated in order to examine the effect on results. Exposures or Interventions: A group “treatment” assignment was simulated, and treated and untreated patients were matched (1:4 with replacement) on baseline treatment propensity (with calipers applied). Main Outcome Measures: The outcome was a continuous variable with a linear trend that was different for the two treatment groups (ie, a higher average rate of increase among treated). Statistical Analysis: In order to analyze the data using PROC GLIMMIX, the dataset was transposed from match-patient-visit level to patient-visit level. Matched set membership was captured via a set of match ID indicator variables, which were included in the COLLECTION specification on the EFFECT statement.

Results: For this particular dataset, the primary results (treatment-by-time interactions) were similar using either MIXED or GLIMMIX. The GLIMMIX approach resulted in more accurate standard errors. The more patients are reused, the bigger the impact of using GLIMMIX.

Conclusions: The EFFECT statement (using the COLLECTION specification) in PROC GLIMMIX allows one to control for reuse of patients across match groups when doing propensity score matching with replacement.

137 | Causal estimation in observational data subject to missing by a machine learning approach

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Background: Observational medical databases find increasing uses for comparative effectiveness and safety research. However, the lack of analytic methods that handle the issues of missing data and confounding bias jointly, and the onus of model specification limits the use of these data sources.

Objectives: To evaluate causal estimation by model-free machine learning (ML) methods in data with incomplete observations.

Methods: We derive ML, a multiply robust method using machine learning based on our early work on its parametric version (MR) to estimate the average treatment effect. We compare the bias, standard error, and coverage probability (CP) of ML to MR, complete case analysis (CC), and regression analysis after multiple imputations (MI). We conduct a simulation study, with data generated from known models of exposure, outcome, and missing mechanism, and thus, the true causal effect is known and used as the benchmark for evaluations. Two settings are studied: a baseline where 40% data are missing and variables relate linearly (on the appropriate scale) to exposure, outcome, or missingness and a challenge where 53% data are missing with non-linearity among variables. For each setting, we generate datasets with sample sizes 1000 and 5000.

Results: Baseline: ML is comparable with MR in bias when all models used in MR are wrong. The CPs of the two methods are mostly comparable. MI is similar to ML and MR in bias and SE. CC is the worst in all three metrics with the wrong outcome model. Challenge: ML's bias is 11% of the bias of MR, when MR's models are all wrong, and MR's CP is 0%. MI's bias is 3 times of MR's bias even when the outcome model is correct for N = 5000; its CP is close to 0% when the outcome regression model is wrong. CC is similar to MI, but with a larger SE.

Conclusions: ML is a robust model-free approach for causal estimation with a minimal bias. This feature lends itself to applications in epidemiological research, when the true data structure is unknown. We recommend ML for large data where the precision is not a concern. When the sample size is moderate or small, we recommend that both MR and ML be performed, with ML used as a supporting tool and MR for producing the causal estimates. If the two estimates are starkly different, more effort is needed in model selection in MR.

138 | Computational algorithms for SAS-based distributed regression software applications for Cox and GLMs

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Background: Previous work has demonstrated the feasibility and value of conducting distributed regression analysis (DRA), a privacy-protecting analytic method that performs multivariable-adjusted regression analysis with only summary-level information from participating sites. However, prior studies utilized R-based algorithms. To our knowledge, there are no DRA applications in SAS, the statistical software used by several large distributed data networks (DDNs), including the Sentinel System and PCORnet. SAS/IML is available to perform the required matrix computations for DRA in the SAS system. However, not all data partners have access to IML as it is licensed separately, limiting the application of DRA.

Objectives: To develop a DRA algorithm using BASE SAS and SAS/STAT modules for use in DDNs.

Methods: We used a distributed iteratively reweighted least squares (IRLS) for generalized linear models (linear and logistic) and distributed Newton-Raphson (NR) for Cox regression. To preserve privacy, only summary data were exchanged between data partners and the analytic center (AC). Both algorithms were implemented using only BASE SAS and STAT modules. The main steps include calculating sums of squares and cross products (SSCP) summary statistics at each site, combining site-specific summary statistics at the AC, and using PROC REG with SSCP-type input to solve the IRLS/NR system of equations and calculate the covariance matrix.

Results: We developed a SAS-based DRA software application and implemented it in the Sentinel DDN. This was successfully tested on several datasets using various options (weights, initial estimates, convergence criteria, stratification [Cox], etc). Overall, the macro computations were in complete agreement with the corresponding pooled patient-level data analyses produced by standard SAS procedures, within machine precision (1E-16).

Conclusions: We successfully developed a DRA software application using only SAS BASE and STAT modules. The application can facilitate the adoption of DRA in national DDNs.

Background: Treatment patterns in oncology constantly evolve, while guidelines offer diverse options for increasingly personalised patient subsets. Defining normative treatment patterns is difficult. Process mining is the application of statistical and graphical methods to extract pathways from event logs and provides a novel approach in pharmacoepidemiology.

Objectives: Using line of therapy information from Flatiron Health's, electronic health record-derived oncology database, we evaluate the use of process mining methodology to aid in the understanding of chronic lymphocytic leukemia (CLL) treatment patterns.

Methods: Three defined case studies were explored using process mining methods: (1) using interactive analysis to identify data collection issues, (2) understanding complex patterns with high variance in treatment pathways within specific populations, and (3) understanding treatment flows leading to specific treatments or outcomes.

Results: Patients with CLL and SLL (N = 2597; 81% CLL/19% SLL) ≥18 years old were selected from the Flatiron Health database. Patients were included if they entered the Flatiron Health network without prior lines, and first-line treatment was between 2011 and 2016. Using process mining methods to explore the data, we were able to quickly identify an unintended artefact of the line of therapy definition, enabling us to account for it in later analyses. We also demonstrated the use of these methods to summarise off-label induction therapy in the non-17p deletion CLL population and defined normative pathways leading to non-frontline treatment.

Conclusions: Application of process mining provided insights on complicated disease flows. The greatest benefit came from introducing process mining as an intermediate step to explore and validate a priori assumptions about potential patterns present in the data. In addition to the statistical methodology developed within the process mining literature, process mining software provides mature and easy to use tools that can enable interactive exploration of complex longitudinal event data.

140 | Misclassification of time-at-risk due to free sample drug use: A simulation study

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139 | Process mining for exploring treatment patterns in chronic lymphocytic leukemia in a real-world oncology database

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Background: In epidemiologic studies relying on claims data, the use of free samples of study drugs may result in both selection bias and misclassification of time-at-risk. New users that experience an event while using free samples may discontinue use and be excluded from the study population. Also, apparent new users may be prevalent users when they are first observed in claims with misclassified time-at-risk. This misclassification is important when monitoring for acute onset adverse events

Objectives: We examined the potential bias created when misclassification of time-at-risk occurs in new-user cohorts by using a plasmode simulation framework.

Methods: We simulated a 1:1 matched population and subsequent follow-up for angioedema following apparent initiation of angiotensin-converting enzyme inhibitors (ACEI) as compared with beta-blockers. Using the plasmode simulation, we modeled time-to-event and total follow-up time based on aggregate data in the Sentinel Distributed Database. In the simulated environment, we varied (a) the true initial hazard ratio and its length in days (eg, 3.0 for the first 30 days following initiation); (b) the proportion of true new users among the treatment group; and (c) the degree to which their time-at-risk was misclassified based on the duration of the free sample supply. Stratified Cox regression was used to estimate the hazard ratio in all of the simulated datasets from the various scenarios.

Results: As expected, there is an underestimation of an early elevated hazard ratio when time-at-risk is misclassified among the treated patients relative to the comparators. The bias scales according to the proportion of misclassified new users and the degree to which the duration of free sample use coincides with the early elevated risk period. That is, if the free sample use partially or completely overlaps the elevated risk period (eg, 60-day free sample use combined with a 30-day elevated risk window following initiation), then the bias is more pronounced.

Conclusions: The presence of misclassified new users with an undocumented history of free sample use will bias estimates of the hazard ratio for early onset, acute events. This potential bias is less problematic for longer or sustained periods of elevated risk following new initiation of therapy. For medical products with suspected free sample distribution, we present a quantitative bias analysis framework that allows investigators to model potential bias.

141 | Effects of time-varying stress-ulcer prophylaxis strategies on risk of ventilator associated events

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Background: Use of acid-suppressive medications for stress-ulcer prophylaxis is common in ventilated patients. However, sustained use may increase risk of infectious ventilator-associated complications (iVACs) including pneumonia. Prior observational studies of these medications on pneumonia failed to appropriately account for time-varying confounders, such as gastrointestinal bleeding, which are affected by past treatment.

Objectives: To estimate the effect of time-varying stress-ulcer prophylaxis strategies on cumulative risks of iVACs and ventilator mortality in ventilated patients, accounting for time-varying and baseline confounders, as well as competing risks.

Methods: Using electronic health records, we identified a retrospective cohort of critically ill patients aged 18 years or older who underwent mechanical ventilation for at least 3 days during an inpatient admission in Brigham and Women's Hospital (Boston, Massachusetts) between January 1, 2009, and December 31, 2014. We considered sustained treatment strategies that treat patients with proton pump inhibitors

(PPIs), histamine-2 receptor antagonists (H2 blockers), or sucralfate starting from ventilation day 3. We estimated the 30-day risk ratio (RR) under each strategy relative to never receiving prophylaxis using the parametric g-formula, an extension of standardization for time-varying treatments and confounders, to appropriately control for time-varying confounding affected by past treatment.

Results: We identified 6133 eligible patients, and H2 blockers were the most commonly used acid-suppressive medications. Compared with never receiving prophylaxis, we estimated a harmful yet non-statistically significant effect of nearly all prophylaxis strategies on iVACs. The effect estimate was strongest for H2 blockers: RR and 95% confidence interval = H2 blockers 1.45 (0.93-2.37), PPIs 1.41 (0.87-2.42), and sucralfate 0.97 (0.34-2.35). Secondary analysis showed different estimates for high- and low-dose PPI strategies: high dose 1.59 (0.89-2.85), low dose 1.29 (0.67-2.39). We found a protective effect on ventilator mortality that was strongest for sucralfate and weakest for high dose PPIs. Sensitivity analyses varying the functional forms for time-varying covariates showed qualitatively similar results.

Conclusions: Despite the consistent direction of effect estimates, we had no sufficient evidence to conclude that sustained use of stress ulcer prophylaxis increases iVACs risk.

142 | Racial heterogeneity in the association of proton pump inhibitors and cardiovascular disease

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Background: Proton pump inhibitors (PPIs) are used for treatment of acid-related disorders and are among the most commonly used drugs in the world. PPI use has been implicated as a risk factor for cardiovascular disease; however, whether the relation of PPIs and cardiovascular disease differs by race is unknown.

Objectives: Therefore, we examined the race-specific relation of PPIs with incidence of cardiovascular disease and its major components (stroke, heart failure, and coronary heart disease).

Methods: The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing, community-based cohort from the United States (n = 15 792) that was designed to examine risk factors for cardiovascular disease. PPI use was assessed via pill bottle inspection at Visit 1 (1987-1989) and up to 10 additional times during follow-up. Participants free of cardiovascular disease at baseline were followed for incident cardiovascular disease (n = 3961) through 2015. Using Cox proportional hazards regression, we computed adjusted hazard ratios of cardiovascular disease outcomes in relation to time-varying PPI use. By including a cross-product term in the model, we tested for differences in the association between PPIs and cardiovascular disease by race.

Results: The crude incidence rates per 1000 person-years of cardiovascular disease, coronary heart disease, heart failure, and stroke were 14, 5, 7, and 3, respectively. Rates of cardiovascular disease, heart

failure, and stroke were higher for African Americans than whites. White PPI users had a 16% higher risk of cardiovascular disease than nonusers (adjusted hazard ratio: 1.16; 95% confidence interval: 1.06, 1.27), whereas African Americans who used PPIs had a 16% lower risk than nonusers (adjusted hazard ratio: 0.84; 95% confidence interval: 0.72, 0.98; race interaction *p* value: 0.0006). This pattern of higher hazard ratios in whites than African Americans was consistent regardless of sub-outcome (ie, coronary heart disease, heart failure, or stroke) and was significant for heart failure and stroke (interaction *p* values for heart failure and stroke, respectively, 0.047 and 0.007).

Conclusions: The association between PPIs and cardiovascular disease was positive in whites but inverse in African Americans. Given the widespread use of PPIs, understanding the risks of PPI use in sub-populations is of critical importance.

143 | Platelet aggregation inhibitors use and risk of recurrent diverticular bleeding among patients with a prior episode of diverticular bleeding

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Background: Colonic diverticular bleeding is the most common cause of lower gastrointestinal bleeding and often recurs. Neither the incidence of recurrent diverticular bleeding (RDB) or its risk factors have been systematically measured.

Objectives: To use administrative medical claims data to calculate the incidence of and risk factors for RDB.

Methods: **Data source:** We used the OptumInsight Clinformatics database, which contains the medical claims of 77.2 million commercially insured patients from 2000 to 2016. **Exposure:** We identified a cohort of patients who had an initial episode of diverticular bleeding during hospitalization using ICD codes. Patients with fewer than 120 days in the database prior to diverticular bleeding or an earlier outpatient code for diverticular bleeding were excluded. **Outcome:** The outcome of RDB was identified by ICD codes during hospitalization. **Statistical analysis:** Incidence rates were age- and sex-standardized to the 2010 United States population. To analyze risk factors for RDB, we identified comorbidities associated with bleeding propensity, platelet aggregation inhibitor use, or anticoagulation. Using pharmacy claims, we assessed exposure to aspirin, NSAIDs, platelet aggregation inhibitors, direct-acting oral anticoagulants, warfarin, and subcutaneous heparins. Covariates were analyzed as time-updating variables. Multivariable Cox regression was used to analyze risk factors for the RDB. Demographics and diagnoses were incorporated into the model using a disease-risk score for RDB to balance covariates among medication exposures. Patients were censored from follow-up if they underwent colectomy.

Results: We identified 24 068 patients with initial diverticular bleeding who met inclusion criteria. The standardized incidence of initial and

second diverticular bleeding were 25.7 (95% CI 25.7-25.7) and 116.3 (95% CI 111.6-121.2) per 100 000 person-years, respectively. Women composed 47.3% of the cohort, and median age was 77 (IQR 69-82) at the time of initial diverticular bleeding. Using Cox regression, platelet aggregation inhibitors were the only medication exposure associated with RDB bleeding (HR 1.40, 95% CI 1.17-1.68).

Conclusions: The incidence of RDB is 116.3 compared with 25.7 per 100 000 person-years for initial diverticular bleeding. When controlling for age, gender, race, and comorbidities, exposure to platelet aggregation inhibitors is associated with a 40% increased hazard for RDB.

144 | Self-reported comorbidity, functional dependence, and health care resource utilization of chronic hepatitis C virus infection patients

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Background: Hepatitis C virus (HCV) is one of the most common causes of blood-borne infections in the United States. Studies are needed to assess the burden on our health care system in terms of their overall health status and health care utilization.

Objectives: To identify the burden of self-reported comorbidity, functional dependence, health care costs, and utilization of chronic HCV and non-HCV patients.

Methods: We conducted a pooled cross-sectional study on Medicare Current Beneficiary Survey 2005-2011, identifying over 65-year-old, chronic HCV patients using ICD-9-CM codes. MCBS is the multi-staged, weighted survey data. Enrollees with no HCV codes were defined as non-HCV. All statistics were reported using pooled (average) weights across multiple years. Instrumental activities of daily living, IADL, and activities of daily living, ADL, stages were determined based on specific activities using prior methods reported.

Results: The HCV prevalence was 0.07% (94 885 out of 127 422 441). Mean age of HCV was 72 and non-HCV was 76.64% of HCV vs 87% of non-HCV were white. The comorbidity prevalence was generally higher in HCV vs non-HCV (hypertension: 73% vs 68%, cancer: 31% vs 20%, myocardial infarction 21% vs 14%, diabetes mellitus: 31% vs 25%). HCV patients reported higher difficulty with heavy housework (44%) than non-HCV (38%) but lower difficulty using telephones (3%) vs non-HCV (10%). IADL stages were lower in HCV vs non-HCV: 73% stage 0 vs 62%. HCV patients had higher difficulty showering (21%) than non-HCV (14%) and using toilets (11% vs 7%). ADL stages were higher in HCV (21% with stage ≥ 2) than non-HCV (13%). The prevalence of falls is 60% (HCV) vs 29% (non-HCV). Mean annual total health care costs incurred were 33 406 (HCV) vs 14 919 (non-HCV). Mean costs were also higher for HCV vs non-HCV for inpatient: 13 024 vs 3628, outpatient: 3116 vs 1374 and prescribed medicines: 3134 vs 2291. HCV patients reported higher number of

events overall (100 vs 85% having >20 events) and by health care settings: inpatient, outpatient, short-/long-term facility, medical providers, prescribed medicines, and office visits.

Conclusions: Despite being younger, chronic HCV is associated with a high burden of self-reported comorbidity, health care events, and costs versus non-HCV but has approximately similar functional dependence. This highlights the overall burden of chronic HCV on the health care system among elderly Medicare beneficiaries.

145 | Incidence and episodes of hypoglycaemia in type 2 diabetes patients: A systematic review and meta-analysis of observational studies

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Background: Diabetes forms a global health concern and is associated with serious complications and multiple comorbidities. Hypoglycaemia is a major challenge in the treatment of diabetes mellitus.

Objectives: To review the existing literature for studies that investigated the incidence and episodes of hypoglycaemia in type 2 diabetes patients.

Methods: The PubMed, EMBASE, and Cochrane Review databases were searched up to July 2017. The search strategy was conducted using both keywords and MeSH terms. Two reviewers independently screened the articles, extracted the data, and assessed the quality of studies included. Observational studies were included in the review with no restrictions on age groups or study designs related to the incidence and episodes of hypoglycaemia in type 2 diabetes and meta-analysis was conducted where appropriate. The pooled estimate for incidence and episodes of hypoglycaemia in type 2 diabetes patients was calculated using the random effect model with 95% confidence interval (CI).

Results: Our search strategy generated 31 288 citations, of which 25 studies representing 9 812 522 type 2 diabetes patients matched our inclusion criteria and were included in meta-analysis. The pooled episodes estimate for hypoglycaemia was 139.42 episodes per 100 patient-years (95% CI, 134.92-143.92). The pooled episodes estimate stratified by treatment regimen was 323.30 per 100 patient-years (95% CI, 196.79-449.80) for insulin-based therapy and 125.24 per 100 patient-years (95% CI, 116.00-134.48) for patients receiving a combination of insulin and oral therapy. The pooled incidence estimate of new cases of hypoglycaemia was 5.99 per 100 patient-years (95% CI, 4.17-7.82).

Conclusions: Hypoglycaemia is very common among type 2 diabetes patients. Further studies are needed to investigate the hypoglycaemia-associated risk factors.

146 | Age- and sex-specific incidence of non-traumatic lower limb amputation in patients with type 1 diabetes mellitus in a US claims database

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Background: Patients with type 1 diabetes mellitus (T1DM) are at an increased risk of developing peripheral arterial disease and amputation. There is limited data on age- and sex-specific incidence rates (IR) of lower limb amputation (LLA) in these patients. Such data can be used for comparison of IR of LLA in clinical trials of new T1DM treatments.

Objectives: To estimate age- and sex-specific IRs of LLA in T1DM patients using a US claims database for years 2007 to 2016.

Methods: Using a retrospective cohort study design, patients with T1DM were identified using a modified approach based on a validated algorithm published by Klompas et al during a study period from January 1, 2007, to December 31, 2016, from the Truven MarketScan database. The index date for a patient was defined as the first date on which a criterion of the algorithm was met. The first event of non-traumatic LLA occurring from the index date till the end of the study period was identified by the presence of ICD-9 or ICD-10 procedure codes in any setting. The follow-up of patients ended on the occurrence of LLA, the end of the study period, or enrollment in the database, whichever occurred first. An overall and age- and sex-specific IRs per 100 000 person-years (PY) of LLA and their 95% CIs were calculated.

Results: Of the 387 993 T1DM patients identified during the study period, 51.6% were males, and 18.7%, 30.3%, 33.8%, and 17.2% were in the age groups of 0-19, 20-39, 40-59, and ≥60 years, respectively. The mean (±SD) follow-up from the index date was 2.6 (±2.3) years. The overall IR (95% CI) of LLA, minor LLA (below the ankle), and major LLA (at or above ankle) per 100 000 PY was 129.8 (122.8, 136.9), 97.1 (91.0, 103.1), and 32.8 (29.2, 36.3), respectively. When stratified by sex, males had a higher IR compared with females regardless of the type of LLA (overall: 170.3 [159.1, 181.5] vs 85.9 [77.7, 94.2]; minor: 131.9 [122.1, 141.8] vs 59.2 [52.4, 66.1]; major: 38.4 [33.1, 43.7] vs. 26.7 [22.1, 31.3]). When stratified by age and sex, an increase in overall LLA incidence was observed in both males and females with an increasing age, with the highest incidence reported in patients aged 50-59 years (males: 350.2 [313.2, 387.1]; females: 180.8 [153.8, 207.8]). When stratified by age and sex, a similar pattern was observed for both types of LLA.

Conclusions: Our study showed that the incidence of LLA increased with an increasing age and was almost twice as high among males compared with females with T1DM, warranting further exploration of risk factors among males.

147 | Systematic review of breast cancer and subsequent risk of hypothyroidism

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Background: Breast cancer treatment may increase the risk of late effects, such as hypothyroidism.

Objectives: We conducted a systematic review to investigate the association between breast cancer and breast cancer-directed radiotherapy (RT) and the risk of hypothyroidism in breast cancer survivors.

Methods: Through December 2016, we searched PubMed and EMBASE to identify all papers on breast cancer and subsequent risk of hypothyroidism, restricting to studies comparing women with and without breast cancer, or comparing two breast cancer treatments. One author screened retrieved papers by title and abstract; included papers were reviewed by two authors for eligibility, data extraction, and risk of bias. The main outcome was the confounder adjusted relative risk (RR) for hypothyroidism. We computed effect estimates (EE) where absolute numbers were presented. Random effects meta-analytic models were used to compute summary EE and associated 95% confidence intervals (CI). We used funnel plots to assess publication bias.

Results: From 580 papers screened by title and/or abstract review, 47 papers were fully reviewed for eligibility. We included 10 observational studies conducted in eight different countries between 1985 and 2016. Based on five studies, there was an overall increased risk of hypothyroidism among women with breast cancer compared with women without breast cancer; pooled EE of 1.5 (95% CI: 1.1-2.0). For cancer-directed RT, three studies investigated the risk according to receipt of RT. The results showed an increased risk of subsequent hypothyroidism among breast cancer patients who received radiotherapy compared with breast cancer patients treated without radiotherapy, pooled EE of 2.6 (95% CI: 0.6-11.2). There was evidence of considerable heterogeneity in the result and indications of publication bias in the funnel plot symmetry in both analyses.

Conclusions: Our review suggests a potential association between breast cancer and hypothyroidism. However, the literature is sparse; thus, high-quality studies are needed to enhance knowledge of hypothyroidism as a late effect in breast cancer survivors.

148 | Racial and ethnic disparities in lower extremity amputation among Medicare beneficiaries with diabetic foot ulceration and infection in the United States

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Background: Minority populations experience a disproportionate rate of diabetic foot ulceration (DFU) and major amputation (above the ankle). Prior studies have primarily focused on whites and African Americans (AAs). Little is known about whether disparity exists in the risk of lower extremity amputation among Hispanics and Native Americans (NAs).

Objectives: To examine the risk of major amputation across different races/ethnicities with diabetic foot ulceration and/or infection (DFI) in Medicare.

Methods: A retrospective cohort study included data from a 5% national sample of fee-for-service Medicare beneficiaries with newly diagnosed of DFU and/or DFI from 2011 to 2015. A multivariable Cox proportional hazard model was used to estimate the risk of major amputation across races adjusting for sociodemographic and health status factors. Adjusted hazard ratios (HRs) with 95% confidence interval (CI) were reported.

Results: Among 92 929 Medicare beneficiaries with DFU/DFI (mean age = 71.9 ± 11.9 years, 54.3% female), 77.7% were white, 14.3% were AA, 3.3% were Hispanic, and 0.7% were NA. The incidence of major amputation within 1 year after diagnosis of DFU/DFI was higher for NA (4.1%) and AA (2.9%) than that for Hispanic (1.6%) and white patients (1.0%, $p < 0.0001$). In a multivariable analysis, NAs (HR = 2.42, 95% CI 1.62-3.62) and AAs (HR = 2.17, 95% CI 1.90-2.47) were associated with an increased risk of major amputation compared with white beneficiaries. Other factors significantly associated with major amputation (all $p < 0.0001$) were male gender (HR = 1.80, 95% CI 1.60-2.03), residing in rural regions (HR = 1.58, 95% CI 1.39-1.80), having a disability status (HR = 1.30, 95% CI 1.13-1.49), insulin use (HR = 1.37, 95% CI 1.21-1.57), end-stage renal disease (HR = 2.53, 95% CI 2.11-3.03), peripheral vascular disease (HR = 4.19, 95% CI 3.48-5.04), a higher Elixhauser comorbidities index (HR = 1.07, 95% CI 1.05-1.09), and a higher diabetes complication severity index (HR = 1.17, 95% CI 1.11-1.24).

Conclusions: Racial minority groups, including AAs and NAs, were associated with an increased risk of major amputation compared with white Medicare beneficiaries, after adjusting for diabetes and comorbidity severity. Multidisciplinary limb salvage team to follow up DFU/DFI management may be helpful to address the disparities for amputation among the minorities.

149 | Allergic rhinitis and subsequent risk of cancer among US elderly adults

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Background: Immune response is increasingly recognized as important in the development of cancer. Allergic diseases, eg, allergic rhinitis (AR), are characterized by an increased immune response and may be associated with reduced cancer risk.

Objectives: To examine the association between AR and cancer using administrative data.

Methods: We used the Surveillance, Epidemiology, and End Results (SEER) Medicare linked database to perform a case-control study. We included first cancer cases (N = 1 744 575) diagnosed during 1992-2013 and aged 66-99. Controls (N = 100 000) were matched on race, sex, age, and selection year. Cases and controls had ≥ 1 month Part A/B coverage and ≥ 1 Medicare claim between study entry and 1 year prior to selection. Participants were classified as having AR if there was ≥ 1 inpatient claim (ICD-9 = 477, 4770, 4772, 4778, 4779) or ≥ 2 physician or outpatient claims >30 days apart in Medicare, with claims between study entry and 1 year prior to selection. Controls could be selected more than once or later become a case. Logistic regression adjusted for race, age, selection year, chronic obstructive pulmonary disease (smoking proxy), markers of health care utilization, and income was used to estimate odds ratios (ORs) for each AR-cancer association. We used a Bonferroni correction to account for multiple testing. Sensitivity analyses were performed in participants selected in 2008-2013, with ≥ 1 -month part D (medication) coverage and ≥ 1 part D claim, where AR was confirmed by the presence of ≥ 1 AR-specific medication claim.

Results: AR was present in 8.4% of controls and 7.9% of cases, but proportions varied by cancer site. AR was inversely associated with many cancers including previously reported cancers (eg, colon, OR = 0.87, 95% CI = 0.84-0.90; rectum, 0.85, 0.81-0.89; pancreas, 0.94, 0.90-0.98) and a few novel sites (eg, esophagus, 0.76, 0.71-0.82; cervix, 0.74, 0.66-0.83; uterus, 0.84, 0.80-0.88). We did not replicate a reported inverse association with brain cancer (OR = 1.02, 95% CI = 0.95-1.09). Sensitivity analyses requiring a part D claim for AR-specific medications did not change most inferences, although associations were stronger for a few cancers (eg, pancreas OR = 0.84, 95% CI = 0.74-0.94; cervix 0.58, 0.41-0.84).

Conclusions: Among elderly US adults, AR is inversely associated with subsequent risk for several cancers. Use of SEER-Medicare is an efficient approach for testing associations of medical conditions with cancer, especially for exposures that are stable at older ages.

150 | Proton Pump Inhibitors Prescriptions and Colorectal Cancer Recurrence Risk: a Danish Nationwide Prospective Cohort Study

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Background: Despite advances in prevention, screening, and treatment, colorectal cancer (CRC) remains the fourth most common cause of cancer related deaths globally. Nearly 3.5 million CRC

survivors worldwide are at risk of adverse CRC outcomes, including a recurrence, most commonly in the first few years after CRC diagnosis. The human gut microbiome is one of the most densely populated bacterial communities known to exist. It plays a vital role in the host's gut physiology and potentially contributes to CRC progression. Several previously published studies found that proton pump inhibitors (PPIs) use is associated with gut microbiota diversity and composition in humans. Furthermore, PPIs use was also shown to be associated with an increased risk for initial and recurrent *Clostridium difficile* infection, leading the US Food and Drug Administration to issue a drug safety warning in 2012 regarding this association. Therefore, given the high prevalence of PPIs use in the adult population (30-40%), and their effects on the gut microbiome, the potential influence of PPIs on the clinical course of CRC is of great public health interest.

Objectives: To assess the association of prediagnostic PPI use with the risk of colorectal cancer recurrence.

Methods: Using data from Danish registries, we followed 21 152 patients (5036 with recurrences) diagnosed with stages I-III CRC during 2001-2011 and registered in the Danish Colorectal Cancer Database. We ascertained information on potential confounders from Danish population-based and medical registries. We examined the association between prediagnostic PPIs use 180 days prior to CRC diagnosis and cancer recurrence, controlling for age, sex, year of diagnosis tumor stage, tumor location, treatment, comorbidities, inflammatory bowel disease, and the use of non-steroidal anti-inflammatory drugs, aspirin, and statins.

Results: In our study population, 20% and 25% of patients were PPIs users 1 year before and after cancer diagnosis, respectively. After adjustment for potential confounders, any PPIs prescription 180 days prior to CRC diagnosis was not associated with recurrence (adjusted hazard ratio [aHR] = 1.02, 95% confidence interval [CI]: 0.94, 1.10). Additional ongoing analyses address cancer-specific and all-cause mortality, the use of PPIs postdiagnosis, and different time-lag periods. These results will be presented at the meeting.

Conclusions: Analyses to date suggest that prediagnostic PPI use is not associated with CRC recurrence.

151 | Identifying patients with metastatic castration-resistant prostate cancers (mCRPC) in the SNDS database: Camerra Study

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Background: Management of mCRPC has evolved significantly since 2011. SNDS is the nationwide health care insurance system database covering 99% of the French population. In the absence of a direct marker, the identification of mCRPC patients within the SNDS database relies on the construction of a complex algorithm.

Objectives: To identify prevalent mCRPC patients in the SNDS database in 2014.

Methods: An algorithm for identifying mCRPC patients was build from an extraction of men over 40 years old with an indicator of prostate cancer (long-term disease and diagnosis codes according to the International Classification of Diseases [ICD 10], hospitalizations and procedures and treatments) and having a 5-year health care history without any gap >1 year. The identification of mCRPC patients depends on two indicators: (1) the date of first management of metastases based on specific acts (radiotherapy, hospitalizations notably for chemotherapy, treatments targeting metastases [denosumab, zoledronic acid, radioisotopes, radiofrequencies, etc], or drugs specific to mCRPC [abiraterone acetate, enzalutamide, docetaxel, and cabazitaxel] associated with imaging procedures); (2) the date of castration resistance based on switch between sequences of anti-androgens and LH-RH analogs, surgical procedures (orchiectomy and pulpectomy), or first dispensing of specific treatments for mCRPC following imaging procedures. A patient was identified as having mCRPC when a date of first management of metastases and a date of castration resistance were identified in his history.

Results: 3192 patients with prevalent prostate cancer in 2014 were identified in the 1/97th sample of the SNDS database (EGB), including 499 metastatic and 254 castration-resistant. Of these 3192 patients, 141 were identified as having a mCRPC in 2014. By extrapolation, 468 142 prevalent prostate cancer patients are expected in the SNDS database in 2014. This estimate concurs with that one of the French National Cancer Institute, 508 699 in 2008. Among these expected prevalent prostate cancers, 20 719 should be an mCRPC.

Conclusions: Considering results of this preliminary study, a functional algorithm for identifying mCRPC patients has been constructed according to complex elements and their sequences, giving rise to a first estimate of its prevalence in the French population from the SNDS.

152 | Global burden of cancer: International comparison of cancer epidemic from geographic and economic perspectives

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Background: Cancer is the most serious of the global burden of disease, and it is becoming one of the leading causes of death, second to heart disease. Previous studies have stated that high-income countries tend to have the highest incidence and mortality for all types of

cancer, while geographical factors are also linked to the prevalence of cancer. Only a few studies have explored the relevance of economic/geographical factors to the cancer epidemic integrally.

Objectives: This study aims to explore the diversities of the overall cancer epidemic rates made by geographic and economic variations, respectively, after adjusting gender, population structure, region, and income level.

Methods: This study collected 183 countries' epidemic data from WHO's the GLOBOCAN project and economic classifications data from the World Bank in 2012. We applied ANOVA with linear mixed models to analyze the variations of 3 epidemic rates (incidence, mortality, and prevalence) between 6 regions (Asia, Africa, Europe, North America, South America, and Oceania) and income levels (high income, upper middle income, lower middle income, and low-income). We identified extreme rates and discuss their reasons and implications and make suggestions regarding the situations.

Results: Among high-income countries, counties in different regions had significant variations of cancer epidemics. Using Asia as the reference and gender as the adjustment, Oceania and North America had the highest incidences, Europe had the highest mortality, and North America had the highest prevalence significantly. Africa had the lowest rates for all epidemics but not significantly. Among countries in Asia, using low-income as the reference and gender as the adjustment, upper middle income countries had significant higher incidence, and high-income countries had significant higher prevalence compared with low-income countries, while there was no significant variation of mortality between counties with various income level.

Conclusions: Except gender, the results show that geographic variation is a stronger key factor for global burden of cancer compared with economic variation. Overall, the cancer epidemic is high in North America, Europe, and Oceania, which is middle in Asia and is low in Africa. However, these epidemics are not able to be significant discriminated by economic level.

153 | Assessing predicted mesothelioma incidence trends in the United States

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Background: Despite decreasing incidence rate, mesothelioma is still a public health concern in the United States. Mesothelioma is caused by prior exposure to asbestos, which remains heavily ingrained in US infrastructure.

Objectives: To determine the temporal pattern of mesothelioma by modelling incidence as a function of asbestos trade figures in the United States.

Methods: This is a retrospective ecological study to project future mesothelioma incidence in the United States. A predictive model was built to assess temporal patterns of mesothelioma incidence. The United States was chosen because it has granular data on asbestos trade; it was a major asbestos consumer with high mesothelioma incidence and using a single country avoided having to control for

macroeconomic heterogeneity. We considered asbestos figures from 1956 to 2014 from the US Geological Survey as an approximation for asbestos exposure. To account for lag effects, asbestos exposure was matched to mesothelioma incidence with a 30-year latency period. The outcome is converted annual mesothelioma incidence count from 1986 to 2014 from SEER. The fitted model predicts incidence for 2015 to 2045, with a graphical depiction of temporal trends. The predictive model was fit and evaluated using generalized linear modelling and stepwise AIC. We used the variance inflation factor to control for multicollinearity. Predictive performance was assessed internally using tenfold cross-validation and externally by inputting WHO mesothelioma mortality counts in the United States from 1999 to 2014 to the best fitting model. Mortality was used as an approximation for incidence because mesothelioma has a deadly prognosis.

Results: The best model included domestic asbestos production ($p < 0.05$) and the square root of asbestos exports ($p < 0.05$), transformed to maintain linearity. No import variables were included in the best model. The model predicts that mesothelioma incidence will drop from 3040 peak cases in 2000 to 2735 (95% prediction interval: 2674, 2797) cases by 2020 and to 2540 (2488, 2593) cases by 2040. Graphical overlays of SEER incidence count and WHO mortality count show that the model is generalizable and not specific to the SEER incidence, given a degree of variability.

Conclusions: Despite no new asbestos entering the United States, the model suggests a lingering burden of mesothelioma. A possible interpretation is that another factor, possibly the accumulation of asbestos in man-made structures, could contribute to prolonged decline of mesothelioma incidence. However, there remains a potential spurious statistical effect.

154 | Estimating the incidence rate of advanced colorectal cancer in Germany based on claims data

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Background: The incidence rate of advanced cancer stages is an important parameter, eg, as a surrogate endpoint to estimate the effectiveness of cancer screening programs. However, information from German cancer registries on tumor stage is often incomplete, especially regarding lymph node involvement and presence of metastases (~30% missings).

Objectives: To explore the potential of estimating the incidence rate of advanced cancer stages based on German claims data, exemplified by colorectal cancer (CRC).

Methods: We used a subsample (~6 million persons) of the German Pharmacoepidemiological Research Database (GePaRD) containing claims data from statutory health insurance providers in Germany. We developed an algorithm based on inpatient and outpatient diagnosis codes (ICD-10 GM) for CRC (C18-21) and secondary malignant neoplasms (C77-C79) to identify incident cases of advanced CRC

(UICC III or IV) diagnosed between 2010 and 2014. We calculated age-standardized incidence rates (ASIR) and age-specific rates per 100 000 persons for each calendar year stratified by sex.

Results: In 2014, the ASIR of advanced CRC in men and women was 18.4 and 13.0 per 100 000, respectively, accounting for ~40% of the total CRC incidence in men and women. The age-specific rates were 6 times (men) and 5 times (women) higher in persons aged 75-79 vs 50-54 years. Compared with 2010, the ASIR in 2014 was ~20% lower in men and women.

Conclusions: The incidence rate of advanced CRC in our study showed plausible patterns, also regarding time trends and the distribution by sex and age. Claims data thus appear suitable to identify advanced CRCs which is an important pre-requisite for various research questions.

155 | International comparison of 10 common cancers' incidence and mortality between 12 Asian countries

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Background: The resource allocation of health care has generated wide interest in for cancer treatment in recent years. In addition to understanding the national past epidemiological trends of the various types of cancer, the results of international comparisons on diverse cancers' epidemiology can also serve as a reference for rationalizing the allocation of cancer medical resources in a country.

Objectives: Focusing on countries in Asia, this study aims to explore the diversities of the epidemics of overall and common cancer types between countries and to furtherly compare the medical capacity of different countries in various types of cancer.

Methods: This study selected 12 Asian countries and acquired their epidemic data (age-standardized incidence and mortality by gender) of multiple cancers from WHO's the GLOBOCAN project report database and Taiwan cancer registry annual report database in 2012. These countries include China, India, Indonesia, Japan, Malaysia, Mongolia, Philippines, South Korea, Singapore, Taiwan, Thailand, and Vietnam. The common cancer types include oral, lung, female breast, liver, oesophagus, stomach, colorectal, prostate, cervix uteri, and melanoma of skin cancers.

Results: Among 12 Asian countries, South Korea (307.8 per 100 000 population) and Taiwan (304.5) had the highest age-standardized incidences of overall cancer, followed by Japan, Singapore, and Mongolia. Surprisingly, China had the highest incidences of lung (36.1) cancer; Mongolia had significantly high incidences of liver (78.1), oesophagus (21.2), and cervix uteri (24.3) cancers; Taiwan had significantly high incidences of oral (22.6) and melanoma (9.8) cancers; Singapore had the highest incidence of prostate (7.4) cancer. In terms of age-standardized mortality, Mongolia (161.0) had the highest mortality of

overall cancer, followed by Taiwan (131.3) and China (122.2). However, Malaysia (18.9) and Philippines (17.8) had the highest mortality of female breast cancer; Philippines (11.3) and Indonesia (9.8) had the highest mortality of prostate cancer; India had the highest mortality of cervix uteri (12.4) cancer. Overall, South Korea, Taiwan, Japan, and Singapore have better medical capacity of cancer treatment than others.

Conclusions: China should pay more attention on prevention and treatment of lung cancer; Taiwan needs to come up with strategies for oral cancer prevention; Mongolia has to overcome the problems of digestion-related cancers; cervix uteri cancer's mortality needs to be improved by India.

156 | Incidence of marrow neoplasms in breast cancer survivors: A national population-based cohort study

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Background: Patients with a history of cancer are at a higher risk of certain types of marrow neoplasms (MN) including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). However, information on the frequency of these MN after cancer in real life are scarce, especially in the recent context of increased cancer survival. In addition, little is known about the incidence of other MN types after cancer.

Objectives: The aim of this study was to estimate the incidence of the various types of marrow neoplasms in breast cancer (BC) survivors in France.

Methods: Data from French National Health Data System (SNDS) were used. All female patients aged 20 to 85 years with an incident primary breast cancer between 2006 and 2015 were included and followed until MN occurrence, death, or December 31, 2016. The main outcomes were cases of MN occurring at least 6 months after breast cancer diagnosis and identified in the database using ICD-10 codes of hospital discharge and long-term disease diagnoses. Incidence rates of the various types of MN in the breast cancer cohort were estimated and compared with those in the general population using direct age-standardization.

Results: 439 704 female patients were included (mean age, 59.3 years) and followed for a mean of 5.2 years. Overall, 3012 cases of MN occurred: 509 acute myeloid leukemia (AML), 832 myelodysplastic syndrome (MDS), 365 multiple myeloma (MM), 123 Hodgkin lymphoma (HL), 810 non-Hodgkin lymphoma (NHL), 106 lymphocytic leukemia/lymphoma (LLL), and 267 myeloproliferative syndrome (MPS). Mean time between BC diagnosis and MN occurrence was 3.9 years overall, ranging from 3.5 years for AML to 4.2 years for MPS. Crude incidence rates per 100 000 person-years of the different types of MN were 22.2 (95% CI 20.3-24.2) for AML; 36.3 (95% CI, 33.9-38.9) for MDS; 15.9 (95% CI, 14.3-17.6) for MM; 5.4 (95% CI, 4.5-6.4) for

HL; 35.4 (95% CI, 32.9-37.9) NHL; 4.6 (95% CI, 3.7-5.6) for LLL; and 11.7 (95% CI, 10.3-13.1) for MPS. Compared with the general population, these incidence rates were higher for AML (standardized incidence rate ratio, SIRR 2.5; 95% CI, 2.2-2.9), MDS (SIRR 4.5; 95% CI, 3.9-5.1), MM (SIRR 1.1; 95% CI, 1.0-1.3), and LLL (SIRR 1.8; 95% CI, 1.2-2.7), while they did not differ for the other types of MN.

Conclusions: Incidences of AML and MDS and, to a lower extent, MM and LLL are higher among breast cancer survivors than in the general population. Further investigations are necessary to assess the role of cancer therapies in explaining these increases.

157 | Recording of colorectal cancer in the United Kingdom and comparison of cancer registrations with diagnoses in other routinely collected data sources—A systematic review of the literature

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Background: Cancer registry data in the United Kingdom (UK) have been used in several randomized controlled trials showing a protective effect of low-dose aspirin against colorectal cancer (CRC). The utility of these CRC registration data is dependent on the extent that true incident cases of CRC are captured.

Objectives: To systematically review studies comparing UK CRC registrations with recorded CRC diagnoses in other UK sources of routinely collected patient data.

Methods: PubMed, Embase, and Cochrane Library databases were searched (up to July 2016) to identify studies that compared CRC registrations in at least one UK regional cancer registry with other sources of patient data in the UK. For inclusion, studies were required to report on either the extent of missingness of incident CRC diagnoses in UK cancer registration data and/or verification of diagnoses with the other data source.

Results: Four studies were included of which two studies evaluated the level of missingness in nationwide cancer registrations (2001-2007), one comparing against electronic primary care data (general practice research database, GPRD), the other against electronic secondary care data (Hospital Episode Statistics; HES). Low levels of missingness were reported: 0.2% (43/1882) and 1.9% (4027/206 794) when comparing against GPRD and HES, respectively. In addition, 19 of CRC registrations in THIN were not found in GPRD, a 1.1% missingness level for CRC in GPRD based on registration data. Two studies verified regional CRC registrations against other sources. Of these, one compared Northern Ireland CRC registrations (1993-1995) with hospital paper case notes, reporting a verification of 72%. The other study compared Scottish CRC registrations (1993) against primary care case notes where 91.2% (198/217) were found to have recorded histological verification. Quality control measures by individual registers were also found to be in place to ensure record correctness.

Conclusions: UK cancer registrations have a high level of completeness and verification for CRC diagnoses compared with other UK data sources.

158 | Prevalence of co-existing chronic health conditions among cancer patients

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Background: Cancer patients often have co-existing chronic health conditions. Nearly two-thirds of patients with cancer had at least one disease in addition to cancer at the time of cancer diagnosis. However, there is a gap in research on the prevalence of chronic conditions among cancer patients in Saudi Arabia.

Objectives: Our study is designed to fill a knowledge gap in the prevalence of chronic health conditions among cancer patients and to assess the number of co-existing chronic conditions among cancer patients.

Methods: A retrospective cross-sectional study design was conducted using data extracted from the electronic health records database for a period of 12 months in a tertiary teaching hospital in Saudi Arabia. Adult patients (age ≥ 18) with cancer diagnosis were included in this study. We identified the prevalence of co-existing chronic conditions among patients with different types of cancer. Descriptive analysis was carried out to describe the data. Frequency and percentage were used to describe categorical variables. The prevalence of chronic health conditions was assessed in a cross-sectional manner. Subgroup analysis was conducted to assess the prevalence of chronic health conditions among older patients. Statistical analysis software (SAS[®] 9.2) was used to analyze the study data.

Results: The study population composed of (n = 699) patients with documented diagnosis of cancer. The most common cancer type among the study population was breast cancer (33%), followed by colon cancer (27.6%), rectal cancer (14.4%), and lymphoma (7.7%). The most common cancer type among older patients was colon cancer (32.1%), followed by breast cancer (22.5%), rectal cancer (14.8%), and lymphoma (7.1%). The majority of the study cohort was women and older patients (age > 60 years old). Almost half of patients with cancer have two or more co-existing chronic conditions in addition to cancer. The most common chronic condition was anxiety (52.2%), followed by hypertension (38.2%), diabetes (27.0%), and dyslipidemia (18.6%).

Conclusions: While anxiety was found the most profound diagnosis, metabolic risk factors (hypertension, diabetes, and dyslipidemia) were the highest among patients with different types of cancer. Further studies are needed to investigate the impact of chronic conditions on health outcomes among patients with cancer.

159 | Chemoradiotherapy treatment patterns and 1-year survival rate among patients with unresectable, stage III non-small cell lung cancer: Time trends from 2009 to 2014

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Background: Non-small cell lung cancer (NSCLC) accounts for 85% of newly diagnosed lung cancer cases. One-third of NSCLC patients (pts) are diagnosed with unresectable stage III disease. The standard of care for these pts is concurrent chemoradiotherapy (CRT) with curative intent followed by active surveillance, but efficacy is poor. Until recently, there have been no major therapeutic advances made.

Objectives: To assess duration of treatment (DoT) and 1-year (yr) survival rate (SR) across yrs in pts with unresectable stage III NSCLC treated with CRT.

Methods: This retrospective study used linked Surveillance, Epidemiology, and End Results (SEER)-Medicare claims data from 2009 to 2014. Pts aged ≥ 65 yrs with a diagnosis of stage III unresectable NSCLC, ≥ 1 claim for first chemotherapy use ("index date") within 90 days of diagnosis, use of radiation during first regimen as defined by SEER, and ≥ 6 months continuous eligibility prior to index were included. Treatment patterns were assessed. Since pts initiating CRT in early 2014 would have ≤ 1 yr of follow-up, 1-yr SR was reported. DoT and survival over 1 yr were modeled using a linear mean model and Cox proportional hazards model, respectively, to assess change across index yr categorized as 2009-2010, 2011-2012, and 2013-2014. Models were adjusted for baseline clinical and demographic characteristics.

Results: Among 2692 study pts, 60% were diagnosed with stage IIIA NSCLC and 40% with stage IIIB. Mean age at diagnosis was 73.5 yrs, 85% were White, and 45% were female. 54% of pts had predicted ECOG score of 0-2, and 45% had squamous histology type. Consistently, the most frequent first chemotherapy regimens were carboplatin + paclitaxel (63%), cisplatin + etoposide (11%), and carboplatin + pemetrexed (5%). DoT (mean $\pm$ SD) was similar across yrs with 91 ± 53 days for pts initiating treatment in 2009-2010, 87 ± 54 for 2011-2012, and 89 ± 47 for 2013-2014 ($p = 0.261$). While 41% of pts died during their first regimen, 38% went on to receive a new agent after 91 ± 52 days on their first regimen. 1-yr SR was 56% for pts initiating treatment in 2009-2010, 58% for 2011-2012, and 58% for 2013-2014 and did not differ across index yrs after adjustment ($p = 0.827$).

Conclusions: Chemotherapy regimens have not changed, and 1-yr SR in stage III unresectable NSCLC pts treated with CRT was stagnant from 2009 to 2014. The lack of improvement in SR observed across yrs indicates an unmet need for more effective therapy for stage III unresectable NSCLC pts.

160 | Disease burden of patients with advanced renal cell carcinoma in Korea

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Background: Although patients with advanced renal cell carcinoma (aRCC) were associated with relatively high levels of resource use compared with other types of renal cell carcinoma, only few studies estimate its costs.

Objectives: To assess the disease burden in patients with aRCC who had at least one vascular endothelial growth factor receptor (VEGFR)-targeted therapy based on current clinical practice. Disease burden is defined as the costs of routine care, adverse events (AEs), productivity loss, and end-of-life care.

Methods: A survey with five Korean oncology experts in major hospitals was conducted to estimate the use of best supportive care (BSC), outpatient visits, hospitalization, diagnostic tests, pain management, and medications for routine care and AEs. The BSC was defined as palliative radiotherapy, metastasectomy, use of bisphosphonate, and nutrition support. The AEs of Grades 3 or 4 of Common Terminology Criteria for Adverse Events (CTCAE) were included in the analysis. The number of missed days from work and the rate of hospice use were also asked to examine the costs of productivity-loss and end-of-life care, respectively. Costs were in 2018 Korean wons.

Results: The cost of BSC was estimated at \$2,686 for the rest of one's life. Health care utilization was differed according to disease stage. In progression free survival (PFS), on average, one outpatient visit, 0.5 days of hospitalization in a general ward, one blood test, 0.5 times of computed tomography (CT), 0.6 times of magnetic resonance imaging (MRI), and 5.6 days of pain management were required per month. In progressed disease (PD), on average, 1.3 outpatient visits, 2 days of hospitalization in a general ward, 0.1 days of hospitalization in an intensive care unit, one blood test, 0.6 times of CT, 0.6 times of MRI, 11 days of pain management were required per month. Among AEs occurred in patients with aRCC, the most burdensome AE was pneumonitis costing about \$657 per episode per patient. The number of missed days from work were estimated at 8 days and 22 days per month and it cost approximately \$116 and \$312 per month in PFS and PD, respectively. At end-of-life, on average, 95% of aRCC patients were admitted to a hospice for 47 days, and end-of-life cost was estimated at approximately \$13,040 per patient.

Conclusions: Findings of this study provide insight on health care resource use associated with routine care, management of AEs and end-of-life care as well as productivity loss in patients with aRCC who had at least one VEGFR-targeted therapy.

161 | Insight into the role of the general practitioner in the management of colorectal cancer: Record linkage of the Netherlands Cancer Registry and the general practitioner database of the PHARMO Database Network

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Background: Little information is available on the role of the general practitioner (GP) in colorectal cancer (CRC) care.

Objectives: To establish a link between the Netherlands Cancer Registry (NCR) and the GP database of the PHARMO Database Network and creating a CRC-GP population.

Methods: A linkage was performed between the NCR—a population-based registry of newly diagnosed cancer patients in the Netherlands—and the GP database of the PHARMO Database Network which comprises data from electronic patient records registered by GPs, including information on diagnoses/symptoms, laboratory test results, referrals, and health care product/drug prescriptions. After pairing records in both databases on gender and birth year, a linkage weight was calculated based on first initial, first letter last name, 4-digit zip code, and presence/absence of cancer-related events as singular variables. Patients diagnosed with CRC between 1998 and 2014 were selected, resulting in a CRC-GP population. The representativeness of this population to the total NCR population was evaluated by comparing the distribution of gender, age at tumour diagnosis, tumour stage, and tumour site.

Results: In total, there were more than 19 000 CRC patients in the linked CRC-GP population, of which 66% were diagnosed with colon cancer, 30% with rectum cancer, and 4% with rectosigmoid cancer. These patients were representative for the cancer patients included in the total NCR. The difference in percentage between these two populations showed that patients who were linked tended to be somewhat younger (68.2 years vs 69.7 years) and were slightly less often diagnosed with an advanced tumour stage (19% vs 21%).

Conclusions: The linked CRC-GP population is representative of the total NCR population. The CRC-GP population will create more insight into the role of the GP in CRC care and will give more opportunities to monitor the patients before, during, and after cancer diagnosis.

162 | Incidence of nonmelanoma skin cancer and related procedures—An analysis of a US medical claims database, 2012 and 2014

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Background: Nonmelanoma skin cancer (NMSC) is the most common form of malignancy among Caucasians and the most common cancer worldwide. NMSC is not captured in US cancer registries; thus, the incidence of NMSC in the US population has been estimated using survey or medical claims data. These estimates have either become dated or were derived from an elderly population.

Objectives: The objectives in this study are (1) estimate overall and age-, gender-, and region-specific incidence rates (IR) of NMSC from 2012 to 2014; and (2) estimate the proportion of NMSC-related procedures among NMSC cases.

Methods: MarketScan[®] Commercial Claims and Medicare Supplemental and COB Databases were used in this analysis. To be considered a case, patients were required to have 2 years of enrollment (1-year lookback plus case year) for each year of 2012–2014 and have at least 2 claims of NMSC (ICD-9-CM series 173 [invasive nonmelanoma cutaneous malignancy] and 232 [in situ nonmelanoma cutaneous malignancy] diagnosis codes occur on the same body location, or include one site specific code and one “other” or “unspecified” site code within a 90-day period between Jan 2012 and Dec 2014). Multiple events could occur when the case defining diagnoses are coded for different body locations or at least 365 days have passed since the last medical encounter.

Results: The incidence rates (IR per 100 000 population) of NMSC for years 2012, 2013, and 2014 were 729 (95% CI 726–732), 833 (95% CI 830–837), and 816 (95% CI 813–820), respectively. Over the same period, the proportion of NMSC-related procedures within 90 days of NMSC diagnosis were 72%, 70%, and 75%, respectively. Patients aged 65+ accounted for 53–56% of cases with age-specific IR of 4080 (95% CI 4057–4102) to 4566 (95% CI 4538–4593) in 2012 and 2014. Males accounted for ~58% of cases with IR of 861 (95% CI 857–866) to 962 (95% CI 957–968). Cases in the south accounted for 37–40% of NMSC with IR of 800 (95% CI 795–805) to 875 (95% CI 869–881). The most frequent site of NMSC was “other and unspecified parts of face” (31–34%) followed by “trunk” (~15%) and “upper limb, including shoulder” (15–16%).

Conclusions: The proportion of NMSC-related procedures accounted for nearly three quarters of all NMSC cases over the study period. Patients with higher IRs for NMSC were elderly, male, and/or living in the south. Future estimates on the incidence of NMSC over time could benefit from using longer periods of observation or different patient populations.

163 | Non-aspirin NSAID use and contralateral breast cancer risk

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Background: Preclinical studies suggest that COX-2 inhibition suppresses development of breast cancer. Observational studies of non-aspirin NSAID use and breast cancer risk have, however, provided inconsistent results. Contralateral breast cancer (CBC) among breast cancer survivors may serve as a useful high-risk model to identify preventive drug effects against breast cancer.

Objectives: To examine the association between post-diagnosis non-aspirin NSAID use and risk of CBC.

Methods: We identified patients with primary breast cancer from the Danish Breast Cancer Group database between 1996 and 2012. Data on non-aspirin NSAID use, CBC diagnoses, and potential confounding factors were obtained from the prescription and various other nationwide Danish registries. Time-varying use of post-diagnosis non-aspirin NSAID was defined as two or more prescriptions with a 1-year exposure lag from the second prescription. Using Cox proportional hazard regression models, we estimated age- and multivariable adjusted hazard ratios (HRs) for CBC and 95% confidence intervals (CIs). We further evaluated various patterns of non-aspirin NSAID use, such as duration and intensity, and stratified according to COX-2 selectivity. In addition, we examined potential effect measure modification by estrogen receptor (ER) status of primary breast cancer or CBC.

Results: The study cohort consisted of 52 723 patients with breast cancer. Among these, 1440 were diagnosed with CBC during a median follow-up of 4.8 years. About one-third (36%) of the breast cancer patients filled two or more non-aspirin NSAID prescriptions during follow-up. We observed no association between post-diagnosis non-aspirin NSAID use and CBC risk (HR: 0.98, 95% CI: 0.87–1.11). Stratification according to COX-2 selectivity revealed similar HRs for COX-2 selective (HR: 1.03, 95% CI: 0.85–1.24) and non-selective (HR: 0.97, 95% CI: 0.82–1.13) non-aspirin NSAIDs. Among women with ER-negative primary breast cancer, post-diagnosis non-aspirin NSAID use was associated with a slightly reduced risk of CBC (HR: 0.82, 95% CI: 0.63–1.08).

Conclusions: In this large nationwide cohort study of Danish breast cancer patients, post-diagnosis non-aspirin NSAID use was not associated with an overall reduced risk of CBC. However, the potential inverse association between post-diagnosis non-aspirin NSAID use and CBC risk observed among women with ER-negative breast cancer warrants further investigation.

164 | The association between statins initiated after a colorectal cancer diagnosis and mortality in a cohort with stage I–III colorectal cancer

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Background: While it has been hypothesised that statin use may be associated with reduced cancer mortality, a recent meta-analysis of post-diagnostic statin use and colorectal cancer (CRC) mortality suggests that statins are not associated with statistically significant

reductions in cancer mortality (HR 0.84, 95% CI 0.68, 1.04). However, the studies included had varying methodological rigor.

Objectives: To further address this question, we examined the association between de novo statin use and CRC mortality and all-cause mortality in a cohort with stage I-III CRC. We also stratified by statin exposure intensity (high/low), type of statin received (hydrophilic/lipophilic/both), and by colorectal cancer site (colon/rectum).

Methods: A cohort of 7544 individuals with newly diagnosed stage I-III CRC were identified from 2001 to 2011, from the National Cancer Registry of Ireland. Post-diagnostic statin initiators were identified from linked pharmacy claims data. Time-varying, multivariate Cox regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for cancer-specific and all-cause mortality (adjusting for age, sex, smoking status, socioeconomic status, comorbidity score, tumour stage, tumour grade, receipt of chemotherapy/radiotherapy/surgery, vitamin D, aspirin, NSAID, and anti-diabetic medication use).

Results: We identified 828 statin initiators, post CRC diagnosis. Statin use initiated after a CRC diagnosis was not associated with a reduction in cancer-specific (HR 0.96, 95% CI 0.78, 1.19) or all-cause mortality (HR 1.04, 95% CI 0.78, 1.19). Results remain unchanged in stratified analyses. The mean follow-up time was just over 4 years, and the mean time to treatment was 2.6 years.

Conclusions: In this population-based cohort of people with stage I-III CRC, new-use of statins after a diagnosis was not associated with reductions in cancer-specific or all-cause mortality.

165 | Lower gastrointestinal bleeding and risk of colorectal cancer in users and non-users of low-dose aspirin

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Background: Lower gastrointestinal (GI) bleeding is a symptom of colorectal cancer (CRC). Aspirin may reduce CRC risk by causing premalignant lesions to bleed thereby bringing patients to medical attention at a stage where cancer development can be prevented.

Objectives: We examined the risk of CRC in users and non-users of low-dose aspirin diagnosed with lower GI-bleeding.

Methods: For 2004-2011, we used the Danish National Patient Registry to identify all patients with a first-time hospital-based diagnosis of lower GI bleeding without a history of cancer or inflammatory bowel disease. We categorized patients according to use or non-use of low-dose aspirin before the diagnosis of GI bleeding. We followed the patients to identify incident CRC. We computed absolute risks of CRC, treating death as competing risk and calculated age-, sex-, and calendar-period standardized incidence ratios (SIRs) by comparing observed cancer incidence among patients with lower GI bleeding to that expected based on national cancer incidence during the study period.

Results: Among 33 886 patients with lower GI bleeding, 4866 (14.4%) patients were users of low-dose aspirin (53% male). The median age at diagnosis was 75.6 years in users and 55.7 years in non-users. We observed 1265 CRCs in the entire cohort. After 5 years of follow-up, the risk of colon cancer was 3.5% (95% CI: 2.94-4.05) in users and 2.1% (95% CI: 1.91-2.25) in non-users, while the risk of rectum cancer was 2.2% (95% CI: 1.82-2.66) in users and 1.6% (95% CI: 1.42-1.71) in non-users. SIRs of colon cancer in users and non-users were 16.9 (95% CI: 14.21-20.03) and 21.6 (95% CI: 19.74-23.66) after 1 year, 1.2 (95% CI: 0.68-1.81) and 1.4 (95% CI: 1.14-1.80) within 1-<5 years, and 1.7 (95% CI: 0.47-4.45) and 0.9 (95% CI: 0.47-1.67) during 5-<8 years of follow-up, respectively. For rectal cancers, the corresponding SIRs in aspirin users and non-users were 27.6 (95% CI: 22.52-33.59) and 37.5 (95% CI: 33.96-41.29) after 1 year and 0.4 (95% CI: 0.09-1.22) and 0.8 (95% CI: 0.51-1.24) during 1-<5 years of follow-up. During 5-<8 years of follow-up, no diagnosis of rectal cancer were observed among low-dose aspirin users, whereas 2 rectal cancers were observed among non-users.

Conclusions: After standardization, aspirin users with lower GI bleeding had a lower estimated relative risk of CRC than non-users. These findings indicate that aspirin may contribute to reduce CRC risk by causing premalignant polyps to bleed, thereby bringing patients to medical attention before manifest cancer.

166 | Statin use is associated with elevated levels of fasting serum insulin and insulin resistance, and increased risk of type 2 diabetes

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Background: Several studies evaluated the association between statins and incident diabetes, but most lack details; the associations between statins use and glycemic traits are unclear.

Objectives: To investigate the associations of statins use with glycemic traits and incident type 2 diabetes.

Methods: Using the prospective population-based Rotterdam Study, we included 9535 individuals free from diabetes at baseline (>45 years) for whom data were available on both exposure and disease during the study period between 1997 and 2012. Linear regression analysis was applied to examine the cross-sectional associations between statins use and glycemic traits including serum fasting glucose and insulin levels and insulin resistance. In a longitudinal follow-up study, using Cox regression model and applying time-dependent exposure to statins, we determined adjusted hazard ratios (HRs) for incident type 2 diabetes. The associations were adjusted for potential baseline confounding factors using two models including: model 1 adjusted for age and gender, cohort (RSI, II and III), smoking status, alcohol consumption, physical activity, and education level and model 2 additionally adjusted for BMI and hypertension. In a series of sensitivity analyses, the model 2 was further adjusted for (i) TC,

or (ii) HDL-C, LDL-C, and TG, (iii) family history of diabetes, and (iv) using proton pump inhibitors (PPIs) at baseline. We further tested an interaction between statin ever use and serum fasting glucose levels.

Results: The mean age at baseline was 64.3 ± 10.1 year, and 41.7% were men. In the fully adjusted model, compared with never users of statins, baseline use of statins was associated with higher levels of serum fasting insulin (β , 0.07; 95% CI: 0.02-0.13) and insulin resistance (β , 0.09; 95% CI: 0.03-0.14). Current use of statins during the study period was associated with a 1.47-fold increased risk of incident type 2 diabetes (HR, 1.47; 95% CI: 1.12-1.94). This risk was more prominent in subjects with impaired glucose homeostasis and in overweight/obese individuals.

Conclusions: Individuals using statins seem more prone to develop hyperglycemia, insulin resistance, and eventually type 2 diabetes. Because the benefit-risk ratio of statins in preventing cardiovascular disease remains favorable, rigorous preventive strategies such as glucose control and weight reduction in patients when initiating statin therapy might help minimizing the risk of diabetes.

167 | Risk of age-related macular degeneration in aspirin uses

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Background: Aspirin is used worldwide for both prevention of cardiovascular diseases and pain control. It brings to some undesired side effects, such as bleeding. Many population-based studies reported higher risk of AMD after aspirin use, though few randomized control studies not.

Objectives: To investigate the risk of AMD in aspirin users.

Methods: This is a retrospective population-based cohort study using the LHID from 2000, 2005, and 2010 in NHIRD. We selected persons who were older than 45 years old in the LHID datasets consisted of 3 million population. The index date as the first prescription date of aspirin in the outpatient department. The comparison group included patients without aspirin use and matched to the aspirin group by age (± 2 years old), gender, and index year in a ratio of 4 to 1. Both groups had same exclusion criteria as followings: 1. at least 1 year of NHI enrollment before the index date, 2. previous history of any diagnosis of AMD by ICD-9-CM codes of 362.5X, and 3. previous use of aspirin (defined as 180 days before the index date). We primarily aimed to estimate the incidence of AMD (ICD-9-CM codes: 362.50-52, 362.57). Secondary outcomes were neovascular AMD (ICD-9-CM: 362.52) and other AMD. The aspirin users were followed up to AMD diagnosis, death, dis-

enrollment of NHI, and the last day of 2013 if no events mentioned above incurred. The comparison group had same censored criteria as the aspirin users. But whenever the aspirin was prescribed to the persons in the comparison group, he/she would be censored. Kaplan-Meier survival curves were used to estimate the time to the events changes and to examine the differences in survival curves between aspirin group and comparison group. HRs and 95% CIs derived from Cox proportional hazard model were used to estimate the incidence of events. We also used propensity score to balance the covariates of these two groups and measure the HRs after PS was applied.

Results: We included 204 085 patients in the aspirin-user group and 478 048 patients in the non-aspirin-user group. Male gender (50.91%) was predominate in aspirin-user group. When univariate Cox regression model was applied, the HR was 2.85 (95% CI, 2.75 - 2.96), while the multivariate Cox model showed HR, 2.54 (95% CI, 2.44-2.65). The incidence of AMD in aspirin uses was 11.95 per thousand person-year, and the incidence in non-aspirin users was 3.92. After PS matching, with 174 129 patients in both groups, the HR was 2.38 (95% CI, 2.25-2.52).

Conclusions: Aspirin users had a higher risk of having AMD compared with non-users.

168 | Plasma potassium and the risk of mortality: A time-dependent analysis from the Stockholm Creatinine Measurements (SCREAM) project

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Background: The clinical recommendation to maintain circulating potassium (K^+) within a narrow range was derived from cross-sectional studies of high-risk populations and single K^+ measurements.

Objectives: This study aims to better quantify the mortality risk associated with K^+ over time by accounting for time dependent confounding factors.

Methods: A retrospective longitudinal cohort study including all patients undergoing plasma K^+ testing in outpatient care in Stockholm, Sweden, during 2006-2011. Cox regression models with restricted cubic splines were used to quantify all cause and cause specific mortality (cardiovascular and non-cardiovascular) associated with K^+ levels over time adjusting for time dependent confounding factors including eGFR measurements, medication use, and comorbidities.

Results: 881 551 patients (median age 54 years, 55% women) contributed with 3.29 million K^+ measurements during a median follow-up of 3.4 (IQR 1.9-4.4) years. 60 243 deaths were registered, of which 22 288 were attributed to cardiovascular causes. Median K^+ increased as eGFR decreased (from 4.0 [3.8-4.3] for eGFR > 90 ml/min to 4.4 [4.1-4.8] for eGFR < 30 ml/min). A U-shaped association was observed between plasma K^+ and mortality with the lowest mortality

risk observed for K^+ within 4.0-4.4 mmol/L (for instance, the HR was 1.10 (95% CI 1.06-1.13) for $K^+ > 4.4$ -4.6 mmol/L, 7.1 (6.12-8.24) for $K^+ > 6$ mmol/L, 1.13(1.10-1.16) for $K^+ > 3.8$ -4.0 mmol/L, and 8.93 (8.17-9.75) for $K^+ < 3$ mmol/L). This was true for both cardiovascular and non-cardiovascular causes of death, but the associations were stronger for non-cardiovascular mortality.

Conclusions: In this large health care-based study, the relationship between K^+ and mortality was U-shaped, with an optimal plasma K^+ range narrower (4.0-4.4 mmol/L) than current clinical thresholds. Future studies are needed to determine whether interventions targeted at maintaining plasma K^+ within a narrow normal range can improve outcomes.

169 | Distribution of CHA₂DS₂-VASC scores in patients with atrial fibrillation treated with rivaroxaban in primary vs secondary care settings

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Background: Since its incorporation in the European Society of Cardiology guidelines in 2010, the CHA₂DS₂-VASC score is widely used to characterise the risk of stroke in patients (pts) with atrial fibrillation (AF). It is frequently calculated in pharmacoepidemiological studies through retrospective application of the component criteria included in the risk score. CHA₂DS₂-VASC Scores of 0, 1, or ≥ 2 indicate low, moderate, or high stroke risk, respectively.

Objectives: To describe the distribution of CHA₂DS₂-VASC scores and individual stroke risk components in two cohorts of pts prescribed rivaroxaban for AF in primary (1°) vs secondary (2°) care.

Methods: Two PASS were conducted to investigate the safety of rivaroxaban in pts with AF in 1° care (modified-prescription event monitoring) and 2° care (specialist cohort event monitoring) (2012-2016). Baseline characteristics were provided by general practitioners (1° care) and specialist prescribers (2° care) using customised questionnaires. An algorithm was used to compute a CHA₂DS₂-VASC score (0-9) for each pt from fixed response options or open questions, according to published guidelines.

Results: The response rate for baseline questionnaires was lower in 1° care vs 2° care (22.3% vs 99.7%). The 1° care cohort consisted of 10225 pts with a primary indication of AF (median age 78 yrs [IQR 70-84]; 5253 [51.4%] male). The median CHA₂DS₂-VASC score was 4 (IQR 3-5) reflecting a high risk of stroke. The 2° care cohort consisted of 965 pts with a primary indication of AF (median age 76 yrs [IQR 69-83]; 517 [53.6%] male), with a median CHA₂DS₂-VASC score of 4 (IQR 3-6). There were a higher proportion of pts with a score of 6-9 in 2° care vs 1° care. The proportions of pts in 1° care vs 2° care with each criterion were age 65-74 yrs (25.7% vs 25.8%) ≥ 75 yrs (61.8% vs 58.0%), female (48.6% vs 46.5%), congestive heart failure/left ventricular dysfunction (14.3% vs 14.6%), history hypertension (82.6% vs 73.2%), history stroke, transient ischaemic

attack (TIA), or thromboembolism (TE) (19.8% vs 46.9%), vascular disease (11.3% vs 26.9%), diabetes mellitus (17.2% vs 18.8%)

Conclusions: These results suggest that pts initiated rivaroxaban for AF in 2° care are more likely to have a history of stroke, TIA, TE or vascular disease than pts treated in 1° care. This may mean that pts considered to be at "higher risk" with greater co-morbidities are more likely to be managed in 2° care, or that co-morbidities may be less well recorded in 1° care.

170 | Characteristics of patients initiated on statin therapy by general practitioners in Quebec, Canada: The obstat cohort

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Background: Statins are widely prescribed for the prevention of cardiovascular (CV) events such as myocardial infarction and CV-related death. The Canadian Network of Drug Effect Studies (CNODES) has conducted several studies examining the side-effects of statins. Therefore, it was of interest to better understand the characteristics of patients prescribed these medications.

Objectives: To describe the characteristics of patients newly prescribed a statin by general practitioners in the province of Quebec, Canada.

Methods: General practitioners located within 2 hours of Montreal, Quebec City, and Chicoutimi were asked to invite patients they were initiating on statin therapy to participate in this prospective cohort study. All patients who were 18 years or older, French-speaking, available for the 2-year study duration, and had no history of statin use were eligible. During their initial visit with a research nurse, a blood sample was taken, and biological parameters (eg, weight and blood pressure) were measured. Using a structured questionnaire, the patient's personal and family history of CV disease and risk factors was recorded. Information on past and present medication use, physical activity, and other lifestyle factors, as well as risk factors for therapy discontinuation (eg, musculoskeletal pain and emotional well-being) was also collected. Patients' risk of a CV event was assessed based on the prevailing Canadian cholesterol guidelines. Baseline characteristics of patients were summarised using descriptive statistics.

Results: Of the 1631 new statin users enrolled in the study, 47.6% were women. Mean age for all patients was 57.4 years. 46.3% of patients were considered at high risk for a CV event. Moderate- and low-risk patients represented 29.2% and 24.5% of patients, respectively. Diabetes was present in 12.8% of patients, and 7.6% of patients had renal dysfunction (mean GFR [all patients] 84.6 ml/min/1.73 m²). Mean LDL level for patients was 3.7 mmol/L and mean HbA1c was 5.8%. Coronary artery disease and peripheral vascular disease were reportedly present in 6.3% and 2.7% of patients, respectively.

Conclusions: Nearly half of all patients initiated on statin therapy had a statin-indicated condition and were considered to be at high risk for a CV event. The remainder of patients were initiated on statins for primary prevention and were almost equally likely to be at moderate or low risk for a CV event.

171 | Body mass index and the risk of cardiovascular disease and all-cause mortality in European primary care databases

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Background: The association between body mass index (BMI) and cardiovascular disease (CVD) and mortality has been previously characterized in cohort studies.

Objectives: We evaluated this association in large routine health care records.

Methods: We extracted records from 18 million adults enrolled for ≥ 1 year in four primary care databases: Health Search Database (HSD, Italy), Integrated Primary Care Information (IPCI, Netherlands), Information System for Research in Primary Care (SIDIAP, Spain), and The Health Improvement Network (THIN, UK). Code lists were harmonized. Patients with a history of CVD or weight-impacting diseases were excluded. We fitted Cox models to estimate the risk of acute myocardial infarction (AMI), stroke, and all-cause of death by BMI categories (using earliest BMI record in adulthood) within databases and pooled results by random effects meta-analyses.

Results: In patients enrolled in 2015, proportions with BMI recorded in the past 3 years ranged from 17.4% in HSD to 50.8% in THIN. Out of a total of 18 408 983 patients ever enrolled across all four databases, 7 050 997 patients had an eligible BMI, with proportion varying from 11.2% of all patients in IPCI to 52.1% in SIDIAP. Median length of follow-up ranged from 1.3 years in IPCI to 4.6 years in HSD. For all-cause mortality, the pooled hazard ratios (HRs) compared with normal BMI (18.5–24.9 kg/m²) and adjusted for age and gender were as follows: underweight 1.49 (95% CI: 0.97; 2.29), overweight 0.99 (0.82; 1.19), and obese 1.20 (0.97; 1.48). HR was non-significant in obese with BMI 25–34.9 kg/m² (HR: 1.13; 0.91–1.41) and became significant in 35–39 kg/m² (1.30; 1.07–1.59) and 40–59.9 kg/m² (1.76; 1.45–2.13) categories. Pooled HRs for risk of CVD versus normal

BMI were as follows: underweight 0.52 (0.26; 1.01) for AMI and 0.74 (0.38; 1.45) for stroke; overweight 1.45 (1.21; 1.74) and 1.21 (0.96; 1.53); obese 1.71 (1.43; 2.04) and 1.38 (1.11; 1.72) (significant in all obese subcategories). After adjustment for risk factors, HRs in obese patients became non-significant for stroke but remained significant for AMI. Associations were significantly stronger in HSD compared with the other 3 databases ($I^2 > 80\%$).

Conclusions: Although we observed disparity in recording of BMI in primary care across Europe, magnitudes of associations with mortality and CVD resembled previous meta-analyses of cohort studies. Routine health care records may be used for cardiovascular research; however, more systematic recording of BMI is recommended.

172 | Primary care recorded NAFLD and the risk of incident MI and stroke: Findings from analyses of 18 million patients in the UK, the Netherlands, Spain, and Italy

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Background: Many consider non-alcoholic fatty liver disease (NAFLD) to be a high cardiovascular (CVD) risk state, but current data stem largely from cohort studies variably adjusted for usual CVD risk factors.

Objectives: We aimed to investigate the association between NAFLD diagnosis recorded in four European primary care databases and the risk of acute myocardial infarction (AMI) and stroke.

Methods: Data were extracted upon ethical approval from The Health Improvement Network (UK), Health Search Database (Italy), Information System for Research in Primary Care (Spain), and Integrated Primary Care Information (Netherlands). Patients with a recorded diagnosis of NAFLD (including non-alcoholic steatohepatitis) were identified after harmonizing clinical codes across databases. Each NAFLD patient was matched by age, gender, practice site, and visit recorded at ± 6 months of date of diagnosis, to up to 100 patients without NAFLD. Patients with a history of AMI or stroke, with < 1 year of enrolment and < 6 months follow-up post index date were excluded. Events of interest were fatal or non-fatal AMI and ischaemic or unspecified stroke. Hazard ratios were estimated using Cox models and were pooled across databases by random-effect meta-analyses.

Results: 121 159 patients with an incident NAFLD diagnosis were identified out of 17.7 million patients. Average follow-up from index date varied between 2.1 and 5.5 years between the databases. The HRs for incident AMI adjusting for age and smoking status ranged from 1.03 (95% confidence interval: 0.90; 1.18) to 1.31 (1.16; 1.49) and pooled estimate was 1.17 (95% CI 1.05; 1.30; I^2 : 66%, p value heterogeneity: 0.032). This pooled HR became non-significant with progressive adjustments for type 2 diabetes, systolic blood pressure, total cholesterol, statin use, and hypertension (1.01; 0.91-1.12; I^2 : 48.4%, p_{het} : 0.121). Pooled HR for incident stroke events adjusting for age and smoking status was 1.18 (1.11; 1.24, I^2 : 29.3%, p_{het} : 0.24), which also became non-significant at 1.04 (0.99; 1.09, I^2 = 0.0%, p_{het} : 0.92) after adjustment for risk factors. Further sensitivity analyses, excluding NASH patients, showed comparable results.

Conclusions: Our study indicates that patients identified in routine care with NAFLD may not automatically be considered as having higher CVD risk as a result of their NAFLD diagnosis; rather, CVD risk assessment in these patients can be conducted in the same way as the general population.

173 | Predictors of outpatient cardiac rehabilitation referral among hospitalized heart failure patients: The Atherosclerosis Risk in Communities (ARIC) study

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Background: US guidelines for heart failure (HF) management recommend exercise and cardiac rehabilitation (CR). However, these services are underused; estimates from the Get With The Guidelines-Heart Failure registry suggest that ~90% of discharged HF patients do not receive CR referrals.

Objectives: To identify factors of HF hospitalizations that predict discharge referral for CR.

Methods: Analyses were based on data from the surveillance component of the ARIC study (2011-2014; 4 US sites) for acute decompensated HF (ADHF) hospitalizations. Model predictors were taken from abstracted patient/hospital records and included patient demographics, medical history, physical exam, precipitating factors for hospitalization (eg, noncompliance of HF meds as noted in record), do not resuscitate status, labs (eg, hemoglobin), CV meds before admission and at discharge, intravenous drug use, prior HF indicators, ARIC site, and academic hospital status. Discharge diagnosis codes for each patient were grouped according to US Healthcare Cost and Utilization Project Clinical Classification Software single-level diagnosis coding. Ridge and elastic net regression were used to identify key patient

and hospital predictors of CR disposition. The outcome was modeled in a 90% subset; performance was evaluated in the remaining 10% using the C statistic and mean squared prediction error (MSPE). Average C statistic, 95% confidence intervals, and average MSPE were reported after 500 random partitions.

Results: The sample included 1934 ADHF hospitalizations (median age 71 years, 48% female, 53% black) of which 64 (3%) included a CR discharge disposition. The full model predicting CR discharge referral had a mean C statistic of 0.678 (95% CI, 0.512-0.843) and an average MSPE of 0.020. Out of 154 tested variables, the influential predictors positively associated with CR disposition included older age; osteoporosis; complications of cardiac/renal devices, implants, or grafts; myocardial infarction; anemia; and other circulatory disorders. Pulmonary heart disease was negatively associated with a CR discharge disposition.

Conclusions: After prediction modeling using high dimensional abstracted data and penalized regression, there remains uncertainty in predicting discharge referral outcomes. Further studies could target factors such as potential CR contraindications (eg, multimorbidity, physical mobility, and frailty) and physician referral behavior.

174 | Cardiovascular outcomes and mortality in type 2 diabetes with comorbid cardio-renal-metabolic conditions in the United Kingdom

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Background: Cardiovascular, metabolic, and renal co-morbidities associated with type 2 diabetes mellitus (T2DM) increase patient morbidity and mortality.

Objectives: We evaluated the occurrence and timing of various cardio-renal-metabolic (CRM) conditions before and after incident diabetes.

Methods: Using Read codes, patients with a new diagnosis of T2DM (index date) were identified in the Clinical Practice Research Datalink (CPRD) database. The occurrence of other CRM conditions (hypertension {HTN}, hyperlipidemia {HPLD}, chronic kidney disease (Stage 2-5) {CKD}, gout, and nonalcoholic steatohepatitis {NASH}) both before and after the time of T2DM diagnosis were identified. Major acute coronary events (MACE), heart failure (HF), and all-cause mortality (ACM) were evaluated in the post-T2DM period.

Results: Between January 1, 2011, and March 31, 2015, 59 362 eligible incident T2DM patients were identified (mean [SD] age: 61.8 [13.6], 55.9% male). Eighty-eight percent of T2DM patients had at least one other CRM disease, and 68% had two or more CRM conditions at T2DM index. The most frequent CRM combinations were T2DM + HTN + HPLD (n = 21 033; 35.4%), T2DM + HTN (n = 16 298; 27.5%), T2DM alone (n = 6767; 11.4%), T2DM + HTN + HPLD + CKD (n = 3681, 6.2%), and T2DM + HPLD

($n = 2136$; 3.6%). Over a mean follow-up time of 2.5 years after T2DM diagnosis, 71.1% did not develop additional CRM conditions, 20.4% were newly diagnosed HPLD, 4.6% were newly diagnosed HTN, and 3.3% were newly diagnosed CKD; and 96.4% have at least one additional CRM condition by end of follow-up. Adjusted hazard ratios (HR) (95% CI) for MACE and HF were 1.50 (1.24, 1.80) and 1.53 (0.99, 2.37), respectively, in patients with DM + HTN + HPLD compared with those with DM only and 1.75 (1.43, 2.14) and 1.72 (0.95, 3.11), respectively, in patients with DM + HTN + HPLD + CKD compared with DM only. HRs (95% CI) for ACM were 1.68 (1.45, 1.94) in patients with DM + HTN + HPLD compared with patients with DM only 3.81 (3.16, 4.60) in patients with DM + HTN + HPLD + CKD compared with patients with DM only.

Conclusions: In patients with a new diagnosis of T2DM, the risk of MACE, HF, and death increased incrementally with greater number of CRM comorbidities, with CKD being the main driver of mortality. These results may have implications for risk factor management, and potentially selection of treatment strategies, among T2DM patients with various CRM comorbidities.

175 | Long-term incidence and risk factors of cardiovascular events in Asian populations: Systematic review and meta-analysis of population-based cohort studies

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Background: Scientific studies on cardiovascular disease (CVD) burden and risk factors are predominantly based on short-term risk in Westerner populations, and such information may not be applicable to Asian populations, especially over the longer-term.

Objectives: This review aims to estimate the long-term (>10 years) CVD burden, including CHD and stroke, as well as associated risk factors in Asian populations.

Methods: PubMed®, Embase®, Web of Science™ were systematically searched, and hits screened on Asian adults, free of CVD at baseline; cohort study design (follow-up > 10 years). Primary outcomes were fatal and non-fatal CVD events. Pooled estimates and between-study heterogeneity were calculated using random effects models, Q and I² statistics.

Results: Overall, 32 studies were eligible for inclusion (follow-up: 11–29 years). The average long-term rate of fatal CVD is 3.68 per 1000 person-years (95% CI 2.84–4.53), the long-term cumulative risk 6.35% (95% CI 4.69%–8.01%, mean 20.13 years) with the cumulative fatal stroke/CHD risk ratio was 1.5:1. Important risk factors for long-

term fatal CVD (RR, 95% CI) were male gender (1.49, 1.36–1.64), age over 60/65 years (7.55, 5.59–10.19), and current smoking (1.68, 1.26–2.24). High non-HDL-c and β -, γ -tocopherol serum associated only with CHD (HR 2.46 [95% CI 1.29–4.71] and 2.47 [1.10–5.61]), respectively, while stages 1 and 2 hypertension associated only with fatal stroke (2.02 [1.19–3.44] and 2.89 [1.68–4.96]), respectively.

Conclusions: Over a 10 years + follow-up period, Asian subjects had a higher risk of stroke than CHD. Contrary to CVD prevention in Western countries, strategies should also consider stroke instead of CHD only.

176 | A cohort study of hypotension among incident heart failure patients using the UK THIN database

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Background: Hypotension is of particular relevance for patients with heart failure (HF) and may impact HF prognosis; furthermore, almost all HF drugs cause lowering of blood pressure (BP). To date, few studies have evaluated the risk of hypotension in a cohort of real-world incident HF patients, while most clinical trials excluded patients with hypotension.

Objectives: To evaluate the incidence and identify risk factors for the occurrence of hypotension among patients with newly diagnosed HF.

Methods: A cohort study with nested case-control analysis in UK general practice was conducted. A previously identified cohort of patients aged 18–89 years, from 2000 to 2005, with a first ever diagnosis of HF ($N = 18\,677$) in The Health Improvement Network was followed to identify cases of hypotension (Systolic BP ≤ 90 mmHg). We matched cases to controls (1:2) according to age, sex, and date. Risk factors for hypotension were identified by calculating adjusted odds ratios (ORs) with 95% CIs, using conditional logistic regression.

Results: In the HF cohort, 2265 patients developed at least one episode of hypotension (13.7%) over a mean follow-up of 3.31 years (SD: 3.97), resulting in an overall incidence rate (IR) of 3.17 cases per 100 p-ys (95% CI: 3.05–3.30). There were 1041 (40%) cases with multiple episodes of hypotension during the follow-up [mean 2.79 (SD: 3.08)] and 288 (11.2%) with symptomatic hypotension (first episode) (IR 0.36 cases per 100 p-ys; 95% CI: 0.32–0.40). Incidence of hypotension was higher in men than in women, but the highest incidence was seen in young females (18–39 years). Increased risk of hypotension was associated with frequency of health care service use (proxy measures for HF severity), as well as with several comorbidities: myocardial infarction, unstable angina, peripheral vascular disease, valvular disease, hyperlipidemia, anemia, renal failure, hypothyroidism, and liver disease. Use of several cardiovascular drugs with known effects on blood pressure appeared as risk factors of hypotension (eg, aldosterone antagonists, loop diuretics, ACE inhibitors, ARBs, beta-blockers,

and nitrates), where the risk was highest within the first month of use and decreased thereafter, but also use of some non-cardiovascular drugs, including asthma drugs, antidepressants, and opioids.

Conclusions: Hypotension occurs frequently in real-world patients with incident HF. The gender and age distribution of hypotension and associations with comorbidities and medications found in the study deserve further evaluation.

177 | Chronic kidney disease (CKD) in US adults with type 2 diabetes (T2D) and/or cardiovascular diseases (CVD): A national estimate of prevalence by KDIGO 2012 classification

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Background: The KDIGO 2012 recommends that CKD is classified based on cause, estimated glomerular filtration rate (eGFR), and albuminuria categories. CKD often occurs in the context of multiple comorbidities, such as T2D and CVD. But data on the prevalence of CKD among US adults with T2D and CVD based on this classification are limited.

Objectives: To provide a national estimate of prevalence of CKD in US adults aged ≥ 18 years with T2D and/or CVD based on KDIGO 2012 classification.

Methods: Using the National Health and Nutrition Examination Survey (NHANES) 2007-2014 data, we conducted a cross-sectional analysis of an adult sample, aged ≥ 18 years. The eGFR and urine albumin-to-creatinine ratio (UACR) were calculated and categorized based on the KDIGO classification. CVD was defined based on self-reported personal interview data on a broad range of health conditions—congestive heart failure, coronary heart disease, angina, stroke, or heart attack. T2D was defined as diagnosed T2D (self-reported provider diagnosis) and undiagnosed T2D (FPG ≥ 126 mg/dL or HbA1c $\geq 6.5\%$ without self-reported diagnosis). Participants who started insulin within a year of T2D diagnosis or were pregnant at the time of health examination were excluded. Appropriate sample weights were used to provide a national estimate. The prevalence of eGFR and UACR categories were calculated in the following 4 subgroups: T2D and CVD, T2D only, CVD only, and neither T2D nor CVD.

Results: The national prevalence of moderately to severely decreased renal impairment based on eGFR < 60 ml/min/1.73 m² (Stages 3-5) in US adults was highest in T2D and CVD subgroup (33.6%), followed by CVD only (21.0%) and T2D only (13.0%), and was lowest in the subgroup of neither T2D nor CVD (3.9%). The prevalence of mildly decreased renal impairment (Stage 2; eGFR = 60-89 ml/min/1.73 m²), regardless of UACR, was highest in the CVD only subgroup (46.4%), followed by T2D and CVD (42.8%), T2D only (35.0%), and neither T2D nor CVD (30.2%) subgroup. However, the prevalence of patients with both stage 2 eGFR and elevated UACR (≥ 30 mg/g)

was highest in T2D and CVD subgroup (13.8%), followed by T2D only (6.9%) and CVD only (6.1%), and was lowest in the subgroup of neither T2D nor CVD (1.9%).

Conclusions: This study applies a global classification of CKD to estimate the frequencies of renal impairment among US adults in a nationally representative sample and confirms the high prevalence of CKD in patients with T2D and CVD.

178 | Cardiovascular and bleeding outcomes in a Nordic cohort of adult patients with chronic immune thrombocytopenia (cITP)

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Background: ITP is a rare condition associated with low platelet counts and an increased tendency to bleed. There is a paucity of real-world data on cardiovascular and bleeding outcomes according to platelet count levels in these patients, as well as how these events influence mortality.

Objectives: To examine the incidence of cardiovascular events and bleeding in association with platelet count levels and the prognostic impact of these events in a population-based cohort of cITP patients.

Methods: Using data from the Nordic Country Patient Registry for Romiplostim, we studied adults diagnosed with cITP (1996-2015), defined as ITP lasting a duration of >12 months. Incidence of cardiovascular events and bleeding requiring inpatient, outpatient, or emergency room hospital contact (via cumulative incidence risk function with death as a competing risk) and all-cause mortality (via Kaplan-Meier method) was estimated. We constructed matched (age, sex, country, and ITP duration) comparison cohorts of ITP patients without these events, and hazard ratios were computed through Cox proportional hazard regression to examine the prognostic impact of cardiovascular events and bleeding.

Results: Among 3584 cITP patients (median age 58; 58% women), absolute 1- and 5-year rates were 1.9% and 5.8% for arterial cardiovascular events, 1.2% and 3.2% for venous thromboembolism, 7.5% and 17.2% for bleeding, and 3.5% and 15.2% for all-cause mortality. After adjusting for important demographic and clinical factors, rates of cardiovascular events were similar across baseline platelet counts (measured within 90 days prior to cITP diagnosis), while patients with baseline platelet counts below $50 \times 10^9/L$ had more than twofold higher 1-year rates of bleeding and all-cause mortality than patients with baseline platelet counts in the normal range ($150-249 \times 10^9/L$). Occurrence of arterial cardiovascular events, venous thromboembolism, and bleeding were associated with subsequent sevenfold, sixfold, and threefold increased 1-year all-cause mortality, respectively, compared with the matched comparison cohorts.

Conclusions: In patients with cITP, rates of cardiovascular events were low; rates of bleeding and all-cause mortality were somewhat higher. Cardiovascular events occurred across all platelet count levels, while low platelet counts were associated with an increased risk of bleeding and all-cause mortality. Cardiovascular and bleeding events were strong adverse prognostic factors for all-cause mortality.

179 | Using existing NHS datasets to determine outcomes of cancer medicines: A feasibility study

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Background: The Chemotherapy Electronic Prescribing Administration System (CEPAS) used in NHS Greater Glasgow and Clyde, along with a number of electronic datasets, provides the opportunity to evaluate outcomes of cancer treatments using record linkage. As this novel method has not been tested thus far, validation is required.

Objectives: To determine the feasibility of using linked, routinely collected health data to analyse clinical outcomes of abiraterone and enzalutamide.

Methods: Retrospective cohort study using two different methods of data extraction: first, individual patient level data retrieval (IPLR); and second, linked electronic data including CEPAS, the Scottish cancer registry, primary care prescriptions, laboratory results, and hospital discharge and death records. Patients initiated treatment with abiraterone or enzalutamide for metastatic castration-resistant prostate cancer between January 2012 and December 2015; end of follow-up was February 2017. Baseline characteristics and treatment outcomes—including treatment duration, time to prostate-specific antigen progression, and median overall survival—were compared between methods using chi square/Fisher exact tests for categorical variables, and 2 sample t test for continuous variables (applying transformation for skewed distributions). To adjust for multiple testing, the Benjamini-Hochberg false discovery rate procedure was applied to control for a 5% significance level over all comparison tests. For outcomes estimated by the Kaplan-Meier method, the median times and corresponding confidence intervals were compared.

Results: 269 and 271 patients were identified using IPLR and record linkage, respectively. Only 2 (4.3%) of the 46 clinical variables compared were significantly different between methods. These variables were the number of patients recorded with metastatic disease at diagnosis (27.7% record linkage vs 60.6% IPLR) and the number of patients subsequently receiving radiotherapy treatment (11.4% record linkage vs 35.3% IPLR). While some variables obtained via IPLR could not be acquired via record linkage, additional variables—mainly with respect to community prescribing—were available using routinely collected health care records.

Conclusions: This study has shown that real-world data on cancer medicines can be provided via data linkage. Electronic record linkage also offers an opportunity to report new outcomes on systemic anti-cancer treatments which previously have been difficult to report.

180 | Using the SEER-Medicare linked databases to identify novel prostate cancer risk factors

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Background: Few known risk factors for prostate cancer exist beyond race and family history.

Objectives: To identify novel prostate cancer risk factors using a medical condition-wide association study (MedWAS) of administrative data.

Methods: We used the Surveillance, Epidemiology, and End Results (SEER) Medicare linked database to perform a case-control study that included first prostate cancer cases (N = 167 366) diagnosed during 2004-2013 and aged 66-99. Controls (N = 334 732) were 2:1 frequency matched on race, age, and selection year. Cases and controls had ≥ 1 month of Part A/B benefits and ≥ 1 Medicare claim between study entry and 1 year prior to selection. We created a disease classification scheme using ICD-9/V/E codes (N = 2202 conditions). Participants were classified as having the condition if there was ≥ 1 inpatient claim or ≥ 2 physician or outpatient claims >30 days apart in Medicare, with claims between study entry and 1 year prior to selection. We split our data into discovery and validation sets, based on optimizing the ability to detect an odds ratio (OR) ≥ 1.2 with 80% power and $\alpha = 2.5E-5$ assuming condition prevalence $\geq 1\%$ in controls. Logistic regression adjusted for race, age, selection year, markers of health care screening and utilization, and income was used to estimate ORs associating each condition with prostate cancer. Conditions associated in the discovery set were examined in the validation set and considered relevant at $p < 5E-4$.

Results: 195 conditions (9.7%) were associated with prostate cancer in the discovery set, of which 131 (67%) were relevant in the validation set. We validated previously observed associations, eg, family history (OR = 2.01, 1.61-2.52), and identified novel associations, eg, actinic keratosis (1.11, 1.09-1.13), seborrheic keratosis (1.14, 1.11-1.17), and osteoporosis (0.85, 0.79-0.90). We also confirmed previously reported inverse associations with diabetes (type 1: OR = 0.79, 0.75-0.84; type 2: 0.88, 0.86-0.90) and tobacco (0.93, 0.89-0.96) and identified expected conditions such as elevated prostate specific antigen (2.96, 2.88-3.05). Numerous other protective associations appeared to reflect frailty (eg, Alzheimer's disease, OR = 0.54, 0.49-0.59).

Conclusions: MedWAS can be used to screen a large number of medical conditions for association with cancer, efficiently identifying novel risk factors. Additional methods to reduce identification of spurious associations due to frailty are necessary. Novel associations need to be validated in external data.

181 | Electronic health records (EHR) vs Medicare claims data: Comparing the relative completeness of non-fatal outcomes in a linked cohort

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Background: EHR capture details about a patient's health and clinical encounters, but research using EHR is challenged by the longitudinal completeness of recorded outcomes.

Objectives: Our objective was to compare the rate of hospital-based encounters in EHR and Medicare (CMS) claims data.

Methods: The cohort included adults age ≥ 65 with a Duke Health EHR encounter in 2009–2014 and a Durham County, North Carolina (NC) address who were successfully linked to CMS claims. The eligibility date was defined as the later of the first EHR encounter date or CMS fee-for-service (FFS) enrollment start date. The index date was after individuals had 12 months of continuous FFS enrollment beyond their eligibility date. Individuals were followed until death, end of Medicare FFS enrollment, move to non-local address, or end of study data. Outcomes of interest were all-cause hospitalizations and 30-day readmissions defined similarly in each data source. Diabetes and heart failure subgroups were identified by ICD-9 CM diagnosis algorithms from CMS claims for encounters that occurred in the year prior to the index date. We estimated incident rate ratios (IRR) with 95% confidence intervals for each outcome using Poisson models to compare the incidence rate of CMS encounters to EHR-based encounters per 1000 person-years, overall, and in the two subgroups.

Results: Among the cohort of 25 225 individuals, 42% were age 65–69 years, 61% were female, and 66% were white. The 5-year incidence rate of CMS encounters was higher than the incidence rate based on EHR encounters; IRR (95% CI): 1.13 (1.11, 1.15) for all-cause hospitalizations and 1.07 (1.02, 1.12) for 30-day readmissions. Estimates within subgroups followed a similar pattern: diabetes subgroup ($n = 8550$), all-cause hospitalizations: 1.11 (1.08, 1.14), 30-day readmissions: 1.05 (0.98, 1.13) and the heart failure subgroup ($n = 4318$) all-cause hospitalizations: 1.11 (1.07, 1.15), 30-day readmissions: 1.08 (0.99, 1.18).

Conclusions: These preliminary results suggest that CMS data captured more hospital-based encounters than EHR data. This finding did not differ within diabetes and heart failure subgroups. Results may reflect care received outside of this health system. However, more research is required to understand the implications of the transformation of EHR data for research purposes on these findings.

182 | Agreement between electronic health records and administrative claims data for patients with multiple myeloma

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Background: To increase the validity of non-experimental studies, researchers are increasingly linking electronic health records (EHR) with insurance claims databases. Exploration of linked data is important to effectively design studies and define key variables.

Objectives: To quantify enrollment overlap and assess the agreement between cancer and non-cancer-related comorbidities for patients with multiple myeloma (MM) within a linked EHR-claims database.

Methods: Patients with incident MM were identified using EHR data from oncology clinics across the United States (Flatiron Health, Inc [FL]) linked with MarketScan[®] (MS) employer-based and Medicare supplemental health insurance claims databases (Truven Health Analytics, Inc). We included patients aged ≥ 18 years with a first MM diagnosis from January 1, 2011, through April 30, 2016, without concurrent cancer or recent prior use of zoledronic acid (ZA) or pamidronate, the intravenous bisphosphonates of interest. We describe enrollment overlap during baseline and follow-up periods and use the kappa statistic to measure agreement in identifying baseline diagnoses and treatments and intravenous bisphosphonate use during follow-up.

Results: There were 1799 patients eligible before implementing an MS continuous enrollment requirement. Requiring 6 months of overlap before the MM diagnosis decreased the sample size by 47%. Requiring 12 months of overlap only decreased the sample size by 8% more. There were 619 patients in the final study population after all exclusions were applied. Half of the follow-up person-months in FL also had continuous enrollment in MS. The prevalence of baseline comorbidities and non-cancer medications was higher in MS data than in FL (eg, opioids: 36% (MS) vs 3% (FL), $\kappa = 0.08$). MM therapies were identified similarly in both data sources (eg, proteasome inhibitors: 43% (MS) vs 46% (FL), $\kappa = 0.84$). While the time from MM diagnosis to the first ZA administration was similar (median number of days: 40 (MS) vs 35 (FL)), more ZA administrations were identified in FL. Lab results and biomarkers were available only in FL.

Conclusions: The oncology-specific EHR captured detailed cancer-related clinical data, while the insurance claims captured broader non-cancer-related health data. The linked data provided more information than either data source alone, which expands the possibilities for observational research, including post-marketing safety surveillance of oncology drugs and non-oncology outcomes.

183 | Developing a multiphase claims-based algorithm for non-live pregnancy outcomes research

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Background: Non-live outcomes occur in about 30% of pregnancies and may be mediated by exposure to medication during pregnancy, depending on various factors including drug type, length, of exposure and/or time of exposure (eg, foetus age/proximity to conception). Understanding the safety of medication exposure during pregnancy is critical but presents methodological challenges. Registries are common, but often yield few cases. Administrative claims data can be used to study large numbers of women if the claims data accurately identify/estimate non-live outcomes, gestational age (GA) at non-live outcome, and medication exposure during pregnancy ending in non-live outcome.

Objectives: To develop a multiphase claims-based algorithm that identifies non-live outcomes (Phase [Ph]1), estimates GA at non-live outcome (Ph2) and estimates medication exposure during pregnancy ending in non-live outcome (Ph3).

Methods: A multiphase algorithm is being developed in stages among women aged ≥ 15 and ≤ 50 years with ≥ 1 end of pregnancy (EOP) ICD-9 code and enrolment and prescription coverage 340 days prior to EOP in the Henry Ford Health System in the United States between January 1, 2013, and September 30, 2015. Algorithms have been (Ph1) or will be (Ph2-3) developed, applied to claims data, and validated against electronic medical records using estimated positive predictive value (PPV), sensitivity, and corresponding 95% confidence interval (CI). The best-performing algorithm in each phase is used in the next phase. Based on previous work for live outcomes presented at ICPE 2017 (abstract 154), Ph1 Algorithm 1 (≥ 1 definitive ICD-9 EOP code) validation was modified to ascertain events ± 30 days from the EOP date (vs 0-7 days). Work is ongoing to assess algorithms that estimate GA at non-live outcome by assigning an estimated GA to 3 or 5 categories of non-live outcomes (Ph2) and to assess drug exposure during pregnancy to long-term (eg, antidepressants) and short-term (antibiotics) medications based on estimated GA (Ph3).

Results: A total of 698 women met the inclusion criteria, and 145 had non-live EOP codes. When validating EOP codes within 0-7 days of the EOP date, the Ph1 Algorithm 1 PPV was 79% (95% CI: 71, 85), and the sensitivity was 97% (95% CI: 96, 99). When validating EOP codes ± 30 days from the EOP date, the PPV was 85% (95% CI: 78, 90), and the sensitivity was 100% (95% CI: 97, 100).

Conclusions: Non-live EOP outcomes can be identified in claims data with high PPV and sensitivity. Further analyses are underway to validate algorithms for Ph2 and Ph3.

184 | Can patients accurately report their drugs?—A comparison of self-reported medication with a national register in Denmark in a subset of the protect pregnancy cohort

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Background: Clinical trials of new drugs are not undertaken exclusively in pregnant women due to unknown teratogenic risks, so analysis of electronic health records (EHR) post marketing is often used to investigate risks and benefits of drugs during pregnancy. While medicine exposure data from EHR is often accurate, there may be limited information on compliance or over the counter drug (OTC) use.

Objectives: One aim of the multicountry PROTECT Pregnancy study was to evaluate if high-quality patient-reported exposure information could be collected.

Methods: Women from the United Kingdom, Netherlands, Poland, and Denmark were recruited into the study via the web. Participants were enrolled from Oct 19, 2012, to Jan 31, 2014, through a dedicated study website. During their pregnancies, women filled in electronic questionnaires of drug use and other data such as demographics and lifestyle factors. By linking with the Danish Register of Medicinal Product Statistics direct comparison of study, prescription information was possible for a subset of women.

Results: 783 Danish women were recruited, and 637 were eligible and filled in the baseline questionnaire. Out of 501 women who had a pregnancy outcome before the study end, 220 women (44%) completed all questionnaires. When compared with national figures, the Danish PROTECT participants were older with higher educational levels. Other parameters like BMI and smoking status were equal. A high recall rate of 86% was found for drugs used regularly and 69% for drugs taken less often. Some medication, especially for migraine, depression, and asthma, were reported only in questionnaires. Antibiotics were the most often category reported as prescribed but not taken. Participants also noted consumption of OTC drugs and those prescribed for friends/family rather than themselves.

Conclusions: This Danish subset validation of the broader PROTECT pregnancy study confirmed that, in our population, women not only provided accurate accounts of drug use but also donated valuable insights on use of non-prescribed and illicit drugs and compliance (eg, prescription drugs were taken on an "as needed" basis, long after they were prescribed). Direct medicines reporting from patients via the internet may be an alternative or additional strategy to traditional methods. There are advantages to taking a patient centric view of drug utilization.

185 | Linking electronic health data in pharmacoepidemiology: Guidance for assessing appropriateness and feasibility

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Background: The linkage of datasets is necessary to effectively utilize available heterogeneous health data. Prior to linking multiple discrete data sources to create novel linked datasets, researchers must assess the feasibility of both scientific aspects (data quality and linkage methods) and operational aspects (access, data use and transfer, governance, and cost).

Objectives: To provide guidance on key aspects of data linkage and methods necessary to plan useful and sustainable linkages that advance pharmacoepidemiology and patient safety.

Methods: An ISPE-supported working group included members from academic, industry and contract research, government, and regulatory sectors. The scope of the activity was determined by querying the group using an online survey to determine the priority content areas; planning and feasibility of data linkage was one of the content areas chosen. Within this topic, scientific and operational considerations were determined, reviewed, and assembled by consensus into key recommendations.

Results: Guidance for feasibility assessment was categorized into key areas: (1) research objectives and justification, (2) data harmonization and quality, (3) the linkage process, (4) data ownership and governance, and (5) overall value added by linkage. Within these key areas, 10 questions were developed as criteria to consider prior to initiation of a linkage to determine if the research objectives are appropriate for the proposed linkage, assess source data completeness and population coverage, and ensure data governance standards and protections are well defined. The planning of a linkage project requires careful evaluation to weigh the resources involved in initiation of a new linkage and the overall potential benefits of answering innovative research questions, expanding the scope of a project, improving classification of existing variables, and increasing the internal validity of population estimates.

Conclusions: These recommendations can help researchers conscientiously assess and design sustainable linked data resources that can be leveraged to fill gaps in data and generate novel, actionable evidence in pharmacoepidemiology.

186 | Concordance of hospitalized endpoints within the linked Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) databases among patients treated with oral antidiabetic therapies

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Background: Pharmacoepidemiologic studies utilizing the United Kingdom's Clinical Practice Research Datalink (CPRD) may seek to identify hospitalized events as outcomes, but the degree to which hospitalizations are captured in this outpatient database is unknown. The ability of Hospital Episode Statistics (HES), which records hospital admission and discharge diagnoses in England, to be linked with CPRD allows determination of the concordance of hospitalizations within these databases.

Objectives: To assess the proportion of (1) hospitalizations in CPRD that are confirmed in the HES database and (2) hospitalizations in HES that are recorded in CPRD.

Methods: We conducted a cross-sectional study from October 2009 to September 2012 among English oral antidiabetic-treated patients in CPRD whose data were available for HES linkage. Within CPRD, we identified initial hospitalizations for any diagnosis for each calendar year of the study period by determining Read diagnosis codes linked to a hospital referral or consultation. We then determined if a hospital admission was recorded in the HES database within +/- 30 days. Next, we identified initial hospital admissions in HES and determined if a hospitalization was recorded in CPRD within +/- 30 days. For each comparison, we determined the median difference (in days) between the recorded CPRD and HES admission dates. Analyses were repeated using HES discharge (instead of admission) dates.

Results: Among 8574 OAD-treated HES-linked patients in CPRD, 6574 initial hospitalizations across the study period were identified in CPRD, and 5188 (79% [95% CI, 78-80%]) were confirmed by a HES admission date within +/- 30 days (median difference, +/- 3 days [IQR, 1-7 days]). Comparatively, among 8609 hospital admissions in HES, 4803 (56% [95% CI, 55-57%]) hospitalizations were recorded in CPRD within +/- 30 days (median difference, +/- 4 days [IQR, 1-9 days]). Similar results were observed when using HES discharge dates.

Conclusions: Our analyses found that, when utilized independently, CPRD captures about 56% of hospitalization events. Pharmacoepidemiologic studies employing CPRD to identify hospitalizations should consider linkage with HES data to ensure adequate ascertainment of inpatient events.

187 | Including primary care data from multiple software systems in a data linkage programme: Results From expanding the Clinical Practice Research Datalink (CPRD)

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Background: CPRD provides anonymised UK primary care electronic health care records linked to a range of datasets including hospitalisations, death certificates, disease registries, and deprivation indices. In December 2017, a new primary care database, CPRD Aurum, based on EMIS software was launched in addition to the long running CPRD GOLD database based on Vision software. Over time, general practices undergo structural changes such as closure, merging, or splitting and may change software vendor. Therefore, some practices will, at different times, have contributed to both databases.

Objectives: CPRD provides linked datasets to researchers for both databases separately but also aims to provide linked de-duplicated data combining the CPRD GOLD and Aurum databases.

Methods: Linkage is performed under rigorous governance conditions on patients from consenting English practices via a trusted third party (TTP) organisation (NHS Digital) using NHS number, postcode, full date of birth, and gender. The TTP uses these identifiers to link the datasets using a sequential eight-stage deterministic algorithm and provides CPRD with anonymised linked cohort files. The practice identifiers are provided so that relevant data from both primary care databases and corresponding linked datasets can be extracted. CPRD then creates two separate linkage datasets for CPRD GOLD and CPRD Aurum. Up-to-date primary care and linked data are provided for currently contributing Vision and EMIS practices. For practices that participated in linkage but stopped contributing data to CPRD, only linked data for patients in the practice at the time of the last data collection are available.

Results: There were 232 English practices with 6.6 million patients in CPRD Aurum and 411 English practices with 10.6 million patients in CPRD GOLD participating in the linkage scheme. CPRD produced a common linkage practice file containing practices that have moved system providers and were in both CPRD primary care databases. There were 47 practices duplicated in both databases, which when removed, left 596 unique practices and 15.9 million unique patients.

Conclusions: Use of duplicated patient information may bias results by artificially inflating data provided from duplicated practices. This can be avoided by identifying duplicated practices and removing them allowing researchers to use the maximum available primary care and linked data regardless of the primary care software system used.

188 | Linking randomized control trials and electronic databases assessing feasibility in 41 countries

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Background: Randomized control trials (RCTs) are usually considered the gold standard for evaluating efficacy and safety of medications. However, conducting RCTs is resource intensive, and generalizing results to real-world patient populations is challenging. Linking RCTs to routinely-collected electronic health care databases can provide a unique opportunity for validating outcomes, long-term follow-up of RCT patients, and capturing outcomes difficult to collect during RCTs. Considering few examples of RCTs and electronic database linkage exist, we investigated country-specific infrastructure and electronic databases that allow such linkage.

Objectives: To assess the feasibility of linking RCT data to real-world patient-level data in 41 countries.

Methods: We conducted extensive web searches and reviewed information available on ISPE and ISPOR websites to identify major electronic databases in each country. We further explored the available literature to assess characteristics of each database based on pre-specified criteria including quality, comprehensiveness, accessibility, regulatory requirements, and availability of unique patient identifiers to facilitate deterministic linkage. We reviewed prior peer-reviewed research conducted on data linkage to better understand the process and feasibility based on any known precedent.

Results: Of the 41 countries evaluated, 6 (15%) were identified as highly feasible for linkage based on the criteria outlined above; these included the UK, US, CAN, FRA, AUS, and NZL. Eleven (26.8%) countries have national databases feasible for linkage but present moderate barriers such as encrypted patient identifiers or lack of outpatient data. Twenty-four (58.5%) countries were identified as likely candidates for linkage of RCTs with certain electronic databases such as national vital statistics. Fewer countries, 17 (41%), were identified as likely candidates for linkage to registry data. We were only able to identify 4 prior examples of linkage of RCT data with electronic databases.

Conclusions: Our findings suggest linking RCT data to electronic databases is feasible in a number of countries. Countries with large RCT populations appear to have an advantage, as their technological infrastructure is usually advanced and regulatory pathways are more transparent. RCTs in countries where patients can be identified in large electronic databases, such as Medicare in the United States and National Health Service (NHS) in the United Kingdom, should be prioritized for linkage.

189 | A comparison of record linkage software and algorithms using real-world data

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Background: Linking medical records across multiple health care settings is critical to delivering high-quality medical care and conducting valid research. Linkage is very challenging in countries without national identifiers and remains an issue elsewhere because of imperfect recording and transfer of identifiers into databases. Researchers must understand the behavior and usability of software used for linkage.

Objectives: To compare 4 record linkage software packages and various algorithms using real EHR data: independent inpatient (n = 69 523) and outpatient (n = 176 154) data sets from a major medical system without a universal identifier.

Methods: We conducted 30 trials, varying the software package (LinkPlus, LinXmart/CUPLE [Curtin University], Merge ToolBox [MTB], and the R *RecordLinkage* package), the algorithm (deterministic or probabilistic; exact or inexact string matching), and the variables used for matching (first name, last name, and gender, and these three plus full date of birth), using year of birth as the blocking variable. We evaluated performance using the matching weights assigned to each of ~132 million compared record pairs. We also assessed computational time and usability of the linkage packages.

Results: Despite substantial similarity, the linkage packages and algorithms did not behave identically. The number of matching weights assigned to the compared pairs ranged over trials from 4 to ~8 million, leading to different decisions when declared matches were pairs whose weights exceed a threshold. In all trials with exact string matching and three matching variables, 30 805 pairs received the maximum weight; with four matching variables, 30 536 pairs did. However, software and algorithms varied in assigning the 2nd, 3rd, and 4th rank weights. For example, some algorithms assigned higher weight to pairs matching on first name and gender but not on last name, and others to pairs matching on first name and last name but not gender. Ordering of the weights also reflected differences in treatment of missing values. Some software packages performed trials more efficiently (eg, 1 minute versus 1 hour for the same algorithm).

Conclusions: Unlike previous linkage work, we have analyzed matching weights assigned to all possible record pairs in each trial, which allows us to describe exactly what match decisions are possible. Because values of weights are not comparable across trials, focusing on ranks is crucial. Software documentation does not yield ready insight into differences.

190 | Using Italian administrative health care data sources to study infusive antineoplastic utilization in clinical practice: A validation study

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Background: In Italy, administrative health care databases (AD) are the most widely used source of information for drug utilization studies. However, studying infusive antineoplastics (IA) utilization remains a challenge. Indeed, IA are administered in hospital settings where patient-level information on drug utilization is only partially captured by AD.

Objectives: To validate the quality of the AD of the Tuscany region, Italy, as a source for conducting drug utilization studies on IA, using rituximab (RIT) as a case study, and hospital pharmacy data as the reference standard.

Methods: All patients aged 18+ with ≥ 1 RIT administration between 2011 and 2014 in the oncology or haematology units of the University Hospital of Siena were extracted from the database of the hospital pharmacy (UHS). Each patient was anonymized using a regional identification code (ID), and information contained in UHS was linked to the Regional AD of Tuscany (RAD). All RIT users in UHS with a valid ID entered the study cohort. The first administration of RIT recorded in UHS was the index date. In both data sources, all records of RIT administration during 1 year from index date were considered. The percentage of RIT users (≥ 1 RIT administration) found in RAD was calculated. The percentage of all RIT administrations recorded in UHS found in RAD was calculated. A RIT administration recorded in UHS and RAD with up to 3 days of discrepancy was considered as the same treatment episode. Among the treatment episodes recorded in both sources, we compared the mean dose.

Results: A total of 307 patients with a valid ID were identified in UHS. Among those, RAD identified 295 patients (96%) as being RIT users. Among RIT users identified in both sources, during the first year from index date, 1758 dispensations were recorded in UHS, and 1382 among them could also be found in RAD (78.8%); 42.1% of the missing in RAD was found among inpatient admission. The mean dose recorded in RAD was 676.5 and over-estimated the UHS dose of 20.8 mg (3.1%).

Conclusions: RAD is very reliable source of information to identify patients treated with RIT. Sensitivity of RAD with respect to treatment episodes was also acceptable: Almost 4 out of 5 administrations recorded in UHS could be also found in RAD. Further investigations are ongoing to assess the validity of RAD in deriving the indication of use and treatment line in RIT users through comparison with UHS data.

191 | Assessment of UK Biobank phenotype data

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Background: UK Biobank (UKB) contains detailed phenotypic data for ~500 000 healthy volunteers that are gathered from several sources with disparate coding systems and varying levels of data capture. Comprehensive definitions for phenotypes necessitate careful mapping across these different coding systems.

Objectives: This GSK-funded study aimed to evaluate the data quality among UKB data sources for 20 phenotypes in the following categories: primary heart failure, pulmonary edema, renal, respiratory disease, osteopathy, and menstruation-related conditions.

Methods: The sources of UKB data are Health Episodes Statistics (HES) from secondary care, UK death registry; questionnaires via nurse interviews for diagnosis and procedures; and the self-reported baseline touchscreen questionnaire. An extensive mapping exercise was conducted to align the phenotypes among the various UKB data sources across the disparate coding systems used: HES and the UK death registry use ICD-10 diagnosis codes; and questionnaires from UKB (diagnosis, procedures, and self-reported baseline) have their own coding system. Medically related terms were determined from clinician review.

Results: HES was the main data source in defining 14 of the 20 phenotypes of interest. Among the UKB data sources, 98.5% of "Bacterial pneumonia" phenotypes and 95% of "Chronic renal failure" phenotypes stemmed from HES data. Two phenotypes were defined by only HES data ("Non-rheumatic tricuspid valve disorders" and "Osteochondropathies"). Phenotypes for "Endometriosis" were evenly defined among HES and UKB questionnaire data, while phenotypes for "Bronchopneumonia and lung abscess" were defined 54% of the time with the UK death registry. UKB questionnaire data from nurse interviews and baseline self-reports were the key source to define cases for four phenotypes, including "Asthma" (93%) and "Other upper respiratory disease" (86%).

Conclusions: Researchers should interrogate all UKB data sources to confidently and comprehensively identify and explore phenotypes algorithms. While HES was the main data source for many phenotypes in this analysis, the list of phenotypes was not exhaustive and the care setting in which phenotypes are likely to be identified should be carefully considered. Some overlaps may be found for more severe phenotypes (eg, those that might appear in death records and hospitalization records) but not necessarily for less severe phenotypes primarily encountered in outpatient settings and likely sourced from nurse interviews and baseline self-reports.

192 | Using real-world data (RWD) in health technology assessment (HTA) practice: A comparative study of 5 HTA agencies

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Background: Reimbursement decisions are conventionally based on evidence from randomised controlled trials (RCTs) which often have high internal validity but low external validity. Real-world data (RWD) may provide complimentary evidence for relative effectiveness assessments (REAs) and cost-effectiveness assessments (CEAs).

Objectives: This study examines whether RWD is incorporated in Health Technology Assessment (HTA) of melanoma drugs by European HTA agencies, differences in RWD use between agencies and across time.

Methods: HTA reports published between 01.01.2011 and 31.12.2016 were retrieved from websites of agencies representing 5 jurisdictions: England (NICE), Scotland (SMC), France (HAS), Germany (IQWiG), and the Netherlands (ZIN). A standardized data-extraction form was used to extract information on RWD inclusion for both REAs and CEAs. A panel of senior HTA assessors representing the 5 agencies was consulted to check the robustness of data extracted and interpretation.

Results: All 52 reports contained REAs; CEAs were present in 25. RWD was included in 28 of 52 REAs (54%), mainly to estimate melanoma prevalence. RWD was included in 22 of 25 (88%) of CEAs, mainly to extrapolate long-term effectiveness and/or identify drug-related costs drugs. Differences emerged between agencies regarding RWD use in REAs; ZIN and IQWiG cited RWD for evidence on prevalence whereas NICE, SMC, and HAS additionally cited RWD use for drug effectiveness. No visible trend for RWD use in REAs and CEAs over time was observed.

Conclusions: In general, RWD inclusion was higher in CEAs than REAs. It was mostly used to estimate melanoma prevalence in REAs or to predict long-term effectiveness in CEAs. Differences emerged between agencies' use of RWD. However, no visible trends for RWD use over time were observed. Future research should explore the use of RWD in HTA of drugs in other disease indications and/or in conditional reimbursement schemes.

193 | Outcomes of cetuximab in first line therapy for metastatic colorectal cancer according to tumor RAS-BRAF mutation status from an update of EREBUS cohort

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Background: Poor efficacy has been recently reported for patients with RAS/BRAF mutation (mt) treated with cetuximab. There are few data about cetuximab benefit in real-life according to tumor RAS/BRAF mt status.

Objectives: To evaluate objective response rate (ORR), metastases resection rate, progression-free survival (PFS), and overall survival (OS) according to tumor mt status: RASmt (whatever BRAF mt status), RASwt/BRAFmt, and RASwt/BRAFwt (ie, 2xWT).

Methods: EREBUS is a multicenter (n = 65) cohort study of KRAS wild-type (wt) unresectable metastatic colorectal cancer (mCRC) patients initiating cetuximab as first-line treatment from 2009 to 2010, followed for 2 years (up to 5 years for vital status). Kaplan-Meier method was used to describe 2-year PFS and 5-year OS. The association between the tumor mt status and the 1-year progression or the 3-year death was evaluated using multivariate Cox analyses adjusted on prognostic factors.

Results: 389 patients were included; tumor mt status was known for 310 (80%): 64 RASmt (21%), 33 RASwt/BRAFmt (11%), and 213 2xWT (69%). Respective baseline characteristics were: median age 65 years, 64 years, and 63 years, male gender 63%, 64%, and 69%, ECOG-PS 0-1 75%, 76%, and 79%, liver only metastases 39%, 33%, and 40%. ORR was 40.6% 95% CI [28.5-53.6] in RASmt patients, 30.3% [15.6-48.7] in RASwt/BRAFmt patients, and 62.4% [55.8-69.0] in 2xWT patients. Metastases resection was performed in 12 RASmt patients (18.8% [10.1-30.5]; 8 radical resections R0/R1/radiofrequency), 2 RASwt/BRAFmt patients (6.1% [0.7-20.2]; 2 radical resections), and 75 2xWT patients (35.2% [28.8-41.6]; 47 radical resections). Median PFS (months) was 8.0 [5.9-9.3] in RASmt patients, 6.0 [2.3-7.2] in RASwt/BRAFmt patients, and 10.4 [9.5-11.0] in 2xWT patients. Median OS (months) was 18.4 [10.9-23.3] in RASmt patients, 9.7 [6.9-16.6] in RASwt/BRAFmt patients, and 29.3 [26.3-36.1] in 2xWT patients. In adjusted multivariate analyses, progression (HR = 2.69 [1.78-4.07]) and death (HR = 3.13 [2.04-4.79]) were more likely for RASwt/BRAFmt patients vs 2xWT patients. In reference to 2xWT patients, HR for progression was 1.41 [0.98-2.04] (p = 0.0618) for RASmt/BRAFwt patients and HR for death 1.63 [1.13-2.35].

Conclusions: EREBUS confirms in real life the difference in clinical outcomes with tumoral RAS/BRAF mutation in unresectable mCRC treated with first-line cetuximab, showing the greatest effectiveness in 2xWT patients.

194 | Evaluation of cabazitaxel in metastatic castration-resistant prostate cancer with real-life use, effectiveness, safety, and quality of life in the FUJI cohort

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Background: Cabazitaxel (CAB) was marketed in March 2012 in France, based on overall survival (OS) benefit in metastatic castrate resistant prostate cancer (mCRPC) in 2nd-line (2L) post-docetaxel (DOC). FUJI is a post-authorisation study of the real-life performance of CAB.

Objectives: To evaluate OS, safety, quality of life (QoL) and pain using specific patient questionnaires (FACT-P for QoL and BPI-SF for pain).

Methods: FUJI is a multicentre (n = 42) cohort study in mCRPC CAB initiators in real-life, included from Sept 2013 to Aug 2015 in a retrospective cohort (follow-up [FU] 18 months [mths]) and from March 2016 to March 2017 in a prospective cohort (FU 6 mths). OS was analyzed using Kaplan-Meier method. A multivariate Cox analysis, adjusted on prognostic factors, evaluated the risk of death.

Results: The retrospective cohort included 401 patients (median age 70) with CAB in 2L (18%), 3L (39%), 4L (23%), or >4L (20%). Treatments before CAB included DOC (100%), abiraterone acetate (ABI 77%), and enzalutamide (ENZ 33%). Median CAB use was 3.4 mths. Median OS was 11.9 mths [95% CI, 10.1-12.9]. In multivariate analyses, factors associated with a shorter OS were grade ≥ 3 adverse event (AE) (HR = 2.05 [1.53-2.73]), visceral metastases (HR = 1.98 [1.40-2.80]), polymedication > 5 drugs (HR = 1.74 [1.23-2.45]), >5 bone metastases (HR = 1.74 [1.20-2.53]), disease progression during DOC (HR = 1.69 [1.13-2.53]) or within 3 mths of last DOC cycle (HR = 1.51 [1.07-2.14]), ≥ 3 drugs such as DOC, ABI, ENZ before CAB (HR = 1.39 [1.00-1.92]), and PSA ≥ 135 ng/ml (HR = 1.36 [1.01-1.82]). Factors associated with better OS were ≥ 10 -yr cancer history before CAB (HR = 0.66 [0.46-0.96]), ≥ 6 mths from last DOC dose to CAB initiation (HR = 0.71, [0.52-0.97]). Grade ≥ 3 AEs occurred in 55%, mainly anaemia (27%), neutropenia (15%), febrile neutropenia (8%), renal failure (7%), septicemia/septic shock (5%). The prospective cohort included 61 patients (median age 72) previously treated with DOC (98%), ABI (61%), and ENZ (61%). 49 patients were evaluable for QoL and 44 for pain. QoL improved in 41%, was maintained in 29%, and deteriorated in 38%. 25% had pain decrease ≥ 1 level, 50% were stable, and 25% increase ≥ 1 level.

Conclusions: Real-life median OS in FUJI was lower than in TROPIC (11.9 vs. 15.1 mths), but very few FUJI patients would have satisfied TROPIC inclusion criteria. There were no new safety issues. Improved/stable QoL and pain were reported by 70% and 75% of patients treated by CAB, respectively.

195 | Direct oral anticoagulants versus low-molecular-weight heparins for venous thromboembolism prevention following total knee replacement: Comparative effectiveness and medical costs from a French nationwide cohort study of around 50 000 patients

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Background: Thromboprophylaxis is recommended after major orthopaedic surgery to prevent the risk of deep vein thrombosis and pulmonary embolism. Three direct-acting oral anticoagulants (DOAC), apixaban, dabigatran, and rivaroxaban was granted a European market authorization for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total knee replacement (TKR) surgery.

Objectives: To assess the benefit-risk and medical costs of DOAC vs low-molecular-weight heparin (LMWH) for VTE prophylaxis following TKR in real-life setting.

Methods: Cohort of all patients with TKR performed in France from Jan 2013 to Sept 2014, home return after discharge, followed-up for 3 months in the French nationwide claims and hospitalization database. Patients treated with a DOAC were 1:1 matched on gender, age, and propensity score with those receiving LMWH. Main outcomes were hospitalization with primary diagnosis of VTE or bleeding, and all causes death during the follow-up or anticoagulant switch. Relative risk (RR) between DOAC and LMWH was estimated using quasi Poisson model, with sub-analyses for each DOAC. Medical costs were calculated according to the collective perspective.

Results: Among the patients who returned home, 15 738 were treated with a DOAC (rivaroxaban 66.2%, dabigatran 22.6%, apixaban 11.2%), 33 497 with LMWH. Mean age was 67.6 (±8.9) years for DOAC patients, 68.5 (±9.5) for LMWH patients, respectively, 52.9% and 53% women, a mean duration of hospital stay of 7.7 days and 8.0 days, a mean IMPROVE VTE risk score = 2, a bleeding risk score = 3.5. Almost all DOAC patients (15 720) were matched to a LMWH patient. For them, the risk of VTE was lower with DOAC than LMWH (1.6‰, 2.3‰ respectively, RR = 0.69

[0.42-1.16]) but not significantly, while the risk of bleeding was significantly lower with DOAC (2.4‰ and 3.8‰, RR = 0.64 [0.43-0.97]), without difference for all cause death (0.6‰ and 0.8‰, RR = 0.96 [0.30-1.62]). The mean total medical costs per matched patient were €442 lower with DOAC (-23%), difference been mainly from drugs, nursing, and hospitalizations.

Conclusions: This study shows a low risk of VTE, clinically relevant bleeding, and death after discharge for patients with anticoagulant for VTE prevention following TKR with a better benefit-risk ratio of DOAC compared with LMWH and associated with cost savings.

196 | Antihistamine use and risk of ovarian cancer: A population-based case-control study

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Background: Preclinical studies have demonstrated anticancer effects of antihistamines; however, epidemiologic evidence is limited. Recently, a Danish registry-based screening study of potential drug-cancer associations suggested an inverse association between use of the antihistamine, fexofenadine, and serous ovarian cancer.

Objectives: To examine the association between antihistamine use and ovarian cancer risk in a nationwide case-control study.

Methods: Cases (n = 5556) comprised all women in Denmark aged 30-84 years with a histologically verified first diagnosis of epithelial ovarian cancer between 2000 and 2015. Age-matched population controls (n = 83 340) were sampled using the risk-set technique. Data on prescription use and patient and demographic characteristics were retrieved from nationwide registries. Conditional logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for epithelial ovarian cancer associated with antihistamine use (≥2 prescriptions). We evaluated associations with various patterns of antihistamine use, ie, cumulative amount, timing, and intensity. In addition, we performed separate analyses for histological subtypes of epithelial ovarian cancer and for individual antihistamines.

Results: Ever use of antihistamines was not associated with a reduced risk of ovarian cancer overall (OR = 0.97, 95% CI = 0.90-1.05), and the neutral association remained in subanalyses of patterns of antihistamine use and of individual antihistamines. In analyses of histological subtypes of ovarian cancer, an inverse association emerged for mucinous carcinomas (OR = 0.74, 95% CI = 0.57-0.96) alone. We also observed inverse associations between antihistamine use and ovarian cancer among premenopausal women (<50 year), notably for serous (OR = 0.63, 95% CI = 0.46-0.87) and clear cell (OR = 0.46, 95% CI = 0.18-1.16) carcinomas.

Conclusions: Antihistamine use was not associated with overall ovarian cancer risk in our study. However, the inverse associations observed between antihistamine use and risk of mucinous ovarian cancer overall and of serous or clear cell ovarian cancer among premenopausal women warrant additional research.

197 | Non-aspirin NSAID use and survival after ovarian cancer

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Background: Preclinical studies suggest that use of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) may improve survival of ovarian cancer; however, the epidemiologic evidence is sparse.

Objectives: To examine the association between postdiagnosis use of non-aspirin NSAIDs and mortality among ovarian cancer patients.

Methods: From the Danish Cancer registry, we identified all women in Denmark aged 30-84 years with epithelial ovarian cancer diagnosed between 2000 and 2012. We obtained information on prescription drug use, mortality outcomes, and potential confounding factors from Danish nationwide registries. Time-dependent Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for the association between postdiagnosis non-aspirin NSAID use (≥ 1 prescription) and ovarian cancer-specific or other-cause mortality compared with non-use (no prescriptions). Additionally, we evaluated associations according to patterns of use (ie, duration, timing, consistency, and intensity/dose) and effect measure modification by tumor histology. The influence of competing risks was evaluated using proportional hazards models for the subdistribution suggested by Fine and Gray.

Results: Among 4117 ovarian cancer patients, any postdiagnosis use of non-aspirin NSAIDs was not associated with either ovarian cancer (HR = 0.97, 95% CI = 0.87-1.08) or other-cause (HR = 0.99, 95% CI = 0.77-1.27) mortality. In analyses of usage patterns, we observed some evidence of a dose-response relationship with lowest HRs for ovarian cancer mortality associated with high cumulative (HR = 0.75, 95% CI = 0.60-0.94) or high-intensity (HR = 0.86, 95% CI = 0.72-1.03) postdiagnosis use of non-aspirin NSAIDs. Associations between non-aspirin NSAID use and ovarian cancer mortality differed substantially with histological subtype of ovarian cancer, with inverse associations seen for serous ovarian cancer (any use: HR = 0.87, 95% CI = 0.77-0.99; high cumulative use: HR = 0.63, 95% CI = 0.47-0.84), the most common subtype of ovarian cancer, but not for other subtypes.

Conclusions: Overall postdiagnosis use of non-aspirin NSAIDs did not reduce ovarian cancer mortality; however, our findings indicate that more intensive use may be associated with improved survival of serous ovarian cancer.

198 | Statin use and progression in men with advanced prostate cancer treated with androgen deprivation therapy

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Background: Statins are found in reducing prostate cancer specific mortality. However, the effect of statins in advanced prostate cancer (PCa) receiving primary androgen deprivation therapy (PADT) and which types of statins would be most appropriate for use is not clear. **Objectives:** To examine the risk of overall survival (OS) and prostate cancer specific survival (PCS) associated with statins in men receiving PADT.

Methods: We conducted a retrospective cohort study using Taiwan Cancer Registry linked to National Health Insurance Research Data from 2008 to 2014. The study included 5749 advanced PCa men receiving PADT during study period. We excluded men who received surgery, radiation therapy, died within the first year of cancer diagnosis, or had missing age or cancer stage. All men were followed until death or the end of the study. We used Charlson's index to assess the burden of comorbidities at cancer diagnosis. A cox proportional hazard model was used to compare OS and PCS of men receiving and not receiving statins while adjusting for propensity score, use of metformin, chemotherapy, or next generation of ADT. Adjusted analyses were performed using inverse probability weighting (IPW). Exposure to statins was treated as a time-dependent variable.

Results: Overall, 2171 (38%) patients were treated with statins at the time of PCa diagnosis. Statin users were slightly younger and more likely to have comorbidities than non-statin users. IPW analysis using Cox regression showed that statin use associated with significantly better OS (adjusted hazard ratio [aHR] = 0.74, 95% confidence interval [CI]: 0.44-0.83) and PCS (aHR=0.72, 95% CI: 0.63-0.82) in metastatic PCa. However, the survival benefit was observed only in OS but not in PCS in men with T3/T4 diseases, and it varied by the type of statins. Patients receiving atrovastatins, pravastatins, rosuvastatins, or pitavastatins showed a significantly better OS and PCS than non-users. The aHR for OS was 0.76 (95%: 0.66-0.87), 0.48 (95%: 0.33-0.69), 0.59 (95%: 0.49-0.72), and 0.22 (95%: 0.10-0.48), respectively. No significant improvement in survival was found in those receiving fluvastatin, lovastatin, and simvastatin. The survival benefit remains after removing those initiating statins before cancer diagnosis.

Conclusions: Statin use is associated with improved survival among metastatic PCa patients receiving PADT. The survival benefit varied by the type of statins.

199 | Receipt and virologic outcomes of HCV direct-acting antivirals by alcohol use and HIV status

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Background: Unhealthy alcohol use is not a contraindication to initiation of direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection. However, the extent to which receipt of DAA therapy and subsequent achievement of cure of chronic HCV are impacted by alcohol use and human immunodeficiency virus (HIV) infection status is unknown.

Objectives: To evaluate receipt of DAA therapy and HCV cure rates by alcohol use category and HIV status.

Methods: We conducted a retrospective cohort study using the Veterans Health Administration (VA) Birth Cohort (>4.5 million patients born between 1945 and 1965). We followed HCV+ patients (all antibody-positive patients excluding those with negative HCV viremia prior to study start) from their first outpatient visit after January 1, 2014, until June 1, 2017. Alcohol use category (abstinent, lower risk drinking, hazardous/binge drinking, and diagnosis of alcohol abuse/dependence) was assessed within the year prior to the index visit based on Alcohol Use Disorders Identification Test-Consumption questionnaire scores and validated ICD-9 codes. Among those with post-treatment HCV viremia results, we determined achievement of HCV cure, defined as persistent absence of HCV viremia ≥ 12 weeks after treatment. We calculated the frequency of DAA initiation and HCV cure rates by alcohol use category and HIV status. Logistic regression models were used to estimate associations between alcohol use categories and HCV cure by HIV status.

Results: Among 124 387 HCV+ patients with known alcohol use status, 4041 (3%) were HIV+. A higher proportion of HIV+ patients received DAA therapy than uninfected (53.9% vs 49.9%; $p < 0.0001$), notably among abstinent and lower risk drinkers. High HCV cure rates were observed across all alcohol use categories (range, 92.1-95.4% among HIV+; 95.2-96.5% among uninfected). However, compared with patients abstinent from alcohol, those with a diagnosis of alcohol dependence/abuse were less likely to achieve HCV cure among HIV+ patients (odds ratio, 0.57; 95% CI, 0.36-0.89) and HIV-uninfected patients (OR, 0.72; 95% CI 0.65-0.80).

Conclusions: HIV+ patients and those with abstinent or lower risk drinking were more likely to receive DAAs. While HCV cure rates were reasonably high across all alcohol categories, those with a diagnosis of alcohol abuse/dependence were significantly less likely to achieve viral cure. These findings indicate a need for provider education and targeted outreach to engage those with unhealthy alcohol use in HCV care and treatment.

200 | Hospitalization after oral antibiotic initiation in Finnish community dwellers with and without Alzheimer's disease

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Background: Persons with Alzheimer's disease (AD) are frequently hospitalized from infection-related causes. There are no previous

studies investigating hospitalization associated with antibiotic initiation in persons with AD.

Objectives: To investigate the frequency and risk of hospitalization associated with oral antibiotic initiation among community dwellers with and without AD.

Methods: We performed a retrospective register-based cohort study using register-based Medication Use and Alzheimer's disease (MEDALZ) cohort. The cohort includes all community dwellers diagnosed with AD during 2005-2011 in Finland. 34 785 persons with AD and 36 428 comparison persons without AD matched by age, sex, and region of residence initiated antibiotic use. Exclusion criteria were prevalent antibiotic use and discharge from hospital within 14 days before antibiotic initiation. Drug use data were collected from the Prescription Register and comorbidities from Special Reimbursement and Hospital Care Registers. Infection diagnoses were collected from the Hospital Care Register. Main outcome was hospitalization within 14 days after antibiotic initiation.

Results: Risk of hospitalization following antibiotic initiation was higher among antibiotic initiators with AD than without AD (adjusted odds ratio 1.37, 95 % CI 1.28-1.46). Hospitalization was associated with comorbidities like epilepsy, active cancer, rheumatoid arthritis, diabetes, and the use of antipsychotics and benzodiazepines and oral glucocorticoids. Among initiators of cephalexin, pivmecillinam, amoxicillin/amoxicillin and enzyme inhibitor and doxycycline, persons with AD were more frequently hospitalized than persons without AD. A quarter of hospitalized antibiotic initiators had infection diagnosis in their hospital care records.

Conclusions: Persons with AD initiating an antibiotic had a higher risk for hospitalization than antibiotic initiators without AD. In both groups, several comorbidities were associated with hospitalization. Further research is needed to determine whether infection-related hospitalization could be reduced.

201 | Monthly intramuscular clindamycin served as a prophylactic antibiotic for recurrent cellulitis: An accessible alternative to penicillin regimen

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Background: Recurrent cellulitis, a common disease, accounted for 40% admission for cellulitis. Guideline recommended prophylactic antibiotics with daily oral penicillin or monthly intramuscular (IM) benzathine penicillin G (BPG) be used in recurrent cellulitis. Previous study also showed significant protective effect of BPG compared with no prophylaxis (incidence rate [IR] 0.73 vs 1.25/person-year [PY]). However, allergy to penicillin or global shortage of BPG leads to lack of convenient monthly prophylaxis.

Objectives: To evaluate if clindamycin (CLD) could be used as an alternative to BPG with equal efficacy for preventing recurrent cellulitis.

Methods: The retrospective cohort study was conducted in 2000 to 2017 using the electronic medical record database in a medical

center. Adults aged above 18 years old with recurrent cellulitis and received prophylactic BPG or CLD were included. Recurrent cellulitis was defined as (1) two or more recurrences or (2) one or more recurrence with known risk factor. The BPG was 1.2 to 2.4 MIU and CLD was 300 to 600 mg MIU monthly. Each recurrence separated more than 30 days was viewed as different episode. Cellulitis at different sites, culture other than *Streptococcus* spp. or *Staphylococcus* spp., irregular prophylaxis, or received other antibiotic during prophylactic period were excluded. Baseline characteristics, risk factors, comorbidities, and cellulitis history were retrieved. Recurrence or loss to follow-up were censored for prophylactic period. Statistics were chi-square or Fisher exact test for categorical variables, *t* test for continuous variables, and Poisson regression for incidence rate ratio (IRR).

Results: There were 82 patients included in the cohort contributing to 192 prophylactic periods with follow-up for 108.93 PY. CLD was used for 58 prophylactic periods, and 134 prophylactic periods were BPG. No significant differences in age, gender (CLD vs BPG, 64.4 ± 16.5 vs 60.0 ± 17.1 y/o, $P = 0.100$; 53.4% vs 56.0% male, $P = 0.747$), or other variables was noted, except for hyperlipidemia and cancer. The 16 recurrence episodes (23.6 PY) in CLD and 43 episodes (85.4 PY) in BPG resulted in IR of 0.68/PY and 0.50/PY. After adjustment, the IRR was 0.91 (95% CI 0.46-1.81, $P = 0.786$) which meant no significant difference in prophylactic efficacy between BPG and CLD.

Conclusions: Monthly IM CLD was revealed to have similar prophylactic effect in compared with BPG; thus, it could be served as reasonable alternative.

202 | Comparative effectiveness of teicoplanin versus vancomycin in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia

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Background: Vancomycin and teicoplanin are both recommended as first-line antibiotic for MRSA bacteremia in Taiwan. Some studies have established comparable efficacy between vancomycin and teicoplanin. However, the effectiveness and safety of different doses of teicoplanin are not fully evaluated.

Objectives: To compare the effectiveness and safety of different doses of teicoplanin versus vancomycin in patients with MRSA.

Methods: We conducted a retrospective cohort study by using data from a medical center in southern Taiwan. We included hospitalized patients with MRSA bacteremia who had been treated initially with either vancomycin or teicoplanin from 2016 to 2017. All MRSA episodes were grouped by the treatments of vancomycin, high (HT; ≥ 10 mg/kg/dose) or low dose (LT; < 10 mg/kg/dose) teicoplanin. We evaluated 7-day microbiological eradication and 30-day all-cause mortality of MRSA as the indicators of effectiveness. We compared

incidence of acute kidney injury among treatment groups. We performed multivariate logistic regression analysis with adjustments of hemodialysis status, body weight, and history of renal impairment to compare the different antibiotic use on clinical outcomes.

Results: We identified a total of 265 MRSA bacteremia patients with age of 70 ± 15 (mean $\pm$ SD) years and 59% were male. The majority were treated with vancomycin ($n = 154$; 58%), followed by low-dose teicoplanin ($n = 68$; 26%) and high-dose teicoplanin ($n = 43$; 16%). The microbial eradication rates were 30.2%, 32.4%, and 20.1%, and mortality rates were 30.2%, 17.6%, and 18.8% for HT, LT, and vancomycin groups, respectively. Compared with vancomycin group, HT (odds ratio, 2.00; 95% CI 0.85-4.69) and LT (1.88; 0.93-3.79) had better outcome of microbial eradication, although no statistical significant. However, the risk of mortality was non-significantly higher in HT (OR 1.91; 0.77-4.78) compared with vancomycin group. We found 3 (7.0%), 2 (2.9%), and 8 (5.2%) cases of acute kidney injury in HT, LT, and vancomycin-treated groups, respectively.

Conclusions: The findings indicated low dose of teicoplanin has higher rate of microbial eradication and lower rates of mortality with fewer cases of acute kidney injury compared with vancomycin. The study could be a strong ground for future analyses including more centers and samples.

203 | The antiretroviral therapy effectiveness in the viral load trend: A 10-year analysis of people living with HIV in Minas Gerais State, Brazil

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Background: HIV transmission has been strongly associated with high viral load (VL). Lowering VL through antiretroviral therapy (ART) can potentially impact HIV transmission at a population-level. Brazil has successfully provided free access to HIV testing, ART and VL assessment.

Objectives: The objective of this study was to evaluate the ART effectiveness on VL of people living with HIV (PLWH) during a 10-year follow-up period in a large Brazilian state.

Methods: Cross-sectional analyses of PLWH in Minas Gerais State, Brazil, who had at least one annual VL result, recorded from 2006 through 2015. Data were obtained from probabilistic linkage of two national health care databases: Medication Logistics and Laboratory Tests Control System, which are required for ART prescription and VL results nationwide. The dispensing of at least one antiretroviral regimen identified the number of PLWH on ART in each year. The ART effectiveness was assessed by the proportion of undetectable VL according to ART use for each year, stratified by gender and age. Chi-square linear trend by odds ratio (OR) was used to compare the proportion of undetectable VL under ART use over time. Significance level considered was 5%.

Results: From 2006 to 2015, most PLWH were male (57.0 to 61.0%). Mean age fluctuated with small differences (37 to 42 years old). During the period study, there was an increase in the number of PLWH who had at least one VL result (16 264 to 30 161) and were on ART (7565 to 26 585). The overall of undetectable VL increased from 43 to 67%, while among ART users this was 25 to 60% and among non-ART users from 19 to 6% ($P < 0.01$). OR showed increased linear trend: 1.00 to 7.41 (p value < 0.05) over the time.

Conclusions: ART has been effective over the time. Although there was an increase in PLWH using ART and in the proportion of undetectable VL from 2006 to 2015, the latter still remains low in order to achieve reduce HIV transmission at a population-level in Minas Gerais. Public health strategies focusing on treating all PLWH and improved adherence among those under ART should be emphasized.

204 | Macrolide empiric therapy is not associated with early clinical improvement in hospitalized patients with pneumonia

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Background: Community acquired pneumonia (CAP) is the leading cause of infectious disease related death worldwide. Guideline-concordant empiric treatment for hospitalized patients with CAP consists of a beta-lactam plus a macrolide or a fluoroquinolone. The benefits of macrolide therapy have recently been considered to extend beyond their antimicrobial nature, leading many to suggest the combination therapy over fluoroquinolones. However, controversy exists in this area, particularly due to the fact that data arise from observational studies and may suffer from bias from confounding by indication.

Objectives: To evaluate the impact of macrolide versus non-macrolide empiric therapy on early clinical improvement in hospitalized patients with community-acquired pneumonia

Methods: This was a secondary analysis of the Louisville Pneumonia Study, a population-based cohort study of adult hospitalized patients with CAP in all nine adult acute care hospitals in Louisville, Kentucky, from June 1, 2014, to May 31, 2016. Two groups were defined: Group 1 consisted of patients who received a macrolide plus a beta-lactam in the first 24 hours of admission but did not receive a fluoroquinolone. Group 2 consisted of patients who received a non-macrolide regimen. Early clinical stability was defined as meeting the 2001 ATS/IDSA clinical stability criteria on or before the third day of hospitalization. A two-stage probit model with an validated Area Deprivation Index as the instrumental variable was used for analysis.

Results: A total of 2406 included, 864 (35.9%) in Group 1, 1542 (64.1%) in Group 2. After adjustment for the instrument, macrolide therapy was not associated with early clinical improvement (OR: 0.7384, 95% CI 0.1115, 4.8883, $P = 0.753$).

Conclusions: This study suggests that confounding by indication is present in the evaluation of empiric treatment on early clinical

improvement in hospitalized patients with CAP. Care should be taken to consider confounding by indication in observational studies of empiric therapy for hospitalized patients with CAP. The benefits of macrolide therapy should be considered an unknown at this time.

205 | Consumption of reserve group antibiotics in Europe

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Background: The World Health Organisation (WHO) grouped antibacterials into three new categories in the latest Essential Medicines List (2017): Key Access, Watch group, and Reserve group antibiotics. Reserve group antibiotics should be kept as a last resort and protected through antimicrobial stewardship programmes.

Objectives: To map the use of Reserve group antibiotics in Europe in 2015.

Methods: Aggregated data on hospital consumption of systemic antibacterials (ATC J01) in European countries in 2015 were provided by the European Centre for Disease Prevention and Control (ECDC). The hospital use of Reserve group antibiotics (tigecycline, 4th generation cephalosporins, 5th generation cephalosporins, aztreonam, polymyxins, intravenous fosfomycin, and oxazolidinones) was analysed. Antimicrobial consumption was expressed as DDD per 1000 inhabitants per day (DID) to allow international comparison (WHO ATC-DDD index, 2017).

Results: Twenty-two European countries provided valid national data on hospital consumption of antibacterials for 2015. The European population weighted mean hospital consumption of Reserve group antibacterials was 0.036 DID, ranging from 0.004 DID (the Netherlands) to 0.173 DID (Greece). Among the Reserve group antibiotics in Europe: polymyxins, 4th generation cephalosporins, and oxazolidinones were the most common. The proportional consumption of polymyxins ranged between 3.3% (Latvia) and 73.7% (Hungary), while 4th generation cephalosporin and oxazolidinone consumption ranged between 2.9% (Portugal) to 70.9% (Estonia) and 4.8% (Malta) to 95.2% (Lithuania), respectively. Aztreonam and intravenous fosfomycin were consumed marginally in a few countries while the use of 5th generation cephalosporins was immeasurable.

Conclusions: This cross-national comparison study showed that the scale and pattern of Reserve group antibiotic use was very diverse in Europe (with an obvious north to south gradient). A comparison with national antimicrobial resistance data is needed to evaluate the observed values.

206 | Trends, disparities, and geographical variation in outpatient antibiotic consumption—A population-based prevalence study

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Background: Antimicrobial overuse and misuse is an important risk factor for antimicrobial resistance, and appropriate antibiotic prescribing behavior is important to ensure patient safety and quality of care. The availability of population-based community pharmacy prescription data at the individual person level in Denmark makes it possible to investigate not only time trends in overall antibiotic utilization but also use of individual antibiotics by patient sex, age group, and geographical residence.

Objectives: To examine trends in antibiotic use in Central Denmark Region between 2006 and 2015.

Methods: Data on all redeemed out-of hospital prescriptions for antibiotics in the adult population of Central Denmark Region (N = 2 943 705) was obtained from the Danish Prescription Database, 2006-2015. We examined recent time trends in the utilization of narrow- and broad-spectrum antibiotics as well as the variation in antibiotic use by sex, age, and municipality of residence.

Results: After an initial increase of 2% between 2006 and 2011, the overall prevalence of redeemed prescriptions for antibiotics per 1000 person-years declined by 17% between 2011 and 2015. Among persons aged over 65 years, decline in use began later (from 2013) and was less pronounced. In 2015, antibiotic use remained much higher among women (289/1000 person-years) vs men (182/1000 person-years) and among the very old (520/1000 person-years in >85 y old) vs middle-aged (204/1000 person-years in 45-65 y old). There was a clear decline over time in antibiotic use in all municipalities with decreasing geographical variation, but striking differences in the use of macrolides and fluoroquinolones remained in 2015, with a 1.6-fold variation in overall use. The overall use of narrow-spectrum antibiotics decreased from 2007 for all patients, while broad-spectrum antibiotics first declined from 2011 onwards. Among women aged ≥65 years and men aged ≥85 years, a continuous increasing trend in broad-spectrum antibiotics was observed from 2006 to 2015.

Conclusions: Antibiotic use has decreased by 19% in Central Denmark after 2011. However, substantial geographical variation in antibiotic prescription remains, and the use of broad-spectrum antibiotics has increased in adults of older age. There seems still to be a need for a more consistent and appropriate clinical practice and sustained attention in relation to the use of broad spectrum antibiotics, especially in adults of older age.

207 | Non-visit-based antibiotic use in a US Medicaid cohort

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Background: Antibiotic prescribing is an important target for safety and quality initiatives. However, antibiotic prescribing outside of visits has not been examined.

Objectives: Assess the frequency of antibiotic prescribing without an associated clinician visit.

Methods: We used 2004-2010 claims data from Medicaid, the US program for low-income individuals, including all filled prescriptions, inpatient and outpatient visits. We identified all filled antibiotic prescriptions and all medical claims in the 7 days prior to the antibiotic prescription. We defined a non-visit-based prescription (NVBRx) as occurring when the patient had no encounter with a clinician in those 7 days. We assessed whether the proportion of NVBRx differed by patient or antibiotic characteristics. We also examined whether the diagnosis codes for the clinician visits were for infectious conditions. Given the massive sample size—all comparisons were statistically significant—we considered differences of 5% clinically significant.

Results: In 7 years of data, we identified 242 million antibiotic prescriptions, dispensed to 46.4 million patients. Most prescriptions (62%) were dispensed to patients under 18 years old, and 61% were dispensed to female patients, 48% to white patients, and 20% to black patients.

For 70.8 million prescriptions (29%), there were no claims for clinician visits in the prior 7 days. NVBRx prescribing rates did not differ by gender (women, 30%; men, 28%) or race/ethnicity (white, 29%; black, 30%; other, 29%), but did differ by age (0-17 years old, 25%; 18-64 years old, 36%). NVBRx were more frequent in the Northeast (37%) and West (36%) than in the Midwest (26%) or South (26%). Among the 5 most commonly-prescribed antibiotic classes, the NVBRx rate was highest for sulfa antibiotics (33%), followed by quinolones (31%), penicillins (28%), macrolides (27%), and cephalosporins (26%).

Of prescriptions associated with a clinician visit, 27% (46 million/171 million) were not associated with a diagnosis code for an infectious condition.

Conclusions: A large fraction of antibiotic prescriptions—tens of millions in absolute terms—were filled without evidence of accompanying clinician visits. NVBRx occurred across the major classes of antibiotics and was more likely in adults and in some regions of the United States. NVBRx may lack clinician assessment and, along with prescribing without an infectious diagnosis code, may increase the risk of adverse effects. Interventions should be developed to address these safety and quality concerns.

208 | The effect of antimicrobial drug use on the composition of the urinary microbiota in an elderly population

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Background: The urinary tract is inhabited by a diversity of microorganisms, known as the urinary microbiota.

Objectives: Here, we investigated the association between the use of antimicrobial drugs and the composition of the urinary microbiota.

Methods: Clean-catch urinary samples were collected from 27 participants in the Rotterdam Study. Bacterial DNA was extracted and the 16S ribosomal RNA gene variable regions V3 and V4 were analyzed using Illumina sequencing. Differences in the urinary microbiota of individuals who did or did not use antimicrobial drugs in the three years prior to sampling were analyzed.

Results: 23 of the 27 participants were included in the analysis. Of 3 persons, too little bacterial DNA was obtained, and in one person, the urine contained almost exclusively *E. coli*. The population consisted of 10 men and 13 women with a mean age of 75 ± 3 years of whom 6 males and 7 females had used antimicrobial drugs in the preceding 3 years. The microbiota compositions showed considerable variability between individuals, but the most abundant species was *E. coli*. No differences were found in the alpha diversities between the individuals who had used antimicrobial drugs versus the ones that had not. However, the use of antimicrobial drugs prior to urine sampling was associated with statistically significant differences in beta-diversity. A lower abundance of *Lactobacillus* was demonstrated in individuals who had used antimicrobial drugs, whereas *Bacteroides* and uncultured members of the *Lachnospiraceae* and *Peptostreptococcaceae* families had higher abundancies.

Conclusions: Prior use of antimicrobial drugs is associated with a different composition of the urinary microbiota. Our results might indicate a long-term effect of antimicrobial drugs on the composition of the microbiota. However, due to the design of the study, we cannot rule out reverse causality. Follow-up studies are needed to differentiate between urinary dysbiosis as a result of antimicrobial drug use or urinary dysbiosis as risk factor for urinary tract infections resulting in increased use of antimicrobial drugs.

209 | 20-year nationwide follow-up study on discontinuation of antipsychotic treatment in first-episode schizophrenia

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Background: It is generally believed that, after the first episode of schizophrenia, the risk of relapse decreases as time goes by. Many treatment guidelines recommend that after stabilization, antipsychotic treatment should be continued for 1-5 years, and longer exposure should be avoided if possible. However, there is no published evidence to substantiate these views.

Objectives: The aim was to study the risk of treatment failure (re-hospitalization or death) as a function of the duration of antipsychotic treatment prior to discontinuation among comprehensive nationwide cohort of first-episode patients with schizophrenia.

Methods: Hospital discharge register was utilized to identify all persons hospitalized for the first time with schizophrenia during 1996-2014 in Finland. Persons who had used antipsychotics during the year before their index hospitalization were excluded, leaving 8738 incident cases. Those who discontinued antipsychotic use ($N = 1714$ discontinuers) were categorized based on duration of antipsychotic use before discontinuation: 0, <1, 1-2, 2-5, and more or equal than 5 years. Zero group refers to non-users. For each patient discontinuing antipsychotic treatment, we matched a user continuing the use at this time point, based on time on antipsychotic. The main outcome was the risk of treatment failure after discontinuation, analyzed with multivariate Cox regression and Kaplan-Meier analyses.

Results: The lowest risk of treatment failure was observed for patients using antipsychotic continuously (adjusted hazard ratio 1.00), followed by patients discontinuing antipsychotic use immediately after discharge from the first hospital treatment (HR 1.63, 95% CI 1.52-1.75), within 1 year (HR 1.88, 95% CI 1.57-2.24), within 1-2 years (HR 2.12, 95% CI 1.43-3.14), within 2-5 years (HR 3.26, 95% CI 2.07-5.13), and after 5 (median 7.9) years (HR 7.28, 95% CI 2.78-19.05). Non-users and patients with early discontinuation of antipsychotics had 174-214% higher mortality compared with those patients using antipsychotic continuously up to 16.4 years ($p = 0.0001$).

Conclusions: Regardless of the underlying mechanisms, the risk of treatment failure or relapse after discontinuation of antipsychotic use does not decrease as function of time during the first 8 years of illness, and long-term antipsychotic treatment is associated with increased survival.

210 | "Real-world" effectiveness of methylphenidate in improving academic achievement of attention deficit hyperactivity disorder (ADHD) students—A systematic review

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Background: Methylphenidate is the most commonly prescribed drug for treatment of attention deficit hyperactivity disorder (ADHD).

Impaired school performance is one of the main reasons for starting ADHD medication, but the evidence of improvement due to methylphenidate is not well established.

Objectives: To evaluate the evidence of the “real-world” effectiveness of methylphenidate in improving academic achievement of ADHD students.

Methods: We have conducted a systematic review of observational studies. Electronic searches were performed in five databases, besides manual and gray literature searches. Observational studies evaluating academic outcomes with methylphenidate compared with no treatment, or other pharmacological/nonpharmacological alternatives used in ADHD were included. These studies were all conducted in scholarly settings, and the participants were students at any level with an ADHD diagnosis. We have assessed the bias risk of selected studies using adapted versions of the Newcastle-Ottawa scale.

Results: Three cohort, two before-and-after design, and two cross-sectional studies were included in the review. They involved 366 children aged 6 to 18 years. The methylphenidate dosages ranged from 10 to 72 mg/day, and the treatment duration from 2.6 months to 4.25 years. In five out of seven studies, the authors concluded that methylphenidate leads to improvement in academic performance. However, among the four lowest bias risk studies, three reached conclusions that the drug is ineffective for this purpose. Four studies assessed the long-term use of methylphenidate (more than one year), and only one concluded methylphenidate is effective, but it had the highest bias risk among these four. The studies have considerable methodological limitations and great heterogeneity regarding academic performance measurement criteria.

Conclusions: Although there are studies indicating that short-term use of methylphenidate may improve academic outcomes, the evidence is weak. The available scientific literature does not conclusively support the “real-world” effectiveness of methylphenidate.

211 | Efficacy and safety of naltrexone for amphetamine and methamphetamine use disorder: A systematic review of randomized controlled trials

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Background: Methamphetamine intake has increased substantially in recent years, being the second most abused illicit substance after cannabis. However, there is currently no effective evidence-based pharmacological treatment for amphetamine or methamphetamine use. Naltrexone, an opioid antagonist has been suggested as a possible treatment option by blocking the rewarding effects of amphetamine and methamphetamine.

Objectives: To evaluate the practicality in using naltrexone as a pharmacological treatment for amphetamine and methamphetamine use disorder.

Methods: We searched PubMed, EMBASE, and Cochrane Library with bibliographies of the retrieved articles screened. Studies investigating the effects of naltrexone on amphetamine or methamphetamine use were eligible for inclusion. Primary outcome was defined as attenuated subjective measures of amphetamine or methamphetamine (eg, level and frequency of drug use). Secondary outcome was rate of abstinence, compliance, adverse events and physiological changes (ie, blood pressure, heart rate). All studies were rated as low risk of bias using the Cochrane tool for risk of bias.

Results: Among 591 identified studies, nine randomized controlled trials were included after eligibility assessment. In total, five studies investigated the effects of naltrexone for amphetamine and four studies for methamphetamine use disorder. Naltrexone modestly attenuated subjective effects for amphetamine users but revealed conflicting results for methamphetamine users. Two amphetamine studies showed conflicting results on abstinence rate and inconclusive results for methamphetamine after treatment. All studies reported well tolerability of naltrexone.

Conclusions: Naltrexone has a modest effect on amphetamine but varying effect on methamphetamine disorder regarding attenuated subjective effects. The effects of naltrexone on the abstinence rate of amphetamine and methamphetamine remains inadequate and inconclusive. The tolerability and safety in both amphetamine and methamphetamine studies appears to be promising and in favor of naltrexone. Due to the limited large-scale studies conducted to confirm the efficacy of naltrexone for amphetamine and methamphetamine use disorder, more high-quality studies are warranted to further evaluate the potential use of naltrexone.

212 | Varenicline is more effective than nicotine replacement therapy during pregnancy: Findings from the smoking mums (maternal use of medications and safety) study

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Background: Studies in the general population suggest that varenicline is more effective than nicotine replacement therapy (NRT) for smoking cessation. However, clinical guidelines recommend against the use of varenicline during pregnancy and suggest NRT be used when the expected benefits outweigh the potential risks.

Objectives: To evaluate whether varenicline was more effective than NRT for smoking cessation when used during pregnancy as evidence on this question is lacking.

Methods: Routinely-collected records of all births (1 January 2011 to 31 December 2012) in New South Wales and Western Australia were used to identify a cohort of women who smoked during the first 20 weeks of pregnancy (self-reported). Pharmaceutical dispensing data were linked to birth records to identify varenicline or NRT dispensing in the first 20 weeks of pregnancy. Smoking cessation was defined as women reported not smoking (ie, quitting) after the first 20 weeks of pregnancy. Inverse probability of treatment weighting with propensity scores were used to account for differences in socio-demographic, obstetric characteristics, and pre-existing co-morbidities between the two treatment groups. Crude and adjusted rate differences (RD) with 95% confidence intervals (CI) were calculated.

Results: Overall, 117 women used varenicline and 135 NRT in the first 20 weeks of pregnancy. In the unweighted sample, more women who used varenicline quit smoking after the first 20 weeks than women using NRT (28.2 vs 11.1%, crude RD: 17.1%, 95% CI: 7.4-26.8%). In the weighted sample, quitting rate was 12.7% (95% CI: 0.8-24.6%) higher in pregnant smokers who used varenicline (27.4% vs 14.7%) when compared with those who used NRT.

Conclusions: Pregnant smokers using varenicline were more likely to quit smoking than those using NRT. This information will assist health care providers to make informed recommendations, but data regarding safety of varenicline in pregnancy are also urgently needed. Future studies with greater statistical power are required to confirm our results.

213 | Abstract Withdrawn

214 | Use of electronic health care data to study the real-world utilization of antineoplastic drugs for the treatment of lung cancer: A systematic review

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Background: During the last decade, pharmacotherapy of lung cancer has evolved rapidly and different new target therapies have been licensed. In this context, studying the real-world use of these medicines to complement information from clinical trials becomes paramount. Routinely collected electronic health care data (EHD) is the data source of choice for those studies.

Objectives: To retrieve and describe published studies providing information on the real-world utilization of antineoplastic drugs for the treatment of lung cancer based on EHD.

Methods: A systematic review of Pubmed database was performed to identify all retrospective, observational studies published between 2012 and 2017. Only studies based on EHD and providing information on the real-world use of drugs for lung cancer were included. Studies with any type of ad hoc data collection were excluded. Each included article was described in terms of data source and study characteristics, and information items used to characterize drug users. A narrative synthesis of evidence provided by the included studies on drug utilization in lung cancer was also performed.

Results: A total of 353 publications were found. After abstract/title screening 307 records were excluded while 45 full-texts were examined. Fifteen studies met the inclusion criteria (ad hoc data collection n=18, no drug utilization informations n = 12). No study was performed in Europe (11 United States, 1 Canada, 1 China, 1 Japan, 1 Korea). In four case, the study cohort was hospital-based, while the remaining were population-based. Study populations ranged from 328 to 24 090 patients. Thirteen studies used data from record linkage of administrative, medical records, and/or cancer registry data, while two used medical records only. Ten studies evaluated target therapy drug utilization including Bevacizumab and Tyrosine kinase inhibitors, while five studies only concerned standard chemotherapy.

Conclusions: This systematic review highlighted the paucity of published studies on the topic. Notably, no study was performed in Europe. The record linkage of different sources of data seems to be necessary to gather sufficient information on lung cancer pharmacotherapy. Other than report on the available evidence from the included studies, final results from this review will provide recommendations for the execution of drug utilization studies in lung cancer patients that will leverage the re-use of routinely collected EHD.

215 | Overall survival and treatment patterns among real-world patients with metastatic non-small cell lung cancer not previously treated with systemic therapy for advanced cancer

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Background: At diagnosis, ~70% of patients with non-small cell lung cancer (NSCLC) have locally advanced or metastatic disease not amenable to surgical resection. Further, prognosis is poor (1-year survival rate: 13-29%). While treatment of these patients is focused on extending survival, real-world treatment patterns and effectiveness data for existing therapies are limited.

Objectives: To retrospectively characterize real-world patients with metastatic NSCLC not previously treated with systemic therapy for advanced cancer, describe treatment patterns, and estimate overall survival (OS) from initial diagnosis of metastatic NSCLC.

Methods: Adults diagnosed with metastatic NSCLC under routine care (excluding those with *EGFR* mutations or *ALK* alterations, or those who previously received systemic therapy for advanced disease) were identified from the US Flatiron Health Oncology electronic medical record (EMR) database. Eligible patients' EMR data (2013-2017) were used to collect patient characteristics; determine treatment patterns, including regimens administered and time from diagnosis to treatment; and estimate median OS (calculated from Kaplan-Meier curves with associated 95% confidence intervals [CI]) from the initial diagnosis of metastatic NSCLC.

Results: In total, data for 9656 patients were analyzed. Mean (SD) age was 68.0 (10.0) years; 54.0% were men; and 88.2% were smokers. Mean (SD) time from diagnosis of metastatic disease to start of first-line therapy was 84.5 (140.7) days, and patients received a median of 1 (range: 1-8) systemic therapy treatment line. Most common (>10% patients) systemic therapy regimens were nivolumab (16.7%), carboplatin + paclitaxel (14.2%), and carboplatin + pemetrexed (12.5%); no treatments were recorded for 26.7% of patients. Median OS was 11.1 months (95% CI: 10.8-11.5) from the initial diagnosis of metastatic disease.

Conclusions: In this retrospective real-world study, more than one quarter of patients were untreated after diagnosis of metastatic NSCLC. Overall, OS was <1 year from initial metastatic NSCLC diagnosis. These findings indicate a need for additional treatment options for these patients, as more patient information such as biomarker testing results are becoming available to physicians at time of initial diagnosis.

216 | Overall survival and treatment patterns among real-world patients with metastatic urothelial carcinoma treated with first-line therapy

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Background: Platinum-based chemotherapy is standard of care for locally advanced or metastatic urothelial carcinoma (UC). However, median overall survival (OS) of patients is 12 to 15 months from start of treatment, demonstrating a need for improved treatments, including the emerging immunotherapies.

Objectives: To characterize real-world patients with metastatic UC treated with systemic first-line therapy, describe general treatment patterns, and estimate OS from start of treatment.

Methods: Adults who were diagnosed with metastatic UC before June 2016 and started systemic first-line therapy were identified from the US Flatiron Health Oncology electronic medical record database (EMR); patients previously treated with immunotherapy were excluded. Eligible patients' EMR data (2011-2017) were used to collect patient characteristics; determine treatment patterns, including most frequently administered regimens and time from advanced/metastatic diagnosis to start of therapy; and estimate median OS from start of first-line therapy.

Results: In total, data from 1811 patients were analyzed. Mean (SD) age was 70.4 (9.5) years; 73.2% of patients were men; and 70% were smokers. Median time from metastatic UC diagnosis to start of first-line therapy was 43 days. Patients received a median of 1 treatment line during follow-up. Mean (SD) treatment duration from start of treatment across all lines was 390.7 (401.7) days. Platinum-based chemotherapy was the most commonly prescribed first-line treatment, most frequently gemcitabine + carboplatin (34.6%) followed by gemcitabine + cisplatin (27.2%); immunotherapy was the most commonly prescribed second-line treatment. Median OS was 12.7 months (95% CI: 11.8-13.4) from initiation of first-line therapy.

Conclusions: Findings from this study of patients with metastatic UC revealed platinum-based therapies were the most frequent first-line systemic treatment used in clinical practice; immunotherapy was the most commonly prescribed second-line treatment; and OS was ≈1 year from start of treatment. The impact of immunotherapy on OS in the real world will become clearer as these therapies are more commonly used.

217 | Chronic myeloid leukemia among veterans from 2006 to 2015: Trends in utilization of tyrosine kinase inhibitors

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Background: Oral tyrosine kinase inhibitors (TKI) have substantially improved treatment and outcomes of chronic myeloid leukemia (CML) since Imatinib approval in 2001. Treatment options for newly diagnosed adult patients expanded with the addition of newer-generation TKIs (NGTKIs), Dasatinib and Nilotinib, as first-line therapies.

Objectives: We examined CML treatment with the three TKIs, Imatinib, Dasatinib, and Nilotinib, across the Department of Veterans Affairs (VA) in the period 2006-2015.

Methods: Retrospective analysis: We identified Veterans newly diagnosed with CML in 2006-2015 using national data from the VA cancer registry and Corporate Data Warehouse. We collected patient characteristics at diagnosis, including age, race, rural/urban residence, clinical comorbidities, and prescriptions for TKI through December 2015. We examined patient characteristics associated with treatments using logistic regression, and overall survival using a Cox proportional hazards model.

Results: Among 468 patients diagnosed with CML, 436 (93%) initiated TKI treatment with a median time of 21 days from diagnosis (interquartile range, 8 to 89 days). Patients not treated with TKI were significantly older than those treated (mean age, 74 years (SD 10) vs 64 (SD 14), $P < 0.001$). In 2010-2015, Imatinib remained the common first-line TKI (average % of first TKI prescriptions per year: 79%, [95% CI, 75%-83%]; versus Dasatinib, 13% [9%-16%], and Nilotinib, 8% [6%-12%]). Controlling for diagnosis year, the use of NGTKIs versus Imatinib was less likely with older age (OR 0.97 [95% CI, 0.95-0.99]), higher comorbidity (OR 0.47 [95% CI, 0.26-0.88] and among patients in rural areas (OR 0.38 [95% CI, 0.17-0.83]; we observed no difference by patient race. Adjusting for age, race and comorbidities, overall survival at three years with use of any TKI was 91%, with no differences by treatment with Imatinib versus NGTKIs.

Conclusions: Most Veterans diagnosed with CML in 2009-2015 received treatment with TKIs, and Imatinib remained the predominant TKI used at VA for CML. Lower use of Dasatinib and Nilotinib among older patients and those with more comorbidities warrant further study. While evidence is growing that NGTKIs may lead to faster and deeper response than Imatinib, appropriateness of use for those patients may vary due to differences in safety profiles.

218 | Impact of psychotropic polypharmacy on health care resource utilization among newly diagnosed non-metastatic cancer patients in the United States

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Background: More than a third of patients with newly diagnosed cancer experience mental health and adjustment disorders due to which these patients are frequently prescribed psychotropic medications.

Objectives: To evaluate the associations between psychotropic polypharmacy and health care resource utilization among newly diagnosed cancer patients in the United States.

Methods: This retrospective cohort study included adult patients diagnosed with the most common cancers (breast, prostate, colorectal, lung) during 2011-2012 from the Optum Clinformatics® Data Mart

(OptumInsight, Eden Prairie, MN) de-identified commercial claims database. Inclusion criteria required continuous enrollment with both medical and pharmacy benefits for at least year prior to and following cancer diagnosis, and ≥ 2 claims for the same cancer in primary or secondary position ≥ 30 days apart. Patients with evidence of metastasis or concurrent cancers were excluded. Psychotropic polypharmacy was defined as concomitant use of two or more psychotropic medications for a period of at least 90 days during the first year following cancer diagnosis. Unadjusted incidence rates for health care resource utilization were calculated as the number of events of interest divided by person-time at risk and adjusted incidence rate ratios were estimated using negative binomial or Poisson regressions.

Results: A total of 5604 cancer patients were included, of which 53% had breast cancer, 31% had prostate cancer, 11% had colorectal cancer, and 5% had lung cancer. Psychotropic polypharmacy was reported in 7.4% of cancer patients during follow-up. Cancer patients with psychotropic polypharmacy had higher rates of health care resource utilization compared with those without psychotropic polypharmacy. In the adjusted regression models, those with psychotropic polypharmacy had 30% higher rates of office and outpatient visits, 18% higher rates of inpatient admissions, 30% higher rates of outpatient visits, than those without psychotropic polypharmacy. The rates of emergency department visits were similar between the groups.

Conclusions: Psychotropic polypharmacy is associated with higher rates of health care resource utilization during the first year after a new cancer diagnosis suggesting that co-morbid mental health disorders and hence psychotropic medication use is an important driver of overall health care resource utilization in this population.

219 | 5- α -Reductase inhibitors prescribing patterns for benign prostatic hyperplasia: Evaluation and cost-effectiveness analysis in an Italian local health care system

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Background: Benign prostatic hyperplasia (BPH) is an age-related condition associated with prostatic enlargement and bladder outlet obstruction with consequent lower urinary tract symptoms that can greatly affect patients' quality of life. Effective treatment for BPH can rely on 5- α reductase inhibitors (5-ARIs): Dutasteride and Finasteride, that reduce global prostate volume and serum prostate-specific antigen level. Dutasteride differs from Finasteride as it can inhibit both 5- α reductase isoenzymes and, thus, results in an almost complete suppression of serum dihydrotestosterone. Although the two drugs efficacy is similar, their costs are significantly different: 1€/DDD for Dutasteride versus 0.28€/DDD for Finasteride. Recently, local health care system recommendations stated Finasteride as a first-line treatment for BPH (more cost-effective drug).

Objectives: The aim of this study is to evaluate general practitioners' (GPs) prescribing patterns for BPH before approval of local recommendations on May 28, 2017.

Methods: We extrapolated, from our regional database, GPs prescriptions of 5-ARIs between January 1, 2016, and June 30, 2017. Prescriptions of drug combinations were excluded. We selected patients receiving a first-time prescription of Dutasteride starting from July 1, 2016, and we verified, in the previous semester, if they already received a treatment with Finasteride.

Results: In total, from January 1, 2016, to June 30, 2017, 8953 patients (median age 74.4 years) were treated with 5-ARIs and, among them, 7073 with Dutasteride. From July 2016, 1669 patients started a therapy with Dutasteride, with 122 patients who had already received a previous Finasteride prescription but with no reports of adverse reactions. Moreover, 144 patients received Dutasteride as a first-line treatment and then were switched to a second-line Finasteride.

Conclusions: The results of this study show GPs' prescribing patterns of 5-ARIs for BPH treatment: 18.9% of patients received a non cost-effective treatment for BPH according to recent local recommendations, but no significant differences were observed between patients receiving Dutasteride vs Finasteride. However, a correct prescription of first-line Finasteride would have resulted in an overall cost saving of 35,037,52 €/year. GPs' education will be implemented to improve adherence to local recommendations.

220 | Drug utilization before and after a diagnosis with sarcoidosis

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Background: Sarcoidosis is a multiorgan disease characterized pathologically by the presence of noncaseating epithelioid granulomas in affected organs in which the lungs are most frequently involved. The disease is often difficult to diagnose. The burden of drug use up to- and after being diagnosed with sarcoidosis has yet to be examined.

Objectives: To assess the pre- and post drug use patterns in patients newly diagnosed with sarcoidosis, with focus on temporal patterns in treatment.

Methods: All adults (≥ 18 years) diagnosed with sarcoidosis (ICD-10: D86) during 2000-2016 who lived on the island of Funen, Denmark (population 490 000) and a comparison cohort of sex- and age-matched (1:10) population controls. We calculated rates of new drug treatment and total drug use and examined use of new and prevalent drugs before and after diagnosis.

Results: In total, 1516 patients and 15 160 controls were included in the study; median age 44 years (Interquartile range [IQR] 34-57 years), 47% were females, 77% cases ($n = 1166$) and 85% controls ($n = 12 932$) had a low burden of comorbidity (Charlson Comorbidity Index 0), and 33% cases and 30% controls had a long education (13+ years). We observed an increasing rate of new drug treatment from 6 to 3 months prior to diagnosis, which peaked in the first month after

diagnosis at 46 new types of drugs per 100 individuals (mainly systemic corticosteroids, non-steroid anti-inflammatory treatment, proton pump inhibitors, and paracetamol). We observed a declining rate to 14 new types of drugs per 100 individuals 1-year post-diagnosis, which was higher than that rate of new drug use among controls after one year (8 new types of drugs per 100 individuals). We found no difference in the number of prevalent drug prior to the diagnosis (median 2 drugs, IQR 1-4) and shortly after the diagnosis (median 2 drugs, IQR 1-5).

Conclusions: We found a substantial increased drug treatment among patients diagnosed with sarcoidosis compared with a control population, which also varied considerably in relation to the time of the diagnosis.

221 | Predictors of tyrosine kinase inhibitor treatment for chronic myeloid leukemia

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Background: Tyrosine kinase inhibitors (TKIs) have dramatically improved survival for patients with chronic myeloid leukemia (CML). While no overall survival differences have been observed between the 3 TKIs approved for first-line treatment of CML, the treatments have distinct toxicity profiles which may influence treatment choice.

Objectives: Describe TKI use for patients newly treated for CML and identify demographic and clinical predictors of treatment with dasatinib, imatinib, or nilotinib.

Methods: We identified patients with 1+ fill for a TKI in the MarketScan Commercial and Medicare Supplemental Databases, 1/1/2011-9/30/2017 (earliest fill = index date). Eligible patients had a diagnosis of CML 6 months pre- or 30 days post-index. A 6-month baseline period was used to measure predictors of treatment and exclude prior TKI use. Multinomial logistic regression was used to estimate predictors of treatment.

Results: Eligible patients included 1528 imatinib, 1177 dasatinib, and 678 nilotinib initiators. In 2011, first-line TKI treatment consisted of 57% imatinib, 24% dasatinib, and 19% nilotinib. Dasatinib use increased over time to 44% of new TKI use in 2017, while imatinib and nilotinib use declined to 44% and 12%, respectively. Nilotinib-treated patients more commonly received a dose consistent with advanced phase disease (15% versus 7% [imatinib] and 5% [dasatinib]). Imatinib patients were older (imatinib: mean [SD] age: 56 [17]; dasatinib: 52 [15]; nilotinib: 54 [14]) and had a higher mean [SD] Klabunde-Charlson Comorbidity Index (imatinib: 0.74 [1.3]; dasatinib: 0.55 [1.0]; nilotinib: 0.60 [1.2]). Vascular, cardiac, pulmonary, and renal comorbidities in the baseline period were less common among patients treated with nilotinib and dasatinib, while liver comorbidity was more common among imatinib-treated patients, but preliminary analyses suggest none were statistically significant predictors of

treatment choice. Gastrointestinal comorbidity was rare but significantly associated with nilotinib versus imatinib treatment (OR 3.00 95% CI 1.03-8.80) and nilotinib versus dasatinib (OR 3.23 95% CI 1.03-10.13).

Conclusions: Despite no evidence of improved overall survival, treatment with dasatinib has increased over time. While older patients with more comorbidities were more likely to receive imatinib than nilotinib or dasatinib, specific comorbidities were not predictive of treatment use, despite varying adverse event profiles. Future analyses will evaluate how predictors have changed over time.

222 | Use of prescription drugs among ovarian cancer patients in Denmark

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Background: Ovarian cancer patients often suffer from chronic diseases at diagnosis. Thus, drug use for prophylaxis or treatment of concomitant disease is considerable at diagnosis of ovarian cancer.

Objectives: To describe general drug utilization among post-menopausal ovarian cancer patients, with focus on temporal patterns in drug use and consideration of tumor characteristics and clinical stage.

Methods: We identified all post-menopausal women diagnosed with epithelial ovarian cancer in Denmark between 2005 and 2012 and a comparison cohort of age-matched (1:4) women without cancer. We calculated rates of new and total drug use and examined use of the most common new and prevalent drug classes before and after ovarian cancer diagnosis. Drug exposure rates were specified by histological type and clinical stage of ovarian cancer.

Results: We identified 2742 ovarian cancer patients. The rate of new drug treatment began to increase from 3-5 months prior to diagnosis and peaked in the first month after diagnosis with 99 new types of drug therapy per 100 patients. Immediate post-diagnosis drug therapy, besides the standard cancer therapy, mainly included anti-emetics, proton pump inhibitors, hypnotics, and opioids. Although declining, the rate of new drug use remained substantially higher among ovarian cancer patients than among cancer-free controls throughout the 3-year post-diagnosis follow-up period. The number of prevalent drugs increased slightly from a median of four drugs (interquartile range [IQR] 2-7) prior to diagnosis to five (IQR 2-8) shortly after the diagnosis. The use of prophylactic drugs, eg, statins, anti-hypertensives, and low-dose aspirin, decreased only slightly after diagnosis. We found little variation according to histological type, whereas the patterns were slightly more pronounced among women with non-localized disease.

Conclusions: Drug use among post-menopausal ovarian cancer patients was substantial and varied substantially in relation to the time of cancer diagnosis, although only limited changes were seen in the use of prophylactic drugs.

223 | Adherence to adjuvant endocrine therapy for breast cancer patients: Impact of a recently implemented outreach program

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Background: Up to 50% of hormone receptor positive (HR+) breast cancer patients do not complete the recommended 5 years of adjuvant endocrine therapy (AET). In 2011, Kaiser Permanente Northern California (KPNC) implemented an outreach program to improve adherence to and continuation of AET. The program includes three contacts with patients with evidence of non-adherence: (1) reminder letter from oncologist, (2) phone call by pharmacist or nurse/oncologist, and (3) second reminder letter from oncologist.

Objectives: To examine the impact of a recently implemented outreach program at KPNC on adherence to and continuation of AET.

Methods: We used the KPNC cancer registry to identify patients diagnosed with HR+ breast cancer during three years before (2005, 2006, 2007) and three years after (2012, 2013, 2014) implementation of the outreach program. Electronic pharmacy records were used to capture prescriptions for AET (tamoxifen, aromatase inhibitors). We defined adherence as a medication possession ratio (MPR) of $\geq 80\%$ and estimated adherence for the periods 0-12, 13-24, and 25-36 months following AET initiation. We defined discontinuation as >180 days since last day supply and generated Kaplan-Meier curves to estimate time to first discontinuation. In addition to the full study population, we conducted subgroup analyses stratified by race/ethnicity, age and medical center.

Results: Approximately 1000 HR+ patients initiated AET in each calendar year of the study. For each of the diagnosis years of interest, adherence to AET ranged from 74-79% during the 12 months after AET initiation, from 67-75% during the 13-24 months after AET initiation and from 57-71% during the 25-36 months after AET initiation. Compared with the pre-outreach period, there was no consistent pattern of improved AET adherence during the period after outreach implementation. Discontinuation ranged from 5-10% in each 12-month period following AET initiation. Cumulative discontinuation rates at years 1 and 2 after AET initiation were similar for the pre- and post-outreach periods, but surprisingly slightly higher at year 3 during the post-outreach period (post = 29%, pre = 22%, log-rank $p < 0.001$). Improvements in adherence and continuation post-program implementation were also not observed in subgroups based on age, race/ethnicity or medical center.

Conclusions: Our results indicate that the outreach program to remind patients to refill their AET had little if any impact on adherence or continuation.

224 | Adherence to oral anticoagulants in patients with atrial fibrillation

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Background: Information on adherence to oral anticoagulants (OAC) and its association with clinical outcomes using real-world data barely exists. Such studies are required in France by health authorities.

Objectives: To describe adherence to OAC in patients with atrial fibrillation (AF), and estimate the associated factors in routine clinical practice.

Methods: This is a population-based retrospective cohort study including patients with AF treated with OAC (VKAs and DOACs), from the PGRx-AF registry in France (2014-2016). Patients were routinely and consecutively included by a practice-representative network of 138 cardiologists and 22 GPs, blind to study objectives, who collected patients' medical data and provided 1-year prescriptions prior to recruitment. Patients were interviewed to inform 1-year history of OAC and bleedings prior to recruitment, and OAC start. Adherence is defined by a combination of proportion of days covered (PDC) and patient self-reporting of compliance (OAC taken every day = 1, regularly [4 to 6 days a week] = 2, or sometimes [≤ 3 days] = 3), resulting in high (PDC $\geq 90\%$ and OAC taken every day) vs low (PDC $< 90\%$ or compliance = 2 or 3) adherence; non-persistence. Clinical outcomes: major (hospitalization) and minor bleedings. Analysis: multivariate logistic regression models to explore the associations between adherence and bleedings and other factors.

Results: Among the 3693 interviewed AF patients, 3147 were OAC users, mostly men (64.5%), with a mean age of 74.5 years [9.4]. The median OAC duration was 23.1 months [3 days; 44.9 years], with 32.8% of incident (4.3 months [3.8]) and 67.2% of prevalent use (5.1 years [5.5]). Overall 5% of users were low adherent with 6.7% vs 4.1% for incident and prevalent users. Among the 2098 patients with at least 12 months OAC duration, non-persistence at 3, 6, 9, and 12 months was 0.2%, 0.5%, 1.0% and 2.0%. Sex, CHA₂DS₂VASc, and HAS-BLED were not associated with adherence. Increasing age was weakly associated with high adherence (0.96 [0.94-0.97]) while permanent AF and prevalent OAC use were strongly (0.39 [0.26 - 0.58], 0.65 [0.46-0.90]). On the opposite bleedings, major or minor, were highly associated with low adherence (3.80 [1.79-8.05] and 2.80 [1.51-5.20]), and OAC switches held the highest association (6.67 [4.47-9.94]). When only patients with a minimum OAC duration of 6 months were kept, results were similar.

Conclusions: A key finding is that occurrence of bleeding, even minor, is one of the main reasons for poor adherence. Adherence still must be improved.

225 | Rituximab use in medicare patients with immune thrombocytopenia (ITP)

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Background: Although it is well-recognized that rituximab can be used off-label as a 2nd-line therapy for ITP, population-based studies on the extent and nature of its use in this setting are lacking.

Objectives: To describe incidence of rituximab initiation and associated patterns of treatment in a population-based cohort of elderly ITP patients in the US.

Methods: Using the Medicare 100% hematologic disease files (2007-2015), we identified elderly Medicare fee-for-service enrollees newly diagnosed with primary ITP in 2010-2014. Patients were followed from ITP diagnosis until the first of rituximab initiation, death, disenrollment, or 09/30/2015. Cumulative probability of rituximab initiation was estimated using the Kaplan-Meier method with log-rank test to assess differences by baseline characteristics. Median (IQR) duration of treatment and number of injections were reported.

Results: Our study included 17 117 elderly patients newly diagnosed with primary ITP (mean [SD] age: 79.1 [7.6] years; 51% female; 89% white). At diagnosis, the most common comorbid conditions were diabetes (33%), coronary artery disease (33%), congestive heart failure (19%), chronic obstructive pulmonary disease (18%), and chronic kidney disease (16%). During follow-up (mean [SD]: 26.9 [20.6] person-months), 1562 patients (9%) received rituximab with a median (IQR) time from diagnosis to initiation of 3 (1-8) months. Cumulative probability (95% CI) of initiating rituximab at 6 months and at 3 years was 6.7% (6.3-7.1) and 10.6% (10.1-11.1), respectively. Those who were white and those who did not have one of the aforementioned comorbid conditions were more likely to receive rituximab than their counterparts. Differences between age groups lacked statistical significance. Among rituximab-treated patients (mean [SD] age, 78.6 [7.1] years; 53% female; 93% white), at initiation, 59% had a history of any bleeding (eg, 19% gastrointestinal bleeding; 17% ecchymosis; 13% epistaxis; 2% intracranial hemorrhage), 4% were splenectomized, and previous use of IV immunoglobulins, IV steroids, and platelet transfusions was 39%, 32%, and 41%, respectively. The median number of injections during the first treatment course was 4 (IQR, 3-4) over a median duration of 4 weeks (IQR, 3-4); 9% of patients received only one dose.

Conclusions: Among elderly Medicare patients diagnosed with ITP in 2010-2014, 9% received rituximab to manage their ITP. Future research on the real-world safety and effectiveness of rituximab in this off-label setting is warranted.

226 | Abstract Withdrawn

227 | Factors influencing non-persistence with antiplatelet medications and statins in patients after an ischemic stroke

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Background: Antiplatelet agents and statins represent an essential component of secondary prevention in patients after an ischemic stroke.

Objectives: The study was aimed at evaluating the extent of non-persistence with antiplatelet medications and statins in patients after an ischemic stroke and identifying risk factors for non-persistence.

Methods: Data for our retrospective cohort study were assembled from the database of the largest health insurance provider of the Slovak Republic. The cohorts of antiplatelet medication and statin users included 6219 patients (51.8% of them women) and 4147 (52.0% of them women), respectively, in whom antiplatelet and/or statin therapy was initiated in association with stroke diagnosis between 1 January 2010 and 31 December 2010. Patients were followed for 3 years. Patients with a treatment gap, defined as a 6-month period without antiplatelet agent or statin prescription, were classified as non-persistent. The Cox proportional hazards model was applied to identify predictors of non-persistence.

Results: At the end of the follow-up period, 2066 (33.2%) of 6219 antiplatelet medication users and 1885 (45.5%) of 4147 statin users were found to be non-persistent. Female sex was associated with increased risk for non-persistence in both groups of antiplatelet medication and statin users (HR = 1.28 [95% CI = 1.17-1.39] and HR = 1.11 [95% CI = 1.01-1.22], respectively). Anxiety disorders increased the risk for non-persistence only in the group of statin users (HR = 1.21 [95% CI = 1.10-1.34]). On the other hand, in both groups of antiplatelet medication and statin users, age ≥ 65 years (HR = 0.61 [95% CI = 0.56-0.67] and HR = 0.76 [95% CI = 0.70-0.84], respectively) and polypharmacy (HR = 0.83 [95% CI = 0.76-0.91] and HR = 0.79 [95% CI = 0.72-0.87], respectively) appeared as factors decreasing the patient's likelihood for becoming non-persistent. Certain comorbid conditions (arterial hypertension, diabetes mellitus, hypercholesterolemia, and dementia) were associated with a decreased patient's probability for becoming non-persistent.

Conclusions: Our results suggest that stroke patients aged < 65 years, women, anxious persons, and those without certain comorbid conditions require special counselling aimed at the improvement of their persistence with secondary preventive medications. The study was funded by grant of the Scientific Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic VEGA 1/0112/17.

228 | Oral anticoagulants initiations in atrial fibrillation patients in France in 2015-2016: Do prescribing patterns have a rationale?

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Background: In nonvalvular atrial fibrillation (AF) patients, direct oral anticoagulants (DOACs) were shown to be as effective as vitamin K antagonists (VKAs) to prevent arterial thromboembolic events without increasing the overall risk of major bleeding events, irrespective of patients' kidney impairment.

Objectives: To assess the patterns of use of DOACs (dabigatran, rivaroxaban, apixaban) in France in 2015-2016 compared with those of VKA in AF patients.

Methods: Using nationwide data from the French National Healthcare databases (Régime Général, 50 million beneficiaries), OAC-naïve AF patients were included if they met the following criteria: (i) continuous health insurance coverage for at least five years before OAC initiation; (ii) at least one reimbursement for DOAC or VKA in 2015-2016 (date of 1st reimbursement = index date) and no reimbursement for OAC in the previous 24 months; (iii) no history of lower limb orthopedic procedure or deep vein thrombosis or pulmonary embolism (DVT/PE) during the 6-week preindex period; (iv) treated for AF (at least one ICD-10 I48 diagnosis in the 5-year pre-index period or classified as AF outpatients using a published algorithm based on proxies discriminating AF from DVT/PE with 95% specificity).

Results: A total of 127 841 DOAC patients with AF initiated DOAC therapy (N = 9085 dabigatran, N = 54 456 rivaroxaban and N = 64 300 apixaban) and 65 010 VKA therapy. Mean age (years $\pm$ SD) was 74.1 (11.6), and 78 (11.3) for DOAC and VKA patients, respectively. Mean CHA₂DS₂-VASc and HAS-BLED scores were 3.7 (1.6) and 4.5 (1.6); 2.0 (0.9) and 2.7 (1), respectively. Proxies of frailty were found in 18.3% and 37.2% of DOAC and VKA new users, respectively. History of hospitalization for chronic kidney impairment was found in 5.2% of DOAC patients vs. 22% of VKA patients. Hospital practitioners were the most common frequent first prescriber in both DOAC (43.8%) and VKA (60.1%) patients. Among DOAC new users, apixaban patients were the oldest and most severe patients.

Conclusions: Despite their similar efficacy profile and potentially DOAC greater safety in terms of intracranial bleeding risk compared with VKA, older patients at higher risk of bleeding were less likely to initiate DOACs than VKAs. These results also observed in North America and in other European countries suggest that the fear of bleeding persist with DOACs for which reversal agents were initially lacking and no objective monitoring of anticoagulation still exists.

229 | Selection bias in studies of non-vitamin K antagonist oral anticoagulant users with atrial fibrillation

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Background: Danish health registries are extensively used in observational studies exploring the safety and effectiveness of non-vitamin K antagonist oral anticoagulants (NOAC) in atrial fibrillation (AF). To date, most studies have required a registered hospital diagnosis of AF for cohort inclusion, serving as a proxy for the indication of NOAC use. However, the capture of indications through this practice may be suboptimal, and potentially leads to exclusion of large amounts of patients receiving NOAC for "non-registered" AF.

Objectives: To explore the potential for selection bias when conducting studies on NOAC users with AF based on Danish registry data and to explore how selection bias may, at least in part, be accounted for when conducting such studies.

Methods: Using the nationwide Danish health registries, we identified all patients filling an incident NOAC prescription between August 2011 and December 2016 ($n = 125\,673$). The assumed treatment indication was identified using registered hospital diagnoses and included AF, venous thromboembolism (VTE), and VTE prophylaxis after arthroplastic surgery. We compared characteristics including comorbidity and comedication in patients with and without a registered indication for NOAC use. Further, we searched for the presence of predefined proxies for AFs (eg, cardioversion) among NOAC users without a registered indication.

Results: The assumed indication for NOAC use could not be identified in 33% ($n = 40\,962$) of initiators. Overall, the characteristics of these NOAC users were more similar to characteristics of users with AF ($n = 55\,362$) than users with VTE or VTE prophylaxis ($n = 15\,507$ and $n = 13\,842$). However, some important dissimilarities, eg, distribution of NOAC type, indicated presence of patients with other indications than AF in the group without an indication. In 34% of users with no indication we identified a proxy for AF, the most common being use of an antiarrhythmic drug (especially digoxin) and/or prior ischemic stroke (63% and 45% of all patients with an AF proxy).

Conclusions: In around one third of Danish NOAC users, an approved treatment indication could not be identified through hospital-based diagnosis registries. While systematic exclusion of these patients in studies on NOAC users with AF may lead to selection bias, systematic inclusion will likely lead to misclassification. A promising solution that requires future validation is to include patients without a registered indication in the presence of proxies for an AF diagnosis.

230 | Use of non-vitamin K antagonist oral anticoagulants during 2008-2016: A Danish nationwide drug utilization study

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Background: With the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) in 2008, a convenient and overall safe anticoagulant treatment alternative emerged. Despite the rapid and extensive uptake of NOACs, the broad clinical use remains to be fully described, as previous studies on the utilization patterns of NOACs have mainly focused on NOAC use for specific indications, eg, atrial fibrillation.

Objectives: To provide detailed utilization data on the total use of NOACs in Denmark since market introduction. Furthermore, to examine potential differences in patient characteristics and treatment persistence according to different indications (including no registered indication) as well as NOACs.

Methods: From the Danish National Prescription Registry, we identified all individuals filling an incident NOAC from March 2008 through 2016. We investigated the development in incident and prevalent use by dividing the number of first-ever and current users per 1000 individuals in the Danish population and explored baseline characteristics and treatment persistence according to registered treatment indication.

Results: A total of 126 688 NOAC users were identified within the Danish population of about 5.7 million inhabitants. The annual incidence and prevalence increased rapidly during the study period reaching 10 and 17 per 1000 individuals in 2016, respectively. The most frequently used NOAC was rivaroxaban (41%), followed by dabigatran (37%), apixaban (21%), and edoxaban (>1%). During the study period, use of apixaban and rivaroxaban increased on the expense of dabigatran. The indication for NOAC use was classified as atrial fibrillation (AF) (43%), venous thromboembolism (VTE) prophylaxis after arthroplastic surgery (17%), and VTE (12%), whereas 28% had no registered indication. Patients treated with NOAC for VTE primarily received rivaroxaban. The proportion of AF and VTE patients initiating the lower dose of dabigatran (110 mg) was 38% and 44% of all dabigatran initiators. Among patients with AF, 45% persisted to treatment after 3 years. Among patients with VTE, 17% was still treated after 3 years.

Conclusions: We documented an accelerating increase in the use of all four NOACs in the first 8 years after introduction in Denmark. We have identified areas requiring further attention, such as a high proportion of NOAC users without a registered treatment indication, potential inappropriate dosing, and the low long-term persistence with NOACs in patients with AF.

231 | Trends in concomitant clopidogrel and proton pump inhibitor treatment among ACS inpatients, 2000-2016

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Background: The Food and Drug Administration (FDA) issued three safety announcements in 2009-2010 warning against concomitant use of clopidogrel and proton pump inhibitors (PPIs) due to an interaction that may attenuate clopidogrel's antiplatelet activity.

Objectives: This study examines trends in concomitant clopidogrel/PPI use among acute coronary syndrome (ACS) inpatients in the United States during 2000-2016, in relation to the FDA safety communications.

Methods: Adult inpatients with a primary diagnosis of ACS were identified from Cerner Health Facts[®] database. The age-, sex-, and race-standardized prevalence of clopidogrel use with PPIs was calculated yearly and quarterly. Findings were stratified by PPIs' potential to inhibit clopidogrel's activity and by age.

Results: A total of 204 506 inpatients were identified. In 2008, the prevalence of concomitant clopidogrel/PPI treatment was 36.9%, decreasing to 24.3% and 15.9% in 2009 and 2010, respectively. The decline was similar across age groups. Treatment with inhibiting PPIs omeprazole and esomeprazole and clopidogrel has continued to decrease since 2010 with the prevalence of these treatments being 0.8% in 2016. A similar reduction was not observed with clopidogrel and non-inhibiting PPIs (pantoprazole, lansoprazole, rabeprazole, and dexlansoprazole). During the FDA warning period, the combined treatment with clopidogrel and H2-receptor antagonists, an alternative to PPIs suggested by the FDA, temporarily increased from 7.3% in 2008 to 12.1% and 13.9% in 2009 and 2010, respectively.

Conclusions: Findings suggest that clinical practice recommendations made by the FDA were followed. Further research is needed to determine how changes in drug labels and availability of new drugs may have influenced the observed trends.

232 | The association between statin medication adherence and subsequent health care utilisation in ageing community dwelling adults: Results from the Irish Longitudinal Study on Ageing (TILDA)

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Background: Adherence to statin medications has been shown to be important in low-density lipoprotein cholesterol (LDL-C) goal

attainment and cardiovascular outcomes. Few studies have explored the association between statin adherence and health care utilisation in ageing community dwelling adults.

Objectives: To establish the association between adherence to statin medication and subsequent health care utilisation in an ageing population in Ireland.

Methods: TILDA is a nationally representative cohort including participants aged 50 and over. Wave one of the cohort (2009/2010) included a computer aided personal interview (CAPI) with each participant recording health and social variables. Data on TILDA participants were linked to pharmacy claims data in a subset of the cohort. Participants were included if they received at least 3 claims for a statin medication (ATC "C10") in the year preceding the time period referred to in the CAPI. Adherence was measured from the claims data using proportion of days covered (PDC) with patients being classified as adherent if PDC was $\geq 80\%$. Negative binomial regression was used to analyse the association between medication adherence and the number of general practitioner (GP), emergency room (ER), outpatient visits and overnight hospital stays in the year preceding the CAPI (adjusted incidence rate ratio IRR and 95% CIs are reported). Covariates adjusted for included age, sex, polypharmacy, depression, socioeconomic status, functional disability, cognitive impairment and social support.

Results: 1059 adults aged 50+ years were eligible for inclusion in the study. 71.2% of adults were considered adherent to statins (PDC $> 80\%$) and the average PDC score was 81% in the study period. There was no statistically significant association between statin adherence and number of GP or ER visits in both unadjusted and adjusted models. Adherent patients were significantly less likely to report outpatient visits than non-adherent patients (adjusted IRR 0.70, 95% CI 0.56-0.88, $p = 0.002$) and less overnight hospital stays (adjusted IRR 0.67 95% CI 0.45-0.99, $p = 0.04$).

Conclusions: Patients who are non-adherent to their statin medication may experience longer hospital stays and more frequent outpatient visits. Interventions should be targeted towards individuals non-adherent to statins in primary care to help reduce the unnecessary burden in secondary and tertiary health care utilisation.

233 | Twenty five year trends in antihypertensive medicine usage in the state sector of Sri Lanka: 1992 to 2016

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Background: Sri Lanka is burdened with an increase in deaths due to cardiovascular diseases and hypertension is a modifiable risk factor.

Objectives: To describe trends in utilization of oral antihypertensive medicines over 25 years in the state sector, adherence to Joint

National committee (JNC) guidelines and highlight gaps between prevalence of hypertension and availability of antihypertensives.

Methods: State sector medicines are supplied by Medical Supplies Division in the Ministry of Health. Data was retrieved from the database from year 1992 to 2016. Antihypertensives were classified according to the 2015 version of Anatomical Therapeutic Chemical classification (ATC) index and consumption expressed as Defined Daily Doses (DDDs) per 1000 population per day. Population utilizing state sector health care, was used as the denominator. Drug Utilization 90% (DU 90%) was used to describe trends. Prevalence rates were obtained from published data.

Results: Over 25 years total DDDs/1000 population/day showed an exponential increase from 6.43 in 1992 to 146.28 in 2016. The DDDs of thiazide diuretics and beta blockers showed a gradual increase from 4.25 to 22.10 and 0.74 to 11.58 respectively. In contrast, DDDs of medicines acting on the renin-angiotensin system, showed an exponential increase from 2000 to 2016 (1.38 to 80.83 DDDs) with losartan being the largest contributor. An exponential increase was seen initially with calcium channel blockers; 50-fold increase from 1992 (0.30) to 2007 (15.06), which slowed to maintain a twofold. NifedipineSR was the largest contributor throughout. The DU90% was determined at 7-year intervals. In 1995, DU90% included; hydrochlorothiazide (HCT, 60%), propranolol, methyl dopa (11% each), and nifedipine (10%). In 2002, HCT was followed by nifedipine (25%). In keeping with the JNC 7 guidelines DDDs of methyldopa had reduced from 11% to 3.2%. DU90% in 2009, included HCT (24%) nifedipine (23%) enalapril (14%) and losartan (12%). By 2016 DU90% had changed in keeping with JNC 8 guideline, with losartan (40%) HCT (15%), nifedipine (11%). Comparison with prevalence of hypertension (estimated around 130/1000 population) a wide shortfall in DDDs was evident from 1992-1995 (8.32DDDs), followed by a gradual positive closure of the gap in 2016 (146.28DDDs).

Conclusions: Utilization of antihypertensives throughout the 25-year period is in accordance with the JNC guidelines and gaps between prevalence of hypertension and availability of anti-hypertensives has closed over time.

234 | When prescriptions fall short: Using CPT codes to augment warfarin prescriptions in claims

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Background: Many have characterized how the introduction of novel oral anticoagulants (NOACs) has changed patterns of anticoagulation in atrial fibrillation (AF) by analyzing proportion of initiators taking NOACs over time and relying on prescription data alone. Whether the introduction of NOACs changed the proportion of time spent anticoagulated and how using Current Procedural Terminology (CPT) codes for international normalized ratios (INRs) changes these estimates is unknown.

Objectives: To assess annual population proportion of days covered (PPDC) by oral anticoagulants from 2005 to 2014 in a commercially insured US adult population with incident AF.

Methods: We identified individuals with incident AF with one inpatient diagnosis code or two outpatient diagnosis codes in the Truven MarketScan database of commercial claims from 2000 to 2014 with a 180-day lookback window to remove prevalent AF. We performed analyses estimating PPDC 6 months, 1 year, 2 years, or 5 years from incident AF for vitamin K antagonist and NOAC prescriptions with a grace period of 50% days' supply. In each year from 2005 to 2014 and for each time window since diagnosis, we estimated annual PPDC by dividing total days covered by prescriptions by days observed of all incident AF patients. We also conducted analyses treating INR CPT codes as warfarin prescriptions as warfarin may be paid for out-of-pocket and therapeutic changes can result in inaccurate days' supply. We computed standard errors with 200 bootstrapped replicates and used Poisson regression to account for yearly region and age variation in secondary analyses.

Results: Our cohort included 593 079 patients with incident AF. Six-month PPDC following incident AF declined from 39.7% (95% C.I. 39.2%, 40.2%) in 2005 to 34.7% (95% C.I. 34.3%, 35.1%) in 2009 and 34.8% (95% C.I. 34.5%, 35.1%) in 2014. One-, two-, and five-year PPDCs declined slightly less. Use of INR CPT codes increased the 6-month PPDC in each year to 47.4% (95% C.I. 46.9%, 47.9%) in 2005, 43.9% (95% C.I. 43.5%, 44.3%) in 2009, and 40.5% (95% C.I. 40.2%, 40.8%) in 2014, with smaller increases when INRs only extended warfarin coverage. Adjustment for region and age increased PPDC in early years but did not remove the temporal decrease.

Conclusions: Introduction of NOACs did not seem to reverse decreases in PPDC from 2005 to 2009, though this could be due to trends in out-of-pocket payment. Use of INR CPT codes increased PPDC suggesting that prescriptions alone may not capture warfarin use and adherence in commercial claims.

235 | Trends in use of rivaroxaban for prophylaxis and treatment in general practice in the United Kingdom between 2012 and 2015

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Background: Rivaroxaban is one of the new alternatives to warfarin for the treatment of venous thromboembolism (VTE) and for stroke prevention in atrial fibrillation (SPAF), yet little is known about changes in prescription patterns of these medications or characteristics of rivaroxaban users since the drug was introduced.

Objectives: To compare the rate of new use of rivaroxaban with new use of warfarin in the UK general population (Jan 2012-May 2015), and to compare characteristics of new users of rivaroxaban across study years

Methods: Using data from The Health Improvement Network (THIN) primary care database, we identified patients aged 2-89 years with a first prescription for rivaroxaban or warfarin. Rates of new use of both drugs were calculated for 2012 and 2015 (Jan-May) using the number of new users divided by total person-years (pyrs) in THIN in the respective year. Among new users of rivaroxaban, we compared changes over time in the proportion with certain characteristics, including indication and co-medication; age- and sex-adjusted odds ratios (OR) were also calculated.

Results: Over study years, the rate of new use of rivaroxaban increased (0.11 to 1.82 per 1000 pyrs), while new use of warfarin decreased (3.05 to 2.21 per 1000 pyrs). There was a higher proportion of new users of rivaroxaban aged 80-89 years in 2015 than in 2012 (31.1% vs 22.8%). The proportion of rivaroxaban new users with no prior record of outpatient anticoagulant use increased (63.8% vs 51.4%; OR: 1.71 [95% CI: 1.36-2.15]). Rivaroxaban was used increasingly for treatment of VTE (33.8% vs 20.9%) and less for hip/knee surgery (19.0% vs 1.6%), while SPAF remained the main indication over time (53.4% vs 51.4%). A higher proportion of patients received anti-hypertensives in the year prior to rivaroxaban initiation in 2012 than 2015 (71.2% vs 64%; OR: 1.37 [95% CI 1.06-1.77]) while fewer received non-steroidal anti-inflammatory drugs (16.5% vs 24.5%; OR: 0.64 [95% CI: 0.49-0.84]). Only minor differences over time were seen in comorbidities, among new users of rivaroxaban

Conclusions: In the UK, use of rivaroxaban as a first anticoagulant has risen substantially while warfarin use has declined. There has been a shift towards rivaroxaban as first-line anticoagulation. There were only small variations in patient's characteristics over the study period.

236 | Database analysis of venous thromboembolism treatment patterns in inpatient vs outpatient settings

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Background: The standard of care for patients with venous thromboembolism (VTE) has been treatment with parenteral anticoagulation therapy, such as low-molecular weight heparin (LMWH), followed by long-term treatment with an oral vitamin K antagonist, such as warfarin. In recent years, novel oral anticoagulants have been approved for treatment and prevention of recurrent venous thromboembolism. There is little in the literature regarding real-world treatment patterns following outpatient diagnosis of VTE.

Objectives: To describe the characteristics of outpatient-diagnosed patients treated for VTE in inpatient and outpatient settings, and characterize treatment patterns for initial treatment and secondary prevention of VTE.

Methods: This study was a non-interventional retrospective observational cohort study conducted within an integrated health care system. Patients were identified using an algorithm comprised of VTE ICD-9 codes in combination with imaging procedures and treatments consistent with VTE. VTEs were verified by medical record review.

Results: Inpatient-treated subjects had a mean age at Index (date of VTE diagnosis) of 65.7 (± 15.1) years while outpatient-treated had a mean age of 61.6 (± 16.3) years ($p = 0.026$). Eighty percent of all patients experienced an isolated deep vein thrombosis (DVT), 10% experienced isolated pulmonary embolism (PE) and 10% experienced PE with DVT. A significantly greater proportion of subjects with PE, alone or with DVT, were treated as inpatient (90%) and a greater proportion of subjects with isolated DVT were treated as outpatient (75%) ($p < 0.001$). Initial anticoagulant therapy consisted of LMWH, warfarin and/or heparin for 90%, 29% or 2% of outpatient-treated and 74%, 88% or 82% of inpatient-treated patients, respectively. Extended anticoagulation consisted primarily of warfarin and/or LMWH for 87% and 81% of outpatient-treated and 76% and 58% of inpatient-treated patients, respectively.

Conclusions: Patients with DVT were more likely to be treated as outpatients and those with any PE were more likely to be hospitalized. Hospitalized patients were older and had more comorbidities and risk factors. Patients treated as outpatients received LMWH as initial treatment but 30% of them also received warfarin. Outpatient-treated patients received LMWH and warfarin as extended therapy. Patients who were hospitalized received LMWH and/or warfarin and/or heparin as initial treatment and received warfarin, and to a lesser extent, LMWH as extended therapy.

237 | Feasibility analysis and data visualization to identify a complex group of cancer in the Simulacrum

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Background: The Simulacrum—simulated artificial data—has been developed to facilitate real-world data (RWD) research in cancer in England. While Public Health England (PHE) has shown Simulacrum can replicate the overall shape of RWD for cancer, more work is needed to more efficiently identify and summarise a complex group of cancers.

Objectives: To explore the possibility of identifying patients with such a complex cancer in the Simulacrum and to apply a data visualization approach summarizing morphological and topographical distribution of identified cancers.

Methods: According to the PHE report, a review of literature was undertaken to update the list of ICD-10 codes and ICD-O2 codes which correspond to topography and morphology of cancers respectively. Then morphology and topography codes were used to further classify cancers in a clinically-relevant and data-driven manner. In order to describe distribution of cancers, Sankey diagrams were generated using

R packages, where each type of morphology or topography can be shown by colour coding and incident counts by the width of each flow.

Results: 11 156 cancers (6 morphological groups across 10 topographical sites in the body) were identified in 2013, 2014, and 2015 in the Simulacrum, excluding 11 157 small cell lung cancers (SCLCs). The PHE report which was based on RWD about all cancers diagnosed in England included 8,726 non-SCLC types among this complex group of cancers in 2013 and 2014, excluding 7908 SCLCs. Overall, morphology and topography distribution of cancers were found to be aligned with those incidences reported from the RWD. In contrast to the traditional information presentation, visual analytics was used to provide a simpler user-friendly presentation of such complex data.

Conclusions: The distribution of a complex group of cancers observed in the Simulacrum was proportionally similar to the distribution reported in the RWD in England. Independent access to simulated data (like Simulacrum), can support a feasibly assessment to facilitate our understanding of complex health conditions (eg, cancers) and ease such iterative processes in RWD epidemiology. A data visualization can be used to summarize distribution of a various patterns in RWD data, telling a story through data.

238 | An application of machine learning for the refinement of an EHR-derived cohort

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Background: Electronic health record databases (EHR) are frequently used for cohort identification in drug and device related studies. A primary challenge is that the EHR query (algorithm) may produce an overly broad list of patients. When this occurs, subsequent manual chart review is required to verify patient eligibility.

Objectives: We employed an open-source machine learning application (CLARK!) to explore its potential as an alternative to manual review of all charts for eligibility verification.

Methods: In 2015, we used a structured algorithm to query a university-based EHR database to identify women with symptomatic uterine fibroids for recruitment into a national comparative-effectiveness registry. Manual review of a random sample of charts showed that 1 in 4 of the women identified by our final algorithm did not have symptomatic fibroids (PPV 76%). Since it is prudent to avoid placing recruitment phone calls to these women for both pragmatic and ethical reasons, we employed CLARK! as an alternative to manual review for eligibility verification. CLARK!'s task was to increase the PPV of our EHR-derived recruitment list by classifying patients as "symptomatic" or "non-symptomatic" based upon the contents of their charts, using the application's random forest option. Two randomly selected sets of charts from our EHR-derived cohort were submitted to CLARK!: a training set (n = 397), followed by a test set (n = 163).

Results: When applied at a high confidence level of 80% or more, as compared with manual review, CLARK! successfully identified 97%

of symptomatic cases, with a PPV of 85%. For further refinement of an EHR-derived cohort of N = 1000 with a PPV of 76%, this improvement represents 110 fewer phone calls placed to ineligible patients (n = 240), at a cost of 23 (of 760) truly eligible subjects, as compared with blind calling of the entire EHR-derived list.

Conclusions: Our results show that machine learning can be used to refine the output of an existing EHR algorithm, allowing study teams to avoid the costs associated with excessive manual chart review or unnecessary recruitment phone calls.

239 | Validation of adaptable computable phenotype as run on health plan common data model

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Background: The ability to use health plan data to accurately identify subjects eligible for pragmatic clinical trials is unknown.

Objectives: To estimate the positive predictive value (PPV) of the ADAPTABLE Computable Phenotype as applied to PCORnet Common Data model (CDM) data. Unlike a drug-safety study, where the objective is to validate the occurrence of a particular event on a particular date, this study aimed to validate the status of a patient as study-eligible or not.

Methods: Design: Validation of patient status as identified through medical and pharmacy claims against a "gold standard" observed in abstracted medical records. Setting, exposures/interventions, and outcomes: Subjects were identified as ADAPTABLE study-eligible by running CDM SAS code in a large commercial health insurer. This validation study was limited to subjects with history of AMI, PCI, or CABG on or after 10/01/2015 (beginning of ICD-10 coding) documented in facility claims. A sample of 300 subjects identified by the computable phenotype were randomly selected, for whom one medical record per patient was requested from a third-party vendor blinded to study objectives. The main outcome measure was whether each patient's ADAPTABLE study eligibility was confirmed by the abstracted medical record. Statistical analysis: The PPV was defined as the proportion of patients identified by the computable phenotype whose abstracted medical records confirmed study eligibility. The PPV was treated as a binomial random variable for the purposes of estimated confidence intervals for the PPV.

Results: Medical records were obtained and abstracted for 185 patients (61.7% of requested records). Of these, 158 patients were confirmed as ADAPTABLE-eligible by the vendor (85.4%, 95% CI, 80.3% - 90.5%). Review of claims histories of the 27 non-confirmed patients frequently showed long histories of AMI, PCI, CABG, or CAD, suggesting that the abstracted medical records were incomplete. Ongoing work is assessing how improved medical-record identification could raise the estimated PPV.

Conclusions: The results indicate that health plan data can reliably identify patients eligible for a pragmatic clinical trial about as accurately as has been reported for safety surveillance in Sentinel (Cutrona et al,

2013 *Pharmacoepidemiol Drug Saf*). These results suggest that health plan data can be a valuable addition to patient recruitment efforts for large pragmatic clinical trials.

240 | Use Chang Gung Research Database for traditional Chinese medicine studies in Taiwan: Patient characteristics and data representativeness

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Background: The Chang Gung Research Database (CGRD), the largest multi-institutional electronic medical records database in Taiwan, contains important patient-level information including laboratory data and pathological reports not in administrative databases. CGRD could be a good study resource for Tradition Chinese Medicine (TCM) effectiveness and safety studies, but the patient characteristic and representativeness of CGRD are not determined.

Objectives: To investigate the representativeness of CGRD for TCM studies.

Methods: We identified a cohort of patients who visited TCM clinic from CGRD and from Taiwan's National Health Insurance Database (NHIRD), respectively, from 2010 to 2015. The NHIRD was considered as reference because it covered most of health care facilities in Taiwan including CGRD hospitals and more than 99.9% of entire Taiwanese populations. We investigated the coverage rates of patients from CGRD over entire TCM patients from NHIRD. We performed chi-square method with alpha level of 0.05 to compare the characteristics of patients between CGRD and NHIRD including age, sex, and 15 health conditions defined by Taiwan's National Health Insurance Administration, such as ICD-9-CM codes of neoplasm: 140-239; mental disorders: 290-319 and endocrine disorders: 240-259, 270-279, 260-269.

Results: We identified more than 71 002 patients from CGRD which accounted for 1.1% of the patients from the NHIRD. The patients from CGRD were older than from NHIRD (+65: 16.6% vs 9.9%; 45-64: 35.0% vs 29.0% for CGRD vs NHIRD). The ratios of female over male patients were 1.7 vs 1.5 ($p < 0.05$) for CGRD vs NHIRD. We found higher patient coverage rates of major conditions for patients from CGRD, specifically for neoplasm 9.2%, mental disorders 6.0% and endocrine disorders 4.8%.

Conclusions: The findings indicated the good patient coverage rates of CGRD for TCM in patients with major conditions. Investigators should pay attentions on possible selection biases because the conditions of patients from CGRD could be relatively more severe than from national administrative databases.

241 | Development of a mobile application for genetic diagnostic (GDx) testing return of results in the Department of Veterans Affairs

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Background: Genetic diagnostic (GDx) testing is an important innovation in diagnosis and treatment of a growing number of clinical conditions. Yet, standardization and incorporation of these tests in electronic health records (EHR) is a work in progress. This has made it difficult for clinical leadership to understand whether GDx tests are used appropriately and it has impeded patients from accessing their GDx test results. In 2012, the Department of Veterans Affairs (VA) began development of a mobile application to provide accurate, timely, structured GDx test results to VA clinicians and patients.

Objectives: To describe development, implementation, and impact of the GDx mobile application.

Methods: The GDx application began as a collaboration between the VA Pathology and Laboratory Medicine Services (P&LMS) and Investigators at VA Informatics and Computing Infrastructure (VINCI). Monthly text data feeds were obtained from contracted reference laboratories. These data illustrated test utilization was tenfold higher than clinical leadership realized. VA established bidirectional electronic interfaces between VA laboratories, reference laboratories, Cerner, and the VA Mobile Application Environment to establish a hub and spoke model of data dissemination. Data between all laboratories are exchanged via secure, Health Level Seven (HL7) messaging. The GDx application displays GDx test orders and results to VA clinicians and patients.

Results: We identified 3.2 million Veterans who had undergone a GDx test over the past 10 years. Within these data, we found evidence of some underutilization, overutilization, and use of GDx tests not in line with guidelines. Linking these data to pharmacy records showed some use of molecularly targeted medications without information about whether the patient had the molecular target. For example, prior to the GDx mobile application, there was underutilization of EGFR testing, a guideline-recommended lung cancer genomic tests that predict response to a targeted treatment (erlotinib). There was also overutilization of erlotinib. When VA clinical leadership saw these data, they developed templates within the EHR to improve appropriate use of GDx tests.

Conclusions: Availability of accurate, structured data documenting GDx testing improved quality of precision medicine for Veterans.

242 | A data-driven automatic method to detect irrational drug use prescriptions: A pilot study

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Background:

Objectives: To test an automatically data-driven irrational drug use prescriptions detecting model in real-world prescription data.

Methods: We used the unsupervised topic modeling approach to analyze prescriptions from the Chinese Monitoring System for Rational Drug Use Database. Multi-view multi-attribute latent dirichlet allocation (MVMA-LDA) algorithm was chosen to generate the topic models using variables including diagnoses (ICD-10), medications (generic name) and medication expenses. After learning all these feature structures, topics could be extracted and interpreted as the latent health status of a patient. Each topic consisted of a set of diagnoses, medications and expenses and their corresponding percentages. These diagnoses, medications as well as expenses were highly related to each topic. For a rational drug use prescription, these features distribution should consist with each other, otherwise prescriptions can be an irrational one. After that, anomaly detection method was used to compare the distribution of prescription regarding to each topics and calculate and rank the dissimilarities. The higher the dissimilarity, the more likely an irrational drug use prescription.

Results: A pilot study was done to test the method. A total of 1.1 million prescription records of 0.26 million patients between Oct 2016 and Dec 2016 from 349 hospitals in mainland China were used to generate topics and detect the rationality. Within the top ten dissimilar prescriptions, 6 of them were confirmed by clinical pharmacists, 2 were actually rational and 2 were unidentifiable in the lack of context.

Conclusions: We successfully applied the MVMA-LDA topic modeling method to automatically detect irrational drug use prescriptions and also got a deeper understanding of pairing relationships between diagnoses and medications in real-world clinical practice.

243 | The InGef research database—A data source for pharmacoepidemiological studies in Germany

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Background: The InGef ("Institute for Applied Health Research Berlin") database (former HRI database) is an anonymized health care database with longitudinal data from approximately 7 million Germans insured in one of 64 contributing statutory health insurance providers. Use of the InGef database for pharmacoepidemiological studies increased during the last years. For pharmacoepidemiological studies, the quality of coding of diagnoses crucial to identify the actual indication of drug use.

Objectives: (1) To describe characteristics of the InGef database and (2) to evaluate the coding quality of diagnoses regarding the indication of drug use.

Methods: Description of characteristics of the InGef database. Analysis of the completeness of primary care and hospital diagnoses for selected index drugs that are directly linked to a certain indication of

use (ie, no relevant off-label use in other indications expected). Selected index drugs were oral antihyperglycemic drugs (type 2 diabetes); antithyroid drugs (thyroid disorders); and antivirals for treatment of hepatitis C virus infections (hepatitis C). For initiators of these drugs, we estimated the proportions of patients with and without a diagnosis of the corresponding indication (from primary or hospital care) in the quarter of drug initiation or the year before. In a sensitivity analysis, the quarter after drug initiation was also considered.

Results: The InGef database covers demographic information; primary care services and diagnoses; hospital data; prescriptions and dispensations of reimbursed drugs, remedies and aids; and information on times of inability to work and of disability. Recent validation studies have shown that there is good overall accordance of the InGef database and the German population in terms of measures of morbidity, mortality and drug usage. For initiators of all index drugs, there was a high accordance of prescriptions with diagnoses of the respective indication (98.0% for type 2 diabetes; 89.6% for thyroid disorders; and 94.9% for hepatitis C). After adding the quarter after drug initiation, the proportions were slightly higher (98.4%, 91.2%, and 95.2%, respectively).

Conclusions: The InGef database is a valuable data source for pharmacoepidemiological studies including studies aiming to identify potential indications of drug use.

244 | Predicting patient anti-arrhythmic drug cessation after catheter ablation for atrial fibrillation

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Background: Catheter ablation is used to treat paroxysmal atrial fibrillation (AF) for patients that fail anti-arrhythmic drugs (AAD). Post ablation utilization of AADs can affect the patient outcomes and is an important consideration when researching ablation outcomes. There is limited understanding of which patients stop AAD use post ablation or which methods to use to accurately predict AAD cessation.

Objectives: Develop and evaluate the performance of prediction models for patient AAD cessation between 91 to 365 days after AF ablation.

Methods: The first catheter ablation (INDEX) for AF for patients ≥ 19 years in Truven Commercial Claims (CCA) from 1/2010 to 9/2015 were identified utilizing ICD-9/CPT codes. One year continuous enrollment before and after INDEX was required. AADs were identified from prescription billing. Patients were required to have AAD utilization 90 days before and after INDEX. Patients were excluded if they had an AF complication (eg, myocardial infarction, stroke, AF related rehospitalization) after INDEX. A total of 80 patient demographic and comorbidity features were utilized. The positive class was AAD cessation defined as a 14-day prescription gap between 91 to 365 days post INDEX. Data was split into 80/20 training/testing.

Linear (support vector classifier [SVC], ridge classifier [RC]) and tree-based (decision tree [DT], random forests [RF]) classifiers were evaluated with tenfold cross-validation. Averaged precision, recall, and F1 for both the positive and negative classes were calculated.

Results: A total of 1376 patients were identified: 76.7% male and 23.3% female. Overall incidence of AAD cessation was 74.7%. Averaged performance for linear classifiers (SVC, RC) was precision (0.56, 0.56), recall (0.75, 0.74), and F1 (0.64, 0.64), and for tree based (DT, RF) was precision (0.62, 0.62), recall (0.59, 0.70), and F1 (0.60, 0.65). These results suggest that linear classifiers performed similar to tree-based. However, for predicting AAD continuation tree based performed better with F1-scores of DT (0.28) and RF (0.13) compared with linear classifiers (SVC, RC) which classified all patients as AAD cessators (undefined F1).

Conclusions: Tree-based performed better than linear classifiers because in this data set the classes were not linearly separable. Predicting AAD cessation in claims databases is challenging likely due to the lack of important factors such as AF burden and ablation complexity. Future work is needed to identify *better* features to predict AAD cessation.

245 | Risk of endometriosis is greatly increased in White women with IUD removal vs insertion

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Background: As part of Translational Epidemiology and Genetics research efforts that are essential for predictive evaluation of real-world performance, we are developing biomarker-based evidentiary approaches for device evaluation in sex/race-stratified subpopulations.

Objectives: To examine the role of Endometriosis (END) as possible intrauterine device (IUD) related adverse outcome.

Methods: National Inpatient Sample from Agency for Healthcare Research and Quality (NIS/AHRQ, 2010-2014) was used for a retrospective analysis of comorbidities in IUD-related discharges, using CCS and ICD9 codes. Using SAS v.9.4 (Proc Logistic: Unadjusted and Adjusted for interactions among age, race, and IUD status), the incidence of END was compared among discharges with no IUD codes (no-IUD) and race-stratified (White, Black, and Rest) discharges with IUD removal (V25.12) and IUD insertion (V25.11).

Results: Compared with no-IUD, overall EDN conditions were less frequent among IUD insertions: OR = 0.38 [95% CI: 0.22; 0.67], but much more frequent among IUD removals: OR = 8.86 [95% CI: 7.13; 11.01]. The highly increased risk of END/Uterus in IUD removals vs. insertions was limited to White women: OR = 33.52 [95% CI: 8.07; 139.3]. A direct comparison between White and Black women with IUD removals showed the borderline trend confirming lower risk of END/Uterus among Black women: OR = 0.43 [95% CI: 0.18; 1.03].

The risk of END/No Uterus was greatly increased in White and Rest women with IUD removals vs. insertions: OR = 152.2 [95% CI: 150.1; 154.3] and OR = 19.66 [95% CI: 19.17; 20.17], respectively. Remarkably, Black women showed an opposite trend for END/No Uterus in IUD removals vs insertions: OR = 0.455 [95% CI: 0.41; 0.50]. The lower likelihood of END/No Uterus in Black women with IUD removals was especially pronounced when compared with their White counterparts: OR = 0.002 [95% CI: 0.0018; 0.0022]. The likelihood of END/No Uterus was also lower among Black and Rest women with IUD insertions, compared with their White counterparts: OR = 0.68 [95% CI: 0.66; 0.70] and OR = 0.75 [95% CI: 0.74; 0.77], respectively. Our in silico queries identified SNPs that can be considered as putative END biomarkers predictive of the enhanced END risk in White women using IUD.

Conclusions: Epidemiologic evidence suggests that IUDs may greatly exacerbate the known inherent risk of END in White women. Further pharmacogenetic research is needed for identifying biomarkers that can predict and mitigate the race-related END risk among IUD users.

246 | Analysis of autoimmune comorbidities among discharges with IUD removals vs insertions suggests increased IUD-related risk which is further modified by race

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Background: As part of CDRH's efforts for predictive evaluation of real-world performance of medical devices, we are developing evidentiary approaches that are aimed at device performance evaluation in sex/race-stratified subpopulations.

Objectives: As part of our project on safety of intrauterine devices (IUD), this study explores the role of Autoimmune Conditions as possible IUD-related adverse outcomes, by comparing their likelihoods among the race-stratified women subpopulations with IUD insertion vs IUD removal.

Methods: National Inpatient Sample from Agency for Healthcare Research and Quality (NIS/AHRQ) was used for a retrospective analysis of allergic and autoimmune comorbidities in IUD-related discharges, as identified by CCS and ICD9 codes. Using AHRQ/NIS data (2010-2014) and SAS v.9.4, the incidence of vascular comorbidities was compared among discharges with no IUD codes (no-IUD) and the race-stratified (White, Black, and Rest) discharges with IUD removal (V25.12) or IUD insertion (V25.11).

Results: When compared with no-IUD discharges, Autoimmune comorbidities in general were found less frequently among women with both IUD insertion and removal: OR = 0.27 [95% CI: 0.19; 0.38] and OR = 0.56 [95% CI: 0.37; 0.85], respectively. In the disease-focused analyses, the likelihood of Lupus was lower among both IUD insertions and removals: OR = 0.28 [95% CI: 0.16; 0.47] and OR = 0.48 [95% CI: 0.24; 0.95], respectively, and the likelihood of Rheumatoid Arthritis (RA) was lower only among insertions: OR = 0.31 [95% CI:

0.19; 0.53]. In the race-stratified discharges with IUD removal vs insertion, White women had borderline increased likelihood of Autoimmune comorbidities in general: OR = 2.37 [95% CI: 0.96; 5.84] and RA in particular: OR = 3.15 (95% CI: 0.94; 10.52), respectively. Black women with IUD insertions had increased likelihood of Lupus, when compared with their White counterparts: OR = 4.73 [95% CI: 1.00; 22.35]. The trends for increased Lupus risk for Black vs White women with IUD removals or for Black women with IUD removals vs insertions did not reach statistical significance.

Conclusions: Epidemiologic evidence suggests that despite an apparent underuse of IUDs in women with autoimmune conditions, IUDs may modify the risk for conditions such as RA. It remains to be clarified if IUD use may enhance the inherent risk for Lupus among Black women. Further pharmacogenetic research on putative race-related biomarkers and risk modifiers is needed.

247 | Characterizing the procedural utilization of mechanical stapler buttress technology in the Premier Healthcare Database

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Background: Buttress is utilized as an adjunctive technology with surgical staplers to mechanically reinforce the ligated tissue staple line. Most utilization is thought to be in stomach and lung but there is a lack of quantitative estimates for which anatomies and procedures have the highest buttress use during surgeries. Estimating buttress utilization is important in understanding current surgical practice and when considering stapler comparative effectiveness.

Objectives: Describe which anatomies have the highest number of cases with adjunctive buttress use in surgical procedures and estimate the proportion of buttress utilization in specific procedures within bariatric surgery, lung resections, and partial pancreatectomy.

Methods: The Premier Healthcare Database from 2013 to 2015 was evaluated. Buttress was identified from the product and technology hospital charge descriptions utilizing a text search algorithm. All discharges with buttress were identified and the primary procedure International Classification of Disease (ICD) 9 and 10 revision procedure codes were identified and grouped into anatomic categories (eg, stomach, lung, appendix, colon, and pancreas). All discharges with these primary procedure codes were evaluated and the proportion of buttress utilization for specific procedures was calculated.

Results: A total of 31 062 discharges with buttress were identified: 2013 (10 420), 2014 (10 936), and 2015 (9706). Over the entire period, the highest proportion of buttress utilization was in stomach (77.3%) followed by lung (8.3%), appendix (4.7%), colon (4.2%), and pancreas (1.4%). For specific procedures, buttress utilization in bariatric surgery was higher in sleeve gastrectomy compared with gastric bypass: 2013 (31.9%, 19.0%), 2014 (30.6%, 19.1%), and 2015 (28.6%, 16.8%), respectively. Within lung procedures lobectomy had

higher utilization compared with segment/wedge: 2013 (5.9%, 2.8%), 2014 (6.9%, 3.0%), and 2015 (6.4%, 2.6%). Utilization in partial pancreatectomy was 2013 (14.3%), 2014 (16.3%), and 2015 (13.5%).

Conclusions: Across various anatomies procedures of the stomach had the largest use of adjunctive surgical stapler buttress and accounted for 3 out of 4 buttress uses. For specific procedures, sleeve gastrectomy had the highest utilization with almost 1 in 3 procedures, followed by gastric bypass, partial pancreatectomy, and lung. Adjunctive technologies are important to consider when performing stapler device surveillance.

248 | Analysis of cerebro/cardio-vascular comorbidities among discharges with IUD removals vs insertions suggests increased IUD-related risk which is further modified by race

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Background: As part of CDRH's efforts for predictive evaluation of real-world performance, we are developing evidentiary approaches aimed at device evaluation in sex/race-stratified subpopulations.

Objectives: As part of our project on safety of intrauterine devices (IUD), the study explores possible adverse outcomes by comparing likelihoods of cerebrovascular (CerebroV), cardiovascular (CardioV), and peripheral vascular (PeriphV) comorbidities among the race-stratified women subpopulations with IUD insertion vs IUD removal.

Methods: The National Inpatient Sample from Agency for Healthcare Research and Quality (NIS/AHRQ) was used for a retrospective analysis of vascular comorbidities in IUD-related discharges, as identified by CCS and ICD9 codes. Using AHRQ/NIS data (2010-2014) and SAS v.9.4, the incidence of vascular comorbidities was compared among discharges with no IUD-related codes (no-IUD controls) and the race-stratified (White, Black, and Rest) discharges with IUD removal (V25.12) or IUD insertion (V25.11).

Results: When compared with no-IUD controls, PeriphV comorbidities were equally less frequent among women with both insertion and removal: OR = 0.43 [95% CI: 0.37; 0.50] and OR = 0.50 [95% CI: 0.39; 0.64], respectively. PeriphV risk remained similar among the race-stratified women with removal vs insertion. Although CardioV comorbidities were less frequent among IUD subpopulations with both insertion and removal when compared with no-IUD controls (OR = 0.26 [95% CI: 0.22; 0.31] and OR = 0.35 [95% CI: 0.28; 0.45], respectively), CardioV risk among IUD removals vs insertions was borderline increased among White women: OR = 1.60 [95% CI: 1.01; 2.54]. When compared with no-IUD controls, CerebroV comorbidities were less frequent among women with IUD insertions, but not removals. Increased CerebroV risk among IUD removals vs. insertions was confirmed for White and Rest women: OR = 2.27 [95% CI: 2.24; 2.31] and OR = 1.95 [95% CI: 1.90; 2.00].

Conclusions: IUD use may increase the risk of various vascular comorbidities. In addition to suggesting their device-relatedness, the revealed risk variations suggest the need for further research on putative race/ethnicity-related risk modifiers and biomarkers.

249 | How to quantify predictive model performance: A case study in predicting repeat incisional hernia surgery in insurance claims

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Background: A common complication after incisional hernia repair surgery (HRS) is recurrence which often requires a second HRS. Population risk factor estimates may benefit from additional contextualization of model predictive performance. But describing clinically meaningful model predictive performance can be challenging.

Objectives: Evaluate tradeoffs of different predictive statistics across several models predicting a second HRS.

Methods: Truven Commercial Claims (CCAE) and Medicare Supplemental (MDCR) databases from 2009-2015 were evaluated. The first incisional HRS (index) for patients ≥ 21 years was identified (ICD-9/CPT codes) and 1-year continuous enrollment was required. Recurrence was defined as a second HRS between 31 and 365 days after index. Baseline covariates ($n = 52$) were used to build the models. Data were split 80/20 training/test. Models considered were logistic regression (LR), Cox proportional hazards (CPH), elastic net LR (ELR), and random forests (RF). Predictive statistics considered were: AUC, sensitivity, specificity, PPV, and F1-score.

Results: Among 102 749 patients (CCAE 78.8%, MDCR 21.2%) with an initial HRS, 5.6% had a second HSR. The AUC values were similar across models (0.630, 0.620, 0.632, and 0.617 for LR, CPH, ELR and RF, respectively). AUC's equal weighting of sensitivity and specificity is less informative for predictions that weigh sensitivity and PPV more than specificity and missed reoperations (false negative rate). The F1-score, a function of the classifier cutoff value, may be a more meaningful statistic. Maximized F1 scores were 0.139, 0.103, 0.139, and 0.136 for LR, CPH, ELR, and RF, respectively. At these respective values, sensitivities were 25.1%, 19.2%, 26.2%, and 29.6%, while PPVs were 9.6%, 7.0%, 9.4%, and 8.8%. While AUC may suggest ELR as the best model, sensitivity and precision shows that LR, ELR, and RF have their respective strengths. Also unlike LR and CPH, ELR and RF hyperparameter selection introduce the tradeoff of increased complexity for potentially greater predictive performance.

Conclusions: Reporting model predictive performance provides perspective on the collective ability of these risk factors in predicting outcomes. Selecting cutoffs, hyperparameters, and predictive performance statistics must balance real-life tradeoffs with careful consideration of clinical context. All models had low AUCs and PPVs. Prediction utilizing claims may be limited due to lack of procedural clinical detail.

250 | Prospective validation of a risk prediction model to identify high-risk patients for medication errors at hospital admission

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Background: Pharmacy-led medication reconciliation is effective to prevent medication errors at admission (MEA). In elective surgery patients medication reconciliation is often performed at the preoperative screening (POS). Because of the time lag between POS and admission, changes in medication may lead to MEA. In a previous study in a general hospital, a risk prediction model for MEA was developed.

Objectives: The objective of this study is to validate this risk prediction model for identification of patients at risk for MEA in a university hospital setting. The secondary objective is to identify potential additional risk factors for MEA in a university medical center.

Methods: The risk prediction model was derived from a study conducted in a Dutch general hospital and validated within a comparable cohort from a University Medical Center. The study received a waiver from the Medical Ethics Committee of the LUMC, as it complied with the Medical Research in Humans Act. Inclusion for the validation cohort took place from October 2016 to August 2017. MEA were assessed by comparing the POS medication list with the reconciled medication list at hospital admission. This was considered the gold standard. For every patient a risk score using the risk prediction model was calculated and compared with the gold standard. The risk prediction model was assessed with receiver operating characteristic (ROC) analysis

Results: Of 368 included patients, 167 (45.4%) had at least one MEA. ROC analysis revealed significant differences in the area under the curve of 0.535 ($p = 0.26$) (validation cohort) versus 0.752 ($p < 0.0001$) (derivation cohort). The sensitivity in this validating cohort was 66%. The specificity was 40%, with a positive predictive value (PPV) of 48% and a negative predictive value (NPV) of 59%. Only the number of medications at admission OR 1.06 (95% CI 1.01-1.12) was significantly associated with the occurrence of MEA. No additional risk factors were identified. **Conclusions:** The risk prediction model developed in a general hospital is not suitable to identify patients at risk for MEA in a university hospital. This is probably due to the more complex patients in university hospitals.

251 | Recording of hospital bleeding events in UK primary care: A linked Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) Study

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Background: UK primary care databases represent a rich source of data for health care research; however, the quality of recording of secondary care events in the databases is uncertain.

Objectives: In order to explore the potential for UK primary care databases to be used to generate real-world evidence on the safety and effectiveness of anti-thrombotic therapy, this study sought to investigate the completeness of coding of secondary care bleeds in primary care records.

Methods: The study population consisted of adults with atrial fibrillation who had at least one bleed recorded in either the CPRD or HES database while receiving prescriptions for oral anticoagulant treatment. All subsequent bleeding events recorded in the HES database were identified and classified according to the location in the body in which they occurred. The proportion of HES bleeds which had a diagnostic code for a bleed recorded in the CPRD in the subsequent 12 weeks was calculated. Cox proportional hazards analyses were carried out to investigate the hazard of bleeding associated with anti-thrombotic treatment strategies using linked CPRD-HES data and using unlinked CPRD data to identify bleeds.

Results: Less than 20% of the 17 456 bleeds identified in HES had a bleed recorded in the CPRD in the subsequent 12 weeks. As a result of the incomplete recording, the hazard ratio comparing vitamin K antagonist treatment to no antithrombotic treatment was overestimated using unlinked CPRD data (adjusted HR 1.31 CI₉₅ 1.13-1.51) compared with linked CPRD-HES data (adjusted HR 1.06 CI₉₅ 0.98-1.15).

Conclusions: Our results add to the evidence base suggesting secondary care events are inadequately recorded in primary care records and illustrate that in studies investigating the risk of bleeding associated with drug treatment the use of unlinked primary care data may produce biased results. Primary care databases should not be used as standalone resources for research into bleeds and other events which commonly present in secondary care, linked datasets should instead be utilised.

252 | Assessment of obesity prevalence and validity of obesity diagnoses coded in administrative claims data for selected surgical populations

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Background: In many types of surgery, the presence of obesity may influence patient selection, prognosis and/or management.

Objectives: Using a large de-identified database of linked electronic health records (EHR) and administrative claims data (Optum Integrated Claims-Clinical Database), this study assessed: (a) the prevalence of obesity and (b) the validity of obesity-related diagnoses coded in administrative claims data for selected surgical populations.

Methods: The study included patients age ≥ 20 years who underwent bariatric surgery, total knee arthroplasty (TKA) for knee osteoarthritis, cardiac ablation for atrial fibrillation, or hernia repair from 2014Q1 through 2017Q1 (first = index). The gold-standard and error-prone measures of obesity (body mass index [BMI] ≥ 30 kg/m²) were measured BMI from the EHR and obesity-related ICD-9-CM/ICD-10-CM diagnosis codes, respectively, recorded during the index procedure or 180 days pre-index. The sensitivity and positive predictive value (PPV) of ICD-9-CM/ICD-10-CM codes for obesity were estimated.

Results: 17 217 surgical cases were eligible for inclusion. Among patients who underwent bariatric surgery (N = 1422), TKA (N = 8670), cardiac ablation (N = 1675), or hernia repair (N = 5450), obesity was present in 98%, 63%, 52%, and 54%, respectively, based on measured BMI as recorded in the EHR. In the administrative claims data: PPVs of obesity-related diagnoses were high, ranging from 92.8% in cardiac ablation to 99.3% in bariatric surgery; the sensitivity of obesity-related diagnoses varied widely, ranging from 41.3% in cardiac ablation to 99.8% in bariatric surgery. For most surgical groups, the sensitivity of diagnosis codes for class III obesity (BMI ≥ 40 kg/m²) was substantially higher, ranging from 58.2% in cardiac ablation to 95.6% in bariatric surgery. Sensitivity was slightly higher in the ICD-10-CM coding era (2015Q4-present) relative to the earlier ICD-9-CM era.

Conclusions: Across all evaluated surgical groups, obesity was present in more than half of patients. Obesity-related diagnosis codes had high PPV (>90%) but lower sensitivity (41-46%)—except in the case of bariatric surgery where sensitivity was also high (99.8%) due to reimbursement requirements. This study provides researchers with valuable information regarding the use cases and limitations of obesity-related diagnosis codes in administrative claims data.

253 | A case study assessing the impact of the new US ICD-10-CM coding system on pharmacoepidemiologic studies—An application between angiotensin-converting enzyme inhibitors and angioedema

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Background: The US Centers for Medicare and Medicaid Services formally set October 1, 2015, as the compliance date for conversion from the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to its 10th Revision: ICD-10 diagnostic (ICD-10-CM) and procedure (ICD-10-PCS) codes. Replicating well-established exposure-outcome associations that span one or both coding eras may help explore the implications of the transition to ICD-10-CM

coding on drug safety analyses, and discover best practices toward minimizing unwanted misclassification.

Objectives: To replicate the well-established association between angiotensin-converting enzyme inhibitors (ACEIs) versus beta-blockers and angioedema in the ICD-10-CM era.

Methods: We conducted a retrospective cohort study of ACEI and beta-blocker initiators in a large US insurance database formatted to the Sentinel Common Data Model. Study periods spanned the ICD-9-CM and ICD-10-CM eras separately and together. We defined covariates and the outcome (angioedema) in ICD-9-CM according to definitions used in a previous study, and conducted simple forward mapping (SFM) and forward backward mapping (FBM) referencing the CMS General Equivalence Mappings to translate them to ICD-10-CM. Patients were followed for a maximum of 90 days. We performed propensity score (PS)-matched and PS-stratified Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: In the ICD-9-CM and ICD-10-CM eras spanning April 1–September 30 of 2015 and 2016, there were 152 017 and 145 232 ACEI initiators and 115 073 and 116 652 beta-blocker initiators, respectively. The PS-matched HR was 4.19 (95% CI, 2.82–6.23) in the ICD-9-CM era, 4.37 (2.92–6.52) in the ICD-10-CM era using SFM, and 4.64 (3.05–7.07) in the ICD-10-CM era using FBM. The PS-matched HRs from the mixed ICD-9-CM and ICD-10-CM eras ranged from 3.91 (2.69–5.68) to 4.35 (3.33–5.70) depending on the mapping technique used.

Conclusions: The adjusted HRs across different diagnostic coding eras and the use of SFM versus FBM produced numerically different but clinically similar results. The HRs observed in this study were higher than estimates from previous studies due to an apparent increasing trend in the incidence of diagnosed angioedema among ACEI initiators over time. Additional investigations as ICD-10-CM data accumulate are warranted.

254 | Adjudicating serious liver injury/disease and interstitial lung disease in electronic health records or claims data

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Background: A retrospective cohort study in electronic health records (EHR) and claims data examined associations of dronedarone, and comparator anti-arrhythmics, with serious liver injury/disease (SLD) and interstitial lung disease (ILD). Complexity in identifying SLD and ILD was compounded by a paucity of diagnostic test results as well as presence of rule-out diagnoses in administrative records. Therefore, suspected outcomes were adjudicated in

order to minimize misclassification and related bias in assessing drug-outcome associations.

Objectives: To review a process used to adjudicate SLD and ILD using EHR and claims data.

Methods: The study used the US Department of Defense Military Health System database and the HealthCore Integrated Research Database for the period from 20 July 2008 to 30 September 2014. Outcome definitions based on inpatient diagnosis and procedure codes were established a priori and used to identify cases for review. Clinicians on three-person SLD and ILD adjudication panels independently reviewed patient profiles created from EHR or medical claims records. Chronological medical, treatment and diagnostic history 1 year prior to the initial study drug fill through 6 months after the suspected outcome was provided for each case with a suspected outcome. Laboratory and radiology results were omitted as they were not available for all patients. Unanimous decisions were considered final. Divergent initial assessments were discussed by the panels and if still lacking consensus were deemed “Indeterminate.”

Given the broad range of symptoms and time to onset of ILD, sensitivity analyses were conducted to assess the impact of changing the ILD definition or risk period for identification and confirmation of those outcomes.

Results: The process found 48 suspected SLD cases, and 146 suspected ILD cases. Of the SLD cases, 38 required panel discussion and final assessments were: 47 not SLD and 1 indeterminate. Of the ILD cases, 96 required discussion, 72 were confirmed, 55 deemed not ILD, and 19 were indeterminate. Sensitivity analyses affirmed the ILD definition and risk period used for the primary analysis.

Conclusions: This study used well-defined algorithms to identify suspected outcomes, and applied succinct adjudication instructions and chronological medical history profiles from EHR and claims data to adjudicate events. A study limitation was the lack of laboratory or radiology reports, which might have aided reconciliation of cases with divergent opinions.

255 | A systematic review of measures for calculating adherence and persistence to multiple medication from prescription data

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Background: Assessing adherence and persistence to multiple medication can be complicated, in particular when medication may be switched within and between drug class level. Inadequate definitions for calculating adherence and persistence from prescription data may lead to misclassifications, and subsequently ineffective and inefficient intervention.

Objectives: To systematically summarize the measures used to calculate adherence and persistence to multiple medication from prescription data, particularly for blood pressure-lowering, lipid-lowering, and/or glucose-lowering (ie, cardiometabolic) medication and to assess

whether studies sufficiently describe the measures used, particularly regarding issues of medication switches and additions at drug class or therapeutic level.

Methods: A comprehensive literature search of Medline, Embase, and PsycINFO databases was conducted to identify studies assessing medication adherence and/or persistence for patients using multiple cardiometabolic medication. The study selection process was performed by two reviewers independently. Data were extracted to determine how adherence and persistence to multiple medication was defined, and whether medication switches and additions were addressed.

Results: We identified 54 studies assessing adherence, 36 (67%) of which clearly described how they calculated adherence to multiple medication. Only 16 of these studies considered switches and/or additions. Five distinct measures were identified from these studies, including adherence to "all," to "any," to "both" medication, "average adherence" and "highest/lowest adherence." We identified 22 studies assessing persistence, 6 (27%) of which clearly described how they calculated persistence to multiple medication. Only one of those studies explicitly considered medication switch. Three measures were identified from these studies, including persistence with "all," with "both," and with "any" medication.

Conclusions: We identified five distinct measures for assessing adherence and three measures for assessing persistence in patients using multiple cardiometabolic medication. Many studies provided insufficient details on how they included multiple medications in their measures, nor did they provide information on how they handled medication switches or addition. More attention in providing adequate measurement definitions is needed for calculation of adherence and persistence to multiple medication.

256 | Using a simple prescription gap to determine warfarin discontinuation can lead to substantial misclassification

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Background: Warfarin remains a widely used anticoagulant and a key comparator of interest in studies of other direct oral anticoagulants (DOACs). As longer-than-needed warfarin prescriptions are often provided to allow for dosing adjustments according to International Normalized Ratios (INRs), the common practice of using a short allowable gap between dispensings to define warfarin and DOAC discontinuation may lead to substantial misclassification of warfarin exposure.

Objectives: To quantify the accuracy of warfarin exposure measurement by different allowable gap thresholds for defining discontinuation

Methods: We linked Medicare claims data from 2007 to 2014 with electronic health records in 2 large anticoagulation management services with comprehensive INR recording. The study cohort comprised patients 65 years or older with non-valvular atrial fibrillation newly initiating warfarin. Based on Medicare dispensing data, we used different allowable gaps (3, 30, 60 days) between warfarin dispensings to determine discontinuation. The performance of an algorithm using an

allowable gap of 60 days but filling larger gaps if there was INR order at least every 42 days (60_INR; proposed by Go et al) was also evaluated. We considered a discontinuation misclassified if there was an INR in the 30 days after the discontinuation date with a value consistent with active warfarin use ($\text{INR} \geq 2$). We then compared Time in Therapeutic Range (TTR, % time with INR between 2-3), a metric of anticoagulation quality, during active warfarin treatment based on each discontinuation definition.

Results: We included a total of 8144 patients. A shorter gap resulted in a shorter mean follow-up time (70, 150, 233, and 301 days for gaps of 3, 30, 60, and 60_INR, respectively; p for trend <0.01). The proportion of misclassified warfarin discontinuations was 64%, 51%, 43%, and 10%, respectively (p for trend <0.01). The mean TTR during active warfarin treatment was 65%, 65%, 65%, and 65%, respectively.

Conclusions: Using a short gap between warfarin dispensings to define discontinuation may lead to a shorter follow-up and higher proportion of misclassified warfarin discontinuations. Incorporating intervening INR codes can reduce misclassification without lowering TTR during person-time classified as exposed to warfarin.

257 | Challenges of using electronic health record (EHR) data for medication exposure and comparison with claims data

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Background: Medication exposure and treatment duration are well defined in electronic claims data. Transition of research to EHR presents a need to assess the use of EHR for defining medication exposure.

Objectives: To evaluate concordance between EHR and claims data in assessing exposure to angiotensin-converting-enzyme inhibitors (ACEI).

Methods: Integrated Heart Failure (IHF) and Integrated ACEI (IACEI) cohorts were created from the Optum Research Claims Database (ORD) and the Optum EHR Database. The IHF cohort included patients ≥ 18 years of age with a diagnosis for heart failure, 12 months recorded EHR history, and overlapping ORD enrollment. Concordance of ACEI use in the ORD and EHR in this cohort was assessed. The IACEI cohort was a subset of the IHF cohort with an ACEI prescription during overlapping ORD enrollment. ACEI treatment duration was calculated in ORD by days' supply and in EHR by days' supply (as available); quotient of quantity prescribed to dose frequency (as available); assumed 30 days' supply (when quantity and dose frequency were unavailable).

Results: 27 963 patients entered the IHF cohort. 2209 had ACEI use in the ORD; 5093 in the EHR; 1328 patients in both sources. 21 989 (78.6%) patients had no ACEI use in either source. Among the remaining 5974 with ACEI use in at least one source, 1328 (22.2%) were found in both sources, 3765 (63.0%) were found in EHR

only, and 881 (14.7%) were observed in claims only. 2290 patients qualified for the IACEI cohort: 1624 had ACEI in the ORD, with a median (IQR) treatment duration of 98 days (38-187). Median (IQR) treatment durations in the EHR were: days' supply (472 patients, 220 days [98.5-406]); quantity and dose frequency (836 patients, 226 days [76-408.5]); assumed 30 days' supply (2290 patients, 82 days [46-316]).

Conclusions: EHR prescription data may require additional cleaning for research use. In Optum EHR, duplicate mentions of prescriptions due to varying data collection processes may result in exposure over-estimation. EHR and claims data may also come from different clinical sources resulting in inconsistencies. Prescription data from EHR will be a useful resource for drug safety research, but further work is needed to understand the underlying data generating mechanisms.

258 | Measurement error in the assessment of oral glucocorticoid exposure using UK primary care electronic health records

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Background: UK primary care electronic health records (EHR) are frequently used to define drug exposure in pharmacoepidemiology studies. They are useful as all prescriptions issued in primary care are captured prospectively. However, estimating true drug exposure using prescription data may result in measurement errors, eg, due to imperfect adherence, and misclassification bias.

Objectives: To assess the extent of measurement error when using UK primary care EHR to define current exposure to oral glucocorticoids (GC)

Methods: This cross-sectional study nested participant-reported drug exposure data within the Clinical Practice Research Datalink (CPRD), a UK primary care research database. Participants were patients with rheumatoid arthritis with at least one oral GC prescription in the 2 years prior to recruitment. Eligible patients were invited to participate via their general practice. On a single day between October 2015 and April 2016 participants reported their use of oral GCs over the past 24 hours using a diary: this was taken to represent "true" current oral GC exposure. Independently, current exposure to and dose of oral GCs, for the same day, were estimated using CPRD prescription data. For current exposure status the sensitivity and specificity of the prescription-based estimates were determined. For current dose the mean absolute difference from, and Spearman's rank coefficient with, self-reported dose were estimated. To assess the potential impact of misclassification we simulated a study with "true" exposure, "observed" exposure (with misclassification) and a binary outcome conditional only on true exposure. The relative risks (RR) were estimated using "observed" exposure.

Results: Current exposure: overall 11/78 participants (14%) were misclassified. 32/38 current users and 35/40 current non-users were correctly classified (sensitivity 84.2%, specificity 87.5%). Current dose

(current users only): estimates were less accurate (correlation coefficient 0.46, mean [SD] absolute difference 3.2 [4.2] mg) but showed no systematic bias (mean difference 1 mg, 95% confidence interval -1, 1.4 mg). Impact: assuming the misclassification rates reported above, "true" RRs of 1.5, 4, and 9 were attenuated to 1.33, 2.48, and 3.58, respectively.

Conclusions: Misclassification of current oral GC exposure was low but sufficient to lead to marked attenuation of the association. Researchers using EHR should assess the likely impact of exposure misclassification on their analyses.

259 | Methods for handling missing ethnicity data and their impacts on the association between ethnicity and type 2 diabetes diagnoses in UK primary care

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Background: Type 2 diabetes (T2D) is a common health condition, known to be associated with ethnicity. Studies examining the association between ethnicity and T2D using UK primary care databases such as The Health Improvement Network (THIN) are hindered by incomplete ethnicity data. Multiple imputation (MI) is increasingly regarded as the standard approach to missing data in medical research. However, standard MI assuming missing at random (MAR) might not yield a plausible ethnicity distribution compared with the general population, potentially due to a missing not at random (MNAR) mechanism. We proposed calibrated- δ adjustment MI which utilises the marginal distribution of ethnicity from an external dataset to deal with data MNAR. The method has been evaluated in simulation studies.

Objectives: To demonstrate the use of calibrated- δ adjustment MI for handling missing ethnicity data in primary care databases.

Methods: Using THIN data, we conducted a cross-sectional study to examine the association between ethnicity and prevalence of T2D diagnoses in primary care. We included eligible individuals who were actively registered in London on 1 Jan 2013 with ≥ 12 months' follow-up. We fitted a logistic regression model adjusted for (complete) demographic variables (age group, sex, deprivation status). For missing ethnicity, we compared (i) a complete record analysis (CRA) (ii) single imputation with the White ethnic group, (iii) standard MI, and (iv) calibrated- δ adjustment MI using the UK 2011 census distribution of ethnicity.

Results: Of 404 318 individuals, 76.6% had ethnicity recorded. In all methods, the odds of T2D diagnosis increased smoothly with age and higher levels of deprivation, and were higher in non-White ethnic groups compared with the White group. Although the Asian group had higher odds of T2D diagnosis in all methods, calibrated- δ adjustment MI yielded considerably lower estimate (OR = 2.35, 95% CI 2.26 to 2.45) compared with CRA (OR = 3.59, 95% CI 3.43 to 3.75), single imputation (OR = 3.63, 95% CI 3.47 to 3.79), and standard MI (OR = 3.58, 95% CI 3.43 to 3.73). A similar tendency was found for the Black group.

Conclusions: Standard MI might not impute ethnicity consistently with the population level when ethnicity is suspected to be MNAR. Appropriately incorporating the census distribution of ethnicity in the imputation can lead to scientifically relevant changes in the estimated associations between ethnicity and prevalence of T2D diagnoses in primary care.

260 | Feasibility of assessing breastfeeding status in electronic health records

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Background: Although breastfeeding status is routinely assessed at postpartum and infant health care visits, data on breastfeeding are difficult to obtain in retrospective studies. Claims databases lack this information and queries to participants long after the postpartum period are subject to recall bias. Electronic health records (EHRs) could possibly fill this knowledge gap.

Objectives: To assess the feasibility of determining postpartum breastfeeding status at the time of intrauterine device (IUD) placement in preparation for an IUD safety study.

Methods: Postpartum women with an IUD insertion were included in the study from 4 health care systems with EHRs: 3 west coast Kaiser Permanente (KP) sites—Northern California (KPNC), Southern California (KPSC), and Washington (KPWA)—and Regenstrief Institute (RI) in Indiana. A random sample of 125 women from each site who underwent IUD placement within 52 weeks postpartum was included—up to 25 women in each of 5 time intervals based on time since delivery. Breastfeeding status was classified as breastfeeding, not breastfeeding, or undetermined at the time of IUD insertion, and the percentage of women in each postpartum time interval was calculated. Evidence of breastfeeding was derived from manual review of mother and infant records (well-child care visits) and clinical notes extracted from EHRs between delivery and 52 weeks postpartum. Breastfeeding classification was validated by clinical experts.

Results: Across all sites, 92% of those sampled with insertion in the first 3 days postpartum were classified as breastfeeding; 90% in the interval >3 days to <4 weeks postpartum; 69%, ≥4 to <6 weeks; 71%, ≥6 to ≤14 weeks; and 41%, >14 to ≤52 weeks. For all postpartum intervals combined, the percentage of women categorized as breastfeeding at each site was 72%, 86%, 80%, and 45% at KPNC, KPSC, KPWA, and RI, respectively. Overall, 94% of the women sampled could be classified as either breastfeeding or not breastfeeding at the time of IUD insertion, with a range of 79%–100% across the sites.

Conclusions: As expected, a high percentage of women were determined to be breastfeeding in the first 4 weeks postpartum. There appeared to be geographic differences in the proportion breastfeeding, which is consistent with breastfeeding patterns reported by the CDC. Breastfeeding status could be ascertained for most women at these sites with EHRs. This study provides evidence that a retrospective study evaluating breastfeeding at the time of IUD insertion can be conducted successfully across sites using EHRs.

261 | Are you really dead? Validation of death and date of death in patients with COPD in CPRD

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Background: The current Clinical Practice Research Datalink (CPRD) death algorithm identifies a large number of deaths and the date of death (DoD). However, improvements are encouraged.

Objectives: To evaluate a process for identifying and verifying cases of death and the DoD in the CPRD.

Methods: Deaths in a nested case-control study of all-cause mortality in a cohort of new users of selected COPD medications (September 2012–June 2016) were identified in the Hospital Episode Statistics (HES), the Office for National Statistics (ONS), and the CPRD General Practitioner Online Database (GOLD) through an electronic algorithm and classified as confirmed (CONF) or potential (for clinical review). In practices not linkable to HES/ONS (NLP), potential deaths were those with recorded clinical information beyond 15 days after the DoD or with missing transfer-out date, and CONF deaths were all others. In practices linkable to HES/ONS (LP), CONF deaths were those with matching DoD in ONS, HES, and CPRD GOLD and, if not matching, those with a DoD in ONS ≤3 days before or after the other sources' DoD. Potential deaths were those with non-matching DoD between ONS, HES, and CPRD GOLD and for which the DoD in ONS was >3 days before or after the DoD in other sources, including patients with missing DoD in ONS or CPRD GOLD. Two physicians blinded to the exposures of interest reviewed the patient profiles of potential deaths to adjudicate the death and DoD.

Results: In CPRD GOLD, HES, and ONS, 3822 deaths were identified in 39 788 users of selected COPD medications. Of these, 3610 (94.5%) were CONF deaths through the electronic algorithm, and 212 (5.5%) were potential deaths. Patient profile review of potential deaths confirmed 209 cases (98.6%; 23 in NLP, 186 in LP). In NLP, the DoD changed for 13 cases (56.5%, 6 cases with an error in the year). In LP, the DoD changed for <5 cases; <5 deaths with DoD missing in ONS were not confirmed. Most of the adjudicated deaths in LP had the same DoD in ONS and HES but a later DoD in CPRD GOLD.

Conclusions: Our electronic algorithm confirmed most deaths and DoD. In NLP, we recommend validation of death and DoD for those

patients with clinical codes beyond 15 days after the DoD or with transfer-out date missing. In LP, HES/ONS DoDs are usually correct, and most CPRD GOLD DoDs were recorded late. This is likely to occur also in NLP. In LP, we recommend validation of cases with >3 days difference between the DoD in HES and ONS, irrespective of GOLD, or those for which the DoD is missing in ONS.

262 | Identifying multiple inhaler triple therapy (MITT) prescribing in COPD patients: An algorithm for UK primary care data

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Background: Multiple inhaler triple therapy (MITT) comprising a corticosteroid (ICS), a long acting beta2 agonist (LABA) and a long acting muscarinic antagonist (LAMA) delivered in 2-3 inhalers is a treatment option for COPD; however, identification of MITT prescribing in primary care databases is challenging.

Objectives: Develop and evaluate an algorithm to ascertain MITT use in COPD based on prescribing records in the UK Clinical Practice Research Datalink.

Methods: The MITT algorithm was developed with Cohort A (125 000 COPD patients with ≥ 1 prescription [Rx] for ICS, LABA, or LAMA). First, Rx information (numeric daily dose NDD, quantity QTY) was assessed descriptively by product and class for all mono and combination Rx for ICS, LABA and/or LAMA. Rules for cleaning and imputing QTY and NDD were informed by the resulting descriptive statistics and knowledge of the health care system. Next, start and end dates for periods of MITT prescribing were identified using a derived duration variable (QTY/NDD). MITT prescribing was defined based on overlapping Rx of the 3 components (ICS + LABA + LAMA). Gaps of <30 days between end and next start date of MITT prescribing periods were allowed, stockpiling was not. Cohort B (43 124 COPD patients with ≥ 12 mths follow-up available) was used to evaluate different patterns of MITT use, relative to a set index date. The proportion of MITT users was estimated using 5 definitions: MITT for ≥ 1 day and on the index date, continuous MITT for ≥ 6 or ≥ 12 mths before index, MITT on ≥ 1 day in 6 mths before index, and MITT for ≥ 1 day in each quarter of year prior to index.

Results: Cohort A included >245 000 Rx for ICS, LABA, and/or LAMA. Availability of QTY and NDD ranged from 27% of LABA/LAMA Rx to 83% of ICS Rx. Cleaning and imputing QTY and NDD to derive duration resulted in minimal changes at class level to median duration, but had larger impact at extremes of the distribution. Median estimated duration was 30 days for all except the ICS monotherapy group (50 days). The proportion of MITT users in Cohort B differed per the definition applied, ranging from 11.4% (continuous overlap for prior 12mths) to 39.6% (overlap of ≥ 1 day in prior 6 mths).

Conclusions: Blanket assumptions about Rx duration (particularly for ICS) may be invalid when exploring MITT prescribing in COPD patients. Care should be taken when defining and estimating MITT use based on overlapping periods of ICS + LABA + LAMA

prescribing—shorter overlap of the MITT Rx components results in higher frequency of use. Funding: GSK PRJ2613 and ODA2778

263 | To pile or not to pile: How to define episodes of use of COPD medications in the CPRD

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Background: In an ongoing COPD study, some patients had long-term overlapping prescriptions (>75th percentile of duration of overlapping prescriptions). Different approaches can be used to define episodes of use of medications in electronic record databases.

Objectives: To assess, among users of 4 COPD medications (LABA, LAMA, LABA/ICS, and LAMA/LABA), the impact on incidence rate (IR) and incidence rate ratio (IRR) of congestive heart failure (CHF) of 8 approaches to define episodes of use of these medications in the Clinical Practice Research Datalink.

Methods: We defined episodes of use separately for the 4 COPD medications, allowing both 7-day and 30-day gaps between prescriptions, using 4 different assumptions: (1) 0% stockpiling (ie, disregarding any overlap between prescriptions), (2) 100% stockpiling for patients below the 75th percentile of duration of overlapping prescriptions and 50% for those above, (3) same as 2 except 75% instead of 50% stockpiling was used, and (4) 100% stockpiling. LABA was the reference for the IRR.

Results: Using a 7-day gap, the highest increase of person-years (PY) of exposure across COPD medications was 6.0%, 7.1%, and 8.7% using 50%, 75%, and 100% vs 0% stockpiling. The highest increase in the number of events was 6.3%, 6.7%, and 8.1% using 50%, 75%, and 100% vs 0% stockpiling. The ranges for IR of CHF per 1000 PY were 19.1-25.6 (0% stockpiling), 19.4-25.5 (50% stockpiling), 19.2-25.5 (75% stockpiling), and 19.0-25.7 (100% stockpiling). The maximum difference across COPD medications comparing all scenarios to 0% stockpiling was 1.2% for the IR and was 0.85% for the IRR, both in the 50% stockpiling scenario. Using a 30-day gap, the highest increase of PY of exposure across COPD medications was 2.3%, 2.9%, and 3.7% using 50%, 75%, and 100% vs 0% stockpiling. The highest increase in the number of events was 2.0%, 3.0%, and 5.9% using 50%, 75%, and 100% vs 0% stockpiling. The ranges for IR of CHF per 1000 PY were 18.6-25.0 (0% stockpiling), 18.7-25.1 (50% stockpiling), 18.7-25.2 (75% stockpiling), and 19.0-25.2 (100% stockpiling). The maximum difference across COPD medications comparing all scenarios to 0% stockpiling was 2.4% for the IR and was 4.0% for the IRR, both in the 100% stockpiling scenario.

Conclusions: As expected, increasing PY of exposure and number of events were observed for increasing stockpiling scenarios, with larger differences for the 7-day gap. Although the differences in IRs and IRRs were larger in the 30-day gap scenario, overall these were small (ie, $\leq 4.0\%$).

264 | A flexible approach to evaluating the validity of commonly used claims-based cancer algorithms

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Background: Algorithms are necessary to identify incident cancer cases in administrative data when pathology information is missing. Cancer validation studies often require a long period of continuous enrollment, but this may limit generalizability and underestimate incidence and positive predictive value (PPV).

Objectives: To develop a cohort to validate a commonly used claims-based incident colorectal cancer definition (≥ 2 ICD-9 codes within 60 days) without strict continuous enrollment criteria.

Methods: We selected all primary CRC cases from the North Carolina (NC) Central Cancer Registry with linkage to NC Medicare claims (85% completeness). Cases were aged ≥ 65 and had a diagnosis from 1Jul06-31Dec13. 17% of non-cases were randomly sampled from all NC Medicare beneficiaries aged ≥ 65 never appearing in the NC cancer registry. Both cases and non-cases had ≥ 13 months of continuous enrollment in Medicare parts A/B at some point between 1Jul06-31Dec13 and ≥ 1 inpatient or outpatient claim, and no evidence of Medicare coverage before age 65. We generated a series of observation windows (OWs) during the study period. Each OW was 365 days plus a period of time before and after the 365 days. This additional time period was based on empirical estimates of average length of CRC diagnosis and treatment. Cases and non-cases were eligible in an OW if they were continuously enrolled during that OW. Starting from 1Jul06, OWs slid forward in time by average CRC diagnosis time increments. Cases could serve as non-cases prior to their case OW. Specificity, PPV, sensitivity and 95% CI were calculated in each OW and overall using generalized estimating equations.

Results: There were 3744 cases and 109 745 non-cases meeting cohort criteria. There were 14 OWs during the study period, each of which was 739 days. CRC incidence weighted for the sampling fraction of non-cases and cases without Medicare linkage in this population was 86.4 per 100 000. Overall specificity and sensitivity were 99.2% (99.2-99.3), and 99.4 (99.3-99.5); PPV was 9.7% (9.3-10.2) after accounting for the non-case sampling fraction.

Conclusions: Because CRC incidence has declined substantially over the past two decades, CRC-identification algorithm PPV has declined even though specificity remains high. Low PPV is not optimal when the goal is to examine the association between a particular exposure and an outcome, or if the cohort consists of individuals identified as an incident cancer case, because a large proportion would be false positive cases.

265 | Assessing the performance and possibility of overfitting of different algorithm development methods used to define advanced stage ER+/HER2- breast cancer

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Background: Case identifying algorithms from claims are often used to define populations and outcomes. These algorithms are developed using different techniques including using clinical knowledge only, post-hoc modification/removal of codes, and predictive modeling.

Objectives: To assess the performance of different algorithm development methods to define advanced stage ER+/HER2- breast cancer using claims, and to assess overfitting.

Methods: We developed several algorithms to define advanced stage ER+/HER2- breast cancer in claims and tested them in a validation study using clinical data for 8800 breast cancer cases from Anthem's Cancer Care Quality Program. The first algorithm included codes utilizing clinical knowledge alone developed prior to the validation study. Next, post-hoc modified algorithms were developed in ten separate training samples (each $n = 150$ to mimic a common validation sample size), with algorithms removing all codes from the first (clinical knowledge) algorithm that were not strongly associated with the outcome (odds ratios < 3.0). We also developed an algorithm through a predictive model using logistic regression with bootstrapping. We then examined if the algorithms were overfit to the training samples using a distinct test sample of 4400 breast cancer cases.

Results: There were 10 distinct post-hoc modified algorithms created from the 10 training samples. The clinical knowledge alone algorithm had a Positive Predictive Value (PPV) of 67.8% (95% Confidence Interval [CI] = 62.9%, 72.7%) and a sensitivity of 33.7% (95% CI = 30.2%, 37.2%). The 10 post-hoc modified algorithms had PPVs ranging from 80.0% to 100% and sensitivities ranging from 18.1% to 50.0% in the training samples. However, there was evidence of potential overfitting for some algorithms, as some of their PPVs and sensitivities were $>5\%$ lower in the test sample with PPVs ranging from 83.2% to 92.0% and sensitivities ranging from 26.8% to 41.1%. The predictive model algorithm had a PPV of 91.4% (89.5%, 93.3%) and a sensitivity of 53.9% (51.3%, 56.5%).

Conclusions: The algorithms developed through predictive modeling and post-hoc modification had improved performance compared with a clinical knowledge alone algorithm in the training samples, but some post-hoc modified algorithms had lower performance in the test sample. Case-identifying algorithms developed through post-hoc modifications can be at risk of overfitting and lack of transportability.

266 | Identification of incident pancreatic cancer in administrative health data: A validation study by the Canadian Network for Observational Drug Effect Studies (CNODES)

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Background: The validity of administrative studies assessing the incidence and prognosis of pancreatic cancer hinges on the accurate recording of this cancer. While government-sponsored cancer registries are the preferred data source for identifying incident pancreatic cancers, these registries are often less readily accessible to researchers than administrative health data. However, few studies have evaluated the accuracy of identifying incident pancreatic cancer in administrative health data.

Objectives: To validate three approaches for identifying incident pancreatic cancer in administrative health data.

Methods: We created a cohort using Ontario (Canada) administrative health data from 2002 to 2012 and identified cases of pancreatic cancer with three approaches, using the Ontario Cancer Registry (OCR) as the reference standard. In the *any diagnosis* approach, cases were defined by primary or secondary diagnostic codes for pancreatic cancer in outpatient or inpatient records. In the *any inpatient diagnosis* approach, cases were defined using only diagnoses in hospital discharge abstracts. In the *algorithm* approach, cases were identified by an algorithm that combined the first two approaches. Comparing each approach to the OCR, we calculated the expected value and 95% confidence interval (CI) of the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). We also compared the event dates using each approach with the diagnosis date recorded in the OCR.

Results: Among the 12 060 837 Ontarians in our base population over the study period, we identified 13 999 incident pancreatic cancer cases in the OCR. Sensitivity ranged from 72.5% (95% CI: 71.8, 73.3%) (*algorithm*) to 97.5% (95% CI: 97.2, 97.8%) (*any diagnosis*), and PPV ranged from 38.4% (95% CI: 37.9, 38.9%) (*any diagnosis*) to 78.9% (95% CI: 78.2, 79.5%) (*any inpatient diagnosis*). Specificity and NPV were ~100% for all approaches. The median absolute difference in time between the cancer event dates and corresponding OCR diagnosis dates ranged from 0 days (*any inpatient diagnosis*) to 15 days (*algorithm*). The *any inpatient diagnosis* method had the highest PPV and moderate sensitivity (86.6%; 95% CI: 86.0, 87.2%). Similar results were obtained in the subset of patients aged 65+ years.

Conclusions: Inpatient diagnoses of pancreatic cancer in Ontario administrative health data are suitable for pancreatic cancer case identification.

267 | Diagnostic accuracy of the International Classification of Disease 10th Revision codes of heart failure in administrative database

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Background: Heart failure (HF) is a common, serious and still poorly known illness, which might benefit from studies in claims databases. However, to provide reliable estimates, HF patients must be adequately identified.

Objectives: This validation study aimed to estimate the diagnostic accuracy of the ICD10 codes I50.x, heart failure, in the French hospital discharge diagnoses database.

Methods: This study was performed in two university hospitals, comparing recorded discharge diagnoses and electronic clinical files (EHR). Patients with discharge ICD10 codes I50.x were randomly selected. Their EHR were reviewed to classify HF diagnosis as definite, potential or miscoded based on the European Society of Cardiology diagnostic criteria, from which the codes' positive predictive value (PPV) was computed. To estimate sensitivity, patients with an EHR HF diagnosis were identified, and the presence of the I50.x codes was sought for in the hospital discharge database.

Results: Two hundred possible cases of HF were selected from the hospital discharge database and 229 patients with a HF diagnosis were identified from the EHR. The PPV of I50.x codes was 60.5% (95% CI 53.7 to 67.3%) for definite HF diagnosis and 88.0% (95% CI 83.5 to 92.5) for definite/potential HF diagnosis. The sensitivity of I50.x codes was 64.2% (95% CI 83.5 to 92.5%). PPV results were similar in both hospitals; sensitivity depended on the source of EHR: a department of cardiology has a higher sensitivity than non-specialized wards.

Conclusions: Diagnosis codes I50.x in discharge summary databases accurately identify patients with HF but fail to capture some of them.

268 | Endpoint adjudication in pharmacoepidemiological research

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Background: Composite clinical outcomes are widely used as endpoints in observational and randomised clinical studies. Potential outcome events can be identified from patient reports, death certificates and increasingly commonly electronic hospitalisation codes. Clinical adjudication of such events has been widely used to validate record linkage methodology and is used in Phase IV post authorisation safety

studies where the PROBE (prospective, randomised, open, blinded endpoint) study design requires independent assessment of blinded endpoints. Adjudicated endpoints may also be required by regulators when either randomised or observational studies are submitted in support of drug licensing applications.

Objectives: To describe the experience and importance of adjudicating cardiovascular endpoints for randomised and observational research in the UK and other European countries.

Methods: Each adjudication process is governed by an endpoint charter. Typically, this process requires abstraction and redaction of secondary care medical records. The abstracted records are then used to complete an endpoint form which is passed to an independent endpoint committee for adjudication.

Results: Reasons for non-adjudication of events include: miscoding of clinical data; re-admission for historical events; events not being the cause of admission; and non-availability of clinical case records. In our studies the positive adjudication rate varies from 50-90%. This variation depends upon the precise definition of the endpoint (for example whether the event is the primary or contributory cause of a hospital admission) and the choice of diagnostic codes used to identify potential events (balancing sensitivity against specificity). Event rates based on non-adjudicated outcomes may be misleading, and with a larger number of events may imply a higher degree of statistical certainty than really exists. The challenges of adjudicating endpoints are many: specially trained staff are needed to access medical records and abstract information, clinical experts are required in the endpoint committees and information governance frameworks are burdensome (a recently completed Scotland-wide validation process required approval from 13 different bodies). The process is time consuming and expensive.

Conclusions: The adjudication of endpoints in clinical studies is an important consideration. The process has been important in the development of the record linkage methodology, is required by regulators and is needed to ensure accurate, unbiased results.

269 | A systematic review of validated suicide outcome classification in electronic health care database studies

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Background: Pharmacoepidemiologic studies measuring suicidal outcomes, including ideation, attempt, or completed suicide, typically use diagnostic code algorithms to identify events, but relatively few studies address the accuracy of these constructs.

Objectives: To identify and describe validated methods for suicidal outcome classification in electronic health care database studies.

Methods: We performed a systematic review of health care database studies that validated methods for suicidal outcomes classification using a standard measure, such as chart review or vital records. We exported PubMed and EMBASE citations meeting our search criteria from January 1, 1990, to March 15, 2016. Abstracts and full texts

were screened by two reviewers using prespecified criteria. Sensitivity, specificity, and predictive value for suicidal outcome measures were extracted by two reviewers using a standardized form. Methods for this review follow PRISMA-P guidelines (PROSPERO: 2016:CRD42016042794).

Results: We identified 2202 citations, of which 16 assessed the accuracy of E-codes, ICD codes, or classification algorithms for suicidal outcomes. Studies estimating the sensitivity of suicidal ideation (V62.84) or E-codes (E950-9) for suicide attempt found sensitivities from 2-5%, though one study found E-codes 19% sensitive among patients with newly diagnosed depression. Six of seven studies found self-harm E-code positive predictive values (PPV) from 83-100%, with one study estimating 55% PPV. We identified two types of multi-criteria definitions: screening algorithms, designed to capture all cases subsequently confirmed by a more specific measure, and outcome algorithms, designed to define a suicidal outcome event. Screening algorithms, often including events with "uncertain" intent, had PPVs of 4-50%. Outcome definition algorithms using ICDs had PPVs from 74-92% with improved sensitivity compared with E-codes. Read code algorithms, in research practice networks, had sensitivities from 14-68% and PPVs from 0-69%, relative to external data sources.

Conclusions: Many commonly used suicidal outcome constructs use E-codes and/or include events with "uncertain" intent. Consequently, many pharmacoepidemiologic studies measuring suicidal outcomes may be under powered or biased towards the null by outcome definitions with poor sensitivity or PPV. Future studies should validate outcomes or use a previously validated algorithm with high PPV in an appropriate population and data source.

270 | Use of patient profiles to enhance the interpretation of the risk of acute pancreatitis among patients on multidrug antidiabetic therapy

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Background: Patients with diabetes often have complex multidrug therapies. In time-on-drug (TOD) analyses, double-counting occurs when cases are attributed to both the study drug and its comparator(s). Patient profiles can offer insights into these patterns to provide broader interpretation.

Objectives: To use claims-based patient profiles to assess the impact of multidrug therapy on the interpretation of TOD analyses, including double-counting of cases, drug switching and concomitant use.

Methods: A new-user, prospective cohort study was conducted using a large US health insurance database (Optum Research Database, 2010-2014). Initiators were adults with observed dispensings for antidiabetic drugs, (AD) with no claim for that drug or drug class during

the preceding 6 months. Acute pancreatitis (AP) cases were adjudicated using medical records. Liraglutide initiators were propensity score-matched separately to individual drug comparators and *all comparator* groupings. Risk ratios (RR) were calculated to compare the AP incidence rates, separately for *current*, *recent* and *past* use, of liraglutide and of comparators. Profiles of claims from AD initiation up to 1 month after the AP diagnosis were reviewed.

Results: In the *all comparator* drugs comparison, 19% of the AP cases in the *current* use category and 33% of the cases in the *past* use category were attributed to both liraglutide and a comparator (ie, included in the numerator and denominator of the RR). Profile review revealed that most double counting was observed due to adjunct therapy with liraglutide (eg, metformin, sulfonylureas, and pioglitazone). Profile review also revealed the complexities of AD therapy, including regular versus sporadic dispensings over time. A range of use patterns will be provided and the impact of these patterns on the interpretation of results will be described.

Conclusions: Interpretation of TOD analyses among AD users should take into consideration the patterns of use, including sporadic and concurrent multidrug therapy. Review of patient profiles assists with identifying the complexities of this analytic approach.

271 | Identifying IBD patients in claims database: A comparison of validated algorithms

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Background: Using validated population-based case definitions is critical for ensuring comparability between retrospective observational studies. There are several existing validated case definitions for IBD but no comparison has been performed.

Objectives: To compare various IBD-identifying algorithms in the same large population-based claims database.

Methods: A literature review was conducted in PubMed database from 2000 to 2016 to select IBD definitions in large population-based databases. Selected algorithms were applied in the Optum Clinformatics DataMart Database between 2000 and 2017. Outpatient IBD drug dispensed, inpatient and outpatient diagnoses for Crohn's disease (CD) (ICD-9: 555.x; ICD-10: K50.x) and ulcerative colitis (UC) (ICD-9: 556.x; ICD-10: K51.x) were used to identify IBD patients. Patients populations identified (UC, CD, unspecified) by each algorithm were compared.

Results: Three IBD definitions published by Herrinton, Rezaie, and McAuliffe were selected based on population, quality, novelty, validation results, and citation numbers. The Rezaie definition had the highest sensitivity, specificity, PPV, and NPV but identified the smallest IBD cohort: 171 537 patients including 70 919 (41%) for CD, 54 953 (32%) for UC, and 45 665 (27%) unspecified. The Herrinton definition had lower PPV but identified the largest cohort: 323 833 IBD patients including 124 899 (39%) for CD, 141 816 (44%) for UC, and 57 118 (17%) unspecified. The most recent McAuliffe definition identified 246 953 IBD

patients including 108 100 (44%) for CD, 117 313 (47%) for UC, and 21 540 (9%) unspecified. The three algorithms together identified 326 439 unique patients in the database, among whom 164 525 (50%) were identified by all three algorithms. Herrinton and McAuliffe algorithms agreed on 80% of CD and UC patients. Most of the UC and CD patients identified by Rezaie algorithm were also identified by the other two algorithms. A major discrepancy was found in the unspecified group where only 5% were identified by all three definitions.

Conclusions: In the same large US population-based claims database, various IBD definition could result in identification of different patient populations and difference estimates of disease incidence/prevalence. When selecting disease definitions, reproducibility should be considered for study population, database, and selected methodology. Validated and robust algorithms should be used in observational studies to allow comparison of results between studies.

272 | Validation of uterine perforation and intrauterine device expulsion in electronic health records

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Background: Health care databases are increasingly used for medication and device safety studies. Data sources with electronic health records (EHRs) have many advantages over administrative claims databases; among them, clinical notes in EHRs that provide additional insight into medical encounters, medical events, lifestyle factors, and health-related behaviors. Methods to utilize these richer data sources must be developed and validated before use.

Objectives: To develop and validate automated algorithms using both structured and unstructured data from health care systems with EHRs to identify uterine perforations and intrauterine device (IUD) expulsions.

Methods: Four sites in the United States participated: 3 Kaiser Permanente (KP) sites—Northern California (KPNC), Southern California (KPSC), Washington (KPWA)—and Regenstrief Institute (RI) in Indiana. The study population included all identified IUD insertions (n=325 582) among women aged ≤50 years (n = 282 028). The study period at each site was from the time the EHR was fully implemented at that site through September 30, 2015. Using structured (eg, International Classification of Diseases codes, Current Procedural Terminology codes, National Drug Codes) and unstructured (Natural Language Processing terms) data, site-specific algorithms for uterine perforation and IUD expulsion were developed and validated by clinical experts via EHR review of a random sample of one-third of the

identified possible cases (up to 100). If sites further refined their algorithm, a second random sample of one-third of the possible cases was selected for review. Positive predictive values (PPVs) of the algorithms were calculated.

Results: The number of possible uterine perforations identified by algorithms at each site ranged from 67 to 444, and the number of possible IUD expulsions ranged from 268 to 4185. Two sites refined their algorithms and selected one or two additional possible-case samples. PPVs for uterine perforation were KPNC, 77%; KPSC, 81%; KPWA, 82%; and RI, 47%. PPVs for IUD expulsion were KPNC, 77%; KPSC, 87%; KPWA, 68%; and RI, 37%.

Conclusions: These results suggest that a retrospective study using algorithms to identify the outcomes of uterine perforation and IUD expulsion can be successfully conducted in these sites with EHRs, although review of possible cases is recommended at the one site that relied solely on unstructured data and in certain subgroups at other sites, to reduce misclassification of outcomes.

273 | Validating updated claims-based algorithms to identify incident fragility fractures

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Background: Although the fracture identification algorithms developed by Ray et al using 1987 Medicare data have positive predictive values (PPVs) ranging from 79-98%, the Health Care Common Procedural Codes used for reimbursement of fracture repair procedures have been modified over time.

Objectives: To validate updated claims-based algorithms for identification of incident fractures.

Methods: We used 2005-2014 Medicare claims linked to the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a prospective, national cohort of Black and White adults ≥ 45 years, to estimate PPVs of updated fracture algorithms. We identified "case qualifying (CQ)" fracture claims among Medicare beneficiaries who were ≥ 65 years with ≥ 12 months of fee-for-service Medicare coverage before and ≥ 6 months coverage after the first fracture claim or who died following their fracture. Fracture status was confirmed using hospital discharge summaries, and/or imaging and surgical reports from medical records. We first matched claims-based fractures to adjudicated-fractures by participant and date (± 180 days). We then performed a manual review of medical records to ensure the claim was appropriately matched to the correct fracture site within ± 30 days. PPV was calculated as the number of confirmed fractures by the total number of claims-identified fractures, overall and by CQ definition.

Results: We identified 8659 fractures from claims among 3818 REGARDS participants. Of these, 38.3% were from fracture sites without a CQ algorithm, and 31.0% were fractures that did not fulfill CQ criteria; thus no retrieval was attempted. Given project resources,

medical record retrieval was attempted for 1400 of the more the recent fractures, and accomplished for 1086 (77.6%). Our final analytic set included 537 fractures, of which 527 (98.1%) were confirmed. The overall PPVs (95% CI) for the hip, wrist, and spine fracture algorithms were 99.1% (95.2, 99.8), 95.9 (90.0, 98.4), and 99.3 (96.3, 99.9), respectively.

Conclusions: Overall, these updated fracture identification algorithms had high validity, even for vertebral fractures, which were not previously evaluated by Ray et al. Our findings suggest that while medical record review and clinical adjudication remains a gold standard for fracture adjudication, claims-based algorithms provide valid fracture ascertainment for case finding and outcome assessment for comparative effectiveness and safety research.

274 | Assessing the impact of missing deaths on survival analyses conducted in an oncology electronic health record (EHR) database

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Background: Real-world data (RWD) sources such as EHRs provide opportunities for deriving clinical insights and complementing clinical trial data when trials are not feasible/ethical. Confidence in these insights are dependent upon confidence in the underlying data.

Objectives: The objective was to assess the impact of missing death data on survival analyses conducted using EHR data.

Methods: Design: Non-small cell lung cancer (aNSCLC) patients with advanced stage disease diagnosed between 1/1/11 and 12/31/15 in an oncology EHR were included in the study. Three analytic use cases were evaluated: absolute risk estimation, relative risk comparing 2 groups within the EHR, and relative risk comparing simulated single arm trial data to an external control identified within the EHR. Setting: The aNSCLC cohort was selected from the Flatiron Health EHR database. National Death Index (NDI) data were obtained on patients in the aNSCLC cohort. Exposures or Interventions: The analyses included a number of survival comparisons for groups defined on the basis of drug exposure or clinical characteristics. Main Outcome: The primary outcome was overall survival (OS), defined as time from first line treatment initiation or advanced diagnosis to death. Patients were censored at their last known structured activity date in the EHR prior to the end of the analysis period. The gold standard for the endpoint was mortality data from the NDI linked data.

Statistical Analysis: The Kaplan-Meier method was used to estimate median OS (mOS), and Cox proportional hazards was used to estimate hazard ratios (HRs).

Results: The study included 10 195 aNSCLC patients. The sensitivity for the mortality endpoint was 90.6%. The mOS using EHR-derived data was 11.6 months (95% CI: 11.3, 12.1) compared with a mOS of 11.0 (95% CI: 10.6, 11.3) using NDI death data. The HR comparing EGFR+ aNSCLC patients to EGFR- was 0.49 (95% CI: 0.43, 0.55) using EHR-derived data, and the HR was 0.49 (95% CI: 0.43, 0.55) when the analysis was conducted using the NDI death data. Other comparisons of groups within the EHR-derived data showed similar lack of bias. A slight bias towards the null was observed in the comparison of single arm data to an EHR-based external control (HR = 0.51 [95% CI: 0.46, 0.57] for the EHR-based data vs HR = 0.48 [95% CI: 0.43, 0.54] when using NDI death data).

Conclusions: EHR mortality data with high sensitivity limits the potential for missing deaths to bias OS estimates. This enables robust conclusions and decision making based on RWD.

275 | Addressing variability of the estimated incidence of acute myocardial infarction across heterogeneous European health care data sources: A strategy from the EMIF project

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Background: European health care databases are heterogeneous in coding and language, but also in terms of data provenance. Some collect diagnoses recorded in primary care practices, others from emergency room, specialist encounters, inpatient care and/or death registries. This must be taken into account in European multi-database studies.

Objectives: To verify the impact of the provenance of data on acute myocardial infarction (AMI) cases retrieval in seven heterogeneous European health care data sources.

Methods: Seven data sources from Spain (ES), Italy (IT), Netherlands (NL), Denmark (DK), United Kingdom (UK) were considered: 2 administrative databases (AD) and 5 medical record databases, 4 from primary (PC) and 1 from hospital care (HC). The Unified Medical Language System was used to project the AMI concept to local terminologies: ICD9CM, ICD10, ICPC, and free text. Records of AMI were separately extracted from primary, emergency, specialist, inpatient care, or death registry. The one year cumulative incidence (CI) of new AMI cases in 2012 among subjects aged 45+, with ≥ 2 year of look-back, was estimated using records of AMI diagnoses with different provenance.

Results: The study population included 8.5 million subjects. CI (cases/10 000 persons) was 43 in AD_DK and 55 in AD_IT, which both used diagnoses from inpatient, emergency care and death registry, but not primary care; in HC_ES, which identified cases mostly from inpatient care but also from specialist care, CI was 40; CI of cases identified from primary care medical records was 8 in PC_IT, 25 in PC_ES, 33 in PC_UK, and 52 in PC_NL. PC_ES could also link diagnoses recorded during inpatient care, and this increased CI to 44: primary care records captured 57% of the total number of cases.

Conclusions: AMI requires immediate medical attention and may lead to death before access to a medical facility. AD data sources, which included AMI from inpatient, emergency care and death registry, likely captured most of the cases in the underlying populations. Assuming consistent reliability of primary and inpatient care diagnoses, sensitivity of primary care records was less than 60% in PC_ES. CI was very variable across PC data sources, possibly due to different local recording habits, such as use of free text. In multi-database studies, the analysis proposed above should be used to better understand the impact of local database characteristics on possible inter-data source variability of findings.

276 | Predicting out-of-hospital death using insurance claims data

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Background: Insurance claims data provide a rich resource for pharmacoepidemiologic research. One important limitation is that deaths are only observable if they occur in-hospital. Out-of-hospital (OOH) deaths result in disenrollment; however, most disenrollment simply reflects a change in insurance provider.

Objectives: To create a claims-based algorithm to distinguish between disenrollment due to OOH death and other types of disenrollment in MarketScan (MSN) Commercial Claims and Encounters (CCAE) and Medicare Supplemental databases (MDCR).

Methods: In preliminary analyses using a 1% random sample of MSN, we identified patients with ≥ 12 months of continuous enrollment before disenrollment in 2006-2011. Using Social Security Death Index

as the gold standard, we used claims in the prior year to predict OOH death ± 30 days from disenrollment. We used logistic regression to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI) for predictors of OOH death. CCAE and MDCR populations were analyzed separately.

Results: Linkage to death data was available for 5902 and 51 206 people disenrolling from MDCR and CCAE, respectively. Of those, 27.6% and 1.1% were OOH deaths in MDCR and CCAE, respectively. In MDCR, disenrollment on Dec 31 (aOR = 0.06, CI 0.05, 0.07), age (aOR = 1.29/5 yrs, CI 1.27 1.30), emergency room visit 3 mo. prior (aOR = 3.2, CI 2.6, 3.9), chronic liver disease (aOR = 1.8, CI 1.2, 2.8), home hospital bed (aOR = 1.8, CI 1.3, 2.7), cancer (aOR = 1.7, CI 1.4, 2.1), and hypertension (aOR = 0.7, CI 0.6, 0.9) were associated with OOH death (c-statistic 0.91). A predicted probability >0.82 identified 9% of MDCR disenrollees for a positive predictive value (PPV) = 80%, sensitivity (se) = 26% and specificity (sp) = 98%. In the CCAE population, hospice in the 3 mo. prior (aOR 17.3, CI 9.9, 30.3) and acute kidney injury (aOR 3.3, CI 2.2, 4.9) were predictors of OOH death in addition to those above (c-statistic 0.94). A predicted probability >0.07 identified 2% of CCAE disenrollees with PPV = 35%, se = 66%, and sp = 99%.

Conclusions: Death is a critical outcome for many research questions and a competing risk for all others. Distinguishing OOH death from other types of disenrollment (administrative censoring) is important for estimating robust treatment effects. The strongest predictor of OOH death was disenrollment any time other than Dec 31. Ongoing work is directed at improving discrimination by considering medications, health care costs and implementing machine learning (eg, random forest).

277 | Validation of an algorithm to identify opioid overdose among US commercially insured individuals

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Background: Insurance claims databases can be used to assess the safety of opioids if they can identify opioid overdose cases and discriminate between intentional (suicidal) and unintentional (accidental) cases. A code-list overdose algorithm comprising overdose codes has been proposed and tested with good results in two electronic medical record (EMR) databases.

Objectives: To assess the accuracy of a code-list algorithm for opioid overdose and an accompanying algorithm classifying intentionality in a further US commercial insurance claims database.

Methods: This validation study was conducted in the HealthCore Integrated Research Database (HIRD), consisting of commercially insured individuals across the United States. We selected at random 159 individuals who had at least one insurance claim-associated diagnosis

consistent with an opioid overdose from 2008 to 2015, and abstracted medical records. Positive predictive values (PPVs) of algorithms and their 95% confidence interval (CIs) were computed, along with the sensitivity and specificity of the algorithm classifying overdoses as unintentional or intentional.

Results: Of the 159 overdose cases identified by the code-list algorithm, 135 (85%) were verified as true overdoses by medical records, providing a PPV of 85% (95% CI = 78%, 90%). The 15% of false positive cases consisted of 12 (8%) patients with opioid adverse events or with anesthesia or surgery related events, and 12 (8%) with no relevant event (miscoded or undeterminable). The 135 overdoses included 88 unintentional and 47 intentional overdoses, as determined by medical record review. The algorithm for unintentional and intentional overdose, provided PPVs of 69% (95% CI = 60%, 77%) and 89% (95% CI = 73%, 97%), respectively, sensitivities of 98% (95% CI = 92%, 100%) and 66% (95% CI = 51%, 79%), respectively, and specificities of 47% (95% CI = 35%, 59%) and 96% (95% CI = 91%, 99%).

Conclusions: A code-list algorithm for opioid overdose was accurate in this large US commercial claims database, with a PPV $>80\%$, which is one standard used for acceptable accuracy. The PPV of 85% in the HIRD was similar to the PPV in the development setting, suggesting the algorithm may have broad applicability in multiple databases. An accompanying algorithm was less accurate in differentiating unintentional and intentional overdoses, partially because some intentional overdoses were incorrectly classified as unintentional.

278 | Validation of electronic health record derived COPD exacerbations using randomised clinical trial data

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Background: Electronic health records (EHRs) are increasingly used to assess medication effectiveness in point of care randomised controlled trials (RCTs), driven by a need to more fully understand the risk/benefit profile, inform reimbursement decisions and cost-efficiency. However, key study outcomes may not be readily available as discrete, easily identifiable events from routine systems, and require derivation using a complex algorithm of diagnostic/medical/drug codes. Establishing the validity of algorithms will enable the use of real-world evidence in regulatory decision making.

Objectives: To validate chronic obstructive pulmonary disease (COPD) exacerbation episodes derived algorithmically in an EHR against researcher-led, prospectively captured exacerbation episodes using a case report form (CRF) from an RCT.

Methods: This analysis used two data sources from COPD Salford Lung Study (SLS) (n = 2269); RCT CRF and the linked primary-secondary care EHR. Exacerbation episodes in the EHR database, identified using an adapted published algorithm, were compared with those

defined in the RCT CRF. Episode characteristics (frequency, duration) were compared, and sensitivity and positive predictive value (PPV) calculated. A match between EHR vs CRF episodes was defined as at least a 1-day overlap; in sensitivity analysis, the definition was relaxed to any part of an EHR episode being within 3, 7, 15, and 30 days of a CRF episode.

Results: In total, 3791 EHR episodes [median length 14d; minimum 1d, maximum 54d] and 4403 CRF episodes [median 7d; min. 1d, max. 372d] were identified. RCT episodes with long duration (≥ 28 days) were not well detected by EHR. Sensitivity and PPV respectively at varying distances between episodes were: 1d overlap - 63.6 and 71.1; 3d distance - 64.8 and 72.1; 7d - 66.3 and 73.1; 15d - 69.1 and 73.6; 30d - 73.7 and 67.6. Relaxing distance between episodes defining matches up to, but not beyond 15d, increased both measures.

Conclusions: In this unique analysis, derivation of exacerbation episodes via EHR compared with RCT CRF recording resulted in slightly fewer episodes, with particularly short and long CRF episodes not well captured; this may be tolerable in new studies of relative COPD exacerbation rates. Performance of the EHR algorithm was acceptable, indicating that EHR derived exacerbation episodes may provide an efficient, valid method of data collection.

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279 | Impact of the definition of osteoarthritis and of the timing of its onset on the association between type 2 diabetes mellitus and osteoarthritis: Clinical Practice Research Datalink

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Background: In a previous case-control study in a large primary care database, the Clinical Practice Research Datalink (CPRD), type 2 diabetes mellitus (T2DM) was associated with a decreased rate of total joint replacement (TJR). As this was in contrast to the hypothesis, selection bias due to the used definition of osteoarthritis (OA) or misclassification of the onset of OA were raised as possible explanations. **Objectives:** To explore the effect of the definition of OA in the CPRD, and hypothesized timing of its onset on the association between T2DM and OA.

Methods: All patients using a non-insulin anti-hyperglycaemic drug (NIAD) between 1989 and 2012 in the CPRD were included and matched to unexposed patients. Cox proportional hazard models were fitted estimating the risk of TJR or OA in T2DM patients compared with patients without T2DM. These analyses were repeated in sensitivity scenarios and joint-specific analyses. To assess whether misclassification of onset of OA may affect the association, analyses were repeated with addition of a latency period of up to 10 years after start of follow-up.

Results: The use of TJR as a proxy for OA (hazard ratio [HR] = 0.74; 95% Confidence Interval [CI] = 0.70-0.78) resulted in a HR that was

approximately 0.2 lower than when OA diagnostic codes were used (HR = 0.93; 95% CI = 0.90-0.95). The joint-specific subgroup analyses, sensitivity scenarios, and latency analyses showed similar results.

Conclusions: When examining the association between T2DM and OA, the use of TJR as a proxy for OA resulted in a 20% lower estimate than the OA diagnosis.

280 | Determining infant age from administrative claims data without birth date: A validation study

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Background: Age is an essential variable for characterizing the demographic distribution of health outcomes. Granularity of this variable may be especially important for young pediatric populations where age is commonly reported in weeks or months rather than years. However, administrative claims databases often provide limited demographic information on enrolled members, generally reporting only birth year.

Objectives: We conducted a validation study to determine if infant enrollment date provides a valid estimate of birth date in administrative claims data.

Methods: We estimated age among infants born during the years 2004-2014 using data from Clinformatics Data Mart (CDM), which provides member birth year but not birth date. The CDM data consist of adjudicated administrative health claims for privately insured members of a large commercial care company affiliated with Optum. Each infant was first linked to their mother via a unique family identifier. We then identified delivery claims for the mother that occurred during the birth year of the infant. We conducted linear regression to compare the service date of the mother's delivery claim to the infant's enrollment date and calculated the intraclass correlation coefficient (ICC).

Results: We identified 406 668 infants from the CDM dataset who were enrolled during their birth year and could be linked to a mother with a medical claim for a delivery filed during that year. The median of the difference between mother's delivery date and infant's enrollment date was 0 days (interquartile range [IQR]: -7-9 days), with a mean of 2 days (standard deviation: 21 days). The linear regression (β : 1.00; p -value < 0.0001) and ICC (0.99) suggested good agreement and high reliability between mother delivery date and infant enrollment date. Stratifying by birth year indicated that these estimates were stable over time; the median difference in 2004 was 1 day (IQR: -7-9 days), and the median difference in 2014 was 0 days (IQR: -7-8 days).

Conclusions: Our findings suggest that enrollment date likely provides a valid estimate of birth date among infants enrolled in private insurance during their birth year. As a result, age granularity can be retained when exact birth date is not present in administrative claims data.

281 | Impact of look-back time on the measurement of prevalence and incidence in health care databases

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Background: Secondary health care databases should enable rapid measurement of disease prevalence and incidence, but studies that report these measurements frequently do so using methodological assumptions that are selected without empirical rationale or are left unstated. These assumptions can involve complex issues concerning observability (contributed person-time) and the amount of look-back time (available data) used to identify prevalent disease.

Objectives: To determine whether variations in observability and look-back time meaningfully affect prevalence and incidence estimates in databases.

Methods: We estimated prevalence and incidence proportion for five chronic diseases (cystic fibrosis, inflammatory bowel disease, schizophrenia, psoriasis, and chronic obstructive pulmonary disease [COPD]) using two de-identified databases (Clinical Practice Research Datalink [CPRD; N = 16 918 695] and the Optum Clinformatics® Data Mart [CDM; N = 56 039 401]). The diseases were chosen for their varied etiology and expected prevalence. For each of 5 consecutive years (2010–2014), we estimated prevalence on Jan 1 and incidence using different look-back times (1-year, 2-year, and all-time look-back) and observability requirements (defining denominator patients as those observable on Jan 1 vs on all days of the year).

Results: Look-back time substantially affected estimate magnitudes. For 2014 in CPRD, use of an all-time vs a 1-year look-back resulted in a 4.3 to 8.3 times higher prevalence (depending on the disease), which reduced incidence by a factor of 1.9 to 3.3. For example, COPD prevalence by look-back time was 0.39% (1-year), 0.65% (2-year), and 1.68% (all-time), and increasing prevalence caused decreasing incidence (0.30%, 0.23%, and 0.16%). All-time look-back also resulted in strong temporal trends that external data did not support. For example, using an all-time look-back, COPD prevalence between 2009 and 2014 saw a 14% increase (from 1.48% to 1.68%), while using a 1-year look-back, it stayed relatively constant (decreasing from 0.41% to 0.39%). Changing observability requirements did not substantially affect estimates. We saw similar results in CDM.

Conclusions: Though prevalence and incidence are seemingly straightforward concepts, careful consideration of assumptions including look-back time is required to obtain meaningful estimates. These assumptions must be informed by expert knowledge of disease etiology and databases' population dynamics and be clearly stated.

282 | Varying numerator and denominator population definitions in annual prevalence proportions estimated from administrative claims data

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Background: Administrative claims are used to estimate annual disease prevalence, but no consensus methods exist for defining numerator and denominator populations. In the literature, cohorts are defined with varying numbers of diagnosis codes, continuous enrollment (CE) lengths, and codes from prior years.

Objectives: To evaluate the sensitivity of prevalence estimates to varying numerator and denominator definitions from the literature for 20 chronic diseases.

Methods: Using Truven MarketScan® Commercial Claims and Encounters database, we identified commercially-insured US patients aged 0–64. We enumerated cases with 20 chronic conditions using 3 published methods: (1) ≥ 1 diagnosis codes in 2016; (2) ≥ 2 codes in 2016; (3) ≥ 2 codes in 2015–16 with ≥ 1 code in 2016. For each numerator, prevalence was estimated with 9 published denominator definitions with CE: (1) ≥ 1 day in 2016, (2) ≥ 1 day in 2016 and ≥ 1 visit; (3) ≥ 6 months in 2016, (4) throughout 2016, (5) throughout 2016 and ≥ 1 visit, (6) ≥ 12 months with ≥ 1 day in 2016, (7) throughout 2015–16, (8) throughout 2015 with ≥ 1 day in 2016, or (9) $\geq$ average CE length of numerator patients. Numerators and denominator CE requirements were the same except for denominator #9. Distributions of the 27 prevalence estimates were examined by disease and between diseases.

Results: Numerator-denominator combinations resulted in varying distributions of prevalence estimates, with the relative magnitude of the standard deviation ranging from 0.3 to 1.2 across diseases. Estimates with highly restricted numerator and denominator populations (eg, numerator with ≥ 2 codes, CE throughout 2015–16) were similar to those with less restricted populations (eg, numerator with ≥ 1 code, CE throughout 2016). Regardless of numerator definitions, prevalence was smaller when populations had CE for ≥ 1 year with ≥ 1 day overlapping 2016 rather than CE over 2016.

Conclusions: The literature includes inconsistent numerator and denominator definitions for annual prevalence estimates, yielding varying estimates for the same disease. We found that estimates with more restricted case and CE definitions were similar to estimates with less restricted definitions, as long as the degree of restriction was similar in numerators and denominators. The results also suggest that definitions should consider both the required CE length and time that CE overlaps the year of interest. Our results can inform decisions about defining populations in future prevalence estimates.

283 | Algorithms for cardiovascular death in administrative claims databases: A systematic review

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Background: Valid algorithms for identification of cardiovascular (CV) deaths allow researchers to reliably assess the cardiovascular safety of medications which is important to regulatory science, patient safety, and public health.

Objectives: To conduct a systematic review of algorithms to identify cardiovascular death in administrative health plan claims databases.

Methods: We searched MEDLINE, EMBASE, and Cochrane Library for English language studies published between January 1, 2012, and October 17, 2017. We examined references in systematic reviews to identify earlier studies. Selection included any observational study using electronic health care data to evaluate the sensitivity, specificity, positive predictive value (PPV) or negative predictive value (NPV) of algorithms for cardiovascular death (sudden cardiac death [SCD], myocardial infarction [MI]-related death, or stroke-related death) among adults aged ≥ 18 years in the United States. Data were extracted by two independent reviewers, with disagreements resolved through further discussion and consensus. The Quality Assessment of Diagnostic Accuracy Studies-2 instrument was used to assess the risk of bias. PROSPERO 2017 CRD42017078745

Results: Five studies ($n = 4$ on SCD; $n = 1$ on MI- and stroke-related death;) were included after a review of 2053 citations. All studies reported algorithm PPVs with incomplete reporting on other accuracy parameters. One study was at low risk of bias, three studies at moderate risk of bias, and one study at unclear risk of bias. Two studies identified community-occurring SCD: one identifying events using ICD-9 codes on death certificates and other criteria from medical claims (PPV = 86.8%); and the other identifying events resulting in hospital presentation using first-listed ICD-9-codes on emergency department or inpatient medical claims (PPV = 92.3%). Two studies used death certificates alone to identify SCD (PPV = 27% and 32%, respectively). One study used medical claims to identify cardiovascular death (PPV = 36.4%), coronary heart disease mortality (PPV = 28.3%); and stroke-mortality (PPV = 34.5%).

Conclusions: Two existing algorithms based upon medical claims diagnoses +/- death certificates can accurately identify SCD to support

pharmacoepidemiologic studies. Developing valid algorithms identifying MI- and stroke-related death should be a research priority.

284 | Comparison of dispensed medications and forensic-toxicological findings to assess pharmacotherapy in the Swedish population 2006-2013

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Background: There is a lack of population-based studies that biochemically have assessed adherence to prescribed non-psychotropic non-addictive drugs.

Objectives: In this nationwide autopsy-based study, we strove to investigate person-level agreement between medication exposure as predicted using the PRE2DUP (a prescription-based design to estimate continuous drug use) method and postmortem toxicological findings, in the Swedish population during the years 2006 to 2013.

Methods: Using the Swedish National Board of Forensic Medicine's toxicology database and the Swedish National Board of Health and Welfare's registries on causes of death, dispensed medications and in-patient care, forensic-toxicological findings were compared with prescription-based estimates of drug use for 27 medications. We modeled expected drug-use periods with the PRE2DUP using an algorithm of demonstrated high validity that evaluates personal drug-purchasing patterns with consideration to possible stockpiling of drugs and package information. Excluding criteria included self-inflicted death and recent in-patient care.

Results: In data from 18 627 performed autopsies, as well as 10 160 instances of dispensed drug use, the agreement between PRE2DUP drug-use periods and forensic toxicology was, overall, moderate (Cohen's kappa: 0.56 [95% confidence interval {CI}: 0.55-0.57]) with a positive predictive value, or predicted adherence rate, of 46.0%. The group-level predicted adherence and agreement were highest for antidepressants, at 71.0% (Cohen's kappa: 0.74 [CI: 0.73-0.76]), and lowest for cardiovascular drugs, at 21.5% (Cohen's kappa: 0.33 [CI: 0.31-0.36]). Predicted recreational use (negative predictive value) was low for all investigated drugs (0.0%-1.4%). The biological half-life explained 29% ($p = 0.003$) of the variability of the false-positive rate.

Conclusions: Measured agreement between PRE2DUP-based drug-use estimates and forensic-toxicological findings is dependent upon a number of factors, including true continuous drug use and postmortem detectability of the investigated drugs, as well as the occurrence of unconventional dosing and true non-adherence.

285 | Review of claims profiles to develop and refine study cohort and outcome definitions

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Background: Accurate identification of study populations and outcomes is critical to draw appropriate inferences in observational studies using health insurance claims databases. Traditional validation methods that rely on review of paper medical charts are costly and time-intensive. Curated patient-level chronological listings of claims data ("patient profiles") may represent a more efficient alternative.

Objectives: To illustrate potential applications of chronological claims profile review using 3 study examples: (1) the development of an algorithm to identify a study population of patients with migraine; (2) rapid review of potential anaphylaxis and hemorrhagic stroke events among influenza vaccine recipients; and (3) refinement of a previously published stroke algorithm.

Methods: The study examples were sourced from a large US health insurance claims database. De-identified claims profiles were created using diagnoses, services, procedures, and medications that generated insurance claims within a pre-specified time range surrounding the diagnoses of interest. In the first example, patients with migraine were identified based on the presence of ≥ 1 of 5 criteria using different combinations of diagnosis codes for migraine associated with inpatient, outpatient physician, emergency room, or neurologist visits, and/or claims for acute migraine treatment. Profile review was conducted on a random sample of 50 patients, 10 meeting each criterion. In the next 2 examples, profiles were created and reviewed for all events meeting a claims-based definition.

Results: Example 1: 6/10 profiles meeting a criterion of ≥ 1 inpatient migraine diagnosis reflected patterns of medical care where the migraine diagnosis claim appeared to represent a more non-specific migraine variant or was part of an inpatient evaluation for conditions such as transient ischemic attack, where migraine might be one of the rule-out diagnoses. The algorithm was subsequently refined to exclude such patients. Example 2: 9/11 anaphylaxis and 11/12 hemorrhagic stroke events were classified as having potential alternate contributing factors or as likely miscodes. Example 3: 20/32 claims-identified stroke events were confirmed through profile review. Of these 20 confirmed cases, 19 were also confirmed by clinical adjudicators with access to the patient medical record.

Conclusions: These examples illustrate the use of chronological claims profile review as an efficient tool to develop and refine study population and outcome definitions.

286 | Cleaning multiple prescription data in general practice datasets

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Background: Data from "real-world" settings are often considered to perfectly reflect clinical practice. However, such data often prove challenging to understand. We examine some of the difficulties in interpreting prescription data. Multiple prescriptions for the same drug can be issued to a single patient at one consultation. There are several set of circumstances that could result in such prescriptions and each may have different implications.

Objectives: To attempt to understand and categorize reasons for multiple occurrences in prescription data and to suggest general rules for handling them in drug exposure studies.

Methods: An examination was made of tramadol prescriptions in the THIN database of UK General Practice data. At 96 66 580 visits at which tramadol was prescribed, 2 or more prescriptions were given on 209 976 (2.2%) of occasions. The maximum number issued at one visit was 28. We examined the product strengths and the specification of daily dose and total quantity to try to infer the reasons for multiple prescriptions and the implications for calculations of exposure periods.

Results: When the same product is given in more than one simultaneous prescription, no additional flexibility is gained with respect to dose. Hence, these are likely to be intended for sequential use. When prescription for different strength tablets are given, the period is often specified for the higher dose and not for the lower dose. Half the multiple prescription (103 282, 49.1%) included two products of different strength. Most (102 632) include just two products. Of these 56 688 (55%) specify clear dosage instruction only for the high strength product. The lower strength is likely to represent rescue medication. 3444 (3.3%) specify such instructions only for the lower strength. 21 336 (20.8%) are unclear for both and 21 164 (20.6%) are clear for both. In 15 083 (71.3%) of these latter cases the exposure periods agree to within $\pm 10\%$ and probably represent an intention to prescribe a non-standard dose. When very different exposure periods are specified the intention may be to vary treatment intensity but sequential or concurrent use is not clear. In some cases of confusion the interpretation of the dosage instruction is not unique and use of a range rather than a single value may help to determine likely exposure period.

Conclusions: In many cases multiple concurrent prescriptions are interpretable in terms of rational prescribing policies but several such policies exist that require differentiating in the analysis.

287 | Validation study with stratified sampling

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Background: In the validation study evaluating the outcome definition when using the chart review as the gold standard, a lot of charts may have to be reviewed to estimate the sensitivity, specificity, positive predictive value (PPV), and the negative predictive value (NPV). The number of chart reviews may be optimized by the stratified sampling where the positive samples of patients who satisfy the outcome definition and negative samples of patients who do not are selected with different extraction fractions.

Objectives: We have proposed a two-step design for the validation study with the stratified sampling where the size of the negative samples is given for the pre-specified absolute precision of the sensitivity.

Methods: In the proposed design, the PPV is estimated first in Step I and is then followed by Step II where the size of the negative samples is calculated for the pre-specified absolute precision of the sensitivity. We used several fictitious scenarios to show how the proposed design works. We also proposed the approximation formulae for the 95% confidence intervals of the sensitivity and specificity and evaluated the formulae by comparing the 95% confidence intervals estimated by the approximation formulae with those by bootstrap percentiles.

Results: The proposed design was shown to provide the size of the negative samples in Step II to achieve the pre-specified precision of the sensitivity for given PPV (estimated in Step I) and the proportion of those who satisfy the outcome definition in the population. For example, if the 95% confidence interval of the sensitivity is pre-specified as within ± 0.1 , ± 0.15 and ± 0.2 of the estimated sensitivity and the number of the true cases in positive samples in Step I is 100, the size of the negative samples in Step II should be at least 3512, 1476, and 849, respectively, provided that PPV = 0.8 and the proportion of those who satisfy the outcome definition is 2% in the population. The approximation formulae gave the 95% confidence intervals of the sensitivity and specificity close to those estimated as bootstrap percentiles.

Conclusions: The proposed stratified sampling method may be useful to optimize the validation study as the size of the negative samples used in Step II can be quantified for the pre-specified precision for the sensitivity.

288 | The impact of increasing allowable inpatient diagnoses in Medicare claims data

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Background: In January 2011, the Centers for Medicare and Medicaid Services (CMS) increased the number of allowable inpatient diagnosis and procedure codes per claim from 9 and 6, respectively, to 25. A sudden expansion of inpatient codes could affect covariate or

outcome measurement in claims-based studies. Using Medicare claims data, we estimated the prevalence of commonly researched medical conditions before and after code expansion.

Objectives: To assess the impact of expanding allowable inpatient diagnosis codes on the measurement of health conditions in CMS claims data.

Methods: We identified Medicare beneficiaries from among patients receiving care within a multi-center metropolitan provider system between 2008 and 2013. Patients entered the study cohort after 180 days of continuous Medicare enrollment, and we recorded the occurrence of 28 medical conditions across all major organ systems over the following 365 days. We divided the medical conditions into (1) covariate type based on both outpatient and inpatient codes and (2) outcome type based on validated algorithms that only used inpatient codes. We then compared the mean yearly prevalence of each condition before (2008-2010) and after (2011-2013) code expansion.

Results: 119 766 eligible patients were identified over the study period. The number of monthly inpatient diagnoses increased by 45% from approximately 14 500 in December 2010 to approximately 21 000 in January 2011. Four of the 18 covariates increased in prevalence after the policy change, with the largest increase for all cancers, which rose from 46.1% in the period before code expansion to 48.6% after. None of the 10 outcomes increased in mean prevalence after the code expansion.

Conclusions: Despite a substantial increase in the number of total inpatient diagnoses, there were no large increases in prevalence for any covariate or outcome after the policy change. This may be because covariates were likely recorded during an outpatient encounter, and outcomes were serious medical events which warranted coding under both the old and new code limits. These findings are reassuring for researchers using CMS claims data, especially when study periods include the date of policy change.

289 | Abstract Withdrawn

290 | Abstract Withdrawn

291 | First insight to national database on electronic prescriptions in Finland

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Background: In Finland, electronic prescribing started in 2010 and became mandatory in Jan 2017. Electronic prescriptions and dispensations are restored in the nationwide Kanta database that has not been used for pharmacoepidemiology research before.

Objectives: To describe the contents of the Kanta database, using prescriptions and dispensations of oral anticoagulants (OAC) as an example and to compare its coverage with the Social Insurance Institution's

Prescription Register (RP), the main data source on medication use in Finland. No information on dosage or indications is routinely available from RP.

Methods: All prescriptions and dispensations for OACs recorded in Kanta in 2012-2016 were retrieved. The distributions of prescriptions, dispensations, and users of OACs in 2016 are described.

Results: The total number of electronic prescriptions for OACs was 257 751 (70% for warfarin, 17% for rivaroxaban, 7% for dabigatran, 6% for apixaban, <1% for edoxaban). Indication was identified in 43% of the OAC prescriptions, atrial fibrillation being the most common of the identified indications (69%). The daily dosage could be determined for 99% of direct OAC prescriptions ($n = 78\,290$). Of the individuals ($n = 202\,584$) prescribed OACs, 7% were <55 years, 11% 55-64 years, 28% 65-74 years, 34% 75-84 years, and 20% 85+ years. The number of dispensations in Kanta were 518 535 (66%) for warfarin, 123 901 (16%) for rivaroxaban, 80 199 (10%) for dabigatran, 63 929 (8%) for apixaban, and 33 (<1%) for edoxaban. The respective numbers identified by PR were 535 812 for warfarin, 89 563 for rivaroxaban, 53 128 for dabigatran, 49 202 for apixaban, and 6 for edoxaban. Based on Kanta, 168 062 individuals used warfarin (vs 173 025 based on PR), 30 464 (24 903) rivaroxaban, 14 108 (10 209) dabigatran, 11 842 (9812) apixaban, and 22 (6) edoxaban. Kanta identified more dispensations of direct OACs than PR since 2014.

Conclusions: The Kanta database is a promising data source for pharmacoepidemiology research in the future. Because of the reimbursement restrictions, use of direct OACs remains severely under-ascertained through the RP.

292 | Feasibility assessment for conducting a multi-country post-marketing safety oncology study using secondary data sources in Europe

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Background: The life cycle of a drug requires a thorough understanding of its safety profile both pre- and post-approval. Use of appropriate real-world data can provide insight into the current post-marketing safety landscape. Secondary data sources in the European Union (EU) with longitudinal data are available for monitoring safety; however, these databases typically lack sufficient patient numbers and have significant data gaps, especially for oncology studies. To better understand these gaps, we evaluated the feasibility of conducting post-marketing safety surveillance research using existing health care databases.

Objectives: The primary objective of this study was to assess the feasibility of conducting a post-marketing small-cell lung cancer (SCLC) drug safety surveillance study within select real-world hematology-oncology databases in the EU.

Methods: Four data sources were qualitatively assessed: The Nordics - Pygargus (Pyg); Germany - German Oncology (GO); United Kingdom

(UK) - Simulacrum (Sim) and Patient Pathway Manager (PPM). Data managers were asked to provide information on database capture of demographic and clinical characteristics, tumor characteristics, therapies received, adverse events, treatment response, and survival.

Results: Annual incident SCLC case counts varied by data source with Pyg at >700 per year, GO and PPM each report ~70 per year (Sim counts are in progress). All four databases had ~80% capture of patient and tumor characteristics. Data on systemic therapies were well captured in all four sources while information on other treatment modalities existed for all but Sim. Adverse events were captured best by GO followed by Pyg. Information on disease progression was poorly captured across all data sources; although, available on patients in PPM by data enhancement through medical record review. Patients in all four databases can be linked to regional death registries for nearly 100% capture of overall survival. Ethics approvals are required for access to Pyg and PPM.

Conclusions: The European databases in this feasibility study had unique tradeoffs that can be leveraged depending on the research questions of interest. However, the Pyg and GO databases had the most consistent coverage of important variables of interest, with complete capture of treatment and adverse events, suggesting these databases present advantages compared with the others contained in this feasibility assessment with respect to post-marketing safety inquiries.

293 | Abstract Withdrawn

294 | Identification of a hereditary angioedema cohort in a US ambulatory EMR database

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Background: Hereditary angioedema (HAE) is a rare disease, characterized by swelling of subcutaneous or mucosal tissue, affecting 1.5-3.3/100 000 people worldwide. Its epidemiologic impact is difficult to quantify due to non-specific diagnosis codes that result in misclassification of patients (pts).

Objectives: To identify representative cohorts of HAE pts for analyses of symptoms, severity, treatments, and outcomes by varying definitions of diagnostic coding and physician notation for HAE within a US electronic medical record (EMR) database.

Methods: A retrospective feasibility study of US ambulatory EMR pts with ≥ 1 diagnosis code (ICD-9 277.6 or ICD-10 D84.1) or mention of HAE in physician notes ("hereditary angioedema" or "HAE") was performed (2007-2017). Pts were included if they had ≥ 1 visit in the EMR ≥ 6 months before and after cohort entry (first date of diagnosis/note). Two mutually exclusive cohorts were created: (1) Pts with ≥ 2 "mentions" (diagnosis code or physician note) of HAE on separate days and (2) pts with only 1 "mention" of HAE. To explore the frequency

of pts with diagnoses vs notes, cohort 1 was further stratified by type of mention: (a) ≥ 2 diagnosis codes, (b) ≥ 2 notes or (c) ≥ 1 diagnosis and ≥ 1 note. An exploratory cohort of pts with ≥ 1 diagnosis code and ≥ 1 note of nonspecific "angioedema" was also created. Cohorts were described in terms of baseline demographic characteristics.

Results: A total of 1692 pts were identified: 194 pts in cohort 1 and 1498 pts in cohort 2. The majority of cohort 1 had a combination of diagnosis codes and notes ($n = 100$, 52%); 24 (12%) had two diagnosis codes and 70 (36%) had notes only. Use of the nonspecific term "angioedema" in combination with ≥ 1 diagnosis code captured 187 pts in exploratory cohort 1. Demographic characteristics were similar across cohorts. Average age ranged from 44 to 48 years; over 60% in each cohort were female. All regions of the United States were reflected, with most from the South (43%).

Conclusions: Despite nonspecific diagnosis coding, it is feasible to identify HAE pts in an EMR system. Physician notes appear to provide valuable additional information. Further evaluation of clinical and demographic characteristics is needed to identify a representative HAE cohort for future studies.

295 | Validation of clinical vs algorithmic definition of line of therapy in multiple myeloma

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Background: Electronic health records (EHR) enable the passive collection of research quality data. Rule-based algorithms can convert recorded treatment events into clinically relevant line of therapies (LoTs) without human abstraction, allowing the creation of meaningful data at scale. While the EHR provides a rich profile of an oncology patient's treatment history, it is important to validate the routinely used algorithmic LoT defined by database providers.

Objectives: Using EHR data from 100 Multiple Myeloma (MM) patients in Flatiron Health's EHR-derived oncology database, we evaluated the inter-rater reliability within clinicians, and comparing clinicians against disease-specific algorithmic LoT.

Methods: Line of therapy was defined by two clinicians independently reviewing de-identified EHR data. Concordance between first line induction and sequence of treatments was calculated between clinicians, and comparing reconciled clinician lines against the algorithm. Treatment duration differences were explored through Bland-Altman plots and summary statistics.

Results: Clinicians identified the same first line induction in 86% of patients (Kappa statistic 0.83; 95% CI 0.75,0.91), agreed on the full induction sequence for 69% of patients and had the same number of lines in 77% of patients. Comparing the reconciled clinical lines against the algorithmic lines, 81% of patients had the same first line induction (Kappa statistic 0.77; 95% CI 0.67, 0.86), 52% the same induction sequence and 67% the same number of lines.

Median difference in the duration of first line between clinicians was 0 days (86 pairs). Clinical lines were a median of 41 days shorter than algorithm lines, with a skewed distribution spanning zero days.

Conclusions: Defining LoT based on observed EHR profiles introduces a degree of uncertainty into classifications. When seen in the context of inter-rater agreement between clinicians, algorithmic performance is comparable with clinician defined lines, while allowing the processing of LoT classifications at scale.

Applying guidelines and working group statements to define periods of induction, maintenance, and consolidation in MM was difficult. Nonetheless, these generally held for the breadth of treatment experiences seen in the real world. Further sub-analysis will identify if standard of care treatment profiles are classified more reliably than non-normative regimes. LoT analyses would benefit from the collection of clinical intent, in addition to raw treatment events, in EHR data.

296 | Utilization of pharmacogenetic testing within the Department of Veterans Affairs

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Background: Despite the enthusiasm around pharmacogenetics (PGx), or the study of how genes affect a person's drug response, little is known about utilization of PGx tests to date.

Objectives: To quantify and describe the characteristics of Veterans who undergo PGx testing as part of routine clinical care.

Methods: The Department of Veterans Affairs (VA) is the largest integrated health care system in the United States. We used secondary data analysis methods to identify VA patients that received PGx testing as part of routine clinical care up until 1/25/2018. We identified all tests associated with a Clinical Pharmacogenetics Implementation Consortium level A gene-drug interaction. These data were manually inspected and categorized. Descriptive analyses of the initial cohort were performed.

Results: We identified a cohort of 308 352 distinctly identifiable Veterans who had 348 427 orders for a PGx test within VA since 1990. Median age was 39.2 years; 19.7% were female; 68.1% were white. G6PD represented the vast majority of test orders ($n = 305\ 841$, 88%), followed by TPMT ($n = 8569$), CYP2C9 ($n = 6821$), IL28B ($n = 4949$), and VKORC ($n = 4456$). We focused on tests for thiopurine methyltransferase (TPMT) to better understand PGx test orders. Azathioprine and mercaptopurine are prodrugs that are inactivated by the enzyme TPMT, encoded by the gene *TPMT*. The expected response to these drugs can be assessed by evaluated by (1) genotyping, or determining whether specific mutations of *TPMT* associated with different levels of drug metabolism are present and, (2) phenotyping, or measuring the activity of the TPMT enzyme. In our cohort, there were 8569 orders for lab tests categorized as measuring TPMT. Of these, 316 (4%) tests were incorrectly categorized as TPMT tests. From the information available regarding the lab results, we were unable to

determine if 786 (9%) of the tests were genotype vs phenotype testing. A much greater proportion of TMPT tests were for phenotype ($n = 6686$, 78%) rather than genotype ($n = 780$, 9%). At least 424 orders (5%) were cancelled or not processed for various reasons.

Conclusions: Over 340 000 PGx tests have been ordered in VA; initial analyses raise several questions. First, it is unclear if tests are being ordered to guide drug therapy or diagnose a clinical syndrome. Second, there are tests to assess both genotypes and phenotypes; how providers decide which test to order is unclear. Finally, several tests are cancelled. Significant investigation into test ordering behavior and result utilization is crucial to further clarify practices.

297 | Information on the expected delivery date in German claims data: Assessing its potential to estimate the beginning of pregnancy

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Background: Estimating the beginning of pregnancy is crucial when studying drug safety in pregnancy, but important information in this regard, such as the last menstrual period (LMP), is generally not recorded in claims databases. The beginning of pregnancy is therefore usually estimated as the date of birth minus an average length of pregnancy for live births, using different periods for term, preterm and postterm births. In German claims data, the expected delivery date (EDD) is calculated based on the LMP or ultrasound examinations in early pregnancy and can be coded once or more often during a pregnancy but it is not obligatory.

Objectives: To assess the availability, plausibility and consistency of information on the EDD in the German Pharmacoepidemiological Research Database (GePaRD).

Methods: We selected all live births documented in GePaRD between 2006 and 2014 among women aged 12 to 50 years who were continuously insured for one year before the birth. For each live birth, available EDDs were extracted in the three quarters before and in the quarter of the birth. We determined the number of EDDs coded per pregnancy and the concordance of the information if ≥ 2 EDDs were coded. To assess the plausibility of the information on the EDD, we examined the difference between the expected and the actual birthdate stratified by preterm, postterm and term birth (=birth not coded as preterm or postterm). Furthermore, we assessed whether the timing of specific prenatal examinations was plausible within each stratum.

Results: We identified 850 245 pregnancies ending in a live birth (7% preterm, 14% postterm, 80% term). For 64% of pregnancies, two or more concordant EDDs which were all concordant, were coded. In 5% of pregnancies, one EDD was coded and 11% had two or more EDDs which were not all concordant. In 20% of pregnancies, no EDD

was coded. In pregnancies with only concordant EDDs, the median difference between the EDD and the actual birthdate in days was -31 for preterm, +9 for postterm, and -4 for term births, and the timing of specific examinations was plausible in >99%. These results were similar for pregnancies with only one EDD and for those with partly discordant EDDs when the EDD coded most often was selected.

Conclusions: One or more EDDs were coded in about 80% of pregnancies ending in a live birth. Our analyses suggest that by using EDD information the beginning of pregnancy can be plausibly identified in German claims data by re-subtracting the biologically expected duration of a pregnancy, ie, 280 days.

298 | Replicating Sentinel Initiative's Cohort Identification and Descriptive Analysis (CIDA) program core functionalities using a novel analytics platform

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Background: Analytics platforms that use a graphical user interface and distributed computing offer rapid results without the need for custom programming. This could be useful for organizations wishing to execute Sentinel's Cohort Identification and Descriptive Analysis (CIDA), but with limited capacity to undertake programming with SAS or other packages.

Objectives: To replicate Sentinel's CIDA Type 1 and Type 2 analysis programs using the Instant Health Data (IHD) analytics platform.

Methods: The Centers for Medicare and Medicaid Services (CMS) Linkable 2008-2010 Medicare Data Entrepreneurs' Synthetic Public Use File (DE-SynPUF) was converted to the Sentinel Common Data Model (CDM) against which CIDA is designed to run. To replicate as many components of CIDA as possible, different types of codes were used to identify index dates for four health outcomes of interest (HOI): National Drug Codes (NDC) only (HOI-A), procedure codes only (HOI-B), NDC codes from drugs within the same class (HOI-C), and a mix of NDC and procedure codes (HOI-D). One event of interest (EOI) and one pre-existing condition (PEC) were also identified. Replication in IHD was first conducted using a Type 1 analysis on patients with at least 183 days of enrollment prior to the first-ever eligible HOI. Then, an intent-to-treat (ITT) Type 2 analysis for each of the 4 HOI was conducted on patients with at least 1 PEC code in the 183 days prior to the first-ever index date of each HOI. The at-risk time was defined from the index date to the earliest of 183 days, disenrollment, EOI, or data end. Equivalence between IHD and CIDA was established based on the total number of patients in each cohort, number of events, time-to-event as well as patient-level matching of HOI index dates, first EOI date and follow-up time.

Results: For both Type 1 and Type 2 analyses, IHD was able to match 100% the output of CIDA. For the Type 2 analyses numbers matched as follows: the HOI-A cohort had 5514 patients, 3270 EOI, and 1664 patient-years; the HOI-B cohort had 524 patients, 458 EOI, and 81

patient-years; the HOI-C cohort had 214 patients, 138 EOI, and 61 patient-years; the HOI-D cohort had 185 patients, 162 EOI, and 29 patient-years. **Conclusions:** This study showed that both CIDA Type 1 and Type 2 ITT analyses can be replicated using the IHD platform and its available functionalities without the use of a specific CDM.

299 | How much reliable is to explore postmarketing antibiotic use in pediatric population through Italian claims databases?

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Background: Prevalence of drug use in pediatrics is quite heterogeneous across countries and, even, between different geographic areas within country. This heterogeneity could be due to variability of underlying prevalence of diseases or pediatricians' prescribing behavior.

Objectives: To evaluate pediatric drug consumption distribution as out of pocket purchase vs coverage by National Health System (NHS) (that is traceable using claims databases) among different geographic Italian areas, as part of the Italian Research and University Ministry-funded MUSiC (Medicines Use and Safety in Children) Project.

Methods: Sales data for retail pharmacies were retrieved in the period Jan-Dec 2015 from "sell-in/private purchase" database owned by IQVIA Italia. Marketing Authorizations codes (AIC) of the most frequently prescribed antibiotics in 2015 in Italy, available only for pediatric use (less than 18 years) and reimbursed by the NHS, have been identified. For each selected medicinal product, the distribution of out-of-pocket purchased vs NHS-reimbursed packages has been evaluated. Finally, the relationship between the price and the amount of private purchase for each medicinal product was analysed using correlation analysis. All the analyses have been stratified by four Italian geographic areas: North-east, Northwest, Centre, South, and Islands.

Results: Overall, 198 medicinal products corresponding to 20 individual antibiotics have been selected. Specifically, the following percentages of packages have been privately purchased for each antibiotic: 30.0% for amoxicillin, 31.3% for ceftibuten, 32.8% for amoxicillin plus clavulanate, 34.6% for ceftazidime, 36.1% for fosfomycin, 37.9% for ceftriaxone, and up to 62.6% for sulfamethoxazole/trimethoprim. We found an inverse correlation between drug package price and amount of private purchase, which however reached statistical significance ($r = 0.541$; p value = 0.0003) only in Southern Italy and Island where the average income is the lowest in Italy.

Conclusions: In Italy, a large amount of antibiotics are purchased privately. The private purchase increases with lowering the price of the drug package, especially in Southern Italy. By using claims databases as up to one third of the drug packages are not traceable through this source thus leading to exposure misclassification which may be differential based on the package price and more specifically to underestimation of antibiotic use in pediatrics.

300 | Advances in epidemiological methods and utilisation of large databases: A methodological review of observational studies on psychotropic drug use in pregnancy and central nervous system outcomes in children

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Background: Various epidemiological approaches have been used to study the association between psychotropic drug use in pregnancy and central nervous system (CNS) outcomes in children in the literature.

Objectives: To identify the methodological characteristics of existing studies in order to examine research gaps and recommend further research in this area.

Methods: A systematic literature search was conducted on observational studies in PubMed that studied psychotropic drug use in pregnancy and CNS outcomes in children up to 21 September 2017. Following independent screening and data extraction, a critical summary including the advancing trend of studies focusing on psychotropic drug use, differences between various data sources, methods to address bias and confounders, and the statistical analysis methods used was presented.

Results: 110 observational studies, 25 case-control studies, and 85 cohort studies were included in this review. Articles targeting antiepileptic drugs (AEDs) use dominated in the early years, but a gradual increase in research on antidepressants (ADs) in recent years contributed to the vast majority of relevant studies to date. No study about antipsychotics (APs) was identified in this review.

Conclusions: Evidence suggests that multiple factors, such as different study designs and data source choices, lead to inconsistent findings in the association between ADs and AEDs use in pregnancy and CNS outcome. Researchers should optimise study design including reasonable exposure period, data source, confounding adjustment methodology, as well as statistical analysis to minimise underlying bias for better precision, validity and generalisability of results.

301 | Increase in diagnosis of depressive disorders contributes to the increase in antidepressant use in adolescents

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Background: Recent studies have shown an increasing use of antidepressants (ADs) among adolescents in European countries and in the USA. In Norway, we have also seen a pronounced increase in the use of ADs, particularly among 16- to 17-year-old girls.

Objectives: To study if the observed increase in use of AD among adolescents (13-17 years old) may be explained by higher incidence

of depressive disorder diagnosis, increasing treatment of other mental disorders or more liberal prescribing practice.

Methods: The study is based on data from a primary health care database, the Norwegian Patient Registry, and the Norwegian Prescription Database, all of which are nation-wide registries. Individual-level registry data were linked using the unique (encrypted) personal identity number assigned to all individuals living in Norway. For each year in the period 2010–2015, we identified individuals with an incident diagnosis of depressive disorders in the primary or secondary health care population. For the individuals with incident diagnoses of depressive disorders in we calculated the annual proportion who were dispensed an AD.

Results: In girls, there was a marked increase in incident diagnosis of depressive disorders from 2010 to 2013, increasing from 7.3 to 11.7 per 1000 in primary health care, and from 5.9 to 11.2 per 1000 in secondary health care, respectively. No further increase was observed between 2013 and 2015. One in four girls with incident depressive disorders was prescribed ADs, and this proportion was stable over time. The proportions of boys and girls with an incident diagnosis of depressive disorder in 2014 treated with ADs were higher with increasing age. This was most prominent for girls with 9.6% treated at age 13 and 29.5% at age 17. The proportion of AD use was higher among those with a comorbid mental disorder in both boys and girls. In boys, 32.8% of those with a comorbidity was treated with AD compared with 20.1% in those without comorbidity. In girls, the corresponding proportions were 30.5% and 17.3%. Among girls treated with ADs the proportion with a diagnosis where AD treatment is indicated increased from 61.1%–66.0%. Further, the proportion with moderate or severe episodes of major depressive disorders was stable and high, 72.9% in 2014.

Conclusions: The only issue studied that could explain increasing AD use in girls was increasing incidence of depressive disorder diagnoses. Most adolescents with incident diagnosis of depressive disorders were not treated with ADs.

302 | Paediatric use of melatonin and other sleeping agents—A register linkage study in Sweden

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Background: The prescription of sleeping agents, in particularly melatonin, to children and adolescent has increased in recent years in Sweden. In 2013, 1% of all children between 5 and 19 years of age had a prescription of melatonin. There are a few registry studies investigating prescription patterns of melatonin among children, and no register study has linked prescription patterns with diagnoses on Swedish data.

Objectives: To assess prescribing patterns, sociodemographic characteristics, diagnoses, and concomitant use of psychotropic drugs in children and young adolescents receiving melatonin.

Methods: Treatment with melatonin or other sleeping agents in Sweden from 2005 to 2016 were identified using the Swedish prescribed drug register and the Swedish patient register.

Results: Preliminary data suggest that prescription of melatonin among children and adolescent has increased almost exponentially since 2005, especially the most recent years. The increase is most prominent among children and adolescent 10–19 years of age and among girls. There is also an increase among other drugs used as hydroxyzine and benzodiazepines, both among boys and girls. Many children have simultaneous prescriptions of both melatonin and other psychotropic drugs. Boys were most commonly prescribed melatonin and drugs for attention deficit disorders. Girls were mostly prescribed melatonin and serotonin reuptake inhibitors. The majority of the prescriptions are performed by doctors specialized in child medicine or doctors specialized in child and adolescent psychiatry. About half of all the children with a prescribed melatonin drug treatment had psychiatric diagnoses.

Conclusions: It is important to further follow melatonin prescription and to support rational use of psychotropic drugs and make efforts to reduce mental illness among children and adolescents in Sweden.

303 | The role of mental disorders in teenage pregnancy

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Background: Recent research efforts sought to characterize the risk of unplanned pregnancy in teenage girls with selected mental disorders, including substance use disorders and mania. The dearth of available data underscores the need to examine more fully risk factors for teenage pregnancy related to mental disorders. To the best of our knowledge, no prior population-based study has assessed teenage pregnancy rates by types of mental disorders.

Objectives: This study aimed to estimate crude pregnancy rates among teenage girls with mental illness stratified by 15 subtypes of mental disorders and to identify age-adjusted relationships between disorder types and teen pregnancy rates.

Methods: We established a retrospective cohort of females aged 13–19 years anytime between 2005 and 2014, using the Truven Health MarketScan Commercial Database. Cohort patients had continuous enrollment for two consecutive calendar years and at least two claims for outpatient or inpatient encounters with mental disorder diagnosis during this time. Patients were classified as experiencing pregnancy if they had at least two claims that indicated pregnancy or pregnancy outcomes including abortions, stillbirth, and live birth. In each two-year interval, the pregnancy rate was calculated as the number of patients whose conception date was in the second of the two years, divided by the total number of patients included in the interval. For each patient, only one pregnancy episodes in a given calendar year was considered.

Results: Pregnancy rates were 18.4 vs 12.8 per 1000 teens with and without mental disorders, respectively. The 5 mental disorders with the highest teen pregnancy rates were 1) substance-related disorders (77.6/1,000), alcohol-related disorders (64.7/1,000), suicide and intentional self-inflicted injury (44.1/1000), bipolar disorders (39.7/1,000), and personality disorders (38/1,000). After adjusting for age in a

multiple logistic regression, substance-related disorders (OR: 3.67 [95% CI: 2.90-4.63]), alcohol-related disorders (3.08 [2.63-3.61]), suicide and intentional self-inflicted injury (2.70 [2.20-3.32]) and bipolar disorders (2.23 [1.93-2.59]) were strongly associated with teen pregnancy compared with those who did not have any mental disorders.

Conclusions: Using 10 years of commercial claims data, we found certain mental disorders were strongly associated with an increased pregnancy rate among teenage girls aged 13-19 years.

304 | Utilisation of neonatal medication error prevention strategies: A clinical practice survey of Australian and New Zealand neonatal units

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Background: Medication errors are common in neonatal care and can lead to significant harm.

Objectives: We sought to explore utilisation of various medication error prevention strategies across Australian and New Zealand Neonatal Units (NNUs) through a clinical practice survey.

Methods: An electronic survey was distributed in October 2016 to relevant staff at each of the 29 Level III NNUs identified as members of the Australian and New Zealand Neonatal Network (ANZNN). The survey contained questions relating to a range of medication error prevention strategies identified from a previous systematic review on the topic. The evaluated interventions targeted different aspects of the medication use process including prescribing, evaluation/checking of orders by clinical pharmacists, transmission, preparation and dispensing of orders, storage of medications, and medication administration.

Results: Responses were received from 20 hospitals (response rate 69%), with responses similar across Australia and New Zealand (70% vs 67%). From the 20 respondents, strategies most commonly utilised were use of smart pumps (n = 18; 90%), and ward-based clinical pharmacists (n = 17; 85%). Interventions least commonly utilised included barcode scanning with medication administration (n = 0; 0%), electronic prescribing and clinical decision support (n = 1; 5%), and dedicated medication administration nurse (n = 2; 10%). The total number of medication error prevention strategies utilised in each NNU ranged from 2 to 10 (median = 7) with 10 of 16 strategies utilised by less than 50% of NNUs.

Conclusions: While evidence supports utilisation of a number of medication error prevention strategies these appear inconsistently utilised across current practice settings.

305 | Locations where medication changes occur for neurologically impaired children

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Background: Children with neurological impairment (NI), such as cerebral palsy or epilepsy, are exposed to multiple medications which increases the risk of adverse drug events. To optimize the integration of pharmacy support into different care settings, we need to understand what types of changes in medications occur at different locations.

Objectives: Describe patient characteristics and types of encounters (outpatient [OP], emergency [ED], or inpatient [IP]) associated with medication changes. Test the hypothesis that IP and ED encounters (vs OP visits) increase daily medication counts.

Methods: Retrospective cohort study of Colorado children with NI enrolled in fee-for-service Medicaid from 0 to 18 years old with 12 months of continuous enrollment. NI status was based on published ICD-9-CM codes. Medications were classified using generic product indicator codes. The primary predictor was type of visit. The primary outcome was an increase in the daily maximum concurrent medication count in 7-day window pre/post visit. We used mixed-effects logistic regression to determine the association between type of encounter and increased medication counts, adjusting for age, sex, and accounting for repeated measures.

Results: A total of 13 660 subjects with NI were predominantly male (57%) between the ages of 1 and 12 (63%), and the most common non-exclusive NI phenotypes were seizures (34%), cerebral palsy/hydrocephalus (23%), and cognitive impairments (14%). These patients had 91 997 visits (OP 81%, ED 16%, and IP 3%). Compared with OP visits, medication counts were more likely to increase after ED visits (OR 1.36; 95% CI: 1.30-1.42) and less likely after IP visits (OR 0.90; 95% CI: 0.80-1.00). The classes of new medications differed by location. Of 50 442 new OP prescriptions, 11% were penicillins, 11% bronchodilators, and 8% anticonvulsants. Of 11 093 ED prescriptions, 18% were penicillins, 9% bronchodilators, 8% anticonvulsants, and 7% opioids. Of 2636 IP prescriptions, 11% were bronchodilators, 10% anticonvulsants, 8% opioids, and 8% penicillins.

Conclusions: Medication counts were more likely to increase after ED visits compared with OP visits, in part due to higher risk anticonvulsants and opioids. Medical homes for children with NI subsequently have to monitor for efficacy and safety of new medications in this fragile population and would benefit from enhanced coordination between ED and OP providers and pharmacists.

306 | Pomme 1 and 2: New cohorts to evaluate long-term consequences of prenatal drug exposure

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Background: While new issues regarding long-term effects of antenatal drug exposure arise (ie, neurodevelopmental effects or childhood diseases), tools available to answer those questions are often inadequate due to limitations such as too short follow-up periods, small sample size, and recall bias.

Objectives: Implementation of databases specifically designed to the evaluation of the long-term consequences of drug exposure during embryonic or fetal development is needed. The cohort POMME has been implemented in southwestern France, in 2011, for this purpose.

Methods: The French cohort POMME (PrescriptiOn Médicaments Mères Enfants) holds anonymous medical information as well as drug and health care reimbursement to the children, from the day of their conception. Data sources included (i) French Health Insurance Database (drugs and medical care prescriptions and reimbursements to children and mothers during pregnancy) and (ii) Mother and Child Protection Centre Database (child health certificates at birth, 9, and 24 months). POMME is composed of two separate cohorts: POMME 1 includes children born between the 1st of July 2010 and the 30th of June 2011 (they reach 6 years of age now) and POMME 2 includes children born 5 years later (ie, between the 1st of July 2015 and the 30th of June 2016).

Results: Among the 8372 children recorded in POMME 1, (50.8%) were boys, 286 (3.4%) were from multiple pregnancies, and 519 (6.2%) were born prematurely. They were prenatally exposed to 9.8 ± 6.1 medications. After birth, drug exposure was greatest in children aged 0-2 years. Children were mostly exposed to paracetamol, anti-infectives, and drugs belonging to R-ATC class (Respiratory system).

Conclusions: POMME provides an overview of drugs and medical care exposure in outpatient children from the first day of intra-uterine life until childhood. The comparison of POMME 1 and POMME 2 will allow the study of variations over time in terms of drugs and medical care use. Monitoring the cohort will give the opportunity to study some long-term effects that raise many questions.

307 | The effects of pneumococcal pneumonia vaccination program for children: An interrupted time-series analysis

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Background: *Pneumococcus (Streptococcus pneumoniae)* is a leading cause of community-acquired pneumonia (CAP) and mainly affect children under 5 years of age and the elder over 65 years of age. Accordingly, the use of pneumococcal vaccines has contributed to the decline in *S. pneumoniae* as a cause of CAP. Taiwan pneumococcal conjugate vaccine (PCV) vaccination program, to reduce *S. pneumoniae* caused by CAP, was implanted for high risk children and children between 2 and 5 years old in 2009 and 2013, respectively.

Objectives: To evaluate the effects of pneumococcal pneumonia vaccination program for children.

Methods: We conducted an interrupted time series analysis (ITS) to exam *S. pneumoniae* hospitalization rates before and after the implementation of the PCV vaccination program. Taiwan Health Welfare Database was used to extract all hospital admissions diagnosed with pneumococcal CAP (ICD-9 code: 481.XX) and other unspecified CAP (ICD-9 code: 486.XX) during 2005-2014. Subjects were stratified to six groups: 2 month-1 y/o, 1 y/o, 2-5 y/o, 6-18 y/o, 19-65 y/o, and more than 65 y/o. We excluded patients who had missing value, aged >100 y/o, hospital stay more than 90 days, and had both diagnosis (ICD-9: 481, 486) during same admission. The CAP hospitalization rate was presented as number of episode per 100 000 inhabitants in each age groups.

Results: A total of 1 123 954 subjects which contributed 1 432 409 episode were included in this study. Among children aged 2-5 y/o, 15% of hospitalization were pneumococcal CAP. The pneumococcal CAP hospitalization rate were 116, 124, 147, 156, 153, 217, 210, 222, 175, and 148 per 100 000 inhabitants, from 2005 to 2014. ITS analysis showed that pneumococcal CAP hospitalization rate was no change in 2009, but marginal decline in 2013 in children who aged 2-5 y/o ($\beta = -618$, $p = 0.05$). There were no statistically significant changes in unspecified CAP (2-5 y/o; $p = 0.29$) or other groups (>65 y/o; $p = 0.66$).

Conclusions: PCV vaccination program reduced pneumococcal CAP admissions in children aged 2-5 yrs after 2013. There some covariate such as immunization rate, healthy policy were not considered in this study, and further study was required.

308 | Severity of adverse drug reactions in Crimean children in 2011-2016. Analysis of spontaneous reports

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Background: Adverse drug reactions (ADR) in pediatrics have major medical and social impact. Spontaneous reporting is simple and informative method to study specific characteristics of ADR.

Objectives: To study severity of ADR in children and compare results of severity assessment methods.

Methods: We analysed local electronic ADR database named ARCADE (Adverse Reactions in Crimea - Autonomic Database), which contains information from "yellow cards" sent by doctors. Time interval was set from 2011 to 2016. For assessment of severity, we used following tools integrated in ARCADE: LDS method, Hartwig-Siegel (HS) scale, and method proposed by Karch and Lasagna (KL).

Results: From January 2011 till December 2016, local pharmacovigilance department received 6254 ADR reports. 1264 (20.2%) cases developed in children (0-17 years old) were selected for severity

analysis. According to KL method, 42 (11.2%) reactions were unsevere, 1006 (79.6%) had moderate severity, and 113 (8.9) were considered as severe. 3 reactions were lethal. One death caused by anaphylactic shock after first dose of Amoxicillin clavulanate suspension, another resulted from unpremeditated overdose of Propafenone tablet and arrhythmia. In one case death was associated with second dose of multicomponent vaccine but later this suspicion was rejected. Results of HS method are following: 12.2% had 1 or 2 level (mild reactions), 76.9% had 3 or 4_{ab} levels (moderate severity), and 10.9% fit criteria for level 5 or higher (severe ADR). Severity assessed in LDS points varied from low intensity (0-4 points) in 837 cases (66.2%) to high (8 points and more) in 39 (3.1%) cases. Other 388 (30.7%) reactions were moderately severe.

Conclusions: All methods for evaluation of ADR severity have shown different results. While most of reactions in children had moderate severity, frequency of severe ADR varied from 3.1% to 11% according to chosen method.

309 | The usability of commercial health care claims data in Japanese pharmacovigilance: A comparison with a prospective postmarketing study

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Background: Postmarketing pharmacovigilance surveillance in Japan has been conducted primarily with prospective, postmarketing studies (PMSs). Studies based on health care claims databases (DBs), however, are expected to come into widespread use in 2018 under a policy change by the regulatory authorities.

Objectives: We investigated the similarities and differences in the results of concurrent datasets. We also performed a time series analysis of claims data covering a longer period to determine whether we could identify changes in drug utilization and tendencies in adverse event (AE) incidences.

Methods: A study conducted by Eisai Co, Ltd, from 2011 to 2013 during the early postmarketing phase of the breast cancer drug eribulin in Japan was used as the PMS ($n = 951$). The data for breast cancer patients treated with eribulin during the same period in a health care claims database provided by Medical Data Vision Co, Ltd, were used as the DB ($n = 551$). The patient characteristics, eribulin treatment status, and incidences of AEs were compared in these two datasets. A time series analysis was additionally performed with the data of breast cancer patients treated with eribulin from 2011 to 2016 ($n = 2814$) who were extracted from the claims database. The Cochran-Armitage test was used for statistical analyses.

Results: In the PMS and DB, women accounted for 99.8% and 99.8% of the patients, respectively, the mean age was 57.8 ± 10.7 and 57.8 ± 10.7 years, respectively, and the mean number of eribulin doses was 10.1 ± 7.8 and 11.1 ± 10.9 times, respectively. The incidences of AEs in the PMS and DB were 7.3% and 8.5% for anemia, 16.9% and

16.3% for peripheral neuropathy, and 11.5% and 7.1% for pyrexia. The time series analysis indicated that there was an increasing tendency in the mean number of eribulin doses. There was a decreasing tendency in the proportion of patients who received hormone therapy combined with eribulin ($p = 0.021$). The incidence of peripheral neuropathy was almost constant throughout the period. The incidence of pyrexia was decreasing ($p = 0.001$).

Conclusions: Patient characteristics, status of drug use, and incidences of AEs between the prospective PMS and retrospective DB were generally comparable. Time series analysis of the DB showed that changes in drug utilization and incidences of AEs can be characterized. These results suggest that the DB could be used in pharmacovigilance like the conventional PMS and is useful for long time series analysis, which may be difficult using the PMS.

310 | Effect of aggressive drug safety measures in reducing adverse drug reactions: Post-hoc analysis of data from all-case surveillance of iguratimod using generalized estimating equations

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Background: Iguratimod (IGU), a novel conventional synthetic disease-modifying antirheumatic drug (csDMARD) sold in Japan, underwent a postmarketing study with all patients who had started taking IGU between September 2012 and April 2013 as subjects¹. During the study period, various safety measures were implemented to reduce drug risk, but the effect of those measures in inhibiting adverse drug reactions (ADRs) has not been quantitatively analyzed.¹ Mod. Rheumatol. 2017 Sep;27(5):755-765

Objectives: We investigated the rate of ADRs occurring before and after implementation of each safety measure to examine the effects of each safety measure in preventing ADRs.

Methods: Post-hoc analysis was performed using data from all-case surveillance of IGU. Subjects of analysis were all patients who received IGU and for whom information on safety was obtained. To confirm the time from the start of administration when ADRs were most likely to be expressed, a generalized linear mixed-effect model was applied for the period from the start of administration to each patient until the occurrence of an ADR. The mean incidence of ADRs per patient before and after the safety measures was compared using generalized estimating equations with a two-sided confidence interval of 5%.

Results: The incidence of ADRs by time period from the start of administration peaked after administration for 8 weeks, then showed a significantly decreasing trend (estimated value of tendency <8 weeks: $0.215 P < 0.001$, >8 weeks: $-0.043 P < 0.001$). However, the overall number of times ADRs were expressed was not related to the number of patients. As a safety measure, the mean incidence ratio of ADRs per patient was compared before and after a precaution was issued for concomitant use with warfarin (Dec 2012), and before and after a

precaution was issued contraindicating concomitant use with warfarin and a warning regarding liver dysfunction (May 2013). The estimated value of the mean incidence ratio of ADRs before and after Dec 2012 and May 2013 were 0.728 and 0.718, respectively, indicating significant decreases after implementation of safety measures ($P = 0.004$, $P = 0.015$).

Conclusions: Implementation of safety measures was effective for inhibiting the overall expression of ADRs. These results appear to show that the ADR profile was properly assessed soon after the launch of IGU and that appropriate usage recommendations could be made.

311 | Use of antipsychotics and the risk of colorectal cancer: A case-control study using data from the linked Netherlands Cancer Registry and Pharmo Database Network population

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Background: The carcinogenetic effect of antipsychotics is unclear and may vary between different types of antipsychotics.

Objectives: This study examines the association between the use of different types of antipsychotics and the risk of colorectal cancer (CRC) using data from the linkage between the Netherlands Cancer Registry (NCR) and Out-patient Pharmacy Database of the PHARMO Database Network.

Methods: Patients who were newly diagnosed with CRC between 1998 and 2014 were selected. The date of diagnosis was defined as index date. Each patient was matched to four controls based on gender, birth year, and year of start enrolment in the PHARMO Database Network. Matched controls received the same index date as their matched case. Cases and controls were not allowed to have a diagnosis of cancer before index date. The association between the use of antipsychotics (either typical, atypical, or lithium) before index date and risk of CRC was estimated using conditional logistic regression.

Results: A total of 29 490 CRC cases and 117 960 controls were identified. The use of any antipsychotic before index date was slightly higher among controls compared with CRC cases [3% vs 2%] resulted in an odds ratio (OR) of 0.64 (95% CI 0.59-0.70) for CRC. Stratification by typical or atypical antipsychotics yielded almost the same OR. A different OR was seen for lithium: 1.17 (95% CI: 0.94-1.45) and increased with long-term use [≥ 5 years: 1.60 (95% CI: 1.12-2.31)]. Also, the OR of lithium differed between tumour sites: [proximal colon: 1.09 (95% CI: 0.78-1.53); distal colon: 1.44 (95% CI: 1.00-2.08) and rectum: 1.04 (95% CI: 0.65-1.65)], which was not seen for atypical or typical antipsychotics.

Conclusions: Overall, no association was seen between the use of antipsychotics and the risk of CRC. However, an increased risk of

CRC was seen with long-term lithium use and differed between specific tumour sites.

312 | Long-term heart-specific mortality among 347 476 breast cancer patients treated with radiotherapy or chemotherapy: A registry-based cohort study

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Background: Breast cancer survival has improved throughout the last decades, but treatment-induced cardiotoxicity remains a major concern.

Objectives: This study aimed to investigate competing causes of death and prognostic factors within a large cohort of breast cancer patients and to describe the heart-specific mortality in relation to the general population.

Methods: In this registry-based cohort study, women diagnosed with breast cancer between 2000 and 2011, who were treated with radiotherapy or chemotherapy and followed until 2014, were identified from the Surveillance, Epidemiology, and End Results-18 (SEER-18) database. Cumulative mortality functions were computed. To investigate heart-specific mortality relative to the general population, long-term standardized mortality ratios (SMR) among treated breast cancer patients, who survived for at least 10 years, were calculated. Prognostic factors for heart-specific mortality were assessed by calculating cause-specific hazard ratios (HRcs) with corresponding 95% confidence intervals (95% CI) using Cox proportional hazards regression. Subgroup analysis on intermediate-term mortality according to molecular subtypes, for which information was available since 2010, was performed.

Results: In total, 347 476 breast cancer patients were eligible to be included in the study. Among all possible competing causes of death, breast cancer accounted for the highest cumulative mortality. Compared with the general population, heart-specific mortality of breast cancer patients treated with radiotherapy or chemotherapy was lower (SMR overall 0.84 [0.79-0.90]). In subgroup analysis, HER2-positive subtype was not associated with increased heart-specific mortality relative to HER2-negative patients (HRcs 0.96 [0.70-1.32]).

Conclusions: Heart-specific mortality among breast cancer survivors is not increased compared with the general population. HER2-positive patients do not have increased heart-specific mortality compared with HER2-negative patients.

313 | Risk of neurological adverse events during tumour necrosis factor inhibitor treatment for arthritis: A population-based cohort study from DANBIO and the Danish National Patient Registry

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Background: Tumor necrosis factor alpha inhibitors (TNFi) have successfully been used for the treatment of immune-mediated inflammatory disorders including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) since 1998. However, several case reports and small case series have indicated that different neurological disorders including multiple sclerosis, inflammatory neuropathies, demyelinating diseases, and optic neuritis may be a serious, although rare, adverse event following TNFi treatment.

Objectives: To investigate the association between new-onset neurological events following TNFi-treatment in arthritis patients compared with non-TNFi-treated arthritis patients.

Methods: 41 026 patients registered in DANBIO (a Danish nationwide quality and research registry for rheumatologists) between January 1, 2000, and January 20, 2017, were identified with a diagnosis of either RA, AS, or PsA. Complete follow-up on mortality, emigration, and newly diagnosed neurological diseases suspected to be associated with use of TNFi until May 10, 2017, was obtained by linkage to the Danish National Patient Registry and the Civil Registration System. A cox proportional hazard model was used to examine the association between use of TNFi and risk of a neurological event.

Results: The DANBIO arthritis cohort experienced 223 861 person-years of observation. 98 patients were diagnosed with a selected neurological disease during follow-up, with 49 contacts among TNFi-treated patients and 49 contacts among non-TNFi-treated patients corresponding to a Hazard Ratio (HR) of 1.51 (95% Confidence Interval [CI]: 1.01-2.27). When including information on gender and year of inclusion, the association was no longer statistically significant ($HR_{\text{adjusted}} = 1.52$; 95% CI: 0.96-2.42). TNFi treatment among RA patients was associated with a non-significant 19% increased risk of a neurological event ($HR_{\text{adjusted}} = 1.19$, 95% CI: 0.65-2.18), whereas PsA and AS patients had a 2.6-fold increased risk of having a neurological event following TNFi treatment ($HR_{\text{adjusted}} = 2.61$, 95% CI: 1.11-6.13).

Conclusions: The use of TNFi for the treatment of arthritis may be associated with increased risk of having a demyelinating disease or inflammatory neuropathy—especially among patients with PsA or AS. Since these events are rare, larger multicenter studies are warranted to further characterize the risk.

314 | Glucocorticoids and the risk of peptic ulcer bleeding: Case-control analysis based on Swiss claims data

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Background: Controversy exists as to whether glucocorticoids (GC) are ulcerogenic *per se* and may thus cause peptic ulcer bleeding (PUB) independent of concomitantly prescribed nonsteroidal anti-inflammatory drugs (NSAIDs).

Objectives: To investigate the association between GC use and PUB with or without co-medication with NSAIDs.

Methods: We conducted a case-control study using administrative claims data from the Swiss health insurance company Helsana. We identified 1191 cases with incident PUB between 2012 and 2016 and matched up to 10 PUB-free controls to each case on age, sex, region, and number of years insured with Helsana. We compared prior GC exposure between cases and controls using multivariate conditional logistic regression analyses controlling for several potential confounders. Patients with or without concomitant NSAID exposure were analysed separately.

Results: Patients with prior exposure to both GC and NSAIDs were five times more likely to experience PUB than patients who neither used GC nor NSAIDs (adjusted odds ratio [adj. OR]: 4.80, 95% CI: 3.55-6.71). Whereas the risk of PUB among patients who used NSAIDs without GC was also increased threefold (adj. OR: 3.20, 95% CI: 2.59-3.95), we observed only a moderately increased risk among patients who used GC alone without NSAIDs (adj. OR: 1.63, 95% CI: 1.20-2.42).

Conclusions: The use of NSAIDs with or without GC was associated with a markedly higher risk of PUB compared with GC monotherapy. Use of GC alone was associated with a moderately increased risk of PUB, which might be causal or attributed to confounding by indication.

315 | Factors associated with arthritis and carpal tunnel syndrome after aromatase inhibitors among female breast cancer population: A nationwide claims data analysis

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Background: Aromatase inhibitors (AIs) showed significant survival benefits. But its use may increase the risk for musculoskeletal adverse events, especially arthritis and carpal tunnel syndrome (CTS) and may thus cause treatment discontinuation. Little is known whether different AIs have different risk profiles of arthritis/CTS using real-world data in Asian populations. Current evidence on factors associated with AI-associated arthritis/CTS such as taxane use is inconsistent.

Objectives: To examine the risk of arthritis/CTS and identify associated factors among women with BC initiating endocrine therapy.

Methods: We identified women with BC initiating tamoxifen (TAM) or AIs between 2007 and 2012 from Taiwan Health and Welfare Database. We excluded women with bone metastasis or with a history of any arthritis/CTS. AIs included anastrozole (ANA), letrozole (LET), and exemestane (EXE). Two primary outcomes were time to first event of claims-based (1) any arthritis and (2) CTS within the first year of the treatment. Using multivariable cause-specific hazard models, we evaluated the association between the risk of arthritis/CTS and factors including types of AI use, taxane use and the history of affective disorders (AD), adjusting for age, comorbidities and pain medication use 12 months before TAM/AI initiation.

Results: Among 37 310 women with BC, 86.3% received TAM and 13.7% received AIs (ANA: 4.3%; EXE: 0.8%; LET: 8.6%). AI users had higher incidence for any arthritis (AIs: 22.1% vs TAM: 15.0%, $p < .0001$) and CTS (AIs: 1.5%, TAM: 1.0%, $p = .0023$). Compared with TAM, LET was the only AI associated with an increased risk of any arthritis (adjusted hazard ratio [aHR] = 1.18, 95% CI = 1.08-1.28). An increased risk of CTS was observed in all AIs (ANA: aHR = 1.79, 95% CI = 1.16-2.78. EXE: aHR = 2.81, 95% CI = 1.23-6.44, LET: aHR = 1.74, 95% CI = 1.25-2.43). Taxane use was associated with a 20% risk reduction of any arthritis (aHR = 0.80, 95% CI = 0.73-0.88) but was not associated with CTS (aHR = 0.98, 95% CI = 0.70-1.34), compared with those receiving other chemotherapy. AD increased the risk of any arthritis by 36% (aHR = 1.36, 95% CI = 1.29-1.43) and by 33% for CTS (aHR = 1.33, 95% CI = 1.07-1.63).

Conclusions: The risk profiles of any arthritis and CTS varied across use of different AIs among Taiwanese women with BC. Taxane use appeared to be related a reduced risk of subsequent arthritis. Patients with a history of AD had an increased risk for any arthritis/CTS after initiating TAM/AI.

316 | Risk of breast cancer in women initiating insulin glargine compared with insulin detemir Or NPH insulin

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Background: Insulin glargine, a long acting insulin analog, has been associated with increased breast cancer risk in women in some studies but not others. A recent study reported an increased risk of breast cancer in prevalent insulin glargine users, especially after long-term use (5 years or more) and at higher doses.

Objectives: We are investigating breast cancer incidence in new users of insulin glargine compared with new users of insulin detemir and to new users of NPH insulin.

Methods: New-user cohorts of female Medicare beneficiaries aged ≥ 65 years initiating insulin glargine, insulin detemir, or NPH insulin between September 2006 and September 2015 were constructed, with follow-up through May 2017 to identify incident breast cancer. Separate analyses will compare insulin glargine use with either insulin detemir use or NPH insulin use. Marginal mean weighting through

stratification will be used to adjust for baseline differences between cohorts. Cumulative exposure to study insulins will be modeled as a time varying covariate defined in terms of cumulative units of insulin, cumulative days' supply and cumulative number of prescriptions received. Separate Cox proportional hazards models will be run for each of our exposure measures to generate HRs and 95% CIs for breast cancer incidence, with a specific focus on longer duration and higher cumulative dose exposure.

Results: There were 317 559 new insulin users identified: 203 159 for insulin glargine, 67 012 for insulin detemir and 47 388 for NPH insulin. Of these new users, 12 243, 2908, and 2017 were long-term users (more than 5 years of cumulative insulin use based on dispensed days' supply), respectively. Across cohorts there was a total of 1 034 912 person-years (PY) of follow-up accrued: 691 880 in insulin glargine users, 199 392 for insulin detemir and 143 640 for NPH. Among long-term users of insulin there were approximately 20 238 PY of follow-up accrued after accumulating 5 years of insulin use for glargine users, 4320 PY for detemir users and 3860 PY for NPH users. There were 6303 incident breast cancers identified across all cohorts (overall incidence rate 6.09/1000 PY). Data analysis has begun and full results will be presented at the meeting.

Conclusions: This is the largest study to date of breast cancer risk associated with long acting insulin use in women, with a focus on the risk associated with higher dose and longer duration of use, which previous studies have not been able to address adequately in new users.

317 | Exposure to phthalate-containing prescription drugs and the risk of colorectal adenocarcinoma: A Danish nationwide case-control study

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Background: Phthalates are suspected endocrine disrupters that have been associated with increased risk of cancers; however, the carcinogenic potential is still unclear. *In vitro* studies have demonstrated that phthalates interfere with several cellular mechanisms involved in colorectal cancer development. Pharmaceuticals are a major source of phthalate exposure.

Objectives: To examine whether there is an association between cumulative pharmaceutical ortho-phthalate exposure and risk of colorectal adenocarcinomas.

Methods: We conducted a Danish nationwide case-control study including all patients with incident colorectal adenocarcinoma 2008-2016 (n = 19 436). Each case was age- and sex matched to five general population controls. Linking information from a database maintained by the Danish Medicines Agency to the Danish Prescription Registry, we quantified cumulative phthalate exposure to ortho-phthalates from orally administered drugs. Further, we specified by exposure to the individual ortho-phthalates diethyl phthalate (DEP) and dibutyl

phthalate (DBP). The association between ortho-phthalates exposure and risk of colorectal adenocarcinomas was estimated using conditional logistic regression.

Results: 6777 cases (26%) and 70 771 controls (27%) had been ever-exposed to any ortho-phthalate from drug products presenting an adjusted OR at 0.97 (95% CI, 0.94-1.00) for the risk of colorectal adenocarcinoma. Major exposure (>500 mg) to any ortho-phthalate exerted an apparent protective effect against colorectal adenocarcinomas with an adjusted OR at 0.88 (95% CI, 0.81-0.95). No clear dose-response pattern was observed. Associations were similar for the individual phthalates. High DEP exposure (>500 mg) yielded an adjusted OR at 0.88 (95% CI, 0.80-0.96) and high DBP exposure (>500 mg) yielded an adjusted OR at 0.87 (0.73-1.05).

Conclusions: In this study, cumulative exposure to more than 500 mg ortho-phthalate as a drug-exipient was associated with a decreased risk of colorectal adenocarcinoma. Our findings were opposite to our study hypothesis and biological rationale.

318 | Androgen deprivation therapy for prostate cancer and the incidence of rheumatoid arthritis

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Background: A recent observational study associated the use of androgen deprivation therapy (ADT) to an increased risk of rheumatoid arthritis (RA) in patients with prostate cancer. However, this study had important methodological limitations, including immortal time bias and not accounting for possible diagnostic delays associated with this outcome. Thus, additional studies are needed to assess this association.

Objectives: The objective of this study was to determine whether the use of ADT is associated with an increased risk of RA in patients with prostate cancer.

Methods: We conducted a population-based cohort study using the United Kingdom Clinical Practice Research Datalink. The cohort consisted of all men at least 40 years of age who were newly-diagnosed with non-metastatic prostate cancer between January 1, 1988, and September 30, 2013, and followed up until 2014. The use of ADT was modeled as a time-varying variable, lagged by 1 year to account for latency and diagnostic delays. Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of RA, comparing ADT use with non-use. In secondary analyses, we assessed whether the association varied with cumulative duration of use with predefined duration categories (<1, 1-2.9, and ≥3 years) and by ADT type. All models were adjusted for age, year of cohort entry, smoking, body mass index,

prostate-specific antigen, and Charlson comorbidity index. In addition, we conducted several sensitivity analyses to assess the robustness of our findings.

Results: The cohort included 32 037 patients, generating a total of 135 559 person-years of follow-up. During the follow-up period, 63 patients were newly-diagnosed with RA, generating a crude incidence rate of 46.5 (95% CI: 35.7-59.5) per 100 000 person-years. Compared with non-use, the use of ADT was not associated with an increased risk of RA (HR 0.84, 95% CI 0.49-1.45). In secondary analyses, there was no evidence of a duration-response relation (<1 years, HR: 0.78, 95% CI: 0.37-1.65; 1-2.9 years, HR: 0.64, 95% CI: 0.29-1.40; ≥3 years, HR: 1.39, 95% CI: 0.62-3.11; *p*-trend = 0.53), and no single type of ADT was associated with an increased risk of RA. Our results remained consistent in the sensitivity analyses.

Conclusions: In contrast to the recent study, the use of ADT was not associated with an increased risk of RA in patients with prostate cancer.

319 | Diuretic use and serum urate levels in the Febuxostat versus Allopurinol Streamlined Trial (FAST)

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Background: The use of some diuretics is cautioned in gout as they can increase serum urate and worsen symptoms. Other non-gout medications are known to have uricosuric action. FAST is an international randomised trial in allopurinol-treated gout patients at cardiovascular risk.

Objectives: To determine: (i) the level of diuretic use and; (ii) the association between diuretics and other medicines on serum urate level in eligible patients screened and randomised for FAST.

Methods: This study used cross-sectional data collected at screening in FAST. Patients were recruited from the UK, Denmark and Sweden. Eligible patients were taking allopurinol for gout and chronic hyperuricaemia, aged 60 or over and had established cardiovascular disease or at least one additional cardiovascular risk factor. Patients were classified as receiving thiazide, loop, "other" or no diuretics. Potentially uricosuric drugs considered were losartan, fenofibrate, and atorvastatin. The primary outcome measure was serum urate measured in µmol/L at screening. Linear regression was used to model serum urate adjusted for other lifestyle and medical factors collected at baseline.

Results: By 31 January 2018, 6142 patients had been screened and were randomised on FAST. Of these 34.9% were taking a diuretic (19.6% on thiazide, 16.1% on loop and 5.2% on "other" diuretics with some using more than one of each). Patients on diuretics had higher serum urate at baseline than then non-users (356 vs 324 µmol/L; *p* < 0.0001) a difference of 31.9 µmol/L (95% CI 27.8 to 36.0). In a multivariate analysis, compared with no diuretic use, thiazide use was associated with a 28.8 µmol/L (95% CI 24.8 to 32.9) higher serum urate, loop diuretics 32.9 µmol/L (95% CI 28.2 to 37.7), and

other diuretics 6.8 $\mu\text{mol/L}$ (95% CI -0.41 to 14.0). Losartan, atorvastatin, and fenofibrate were associated with lower serum urate. Covariates significantly associated with serum urate were allopurinol dose, BMI, age, sex, renal impairment, and recruitment region.

Conclusions: Despite being cautioned for use in gout, thiazide and loop diuretics were widely used and associated with higher serum urate. Use of other potentially uricosuric non-gout medications was associated with lower serum urate.

320 | Administrative claims data to support pragmatic clinical trial outcome ascertainment using PCORnet adaptable trial as an example

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Background: Administrative claims data present a potential cost-efficient alternative to traditional trial-specific ascertainment of clinical events.

Objectives: To demonstrate the utility of administrative claims data to improve the capture of end points for longitudinal pragmatic trials.

Methods: We conducted a retrospective, observational cohort study following the design of the ADAPTABLE trail (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term Effectiveness). The trial is being conducted by the Patient-Centered Clinical Data Research Networks (PCORnet CDRNs) with outcome data collected through a common data model (CDM) of EMRs from participating institutions. We utilized Anthem administrative claims data extracted into PCORnet CDM to identify eligible members using the ADAPTABLE computable phenotype. We identified potential membership overlap with PCORnet CDRNs based on facility identifiers for members having received treatment for myocardial infarction (MI) or coronary revascularization procedures (PCI/CABG) at any PCORnet CDRNs within 2 years prior to an index date of 4/1/2014. We followed the population for 2 years for ADAPTABLE outcome events (1) Cardiovascular (CVD) hospitalizations including MI, stroke, or PCI/CABG, (2) hospitalizations of major bleeding, and (3) in-hospital death. Each event was classified as within or outside the potential PCORnet CDRNs using the affiliated facility identifier. Incidence rates were reported from the perspective of data available to CDRNs and full administrative claims data available.

Results: 11 101 patients were identified as being ADAPTABLE eligible members at PCORnet CDRNs, with average age of 70 years old, 71% of male, and average follow-up of 20.7 months. The patients had 1521 hospitalizations for CVD (37.5% occurred outside CDRNs), 710 for major bleeding (41.7% outside CDRNs), and 196 death at hospital (34.2% outside CDRNs). Incidence rates (events per 1000 patient-months) differed from the perspective of CDRNs and health plan: CVD 4.1 (95% CI: 3.9, 4.4) vs 6.6 (95% CI: 6.3, 7.0), major bleeding 1.8 (1.6, 2.0) vs 3.1 (2.9, 3.3), and in-hospital death 0.56 (0.47, 0.67) vs 0.85 (0.74, 0.98).

Conclusions: This study demonstrated the value of administrative claims supplementing longitudinal clinical studies and suggests that administrative claims data together with EMRs will serve as a good vehicle to completely capture patient's treatment journeys.

321 | Can cluster randomisation of prescribing policy be used to efficiently generate drug safety and effectiveness data? Pilot phase of the evidence study

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Background: The randomisation of prescribing policies has the potential to answer important clinical questions in the absence of head-to-head comparative effectiveness data. In 2011, the UK National Institute for Health and Care Excellence (NICE) hypertension guidelines recommended that indapamide or chlortalidone (thiazide-like diuretics) should be used in preference to bendroflumethiazide (thiazide diuretic) in the management of hypertension. The guideline has been criticised for lacking evidence and has not been fully implemented with bendroflumethiazide remaining the most widely used thiazide or thiazide-like diuretic across Scotland. The Evaluating Diuretics in Normal Care (EVIDENCE) study aims to demonstrate whether the cluster randomisation of prescribing policies embedded in the routine practice of NHS Scotland can be used to compare the comparative effectiveness of bendroflumethiazide and indapamide.

Objectives: To describe the pilot phase of the EVIDENCE study.

Methods: EVIDENCE uses a cluster randomised, parallel group design to evaluate the NICE recommendation. Randomisation is at GP practice level with allocation to either bendroflumethiazide or indapamide as preferred diuretic for use in hypertension. Routine prescriptions are switched, where necessary, to comply with the policy, using established "drug switch" mechanisms. The effectiveness and impact of the intervention will be assessed through the record linkage of routinely collated prescribing and outcomes data.

Results: The EVIDENCE study protocol has been approved by a Research Ethics Committee, and the initial pilot phase has commenced in Tayside, Scotland. Initial experience suggests that implementation of the intervention can be delivered at a practice level. The numbers of patients prescribed study medications before and after the policy implementation along with measures of adherence to applied switching and reasons for non-adherence will be analysed. It is likely that cardiovascular events in this pilot phase will be few, but results will demonstrate the utility of routinely collected data.

Conclusions: EVIDENCE will test a novel methodology for conducting comparative effectiveness research efficiently within the NHS in Scotland. It is anticipated that this methodology will be applicable to the assessment of many diverse medications and interventions in current routine use where there is insufficient evidence to guide clinical practice.

322 | Using a single non-inferiority margin or a single preserved fraction for an entire pharmacological class may be invalid for the analysis of non-inferiority: A case study of statin non-inferiority trials

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Background: The use of a single non-inferiority margin or a single preserved fraction (PF) in non-inferiority trials for an entire pharmacological class will spare investigators from the extensive efforts required to define a new margin each time a member of this group is chosen as an active comparator (the recommended approach by regulators). However, the validity of this approach has not been assessed.

Objectives: To assess the validity of using a single margin or a single PF for all non-inferiority trials within a pharmacological class (statins).

Methods: A search in PubMed, EMBASE, and CENTRAL resulted in 7 active-controlled non-inferiority trials for treating hyperlipidemia. The impact of using a single margin (6% reduction of low-density lipoprotein cholesterol from the baseline) was assessed by evaluating how this margin corresponds to the PF for each comparator statin in the 7 trials. PF is the fraction of the effect of the comparator statin that was preserved by the test statin (the higher the PF the stricter the margin). The use of a single PF was assessed by re-analyzing non-inferiority in the included trials with new margins (based on the single PF) for each comparator statin and compare the new results with those of the original trials (in which a PF was assumed to be chosen for each comparator in each trial).

Results: The use of a single margin resulted in PFs that range between 81% and 89% for the different comparators. This means that the stringency of demonstrating non-inferiority, in terms of the PF, varies among the comparator statins. For example, non-inferiority of a test statin to 10 mg atorvastatin will be demonstrated if it at least preserved 84% of the effect of atorvastatin that was pooled from the historical placebo-controlled trials (both the test and comparator statins are equipotent). However, this PF may become higher or lower if another equipotent statin is chosen as a comparator instead of 10 mg atorvastatin. The use of single PF resulted in 4 of 9 (44%) different non-inferiority conclusions compared with the original analyses. This means that the new margins were either wider or narrower compared with the original ones.

Conclusions: The threshold of demonstrating non-inferiority with a single margin or single preserved fraction of the effect per pharmacological class may not be consistent with using a margin/PF for each comparator separately, which may also be invalid for the analysis of non-inferiority.

323 | Regulatory challenges in the design of non-inferiority trials: Evaluating scientific advice letters from the European Medicines Agency (EMA)

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Background: Non-inferiority trials are associated with methodological challenges. The European Medicines Agency (EMA) does not have a guideline on designing non-inferiority trials and recommend to define the non-inferiority margin based on clinical and statistical considerations. However, they do not recommend a specific method to determine the margin.

Objectives: To assess the challenges in designing non-inferiority trials for drugs intended to be marketed in Europe.

Methods: Using the database of the Dutch Medicines Evaluation Board (MEB), a search in recent (2014 and 2015) final EMA scientific advice letters was conducted to identify design proposals that were sent by pharmaceutical companies to the EMA about non-inferiority trials. Each scientific letter is for one drug, and it includes proposals for different aspects of the trial with a response from the EMA to each proposal. The proportion of the accepted proposals by the EMA was assessed taking into account the therapeutic class and the type of the drug application (orphan vs other drugs) using generalized estimating equations with an exchangeable correlation matrix to account for clustering of proposals within letters.

Results: The EMA accepted 142 of 232 (61%) of the total proposals. Almost 65% of the proposals were for three therapeutic classes: anti-infectives (most common), drugs for endocrine disorders (mainly anti-diabetics), and oncology drugs. The EMA acceptance did not differ between proposals for endocrine drugs vs anti-infectives (OR: 1.30, 95%CI 0.52 to 3.24) and between oncology drugs vs anti-infectives (OR: 0.54, 95%CI 0.12 to 2.47). The EMA acceptance also did not differ between orphan vs other drug applications (OR: 0.47; 95%CI 0.19 to 1.14). The non-inferiority margin was the main challenge, only 25 of 61 (41%) proposals for the choice of the margin were accepted. There was no common approach proposed by pharmaceutical companies to define the margin (the recommended approach by the EMA was proposed for only 18 of 61 margins) nor a common method of the recommended approach.

Conclusions: There are many questions about the design of non-inferiority trials with the choice of the inferiority margin as the main challenge. We did not find that the challenge was related to one of the three most common therapeutic classes or to a type of drug applications. This study shows that more explicit guidance from the EMA on the rationale for choosing different approaches to define the margin is needed.

324 | The landscape of clinical trials for testosterone: Potential indications

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Background: Testosterone is approved for treatment of male hypogonadism, but ever since the drug was invented, it has been surrounded by speculations about other potential indications.

Objectives: Using global data on registered clinical trials, the aim was to study research activity for potential indications for testosterone.

Methods: The study is descriptive. Data were retrieved from the Biopharma Navigator Database (Expert System), which gathers information about clinical trials from clinicaltrials.gov (the United States), the WHO International Clinical Trials Registry Platform, The European Union Clinical Trials Register, The Australian New Zealand Clinical Trials Registry, the International Standard Randomised Controlled Trial Number Register, and UMIN (Japan). We used the selected interventions testosterone, testosterone undecanoate, methyltestosterone, testosterone enanthate, dihydrotestosterone, testosterone decanoate mixture with testosterone propionate, testosterone 17-phenylpropionate, and testosterone isocaproate, testosterone cypionate, 1-testosterone, conjugated estrogens mixture with methyltestosterone, megestrol acetate and testosterone. Ongoing and completed clinical trials (phase 2 to 4) from 2005 to 2017 with administration of testosterone to human patients were included. Trials only testing pharmacokinetics on healthy volunteers or bioequivalence were excluded. The search yielded 460 trials. After removal of duplicates and trials not fulfilling inclusion criteria, 346 remained. For each trial, the indications were manually categorised according to the 2016 Medical Subject Headings (MeSH).

Results: Of the 346 included studies, 253 included only men, 70 only women, and 23 both sexes. Five included children under 18 years, and the rest only included adults. Countries with the highest number of trials were the United States ($n = 130$), the United Kingdom ($n = 37$), and Australia ($n = 31$). The five most common indications were hypogonadism ($n = 162$), glucose metabolism disorders ($n = 43$), psychological sexual dysfunction ($n = 26$), overnutrition ($n = 20$), and physiological sexual dysfunction ($n = 19$). Selected examples of other indications were treatment of burns, anorexia nervosa, gender dysphoria, and development of male contraceptives.

Conclusions: Clinical trials with testosterone concern a wide spectrum of potential indications. Areas where research activity seem particularly high are glucose metabolism, sexual dysfunction, and overnutrition.

325 | A precision medicine trial to study heterogeneity in paediatric asthma: Design of the PUFFIN trial

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Background: There is large heterogeneity in treatment response to asthma medication, and a one-size-fits-all approach based on current guidelines might not fit all children with asthma. It is expected that children with one or more variant alleles (Arg16Arg and Arg16Gly) within the beta2 adrenergic receptor (ADRB2) gene coding for the beta2 receptor have a higher risk to poorly respond to long-acting beta2-agonists (LABA) comparing with the Gly16Gly wild type [1,2].

Objectives: To study whether ADRB2 genotype-guided treatment will lead to improvement in asthma control in children with uncontrolled asthma on inhaled corticosteroids (ICS) compared with usual care.

Methods: A multicentre, double-blind, precision medicine, randomized trial will be carried out within 15 Dutch hospitals. 310 asthmatic children (6-17 years of age) not well controlled on a low dose of ICS will be included and randomized over a genotype-guided (intervention) or non-genotype-guided (control) arm. Intervention arm children with Arg16Arg and Arg16Gly will be treated with double dosages of ICS and with the Gly16Gly wild type with add-on LABA, respectively. Control arm children will be randomized over both treatment options. Lung function measurements, questionnaires focussing on asthma control (ACT/c-ACT), and quality of life will be obtained in three visits within 6 months. The primary outcome will be improvement in asthma control based on repeated measurement analysis of c-ACT or ACT scores in the first 3 months of the trial. Additional cost effectiveness studies will be performed [3].

Results:

Conclusions: Currently, pharmacogenetics is not used in paediatric asthma. This trial may pave the way to implement promising results for genotype-guided treatment in paediatric asthma in clinical practice. We are aiming to start the trial in April 2018.

326 | Relationship between migraine trigger factors and auras

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Background: Migraine trigger factors are precipitating factors that can contribute to a migraine attack by increasing the probability of a migraine occurring. For some migraineurs, the headache phase is preceded by a transient disturbance in neurological function (an aura). An aura could be visual or sensory in nature. Few studies have investigated the relationship between migraine trigger factors and auras.

Objectives: The primary aim of the study was to identify if there was a relationship between migraine trigger factors and auras in a sample of migraineurs.

Methods: A questionnaire survey was conducted in 2014 in Port Elizabeth, South Africa, under migraine patients who frequented pharmacies, physiotherapy practices, and health shops. Purposive sampling was used. A total of 173 questionnaires were analysed. Basic descriptive and inferential statistics were calculated.

Results: Of the 173 respondents, 89.3% ($n = 151$) were female with 58.4% between 30 and 49 years of age. Most respondents (82.3%) reported that the onset of their migraines was before 30 years of

age. Most of the respondents (72.5%) experienced one to three migraines per month. Experiencing an aura before a migraine attack was reported by 43.9% of respondents, with 22.5% of respondents indicating that they only “sometimes” experience an aura. Visual auras were experienced by 92.0% of respondents who indicated that they suffered from migraine with aura and sensory auras by 71.5% of respondents. Nearly two-thirds (62.8%) of respondents experienced both visual and sensory auras. Trigger factors were experienced by 89.0% of respondents. There was no statistical relationship between trigger factors and aura, but there was a statistical relationship between trigger factors and visual aura at the 5% level (chi-square = 7.966, $df = 1$, p -value = 0.005). Cramér's V showed a small practical significance at 0.218.

Conclusions: There appears to be a statistical relationship between visual auras and trigger factors, but further studies need to be conducted to substantiate these findings. The different types and combinations of trigger factors are important to include in studies.

327 | Evaluation of opioid overutilization criteria suggested by Centers for Medicare and Medicaid Services among privately insured or Medigap population

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Background: The Centers for Medicare and Medicaid Services (CMS) have employed overutilization criteria (high dose/number of prescribers/number of pharmacies) in 2013 and updated in 2017 to identify beneficiaries at risk for opioid use disorder (OUD) or overdoses. The predictive validity of this algorithm has not been evaluated.

Objectives: To examine the proportion of OUD patients who met the high dose criterion within 1 year before the diagnosis.

Methods: Using 2005–2015 Truven Marketscan Commercial and Medigap Databases, we included patients with OUD (ICD-9:304.0x and 304.7x or ICD-10: F11.xx) who had (1) 1 year of continuous enrollment before the first observed OUD diagnosis; (2) at least one prescription fill for opioids; and (3) no cancer diagnosis or hospice care during the 1-year pre-diagnosis period. We calculated the proportion of OUD patients who met CMS' 2013 criterion as “cumulative daily morphine equivalent dose (MED) > 120 mg for ≥ 90 consecutive days.” The 2017 high dose criterion was “average daily MED ≥ 90 mg for any duration in the most recent 6 months.” The proportion was calculated among patients who had at least one prescription during the period of interest, in the entire sample and a subgroup of elderly patients (age ≥ 65).

Results: Of 133 203 OUD patients, 12.6% (16 862 patients) were identified as high dose users according to the 2013 criterion. The proportion decreased from 13.3% to 10.9% over the study years. Using the 2017 criterion, 26.6% and 28.3% of patients were identified as high dose users in the 0- to 6-month period and 7- to 12-month period before the diagnosis. In both periods, the proportion decreased

during the study years (27.5% to 23.8% and 29.4% to 24.3%, respectively). In the elderly subgroup ($n = 8328$), the 2013 criterion identified 1066 patients (12.8%) with a decrease in the proportion over time (17.2% to 10.5%). The 2017 criterion captured 2280 patients (30.5%) in the first period ($n = 7467$), and the proportion decreased from 41.5% to 26.4% over time. In the second period, 2437 (31.0%) patients were identified as high dose users ($n = 7855$) with a decrease from 38.5% to 27.4%.

Conclusions: The CMS high dose criterion may not be a sensitive measure to identify high-risk patients in privately insured or elderly populations. As the full criteria include two other elements involving the number of providers, the algorithm sensitivity is expected to be lower.

328 | Multiple source of information to characterize the clinical, therapeutic management and economic burden of patients with multiple sclerosis in France

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Background: New disease-modifying treatments (DMTs) approved since 2006 have probably changed the management of multiple sclerosis (MS) patients in current medical practice. However, few recent data are available on real-life therapeutic strategies implemented in MS patients.

Objectives: The objective is to describe the characteristics, therapeutic management, and cost of multiple sclerosis (MS) in France by using different data sources.

Methods: The French regional MS Lorrain registry (ReLSEP) contains MS patients' characteristics, clinical data, and therapeutic management, but no associated costs. Selected populations for this analysis were MS patients with first symptoms between 2000 and 2014. The French health insurance databases (SNIIRAM and EGB) contain drug/medical device consumptions, medical visits, hospitals stays, and associated costs, but limited patients' characteristics, no clinical information, and no possibility to distinguish the form of the disease. Selected population for this analysis was prevalent MS patients in 2014. SNIIRAM is exhaustive (all French insured population), and EGB is a 1/97th representative sample of the SNIIRAM.

Results: From the 6090 MS patients registered in the ReLSEP database, 1926 MS patients met all the predefined selection criteria: 72% were female, and mean age at first symptoms was 33 ± 11 years. 1663 patients with remitting form of MS (RRMS) at initial diagnosis (86%) and 263 (14%) with primary progressive (PPMS). 180 (11%) RRMS and 73 (28%) PPMS patients have never been treated during the observation period. Median follow-up was 9 years (Q1–Q3: 5–12). From the 940 MS patients extracted from the EGB database, 71% were female and mean age at extraction was 51 ± 14 years with more than 50% of patients having first MS long-standing condition

status of >10 years. In 2014, 70% of cost resulted in drug expenses/hospitalizations, while 56% of patients had no delivery of treatment and 94% no hospital stay. From the SNIRAM database in 2014, around 90 000 patients were diagnosed with MS. Cost of MS patients represented 0.8% of the annual spending in France.

Conclusions: Multiple source of information is necessary to evaluate clinical, therapeutic, and economic burden of multiple sclerosis in France, as complementary/confirmatory information is retrieved.

329 | Treatment resistant depression as a risk factor for substance use disorders—A national register-based cohort study

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Background: Up to 50% of patients with major depressive disorder (MDD) do not achieve remission despite two adequate antidepressant treatment attempts, commonly defined as treatment resistant depression (TRD). The risk for developing SUD among patients with TRD compared with other depressed patients has not previously been studied.

Objectives: To investigate the risk of developing SUD among patients with TRD compared with other depressed patients using nationwide administrative Swedish registers.

Methods: This prospective cohort study was based on data from combined Swedish national registers in the years 2006–2014. All patients with an MDD diagnosis in specialized psychiatric care who had received at least one antidepressant prescription (N06A), and with no previous prescription of antidepressants or the potential augmentation medications of antipsychotics (N05A), or anticonvulsants (N03A) within the previous 180 days, were included ($n = 121\,669$). Patients with a diagnosis of psychotic disorder, bipolar disorder, and dementia were excluded. Patients who received at least three treatment episodes of antidepressants, antidepressant augmentation, or brain stimulation therapies, within a single depressive episode, were classified as having TRD. TRD patients were compared with the whole MDD cohort regarding risk for SUD, using proportional hazards regression. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated for being diagnosed with or prescribed treatment for SUD. Patients with and without previous SUD diagnoses were analyzed separately. Analyses were adjusted for sociodemographics, anxiety disorders, and personality disorders.

Results: 15 631 (13%) of the MDD patients were classified as having TRD. An equal proportion of patients in both groups had a previous SUD diagnosis at start of follow-up (MDD 11.2% vs TRD 11.9%). Mean follow-up was 4.2 years. Among the patients with no previous SUD, TRD patients had an overall risk increase for SUD, HR 1.6 (95% CI 1.5–1.7). In the specific SUD categories, risks for use of alcohol (1.2; 1.1–1.3), opioids (2.1; 1.7–2.6), sedatives (2.8; 2.4–3.3), and multiple drugs (2.3; 2.0–2.6) were elevated. Among the patients with

a previous SUD diagnosis, risks for any SUD (1.3; 1.2–1.4), use of sedatives (2.9; 2.3–3.7), and multiple drugs (1.7; 1.5–2.0) were elevated among TRD patients.

Conclusions: Patients with TRD, with and without previous SUD, are at greater risk for SUD compared with other MDD patients with antidepressant treatment.

330 | Alcohol-specific mortality in people with epilepsy: Population-based matched cohort study

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Background: The need for accurate estimates of cause-specific mortality in people with epilepsy has been recognised, including the specific contribution of alcohol.

Objectives: To estimate the relative risk of alcohol-specific death in people with epilepsy vs unaffected individuals, and to determine the proportion of these deceased persons who had prior alcohol-related primary care referral, treatment, or hospital admissions.

Methods: From the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality records in England, we delineated a cohort of people with incident epilepsy. This was defined as the first diagnostic code for epilepsy and associated antiepileptic drug prescription (AED). Individuals were eligible for inclusion if they were aged 18 or over and entered between 01/01/1990 and 31/03/2014. Individuals were matched with up to 20 people without epilepsy on year of birth (± 2 years), gender and general practice and followed up until death, transfer out of practice or study end. We applied the ONS definition of alcohol-specific death using ICD-10 codes and estimated hazard ratios using stratified Cox proportional hazards models adjusted for area-level deprivation. Amongst those who died from alcohol-specific causes, we estimated the proportion previously treated, referred for primary care intervention, or admitted to hospital for their alcohol problems.

Results: We matched 9871 people with incident epilepsy to 185 800 individuals without the condition. There were 29 alcohol-specific deaths in the epilepsy cohort and 106 in the comparison cohort, and the deprivation-adjusted hazard ratio was 5.43 (95%CI 3.80–7.75). Amongst those who died by alcohol-specific death, the following proportions had received care for alcohol problems in the epilepsy and comparison cohorts, respectively: treated for alcohol dependence (24.1% vs 9.4%), received support in primary care (20.7% vs 11.3%), and hospitalised for alcohol-related illness (51.7% vs 38.7%).

Conclusions: People with epilepsy are at a greatly elevated risk of alcohol-specific death. Not all of those who died by alcohol-specific death had specialist intervention prior to death. This could be a missed opportunity for identification and intervention targeted towards those most at risk of alcohol-specific death.

331 | Substance use disorders are risk factors for treatment resistant depression

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Background: Treatment resistant depression (TRD), defined as non-response to at least two treatment attempts, is common among patients with major depressive disorder (MDD). Substance use disorders (SUD) can co-occur in MDD and may lead to worse treatment outcomes. However, in previous clinical studies, SUD have not been identified as risk factors for TRD.

Objectives: To investigate whether SUD are risk factors for TRD, using national health care register data in a nested case-control study comparing TRD with other MDD patients.

Methods: Nationwide Swedish register data on pharmacological prescriptions, diagnoses from specialized psychiatric care, and various sociodemographic variables were used to establish a prospectively followed antidepressant-treated MDD cohort ($n = 121\ 669$) in the years 2006-2014. 15 631 patients (13%) were defined as TRD cases, having at least three registered antidepressant (N06A) or neurostimulatory treatment attempts within a single MDD episode. Patients with a previous prescription of antidepressants or the potential augmentation medications of antipsychotics (N05A) or anticonvulsants (N03A) within the previous 180 days were excluded, as were patients with a diagnosis of psychotic disorder, bipolar disorder, or dementia. Each case was closely matched on sociodemographic data with five non-TRD MDD controls using incidence density sampling. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the risk of having a SUD diagnosis, or treatment, for alcohol, opioids, cannabis, central stimulants, cocaine, hallucinogens, volatile solvents, or multiple drug use before entering the MDD cohort. Analyses were adjusted for education level, anxiety disorders, and personality disorders.

Results: Adjusted OR for history of any SUD was 1.16 for TRD cases compared with non-TRD controls (95%CI 1.10-1.22). When investigating specific SUD diagnoses, OR were significantly elevated for opioids (1.53, 1.01-2.30), central stimulants (1.44, 1.31-1.58), and alcohol (1.36, 1.22-1.53).

Conclusions: A history of SUD increases the risk for TRD among MDD patients in specialized psychiatric care. The impact of comorbid substance use should be considered when planning antidepressant treatment.

332 | Prevalence and predictors of dementia in older adults with employer-sponsored health insurance

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Background: Dementia is an area of growing concern worldwide. While dementia prevalence has been estimated using administrative claims data and survey data, little is known about dementia in elderly individuals with employer-sponsored health insurance in the United States.

Objectives: To determine the prevalence of dementia during two time periods (2009-2011 and 2013-2015), and to identify factors associated with dementia diagnosis.

Methods: In this study using Truven Health Marketscan Research Database[®], we identified subjects with dementia between 2009-2011 and 2013-2015. We required subjects to be continuously enrolled, 65 years or older, and have at least one medical claim in the study period. We compared demographics, comorbidities, and potentially inappropriate medication use (defined using Beers' criteria) between these two periods using two-sample mean and proportion tests where appropriate. In a subgroup analysis of subjects continuously enrolled 2009-2015, we used logistic regression to identify factors associated with incident dementia after the first period.

Results: After all inclusion and exclusion criteria were applied, 2 042 598 subjects were analyzed for the first period (54.9% female, mean age 74.4 years) and 1 291 834 were analyzed for the second (55.5% female, mean age 74.4 years). Prevalence of dementia increased (8.15% versus 9.94%; $p < 0.001$). In both periods, subjects with dementia were older, more likely to be female, had more comorbidities, and used more potentially inappropriate medications ($p < 0.001$). In the subgroup analysis, predictors of dementia included age, Parkinson's disease, depression, traumatic brain injury, and epilepsy. Use of potentially inappropriate anticholinergic and genitourinary medications was also associated with higher odds of incident dementia (OR 1.25 [1.22-12.8] and 1.44 [1.03-1.99], respectively).

Conclusions: Prevalence of dementia increased from 2009-2011 to 2013-2015 in a population of elderly subjects with employer-sponsored health insurance, but remained lower than estimates in other populations. Older subjects with more comorbid conditions and potentially inappropriate medication use had higher odds of developing dementia. More investigation needs to be done to determine how this unique population is different than other elderly populations, including those with Medicare.

333 | Abstract Withdrawn

334 | Epidemiologic temporal trends of neuromyelitis optic spectrum disorder in the United States from 2000 to 2015

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Background: Neuromyelitis optic spectrum disorder (NMOSD) is a rare autoimmune disease with unknown etiology that attacks the central nervous system leading to progressive disability. Population-based incidence and prevalence time trends of NMOSD in the United States (US) general population are insufficiently described, yet are needed to better understand the unmet medical need and evolving health care burden of this disease.

Objectives: To describe overall and age-specific prevalence, incidence, and time trends of NMOSD in the US using an electronic claims records database.

Methods: All patients in the Truven Health MarketScan® Commercial, Medicare and Medicaid databases between January 1, 2000, and December 31, 2015, who met the following case definition were included in the NMOSD cohort: (1) ≥ 1 claim of NMO in the inpatient setting and ≥ 1 claim of NMO in the inpatient or outpatient setting that are at least 60 days apart or (2) ≥ 2 claims of NMO in the outpatient setting that are at least 60 days apart. Counts for overall distribution by year, gender, and age were calculated, and prevalence and incidence rates were obtained with 95% confidence intervals (CI) by age and year.

Results: There was a total of 2187 patients in the NMOSD cohort, which was predominantly female (78%). The majority of patients were between the ages of 40 and 60 years. Beginning in 2005, a steady increase in annual and cumulative prevalence was shown from 0.35 (CI: 0.17, 0.64) per 100 000 in 2000 to 1.99 (CI: 1.81, 2.19) per 100 000 in 2015 and 0.35 (CI: 0.17, 0.64) per 100 000 in 2000 to 2.65 (CI: 2.44, 2.85) per 100 000 in 2015, respectively, in the overall NMOSD cohort. Steep increases were shown in patients starting at age 40 years. An increase in incidence was shown beginning in 2003 (0.14 (CI: 0.06, 0.27) to 0.44 (CI: 0.33, 0.58) per 100 000), with a dip in 2007, followed by a continued steady increase thereafter up to 2013, reaching a maximum of 0.63 (CI: 0.52, 0.76) per 100 000, possibly reflecting the impact of new diagnostic criteria for NMOSD in 2006. Over time, incidence rates were highly variable across age groups, with patients aged 55 to 70 years showing incidence rates reaching greater than 1 per 100 000 in some years.

Conclusions: Results from this study showed increases in prevalence and incidence of NMOSD over a 15-year period, overall and especially in adults over 40 years in the US. These data suggest the potential impact and implications of NMOSD on health care and societal resources in this predominantly working-age population.

335 | Comparison of characteristics and management of embolic strokes of different sources

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Background: Embolic stroke of undetermined source (ESUS) is a recent clinical entity corresponding to patients with ischemic stroke for whom the etiology of embolism remains unidentified and accounts

for up to 30% of ischemic strokes. However, the diagnosis of ESUS depends on the extent and quality of investigations performed or classification used.

Objectives: To compare characteristics and management of ESUS, with AF presumably related- and other etiology-related (OER) strokes, as diagnosed by stroke physicians in real-world practice.

Methods: Data from the French PGRx-Stroke registry were used. A representative network of 68 stroke units (65% of all), blind to study objectives, recruited consecutive incident stroke cases (2014-2016). An oversampling of ESUS was also conducted. For each stroke case, a case report form was filled out and the hospital report for stroke hospitalization obtained.

Results: Out of the 3705 ES kept, 1975 were presumably AF related, 905 ESUS, and 825 OER-ES. They were male in 52.7%, 63.5%, and 69.9% of cases, respectively. AF patients were the oldest and ESUS the youngest (78.8 [10.3], 56.0 [13.4], 57.3 [12.7]). 1.5% of AF patients died from their stroke vs 0.1% in each of the other groups. 99.99% of all patients were investigated by a CT-Scan or MRI. Supra-aortic atherosclerosis in 13.2%, 10.8%, 21.5%, intracranial atherosclerosis in 1.7%, 2.7%, 4.5%, and small vessel disease in 5.6%, 3.0%, 5.7% of cases. ESUS patients showed the lowest proportion of severe stroke (NIHSS ≥ 16) and AF patients the highest [17.3%, 5.6%, 6.9%]. Acute management was thrombolysis in 22.3%, 27.1%, 24.5% and endovascular treatment in 5.4%, 4.9%, 3.3%. During hospitalization, heparin was given to 19.5%, 10.0%, 18.3% of patients, oral anticoagulation (OAC) to 65.5%, 7.4%, 25.4%, antiplatelet drug (AP) to 43.8%, 87.1%, 75.0%, and both of them in 11.4%, 3.6%, 8.3%. At hospital discharge, patients were prescribed OAC in 67.1%, 3.5%, and 19.8% of cases, heparin in 28.3%, 19.0%, and 25.1%, AP in 34.0%, 93.4%, and 78.7%, antihypertensive drugs in 86.4%, 49.2%, and 54.1%, antiarrhythmic 29.6%, 0.9%, and 1.8%, and lipid-lowering drug in 56.6%, 75.0%, and 72.1% of patients. A dual AP therapy was prescribed in 1.9%, 8.6%, and 13.6% and OAC and AP combination in 11.3%, 0.2%, and 3.0% of patients.

Conclusions: ESUS patients are more male, younger, and less severe ES than the others. Surprisingly 19.8% of OER-ES are prescribed OAC at discharge. This result needs more exploration.

336 | Part 1 descriptive characteristics of incident dementia patients in four electronic health record databases in Europe

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Background: Epidemiological studies in dementia tend to focus on incidence, prevalence, and risk factors using cohort studies. The European Medical Information Framework (EMIF), a European Innovative Medicines Initiative (IMI) project, provides a platform for working with real-world patient health care data to elucidate differences in dementia epidemiology between countries.

Objectives: To evaluate newly diagnosed dementia patient characteristics, comorbidities, and medication use.

Methods: We obtained ethical approval to access 4 databases: The Health Improvement Network (THIN, UK), the Integrated Primary Care Information (IPCI, The Netherlands), the Health Search Database (HSD, Italy), and the Aarhus University Hospital database (AUH, Denmark). Dementia patients were identified from registration to database end, with their incident diagnosis recorded at age ≥ 55 with at least 1 year registration prior to dementia diagnosis. Dementia therapies included donepezil, galantamine, rivastigmine, and memantine. Other therapies included sleeping medications, anxiolytics, antidepressants, antipsychotics, antidiabetic medications, antihypertensives, statins, anti-inflammatories, and mood stabilizers.

Results: We identified 191 933 dementia patients. 133 751 dementia patients fulfilled our inclusion criteria with a higher proportion of females compared with males identified. There was a substantial difference in mean age at time of diagnosis between HSD (70.5) and IPCI, AUH, and THIN (range 81.4-82.2). Follow-up after dementia diagnosis ranged from 1.4 to 5.6 years. The most common comorbidities were diabetes and hypertension. The proportion of patients initiating a dementia therapy in the year prior to diagnosis was almost half in IPCI and AUH, while only a quarter in HSD and THIN. In the year after diagnosis, over 85% of all patients had initiated therapy. In the year after diagnosis compared with year before, the use of antipsychotics (4 databases), antidepressants (3 databases), anxiolytics, mood stabilizers, and sleeping medications (2 databases each) was significantly higher.

Conclusions: We provide a real-world insight into differences in dementia patient characteristics and medication utilisation across Europe.

337 | Comorbid conditions and medication utilization among patients with major depressive disorder in the United States

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Background: Estimates of comorbid conditions and drug utilization among patients with Major Depressive Disorder (MDD) vary by database and impact the characterization of MDD populations.

Objectives: This study describes the demographics, comorbid conditions, comedications, and drug utilization among patients with MDD in the United States.

Methods: The PharMetrics Plus health-insurance claims dataset (years 2007-2016) was used for this cross-sectional analysis. MDD cases were defined as those with ≥ 1 ICD-9-CM/ICD-10-CM claim for

MDD anytime during the study period. For each case, up to 2 controls without MDD were matched on birth year, gender, time in the database, and pharmacy benefit eligibility. Comorbidities were assessed based on ≥ 1 ICD-9-CM/ICD-10-CM diagnosis code and were grouped according to the CCS (Clinical Classifications Software) level 2 categories. Medication exposure was based on ≥ 1 NDC code occurring in the outpatient setting and grouped by Redbook classification. Comparisons of comorbidities between patients with MDD and controls were estimated using odds ratios (ORs) and 95% confidence intervals, adjusting for number of months of enrollment and enrollment start date.

Results: During the study period, out of 5 732 511 identified patients with MDD, about 67% were female. Mean age at diagnosis was 40.7 years. There were 11 383 015 controls selected. Patients with MDD had increased odds of the following comorbidities compared with controls: suicide (OR = 58.44, 95% CI: 57.00-59.92); personality disorders (OR = 21.39, 95% CI: 21.25-21.54); anxiety disorders (OR = 11.00, 95% CI: 10.98-11.02); substance-related disorders (OR = 6.41, 95% CI: 6.39-6.43); and attention deficit conduct and disruptive behavior disorders (OR = 5.53, 95% CI: 5.52-5.55). Common concomitant medications dispensed to patients with MDD included analgesics/opiates (56%), antibiotics/penicillins (45%), NSAIDs (44%), corticosteroids (40%), and benzodiazepines (37%). Among antidepressants, sertraline (22%), fluoxetine (17%), citalopram (17%), bupropion (16%), and trazodone (16%) were the most prevalent therapies dispensed.

Conclusions: Patients with MDD have a higher odds of mental health and substance-related comorbid conditions as compared with patients without MDD. The use of concomitant medications such as opiate agonists and benzodiazepines is prevalent among this MDD population. Future work using other data sources is needed to further characterize this highly prevalent patient population.

338 | Depression and anxiety and health-related quality of life (HRQoL) among cancer patients

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Background: Cancer is a life-changing experience and many cancer patients may suffer from depression and anxiety. However, there is a gap in research on the prevalence of depression and anxiety and the impact of these mental conditions on health-related quality of life (HRQoL) among Saudi cancer patients. Therefore, this study is designed to fill this knowledge gap among adult cancer patients with different types of cancer.

Objectives: (1) Identify the prevalence of depression and anxiety among patients with different type of cancer. (2) Identify the association between depression and anxiety and cancer patients' health-related quality of life.

Methods: A prospective cross-sectional study design was conducted among 217 patients. Data for this study were self-reported by the patients and were also derived from patients' electronic medical

records. Depression and anxiety were measured using Hospital Anxiety and Depression Scale (HADS). The HRQoL was measured using the European Organization of Research and Cancer Treatment scale (EORTC QLQ-C30). Descriptive statistics were used to describe the data. Multinomial regression analysis was used to examine the adjusted association between independent variables and depression and anxiety.

Results: A total of 217 patients were contacted to participate in this study, and all patients consented to be a part of the research. The majority of the study sample was women (66%) and has breast cancer diagnosis (51%). We found that 25% of cancer patients have depression and 18% have anxiety. Depression was significantly associated with the gender, income, stage at cancer diagnosis, and number of comorbidities. Anxiety was significantly associated with age, gender, social status, income, and stage at cancer diagnosis. We found that depression and anxiety were negatively correlated with physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, and global health status.

Conclusions: This study found that depression and anxiety were highly prevalent among cancer patients. Both depression and anxiety were significantly related to poor HRQoL. Health care providers may need to routinely screen cancer patients for depression and anxiety, especially those with an advanced stage of cancer and those with multiple conditions.

339 | Diabetes treatment in Brazil: Affordable choices and good coverage

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Background: Diabetes is a leading cause of disability. The use of pharmacological agents to control the glycemic levels remains the main strategy when managing diabetes, playing a vital role in preventing or delaying the onset and progression of complications.

Objectives: To describe the pharmacological treatment in use by the Brazilian people with medical indication to treat diabetes and to explore the users' characteristics.

Methods: Descriptive study of the use of antidiabetic medications in adults (aged ≥ 18 years—32 758 people) using data from the National Survey on Access, Use and Promotion of Rational Use of Medicines (PNAUM). The data were self-reported accounts for the urban living Brazilian population. The diabetes treatment was categorized in medications to treat hyperglycemia and medications related to diabetes (antiplatelet agents, statins, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers). Prevalence estimates and their 95% confidence intervals [95% CI] were calculated.

Results: Self-reported diabetes prevalence was 6.5% [95%CI 6.1-6.9], going up to 20.0% [95%CI 17.7-22.5] in those aged 75 or more. 16.2% [95%CI 14.4-18.2] of the diabetic referred being diagnosed within 1 year before the survey and 85.7% [95%CI 83.6-87.5] referred medical indication to treat it with medication. From those with treatment recommendation, 92.7% [95%CI 90.8-94.2] were in use of antidiabetic medication, being 58.6% [95%CI 55.8-61.4] using biguanides, 32.3%

[29.9-34.8] sulfonylureas, 3.5% [95%CI 2.6-4.5] DPP-4 inhibitors, and 14.4% [95%CI 12.7-16.4] declared to be insulin users. No occurrence of the use of rosiglitazone. From the ones who referred diabetes, 84.6% [95%CI 82.4-86.6] also referred other chronic conditions, being hypertension the most prevalent (72.6% [95%CI 70.2-75.0]), followed by hypercholesterolemia (36.5% [95%CI 33.9-39.2]) and heart conditions (21.6% [95%CI 19.2-24.2]), which lead to the use of medications related to diabetes (32.2% [95%CI 29.7-34.7]). Regarding living with diabetes, 65.8% [95%CI 63.4-68.2] of the diabetic said the disease do not limit their daily life and 19.1% [95%CI 17.2-21.3] said it limits a little.

Conclusions: The data suggest affordable pharmacological choices having old agents (biguanides and sulfonylureas) as the most used ones; good coverage regarding diabetes treatment (92.7%) and satisfactory control over the disease with most people facing little or none daily limitations. Further investigation on the patterns of use of these medications is desirable.

340 | Real-world use of dulaglutide in Europe: A multi-country drug utilization study

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Background: Dulaglutide is a long-acting glucagon-like peptide-1 receptor agonist approved in Europe for the treatment of type 2 diabetes.

Objectives: This study aimed to characterize dulaglutide utilization patterns in real-world conditions in subpopulations of patients for which little data exist.

Methods: Electronic medical record databases in France (FR), Germany (GE), Spain (SP), and Sweden (SW) were used to evaluate dulaglutide use in the following subpopulations of interest: patients with severe renal failure, heart failure, liver disease, and severe gastrointestinal (GI) disease; children and adolescents (<18 years); elderly (≥ 75 years); and pregnant and breastfeeding women. Eligible patients were those who initiated dulaglutide between 2015 and 2016 with ≥ 6 months of continuous history before dulaglutide initiation. Subpopulations of interest were defined by ICD-10-CM diagnosis and procedure codes for respective conditions. Patients with a recorded diagnosis of severe renal failure or an estimated glomerular filtration rate of <30 ml/min/1.73 m² recorded closer to the index dulaglutide initiation date were considered having pre-existing severe renal failure.

Results: A total of 4750 dulaglutide initiators were identified, corresponding to 441 in FR; 2760 in GE; 853 in SP; and 696 in SW. Mean age was 61 years in FR; 60 years in GE; and 59 years in SP and SW. Except in SP, the majority of dulaglutide users were males. All dulaglutide initiators in GE and SP and the vast majority (99%) of those in FR and SW were diagnosed with type 2 diabetes, with preponderance of patients using dulaglutide as add-on type 2 diabetes therapy (FR 84%; GE 86%; SP 100%; and SW 99%). Only 1 patient in FR was an adolescent (<18 years old). About 9% of patients in GE (and 7% in other countries) were elderly. Among women treated with

dulaglutide, only 4 (0.1%) in GE were pregnant at the time of starting dulaglutide. None were breastfeeding. Few to no patients had pre-existing severe renal failure (none in FR; GE 0.7%; SP 1.2%; and SW 0.3%). The frequencies of other pre-existing conditions were liver disease (FR 0.9%; GE 3.5%; SP 18.1%; and SW 1.9%), heart failure (FR 1.6%; GE 11%; SP 6.6%; and SW 5.3%), and severe GI disease (FR 5.2%; GE 7.4%; SP 11.6%; and SW 7.5%).

Conclusions: This study showed that dulaglutide is not widely used by patient groups of interest and is used by the intended population as an add-on therapy rather than first-line type 2 diabetes therapy according to the labeled indication in these 4 European countries.

341 | Comparison of diabetic patients' baseline characteristics in clinical trials versus real-world settings

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Background: Data about *real-world* patient treatment help fill the knowledge gap between *clinical trials* and clinical practice.

Objectives: Are there differences in the baseline characteristics of type 2 diabetes (T2D) patients in large clinical trials (prior to the approval of a new drug) and T2D patients in clinical practice (after a drug has been approved)?

Methods: The baseline characteristics of patients from two large clinical studies on sitagliptin (464 patients) and vildagliptin (362 patients) published in Diabetes Care were compared with the baseline characteristics of patients treated with sitagliptin and vildagliptin in Germany (20 123 sitagliptin and 4372 vildagliptin patients). Anonymous patient data from 1029 general and internal medicine practices in Germany (including specialized diabetological practices) (IMS[®] Disease Analyzer database; 2007 to 2016) were used for the comparison.

Results: There were significant differences in age, gender, HbA1c levels, body mass index (BMI), and co-therapy between the characteristics of patients in clinical trials and those in clinical practice. For example, sitagliptin patients in the clinical trial were 54 years old on average, while comparable patients in clinical practice were 66 years old; for vildagliptin ($p < 0.01$), the ages were 54 versus 69 years ($p < 0.01$), respectively. The proportions of male patients were 56% in the clinical trial versus 53% in clinical practice for sitagliptin ($p < 0.01$) and 47% versus 51% for vildagliptin ($p < 0.01$). The average HbA1c levels were 8.0 versus 7.9 for sitagliptin (difference not significant) but 8.4 versus 7.7 for vildagliptin (significant difference; $p < 0.001$). The average BMI values were 31 versus 32 for vildagliptin patients ($p = 0.15$) and 33 versus 31 for sitagliptin patients ($p < 0.01$). While all sitagliptin and vildagliptin patients in the clinical trials received metformin co-therapy, the same was true for only 60% and 65% of patients in clinical practice, respectively.

Conclusions: The retrospective database analysis shows that patients being cared for in everyday clinical practice differ from those in the prospective clinical trials. A combination of clinical trials and retrospective epidemiological studies (real-world evidence) would be necessary in

order to design future clinical trials in line with clinical practice and to address the target population in a more specific manner.

342 | The treatment patterns of patients with type 2 diabetes in urban China

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Background: Type 2 diabetes (T2D) is one of the well-recognized causes of premature death and disability worldwide, and proper treatment may help to improve prognosis of cases with T2D. So far, little is known about the T2D treatment in China.

Objectives: To elucidate the T2D treatment patterns and its relationship to the duration of T2D among patients in heavily populated Chinese cities.

Methods: A cross-sectional study was carried out in 15 hospitals of Beijing, Guangzhou, Shanghai and Chengdu. Eligible subjects were face-to-face interviewed by trained interviewers using a structured questionnaire, and data were collected on their socioeconomic, lifestyle, and T2D-related clinical variables. Descriptive statistics were used to evaluate the data with proportions/percents presented for categorical and mean/median for continuous variables. The chi-square for trend was used to test the relationship between numbers of oral antidiabetic drugs (OAD) and the duration of T2D.

Results: Totally, 1524 of 1530 eligible subjects were analyzed. Their average age was 63.4 ± 10.2 years old, and 58.2% were female. Nearly two thirds (65.5%) and about one quarter (24.5%) used OAD alone and OAD + insulin, respectively. Also, few (1.5%) were treated solely with lifestyle intervention. More than half (56%) of OAD-treated subjects took metformin. Nearly half (46.1%) were treated with dual OAD therapy; combination of metformin + sulfonylurea was the most frequently used for them. The number of OADs used significantly increased as the increasing duration of T2D ($P < 0.001$).

Conclusions: OAD are commonly used in patients with T2D in urban China, consistent with the clinical guidelines. Treatment pattern should be adjusted over time to maintain T2D control.

343 | Changes in diabetes medication adherence in older cancer patients versus matched cancer-free cohorts: A difference-in-difference analysis

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Background: Diabetes is a common comorbid condition in older adults with cancer. Given the favorable prognosis for many early-stage cancers, continuous and coordinated management of comorbidities, like diabetes, across the trajectory of cancer care is important. Yet few studies have characterized how a cancer diagnosis influences antidiabetic medication adherence.

Objectives: We evaluated changes in adherence to non-insulin diabetes medications in older adults diagnosed with non-metastatic cancers and matched cancer-free cohorts in the 6-months pre- through 6-months post-cancer diagnosis or matched index date.

Methods: Adults aged 66+ years with prevalent diabetes, non-metastatic breast, colon, lung, or prostate cancer, and a prescription fill for a non-insulin diabetes medication from 18 to 6 months prior to cancer diagnosis were identified using linked cancer registry and Medicare claims data from 2007 to 2013. Four cancer-free cohorts were identified using coarsened exact matching on age, sex, race, region, and presence of a diabetes diagnosis and medication fill. Medication adherence was measured using ambulatory proportion of days covered (aPDC). Changes in aPDC attributable to a cancer diagnosis were estimated for each cancer and matched non-cancer cohort using difference-in-difference methods and linear regression models.

Results: In total, 10 531 breast, 11 393 prostate, 6366 colon, and 6511 lung cancer patients and corresponding 4 165 569, 4 834 095, 2 423 257, and 2 552 977 matched cancer-free adults were included. Mean aPDC ranged from 80% to 82% in the cancer cohorts and 79% to 80% in the matched cancer-free cohorts in the 6 months prior to diagnosis or matched index date. In the following 6 months, mean aPDC dropped in the colon and lung cohorts (71% and 73%, respectively), but was stable in the matched cancer-free cohorts, with difference-in-difference estimates of -8.4% (95% CI: -6.1%, -10.7%) and -6.3% (95% CI: -3.8%, -8.8%), respectively. No significant differences were observed in adherence trajectories between breast and prostate patients and matched cancer-free cohorts.

Conclusions: Changes in mean aPDC following a cancer diagnosis varied by cancer type; future work will stratify results on prognosis and extend follow-up beyond the initial treatment phase of care. These findings could inform targeted interventions to improve care coordination and comorbid disease management in older adults with cancer.

344 | Federal provision of insulin in Brazil: Volumes and expenditures 2009-2015

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Background: Prevalence of diabetes in Brazil is 6.2% of population over 18. Federal public insulin provision involves tendering by the Department of Health Logistics of the Ministry of Health (DLOG-MOH) and reimbursement of private retailers by Brazilian Popular Pharmacy Program (PFPB).

Objectives: To analyze NPH and Regular insulin provision volumes and expenditures by the Brazilian Federal government, from 2009 to 2015.

Methods: We conducted a quantitative drug utilization study using procurement and reimbursement data as proxy for consumption. Tendered insulin volume and expenditure data were provided by the General Services Administration System (SIASG). PFPB reimbursement data were provided through the Freedom of Information Act. Total volumes were calculated in units. Number of DDDs were expressed as DDD/1.000 inhabitants/day. Expenditures were calculated using total volume and unit price, adjusted to December 2015 reais (BRL), according to the Brazilian Consumer Price Index, and converted to US dollars (USD) using yearly average Brazilian Central Bank values. Data were analyzed according to provision source, insulin type, and the expenditure:volume (represented by (DDD)/1.000 inhabitants/day) ratio.

Results: A total of 133 565 553 units of NPH and Regular insulins were provided by DLOG-MOH and PFPB between 2009 and 2015, showing a growth during the period, representing a total expenditure of 748 467 888.99 USD. NPH insulin presented greater volumes and expenditures in total federal government purchases compared with regular insulin. PFPB presented increase in volume and expenditures for both insulin types, with expenditures presenting a steeper increase. Despite the growth of PFPB, DLOG-MOH was the main provider of insulin, with total volume peak in 2014 (13.04 DDDs/1000 inhabitants/day) and total expenditures peaking in 2013 (155.51 million USD). The expenditure:volume ratio was 3-fold higher for PFPB compared with DLOG-MOH, which may demonstrate higher expenditures for PFPB for the same number of DDD/1000 inhabitants/day.

Conclusions: Federally supplied insulin volumes and expenditures showed growth during the period. NPH apparently drove federal procurement volumes. PFPB provision grew but was not able to cover DLOG-MOH provision. There were higher expenditures per DDD/1000 inhabitants/day by PFPB, possibly indicating higher prices.

345 | Prescription pattern of anti-diabetics agents in the patients with end-stage renal disease and type 2 diabetes mellitus: A national database from Taiwan

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Background: It is difficult to decide optimal antidiabetic therapy for type 2 diabetes (T2D) patients with and end-stage renal disease (ESRD) because most treatments are affected by renal function and their use may be contraindicated in this patient population. As a result,

the prescription pattern of antidiabetic regimens in T2D patients with ESRD appears to be inconsistent in clinical practice and is lack of investigation.

Objectives: To understand the use of antidiabetic treatments among T2D patients with ESRD in Taiwan, particularly assessing (1) the changes in the use of antidiabetic treatment at 1 year before and after dialysis and (2) patients' characteristics according to antidiabetic drug exposure after dialysis.

Methods: The Longitudinal Cohort of Diabetes Patients 1996-2013 from the National Health Insurance Research Database were utilized. We included T2D patients newly on dialysis in 2009-2012. We analyzed the pattern in antidiabetic treatments, in terms of prescription refills and defined daily doses (DDD), at 1 year before and after dialysis. Study patients were further stratified according to antidiabetic treatment exposure (eg, mono, dual, and triple therapy), and only stable users were included for analyzing their clinical characteristics. The stable user was defined as medication possession ratio ≥ 0.8 at 1 year after dialysis.

Results: A total 12 471 T2D patients starting dialysis during 2009-2012 were included, in which 2767 patients were stable users of antidiabetic treatment. The pattern of antidiabetic treatments has significantly changed at 1 year before and after dialysis. At 1 year after dialysis, there were total 6118 antidiabetic prescriptions with 1 770 692 DDDs prescribed, in which the most prescribed drug was insulin (33.48%) with 72.28% of DDDs, followed by sulfonylurea (18.63% of prescriptions, 9.90% of DDDs), and DPP4i (18.63% of prescriptions, 9.80% of DDDs). Among stable users of antidiabetic drugs, most patients were on monotherapy (20.10%), in which insulin users accounted for majority of population (35.22%), while 0.94% patients were stable on dual therapy and 0.10% patients had stable use of triple therapy.

Conclusions: Among T2D patients with ESRD undergoing dialysis, insulin was the most frequently prescribed therapy, while sulfonylureas, meglitinides, and DPP4i were common oral antidiabetic drugs. The prescription pattern of antidiabetic therapy significantly changed after dialysis.

346 | Mining treatment patterns of glucose-lowering medications for type 2 diabetes in the Netherlands

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Background: Guidelines for treatment of type 2 diabetes (T2DM) exist in the Netherlands. In this study, we want to assess how T2DM treatments are implemented in clinical practice.

Objectives: We aim to (1) investigate the prevalence of different classes of glucose lowering medications in T2DM during 6 years after the onset of the disease and (2) show the most frequent treatments steps in treatment of T2DM and the duration between switching

from monotherapy to combination therapy. We also aim to (3) find a method that helps describe the patient journey through treatment steps. This journey is complex, due to the large number of paths that exist.

Methods: We studied a cohort of 53 482 patients, aged >45 years with a first prescription for oral glucose-lowering medication, from 2012 to 2017. We used the NControl database that includes dispensing data from 527 pharmacies in the Netherlands. The date of first ever-oral glucose-lowering medication dispensing was selected as the cohort entry date (index date). We calculated annual and overall prevalence rates of each medication class in the period after index date. We used SQL Server to develop an algorithm to mine sequential patterns and study treatment steps. Treatment steps were compared between age categories (45-55, 56-65, and >66 years) and gender, using chi-square test.

Results: Mean age at index date was 64 ± 11 years, and 54% were men. The majority of patients with T2DM were aged ≥ 66 years (46%). Overall prevalence rates of biguanides (BIGU) and sulfonylureas (SU) were 97% and 37%, respectively. The prevalence of BIGUs decreased from 97% to 87% in the 6 years after index date. During this period, use of SUs increased from 22% to 37%. Use of dipeptidyl peptidase-4 inhibitors (DPP-4i) increased from 2% to 5%. We were able to mine stepwise patterns of medication treatment. 58% of all patients only received biguanides (BIGUs) until the end of the study, 20% of all patients start on BIGU and then switch to biguanides + sulfonylureas (BIGU + SU). The time between switching from monotherapy to combination therapy was roughly 30 months. We found 5285 (9.9%) patients that used insulin during follow-up.

Conclusions: This study shows the trends and treatment steps in the Dutch population with T2DM. BIGUs are the main first choice to manage T2DM. SUs are mostly added to this treatment. Sequential pattern mining can be used to give a clear overview of the most frequent steps in the patient journey in T2DM, which would otherwise be too complex to describe.

347 | Utilization of new antidiabetic drugs between 2008 and 2017 in Hungary

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Background: During the last 10 years, new antidiabetic drug groups (NADDs) have been authorized and reimbursed in Hungary: DPP-4 inhibitors (DPP4i) in 2008, GLP-1 analogues (GLP1A) in 2010, and SGLT-2 inhibitors (SGLT2i) in 2014. These agents are now included in the treatment guidelines for type 2 diabetes after metformin or in combination with metformin.

Objectives: Our aim was to analyze the utilization changes of NADDs and to detect the share of these agents out of the total antidiabetic drug use in Hungary between 2008 and 2017.

Methods: Crude national drug utilization data including the entire population of Hungary were obtained from the Hungarian National Health Insurance Fund. The study period was between 2008 and

2017. Data were analyzed using the WHO's ATC/DDD system (version 2017, ATC: A10) and were expressed in defined daily dose per 1000 inhabitants per day (DDD/TID).

Results: Between 2008 and 2017, the total NADD use increased from 0.045 DDD/TID to 11.873 DDD/TID and the share of NADDs rose to 16.13% of the total antidiabetic use by 2017. The most frequently used NADD drug group was the DPP4Is. The whole DPP4I use was 0.07% of the total antidiabetic use in 2008, which emerged to 10.50% in 2017. Since 2008, the DPP4I use has constantly emerged from 0.039 DDD/TID to 1.871 DDD/TID and the DPP4I + metformin use from 0.006 DDD/TID to 5.844 DDD/TID. The DPP4I + thiazolidinedione use was marginal, only 0.013 DDD/TID in 2017. In 2017, the most widely used DPP4I was sitagliptin followed by vildagliptin and linagliptin. Regarding GLP1As, the utilization was lower but showed a growing tendency, 0.058 DDD/TID in 2010 and 1.446 DDD/TID in 2017, while GLP1A + analogue insulin was 0.268 DDD/TID in 2016 and 0.527 DDD/TID in 2017, the total GLP1A utilization was 1.96% of the total antidiabetic use in 2017. Although SGLT2Is was authorized only in 2014, the consumption was growing dynamically from 0.019 DDD/TID in 2014 to 1.492 DDD/TID in 2017 and the SGLT2I + metformin from 0.010 DDD/TID to 1.207 DDD/TID. The share of the total SGLT2I use was 3.67% in 2017.

Conclusions: The last 10 years have brought a lot of changes in the treatment of diabetes mellitus. As the NADDs were authorized, reimbursed, and included in the therapeutic protocol, the utilization of these drugs showed a constantly growing tendency.

348 | Description of the utilization patterns of SGLT-2 inhibitors in type 2 diabetic patients in Korea

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Background: Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are a new class of oral antidiabetic medications approved for treating type 2 diabetes mellitus in Korea. Due to a relatively short period of time after approval, use of SGLT-2 inhibitors is largely uncharacterized.

Objectives: To describe the utilization patterns of SGLT-2 inhibitors and examine baseline demographic and clinical characteristics of patients with SGLT-2 inhibitors.

Methods: We performed a large nationally representative study using the Korean National Health Insurance claims data from 2013 to 2016. We identified type 2 diabetic patients (aged ≥ 18 years) initiating metformin. We then investigated the patterns (eg, continuation, switch, add, drop, and stop) of use of antidiabetic medications and duration of therapy. We also developed multivariable logistic regression model to identify independent predictors on initiation with SGLT-2 inhibitors versus other second line oral antidiabetic medication therapy (ie, dipeptidyl peptidase-4 inhibitors [DPP4I], sulfonylurea, thiazolidinedione, meglitinide, and alpha-glucosidase inhibitors).

Results: We identified 3228 type 2 diabetic patients with initiation of metformin. Among them, 67% were continued the first metformin therapy, 18.4% were switched their therapy to other diabetic medications, and 14.5% were added other medications. The most frequent medications to switch or add were DPP4I. Independent predictors on SGLT-2 inhibitor users were concomitant use of anticoagulant (adjusted odds ratio [aOR] 8.11, 95% confidence interval [CI] 1.29-51.02), followed by history of myocardial infarction (aOR 6.18, 95% CI 1.73-22.13), use of statins (aOR 2.96, 95% CI 1.60-5.48), body mass index (aOR 1.17, 95% CI 1.09-1.27), and calcium channel blockers (aOR 0.48, 95% CI 0.25-50.92).

Conclusions: Safety concerns were rising surrounding use of SGLT-2 inhibitors. While taking these baseline differences into account, future research may be needed to assess real-world outcomes after use of SGLT-2 inhibitors.

349 | Methodological approaches to reduce immeasurable time bias: The case of beta-blockers and the risk of mortality in patients with heart failure

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Background: Immeasurable time bias, which is induced by the unavailability of inpatient medication data, may exaggerate the benefits of drugs, particularly among populations where periods of prolonged hospitalization may precede the event of interest. While several methodological approaches have been proposed to reduce immeasurable time bias, the optimal approach remains unclear.

Objectives: To compare the ability of different methodological approaches to minimize immeasurable time bias using the example of beta-blocker use and all-cause mortality among patients with heart failure.

Methods: We conducted a retrospective cohort study of patients with incident heart failure between January 2003 and December 2013 using the nationwide sampled health insurance database of South Korea, linked to vital statistics. New users of beta-blockers were propensity matched to non-users at cohort entry (the date of heart failure diagnosis). Exposure to beta-blockers was defined using a time-dependent approach with current exposure defined by any prescription whose duration + 30-day grace period overlapped with the risk set date. We first estimated the hazard ratio (HR) and 95% confidence interval (CI) by including in-hospital and outpatient medication data as part of our exposure assessment (gold standard analysis). To estimate the magnitude of the immeasurable time bias, we then repeated analyses restricting exposure assessment to outpatient data. Finally, we compared 3 different approaches to minimizing this bias: (1) restriction to non-hospitalized patients; (2) adjustment for hospitalization; and (3) weighting by exposed time.

Results: In our 1:1 propensity-score matched cohort of 14 774 patients, we found a HR for current exposure to beta-blockers of 1.09 (95% CI: 1.01-1.18) when considering both inpatient and

outpatient prescriptions. In contrast, when exposure assessment was restricted to outpatient prescriptions only, beta-blockers were associated with a significantly protective effect (HR = 0.83, 95% CI: 0.77-0.89). Restriction to non-hospitalized patients (HR = 0.84, 95% CI: 0.77-0.91) and adjusting for hospitalization (HR = 0.84, 95% CI: 0.78-0.90) did not reduce the bias. However, weighting by follow-up time produced results (HR = 1.02; 95% CI: 0.98-1.07) that were consistent with those of the gold standard analysis.

Conclusions: Weighting by follow-up time appears to be the most appropriate approach to reduce the impact of immeasurable time bias.

350 | Healthy user bias in comparative safety studies for brand versus generic products: The example of warfarin

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Background: Warfarin was selected as a case study to examine manufacturer-level confounding because it is a narrow therapeutic index drug with prevalent beliefs of brand-name superiority.

Objectives: To explore confounding considerations in manufacturer-level comparative safety studies.

Methods: Medicare beneficiaries ≥ 65 years of age were identified with an incident outpatient warfarin dispensing for atrial fibrillation between 2006 and 2015. Medication and medical covariates were obtained through Medicare inpatient, fee for service, and prescription coverage and physician specialty through the Provider Enrollment, Chain and Ownership System. Demographic and socioeconomic indicators were obtained through linkage with the American Community Survey. Unadjusted comorbidity imbalances were explored using standardized mean differences.

Results: The cohort included 746 098 warfarin users taking brand-name BMS ($n = 48\,962$) and generics: USL ($n = 36\,931$), Taro ($n = 262\,453$), Teva/Barr ($n = 281\,809$), and Zydus ($n = 115\,943$). BMS users had the lowest rates among all manufacturers for 42 of 63 (67%) pre-specified covariates for clinical comorbidity, including nearly half the rates of smoking, obesity, and alcohol abuse (lifestyle factors). BMS users were more likely to receive warfarin from a cardiologist (47% BMS vs 34-36% generics), have recent primary care visit (72% BMS vs 61-67% generics), and have no recent emergent care visits (84% BMS vs 71-79% generics). Brand-name BMS users were more likely to live in areas with average income over \$100 000 (by 5-8%) and where >50% of people have a bachelor's degree (by 6-10%). Further imbalances between BMS and generics were observed for the impact of exclusion criteria, treatment adherence, pharmacy setting (eg, retail, mail-order), and time-varying changes in comorbidity risk scores. Beneficiaries who requested brand-name BMS or had a prescriber that did not allow substitution (92% of BMS) had

considerably different demographics and clinical comorbidities than beneficiaries receiving warfarin without direct request (eg, brand name required by law or generics out of stock).

Conclusions: Users of brand-name BMS were healthier than generic users across an array of clinical comorbidity and socioeconomic status markers. These differences likely stem from patient and/or provider beliefs regarding the superiority of the brand-name product, and they impose healthy user bias in the comparison of brand name versus generic warfarin.

351 | Negative control time window to identify residual confounding in comparative effectiveness study: An example of bisphosphonate use and risk of fracture

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Background: Negative controls are often used in pharmaco-epidemiology to identify residual confounding although their use is limited. Time windows of no drug activity (negative control time windows) have been identified from preclinical/RCT data for most preventative therapies: Bisphosphonates have no effect on fracture risk for the first 6+ months after initiation, providing an opportunity to test the method.

Objectives: To identify whether early treatment windows can be used as a negative control in a study assessing fracture risk after bisphosphonate (BP) use in patients with chronic kidney disease (CKD).

Methods: Patients with stage 3B+ CKD (eGFR < 45), aged ≥ 40 , were extracted from UK primary care records (CPRD). Main outcome was major osteoporotic fracture. BP users were matched up to 5 non-users using propensity scores. Fracture rates were calculated per 1000 person years for both groups. Hazard ratios were calculated using Cox proportional hazards (CPH) models for the full models and censoring at 180 and 360 days.

Results: 10 694 bisphosphonate users were matched to 42 445 non-users with CKD. Risk of fracture was increased in bisphosphonate users HR (95% CI) 1.38 (1.28, 1.49) with rates of 36.3 (34.0, 38.9) and 26.2 (25.3, 27.0) in the exposed and unexposed patients, respectively. Risk of fracture in the first 6 months (180 days) was considerably higher HR 2.00 (1.69, 2.36). At this time, rates of fracture in users were considerably higher than later 56.1 (49.8, 63.2), but stable over time in the non-users 28.2 (25.9, 30.7). By the first year, risk of fracture had decreased to HR 1.78 (1.57, 2.01) with rates of 47.5 (43.2, 52.2) and 26.7 (25.1, 28.5) in the exposed and unexposed patients, respectively, suggesting residual confounding by indication.

Conclusions: Risk of fracture in the first 6 months may be suitable for use as a proxy for a negative control time window. Risk of fracture

was 2-fold in the first 6 months compared with 1.4 times throughout follow-up suggesting the risk calculated throughout follow-up is biased by the initial increased risk. More research is needed to explore the usefulness of this method to estimate actual (un-biased) treatment effect/s.

352 | Adherence to statin therapy and the traumatic injury: An investigation using claims database in Japan

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Background: The healthy adherer bias arises when patients who adhere to preventive therapy are healthier or more health oriented than their non-adherent counterparts. Dormuth et al reported that patients more adherent to statin therapy were less likely to have accidents than less adherent patients, even after adjusted by various covariates.

Objectives: To investigate whether the healthy adherer bias associated with statin use arises in Japanese health care setting, we examined the association between adherence to statin therapy and traumatic injuries.

Methods: We conducted a cohort study, using claims database of the Japan Medical Data Center. We identified patients aged ≥ 20 who newly started a statin between January 2005 and July 2014. Patients were classified as adherers if they filled ≥ 2 prescriptions but as non-adherers if they filled only one prescription for a statin during a 1-year ascertainment period. They were then followed-up further for up to 365 days to see whether they had the incident traumatic injuries including burn, fracture, open wound, and poisoning. We estimated hazard ratios (HRs) for those events adjusted only by age and sex first, then adjusted fully by age, sex, various comorbid conditions, number of drugs, number of outpatient visits, days in hospital, and Charlson comorbidity index.

Results: We identified 41 462 new users of a statin where 36 304 were adherers (mean age $\pm$ SD: 50.7 ± 9.3 ; male: 62%) and 5158 were non-adherers (mean age $\pm$ SD: 47.1 ± 9.9 ; male: 67%). HRs adjusted only by age and sex were 0.96 (95%CI: 0.87-1.06) for all traumatic injuries, 0.89 (0.65-1.23) for burn, 0.99 (0.85-1.15) for fracture, 0.96 (0.83-1.19) for open wound, and 1.06 (0.84-1.33) for poisoning, respectively. The fully adjusted HRs were 0.91 (0.83-1.01) for all traumatic injuries, 0.80 (0.58-1.10) for burn, 0.96 (0.82-1.12) for fracture, 0.92 (0.78-1.06) for open wound, and 1.00 (0.80-1.26) for poisoning, respectively.

Conclusions: No reduction of the hazard of traumatic injuries was observed in Japanese patients adherent to statin therapy compared with less adherent patients after adjusted by various covariates. However, the confidence interval of HR was wide and about $\pm 11\%$ of the estimate (0.91). Further studies in a larger population are warranted.

353 | Methods for estimating treatment episodes—Dosage assumptions versus real prescribed dosage accounting for treatment gaps and overlaps

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Background: Defining exposure is crucial in a statistical analysis plan to reduce bias in treatment effect estimates. When constructing treatment episodes in observational studies, information about dosage, duration, and the presence of gaps and overlaps among prescriptions should be properly considered.

Objectives: To compare treatment episode durations estimated using real prescribed dosage versus estimates based on different assumptions of prescribed dosage and different approaches to account for gaps and overlaps among prescriptions.

Methods: Data from the Swedish Prescribed Drug Register were used to estimate treatment episodes for patients exposed to citalopram and mirtazapine during 2005-2014. Three methods were used: Method A, which is used as the gold standard, is based on real dosage extracted from free text format. Methods B and C are based on 1 unit of drug per day (in the specific marketed form) and 1 DDD per day assumptions, respectively. Moreover, the three methods were used to estimate treatment episodes accounting for different assumptions on gaps and overlaps between prescriptions.

Results: For citalopram users, the cumulative duration in number of days (median 260, interquartile range [IQR] 612) is underestimated using method C (median 230, IQR 618) and overestimated using method B (median 294, IQR 668). The cumulative duration for mirtazapine users (median 130, IQR 340) derived using method C is underestimated (median 100, IQR 300), and it is well estimated with method B (median 130, IQR 346). The episode's duration and the number of treatment episodes for citalopram and mirtazapine users are strongly affected by different allowed gaps (0, 10, 30, 60, 90, and 180 days).

Conclusions: Depending on the research question and the therapeutic area, dosage assumptions involved in the exposure definition require careful evaluation. Different assumptions result in underestimation or overestimation of treatment episodes, which may introduce bias in the estimates of treatment effects or association. When considering a time-varying exposure, the presence of gaps and overlaps needs to be taken into account in the treatment episode estimation. Further work is needed to test the effect of different exposure definitions on the risk of specific outcomes such as hospitalization.

354 | Quantifying the impact of mortality underreporting on analyses of overall survival

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Background: Underreporting of mortality in real-world data sources leads to overestimation of survival times and to potentially biased overall survival (OS) comparisons. In principle, the magnitude of bias in OS outcomes can be directly measured through linkage to a second (assumed perfect) source of mortality information [1]. However, this is often not possible or practical.

Objectives: In this study, we explore a theoretical approach to quantify the magnitude of bias when comparing OS from data sources with different levels of mortality underreporting.

Methods: Mathematical formulae were developed to predict the magnitude of bias introduced into OS hazard ratios between datasets with different levels of underreporting of mortality information, denoted by sensitivity parameter s . Predictions were verified using simulated data: Publicly available data from 1098 patients with invasive breast cancer [2] were bootstrapped, and the data were artificially censored at time of death in a proportion $1-s$ of patients with a death event.

Results: The formulae predict that an OS hazard ratio between two cohorts should be biased by a factor equal to the ratio of the sensitivity parameters in each dataset. There was almost perfect agreement with the simulation results. Under the assumption of exponential survival, a dataset with sensitivity parameter s is predicted to overestimate median OS by a factor $1/s$. Agreement with simulation results was only approximate in this case, presumably due to non-exponential survival in the breast cancer data.

Conclusions: This method predicted the magnitude of bias in a OS hazard ratio given the ratio of sensitivity parameters in either cohort. The results imply that hazard ratio estimates could be unbiased even with high levels of missing death information, as long as this is balanced between the arms. This study assumes that death information is missing at random. Further research will have to investigate accuracy of our predictions when this assumption is violated.

References

1. Møller H, Richards S, Hanchett N, Riaz SP, Luchtenborg M, Holmberg L, et al. Completeness of case ascertainment and survival time error in English cancer registries: impact on 1-year survival estimates. *Br J Cancer*. 2011 Jun 28;105(1):170-6.
2. The Cancer Genome Atlas Home Page [Internet]. The Cancer Genome Atlas—National Cancer Institute. [cited 2018 Feb 14]. Available from: <https://cancergenome.nih.gov/>

355 | How is outcome misclassification addressed in pharmacoepidemiology database studies?

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Background: Outcome misclassification can lead to a type of information bias with a particular concern in electronic database studies, because both false positive and false negative errors can occur when using diagnostic and treatment codes collected for purposes other than research. This misclassification can be quantified in validation studies as estimates of sensitivity, specificity, positive predictive value, and negative predictive value. Effect estimates can be biased unless misclassification is addressed in the analysis. Confounding is another possible source of bias. Methodological guidance documents of the Food and Drug Administration and of the European Medicines Agency discuss adjustment for confounding as well as validation, but not methods for addressing misclassification.

Objectives: To investigate the reporting of outcome validation and adjustment for misclassification in comparative pharmacoepidemiology studies.

Methods: Medline was searched using “Pharmacoepidemiology and drug safety”[Journal] AND (“2017/01/01”[PDAT]: “2017/06/30”[PDAT]) (n = 137 publications). Comparative studies were selected (n = 33), and 30 studies were reviewed using a common spreadsheet after excluding 3 having drug utilisation as outcome. The following key parameters were described for each selected study: discussed outcome misclassification, reported on validation metrics, adjusted for misclassification, and addressed confounding.

Results: Outcome misclassification was discussed in some manner by 14 (47%) studies. Six (20%) studies reported either internal (4) and/or external (4) estimates of validity (13% each). Among the four studies with internal estimates, 2 (6%) restricted the analysis to validated outcomes and 1 (3%) adjusted the results to account for overall misclassification. Confounding was addressed by design or/and at the analytical stage in 25 (83%) studies.

Conclusions: In our sample of pharmacoepidemiology studies, a minority reported validity indices and quantitative misclassification adjustment was uncommon, while adjustment for confounding was usually included. This lack of misclassification adjustment may reflect the omission in methodological guidance. An ISPE sponsored initiative aims to raise awareness of the impact of misclassification bias, to disseminate methods for quantitative adjustment in a manuscript, and to develop an online tool to support this adjustment.

356 | Conditioning on calendar time in studies of newly marketed drugs

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Background: Calendar time is often a strong predictor of treatment receipt in studies of newly marketed drugs, leading some authors to propose using calendar time as an instrumental variable (IV), particularly if uptake of the new drug is rapid. In contrast, other authors recommend conditioning on calendar time to capture the natural evolution of medical practice in studies of newly marketed drugs in an attempt to reduce confounding. However, adjustment for IVs has been shown to amplify unmeasured confounding and reduce precision, raising the question of whether calendar time should generally be adjusted for.

Objectives: We sought to determine whether adjustment for calendar time, a potential IV, may impede estimation of treatment effects in real-world studies of newly marketed drugs. In particular, we sought to determine if evidence for bias amplification or precision reduction could be observed across several diverse example studies.

Methods: In four example studies, we compared newly marketed drugs to established alternatives during their first 2 years of marketing and assessed the impact of conditioning on calendar time in propensity score-based analysis. We examined calendar time trends in treatment preference, outcome incidence, and covariate balance, as well as effect estimation.

Results: In three of four example studies, there was a trend toward decreasing covariate imbalance over time. However, propensity scores that conditioned on calendar time did not achieve better overall balance than those that did not (maximum difference in average absolute standardized differences of 0.013). There were no consistent differences in treatment effect estimates or their standard errors whether conditioning or not conditioning on calendar time.

Conclusions: While there is theoretical potential for calendar time to act as a proxy for trends in unmeasured risk factors or as an instrumental variable in studies of new drugs, we did not observe meaningful differences in effect estimates with or without adjusting for calendar time in four examples. Researchers should consider whether adjusting for calendar time is likely to aid or impede confounding control.

357 | Do regression models with better goodness of fit ensure less biased treatment effect estimates?

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Background: There is widespread misconception that goodness-of-fit statistics are critical in determining whether treatment effects estimated from a regression model are unbiased.

Objectives: We aimed to examine whether regression models with better goodness of fit ensure less biased treatment effect estimates.

Methods: We constructed a simulated dataset of 10 000 patients to compare two treatments on a continuous outcome of a prognostic score (mean: 0.82; range: -6.2 to 8.0) wherein a higher score indicates a higher risk of mortality within 1 year. By design in our simulation, the new treatment would lower the prognostic score by 0.1 compared with the traditional treatment. We then generated two study designs using this dataset: (1) a randomized controlled trial (RCT) with randomly assigned treatment and (2) an observational study design wherein patients receiving the new treatment tended to be sicker on observed (eg, older age, higher comorbidity score) and unobserved covariates. Treatment effect estimates were obtained from the observational study design using (1) multivariable linear regression accounting for observed covariates and (2) instrumental variable two-stage least squares (2SLS) regression accounting for observed and unobserved confounders and were compared with (3) the regression results from the RCT. Bootstrapping with 1000 resamples and standardized errors (SE) were used to estimate out-of-sample prediction for each of the three regression models.

Results: Across the three regression models, multivariable linear regression had the highest goodness of fit (adjusted *R*-squared 0.215) and best out-of-sample prediction (SE: 2.15), but very biased treatment effect estimates due to unmeasured confounders (bias: 1.119, 95%CI: 1.101 to 1.137). The RCT regression had the lowest *R*-squared (0.001), and 2SLS had an *R*-squared of 0.122. Both RCT (bias: 0.003, 95%CI: -0.017 to 0.024) and 2SLS (bias: 0.004, 95%CI: -0.039 to 0.046) had unbiased estimates.

Conclusions: Regression models with better goodness of fit would have better predictive power but do not ensure less biased treatment effect estimates. Correct study design and model specification are important for unbiased treatment effect estimates.

358 | Sample size needed to achieve covariate balance

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Background: Subclassification on a propensity score (PS) will balance measured variables used to estimate the PS, over a sufficiently large

sample. When subgroups of patients are matched on the propensity score or when analyses are conducted by stratifying on the propensity score, investigators may wish to examine covariate balance within subgroups or strata, often using standardized differences. With small subgroups or strata, balance may not be achieved due to chance even if matching or stratification is effective in balancing covariates in the overall study cohort.

Objectives: To determine how large a subgroup, stratum, or even an overall study sample must be to achieve adequate covariate balance.

Methods: We conducted simulations to evaluate balance for a single binary covariate, varying sample size and covariate prevalence. We assumed an equal number of patients in each of two treatment groups and generated samples of 100, 200, 500, 750, and 1000 patients in each group. For each treatment group at each sample size, we simulated a binary covariate with the same true prevalence (50%, 25%, 10%, 5%, and 1%) in each group using a binomial distribution. We generated one million samples of each size and covariate prevalence and calculated the proportion of samples in which the standardized difference of the covariate was >0.10 .

Results: In samples with 1000 individuals in each group, $<1\%$ had standardized differences >0.10 at all five levels of covariate prevalence. At a sample size of 750 patients in each group, the probability of obtaining a standardized difference of >0.10 was 2% across all levels of covariate prevalence; this increased to 5-6% at a sample size of 500 in each group. In samples with 200 patients in each group, the standardized difference was >0.10 in 21% of replicates for a covariate with a true prevalence of 50%; this increased to 29% for a covariate with a prevalence of 1%. With only 100 patients in each group, the probability of a standardized difference of >0.10 ranged from 36% to 53% across the levels of covariate prevalence.

Conclusions: In samples sizes with <500 (and especially >200) patients in each group, investigators should not necessarily expect to achieve balance even when the two groups have the same true prevalence of the covariate. Even when overall study cohorts are well balanced, imbalances due to chance on at least one covariate are likely to be observed in small strata or subgroups when using a propensity score to balance multiple covariates simultaneously.

359 | Maternal ADHD medication use during pregnancy and the risk of ADHD in children

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Background: The association between maternal attention deficit with or without hyperactivity disorder (ADHD) medication use during pregnancy and the risk of ADHD in offspring is controversial. The etiology of ADHD remains unclear, but genetic trends and environmental risk factors are likely involved in offspring and adult onset of ADHD.

Objectives: We sought to evaluate the risk of ADHD in offspring associated with overall and class-specific intrauterine exposure to ADHD medication.

Methods: We performed a cohort study in the Quebec Pregnancy Cohort (QPC), an ongoing population-based cohort, which includes data on all pregnancies of mothers covered by the provincial prescription drug insurance in Quebec and their children from January 1, 1998, to December 31, 2015. Singleton full-term liveborns and mothers with continuous prescription drug coverage for at least 12 months before and during pregnancy were included. ADHD medication exposure during pregnancy was defined according to trimester of use and class-specific medication (ADHD-specific stimulant and non-stimulant). ADHD in children was defined as having at least 1 diagnosis of ADHD or 1 prescription filled for ADHD medications between birth and the end of the follow-up. Cox proportional hazards regression models were used to calculate crude and adjusted hazard ratios (aHR) with 95% confidence intervals (CIs).

Results: A total of 166 047 full-term singleton live births were considered for analyses. During follow-up, 25 454 infants (15.3%) were identified with ADHD; boys outnumbered girls by a ratio of 2:1. The mean age ($\pm$ standard deviation [SD]) at first ADHD diagnosis was 8.19 ± 3.11 years. Adjusting for potential confounders, including maternal history of ADHD, which is a risk factor for childhood ADHD, and other psychiatric conditions, maternal exposure to ADHD medication was associated with an increased risk of ADHD in the offspring (aHR = 2.04; 95% CI 1.27-3.27; 133 exposed cases). More specifically, use of ADHD medication during the 1st trimester was associated with an increased risk of ADHD in the offspring (aHR = 3.70; 95% CI 2.36-5.79; 130 exposed cases); 2nd and 3rd trimester use did not significantly increase the risk. Methylphenidate was associated with an increased ADHD risk in the offspring.

Conclusions: Our findings suggest that maternal exposure to ADHD medication increases the risk of ADHD in the offspring, specifically following 1st trimester exposure. Additionally, methylphenidate was associated with an increased ADHD risk in the offspring.

360 | Multiple imputation of clinical variables in FFS Medicare population

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Background: Trials suggest GLP1 receptor analogues (GLP), a class of injectable antidiabetics, may increase the risk of diabetic retinopathy (DR). Assessing drug effectiveness and safety in fee-for-service Medicare beneficiaries (FFSMB) offers unique opportunities to examine this signal, but presents challenges due to lack of clinical detail. CPT II codes, which provide information on clinical measures (eg, hemoglobin A1c, blood pressure, cholesterol), may provide additional control for confounding, but are not reported for all patients.

Objectives: Use multiple imputation (MI) for clinical variables available in an internal validation study to further balance cohorts for diabetes severity to assess whether GLP increases DR risk.

Methods: We identified FFSMB initiating GLP or long-acting insulin (LAI) 2007-2015, excluding patients with blindness, low vision, or DR therapy. We defined DR as a procedure code for photocoagulation, intravitreal injection, or vitrectomy with 1+ DR or diabetes code on the same claim. We conducted MI stratified by exposure using fully conditional specification with logistic regression for clinical variables (A1c, SBP, DBP, and LDL) in arbitrary missing pattern allowing generalized logit model for nominal response data. We used propensity scores to balance measured and imputed confounders and estimated adjusted hazard ratios (aHR) and 95% confidence intervals (CI) using standardized mortality ratio-weighted Cox proportional hazards models censoring for treatment changes.

Results: A1c was available for 11% of GLP ($n = 11\,510$) and 7% of LAI ($n = 110\,423$) initiators. The prevalence of A1c category <7%, 7-9%, and >9% was 29%, 51%, and 20% in GLP and 23%, 44%, and 33% in LAI, respectively. The crude rates of treated DR per 1000 person-years were 3.4 in GLP and 8.7 in LAI over a median duration of 0.75 and 0.97 years, respectively. Comparing GLP with LAI, the aHR ignoring clinical measures was 0.41 (CI 0.29-0.59); adjusted for imputed clinical measures, the aHR was 0.45 (CI 0.31-0.67) in the full cohort and 0.57 (CI 0.32-1.03) in patients with A1c $\leq 9\%$.

Conclusions: Among older US adults treated with GLP or LAI, ~7% have some information on diabetes severity/control in claims data. Using MI to leverage this information moved the aHR slightly towards the null. Residual confounding is likely, due to the broad A1c categories, particularly in the highest A1c stratum. Identifying comparator drug classes with balance of clinical variables may still be the most robust approach to controlling for diabetes severity.

361 | Assessing residual confounding of comparative mortality risk of antipsychotics use in elderly patients with ischemic stroke

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Background: Selection of antipsychotics (APs) with lower mortality risk is important for the control of psychosis in post-stroke elderly patients. However, evaluations on comparative mortality risks of APs

could be biased due to residual confounders, such as stroke severity and the functional status, which are not observed in claims data.

Objectives: To evaluate the confounding effects due to unmeasured factors, including stroke severity (NHSS scores), functional status (Barthel index and mRS scores), and other health factors (smoking history and BMI).

Methods: Design and setting: We conducted a retrospective cohort study to identify the patients aged above 65 years old and admitted for ischemic stroke in National Health Insurance Research Database (NHIRD) from 2001 to 2012. These patients were not prescribed APs before discharge date and followed them until they started to receive APs treatment. The measured factors were retrieved from claims during the 1-year look-back period prior to index date. We then used stroke registry database to link NHIRD by deterministic linkage method to identify five unmeasured factors. **Exposures:** APs included chlorpromazine, haloperidol, olanzapine, quetiapine, risperidone, and sulpiride. **Main outcomes:** 1-year all-cause mortality. **Statistical analysis:** We first estimated hazard ratio was adjusted for measured confounders for mortality risk of APs use in NHIRD, and then estimated fully adjusted relative risk (RR) was corrected by external adjustment with five unmeasured confounders. The sensitivity analysis was used to evaluate the bias and variation of RR of each AP.

Results: Comparing quetiapine users, we found did not adjusting Barthel index score led to the most underestimation for the mortality risk in sulpiride users (~20.0%). After correction of combination of five unmeasured confounders, the mortality risk compared with quetiapine was slightly increased in chlorpromazine (RR 1.48; 95% CI 1.37-1.59), olanzapine (RR 0.88; 95% CI 0.72-1.09), risperidone (RR 1.07; 95% CI 1.01-1.14), and sulpiride (RR 0.82; 95% CI 0.74-0.90).

Conclusions: The findings indicated we would underestimate the differences of mortality risks between APs because of residual confounders. Although active comparator designs could be one of the best approaches to deal with unmeasured confounders for observational studies, the finding warrants attention on possible bias toward to null without considerations of residual confounding factors.

362 | Variation in risk estimates from different cohort selection strategies when using recurrent index events

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Background: In database studies, we often assemble analytical cohorts by anchoring look-back and follow-up to a recurrent index event (eg, outpatient visit, hospitalization, or prescription). While it is common to take the first eligible index event, there is little guidance on best practices for assembling cohorts when patients have multiple eligible index events.

Objectives: To examine the effect of three different selection strategies on estimated 30-day all-cause mortality after an index outpatient visit.

Methods: Using a 20% random sample of US fee-for-service Medicare beneficiaries, we identified all routine outpatient visits in 2010 at which a beneficiary was ≥ 66 years of age and had ≥ 12 months of continuous baseline enrollment. We assessed 30-day all-cause mortality after each eligible index visit. We then explored three strategies for assembling an analytic cohort: (1) keeping all eligible visits, (2) randomly selecting one outpatient visit per beneficiary, and (3) selecting the first outpatient visit per beneficiary. For each strategy, we estimated the overall risk, as well as the risk by date of the visit to examine temporal trends.

Results: We identified a total of 20 054 972 eligible outpatient visits for 2 118 572 unique beneficiaries, with 83 015 of those outpatient visits being followed by a death within 30 days. The overall 30-day mortality estimates were 0.41% (95% confidence interval: 0.41, 0.42), 0.79% (0.78, 0.80), and 0.35% (0.34, 0.36) when using all visits, a random visit per beneficiary, and the first visit per beneficiary, respectively. When all visits were used, risk was roughly constant over time at around 0.4%, and the same was seen with the first visit strategy, but with greater variation towards the end of the year when fewer visits were available. When one visit was randomly selected per beneficiary, risks were elevated (~4%) and decreased exponentially over the first 4 months of the year before settling at a level similar to the other two methods.

Conclusions: Risk estimates varied based on the approach used to select visits, suggesting that the choice of selection strategy is important when a population indexed on a recurrent event is itself of interest, or to be used as a comparator. Randomly selecting one visit per beneficiary should be avoided as it conditions on the future—each visit's selection probability depends on the number of other visits the beneficiary had, which is a function of whether or not the mortality outcome has occurred.

363 | Implementation of the prevalent new user study design in the US Medicare population: Benefit versus harm

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Background: Thiazolidinediones (TZDs) are known to increase the risk for congestive heart failure (CHF). Active comparator, new user (ACNU) studies can replicate this finding compared with a clinical alternative 2nd line antidiabetic drug class, dipeptidyl peptidase 4 (DPP). The ACNU design has been criticized because it might lead to smaller sample size if many new users of one of the drug classes compared have been treated with the other drug class previously. The prevalent new user (PNU) design has been proposed to overcome this but changes the causal interpretation of the treatment effect estimates.

Objectives: Compare 1-year CHF hospitalization rates among new users of TZD with DPP, allowing for new users of DPP to switch from TZD.

Methods: Using Medicare claims, exposure sets were created for all new users of DPP 2008-2015 to group each traditional new user of DPP with all traditional new users of TZD who are not yet exposed to DPP with both the same duration of TZD supplied and a TZD prescription claim within ± 30 days. A 1:1 matched cohort without replacement was subsequently created based on the propensity to initiate DPP among all exposure sets conditional on each exposure set. Cox proportional hazards models were used to obtain the hazard ratio (HR) and their 95% confidence intervals adjusted for calendar year of the matched index date, using 2011 as the referent year.

Results: Overall, there were 97 102 TZD initiators. Among the 205 156 DPP initiators, 16.9% had TZD during the 180-day washout period. Among the 88 202 matched sets, DPP patients were more likely to have use of angiotensin receptor blockers, loop diuretics, and statins and higher baseline CHF prior to the matched index. Switching from TZD to DPP was associated with an increased risk for HF (HR = 1.67 [0.50-5.56]) compared with staying on TZD, whereas the corresponding ACNU estimate was 0.98 [0.97-1.00].

Conclusions: DPP new users who switched from TZD had a higher outcome risk, which could potentially be attributed to confounding by contra-indication. This implementation of the PNU design in the US Medicare population shows little advantage with respect to sample size compared with the ACNU design and highlights some pitfalls in the causal interpretation of PNU results.

364 | The case-crossover design for drug interaction studies: Interaction term model versus a novel fully saturated model

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Background: The case-crossover design may be useful for evaluating the clinical impact of drug-drug interactions (DDI) in electronic health care data. In the context of two interacting drugs, a traditional 3-parameter model with a product term for the two exposures may be vulnerable to confounding by indication for one or both drugs.

Objectives: To compare the 3-parameter model with the interaction term to a novel, fully saturated 6-parameter model in the context of case-crossover studies of drug interactions.

Methods: Using five US databases (1998-2013), we conducted case-crossover analyses of two DDI examples with prior evidence of harm: (1) cytochrome P450 (CYP)3A4-metabolized statins + CYP3A4-inhibiting antibiotics (clarithromycin, erythromycin) and rhabdomyolysis and (2) clopidogrel + CYP2C19-inhibiting selective serotonin reuptake inhibitors (SSRIs; fluoxetine, fluvoxamine) and ischemic events. We considered the exposure histories of all eligible cases and conducted analyses with (1) a 3-parameter model with an interaction term and (2) a saturated 6-parameter model that distinguished initiation order of the two drugs and chronicity of drug use prior to DDI

encounter. Negative controls (azithromycin and SSRIs not known to interact with CYP2C19) were utilized as active comparators qualitatively and in case-case-time-control analyses.

Results: In the statin example, the 3-parameter model produced estimates for the interaction term that were consistent with prior evidence both with the active comparator (odds ratio [OR] 2.05, 95% confidence interval [CI] 1.00-4.23) and without (OR 1.99, 95% CI 1.04-3.81). In the clopidogrel example, this model produced results opposite of expectation (interaction term OR 0.78, 95% CI 0.68-0.89) unless the active comparator was used (OR 1.03, 95% CI 0.90-1.19). The saturated 6-parameter model showed considerable heterogeneity across strata; strata with concordant clopidogrel exposure likely produced the least biased estimates.

Conclusions: The traditional model for interaction can be useful for evaluating outcomes of DDIs in case-crossover studies in the absence of strong confounding by indication. A more complex saturated model can help identify heterogeneity and differences in confounding across strata. Restricting to specific strata or use of an active comparator may be necessary when confounding is present.

365 | Minor differences, major consequences? Lessons learned from replication of a claims-based drug safety assessment

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Background: Minor specification changes in key parameters can potentially define different analytic cohorts and subsequently affect causal inference in pharmacoepidemiological studies. Understanding the impact of these changes is important for consistency improvement in future investigations.

Objectives: To examine the impact of specification changes in claims-based drug safety evaluations.

Methods: This study conceptually replicated a published retrospective cohort assessment for dabigatran versus warfarin use on risk of myocardial infarction (MI), gastrointestinal bleeding (GIB), and intracranial hemorrhage (ICH), using data from the 2010-2015 Truven Health MarketScan[®] Research Database. Initial analysis identified the following minor but high-impact factors in the reference study: 1) baseline inclusion of exposure index date; 2) baseline heparin use; 3) dispensing-stockpiling algorithms; and 4) health utilization metrics inclusion in propensity score (PS) estimation model. We covaried these factors, performed analyses using 1:1 PS-matching methods and Cox proportional hazards models, and examined changes in cohort size, time-at-risk, and effect estimates.

Results: Co-presence of the baseline inclusion of the index date and heparin use led to the most substantial but differential increase in the unmatched cohort size for dabigatran and warfarin treatment

groups (in MI cohorts, increase by 10% and 14% respectively). Similar differential increase was observed for generous stockpiling in extending time-at-risk (in unmatched cohorts, minimum increase across all outcomes by 26% and 44% respectively). Among the co-varying factors, safety estimates varied from adjusted hazard ratios (HRs): HR_{MI} 0.75 (95% CI: 0.54-1.04), HR_{GIB} 1.04 (0.85-1.26), HR_{ICH} 0.54 (0.38-0.75) for the smaller cohorts to HR_{MI} 0.98 (0.74-1.31), HR_{GIB} 1.10 (0.93-1.30), HR_{ICH} 0.49 (0.37-0.64) for the bigger cohorts. Baseline inclusion of the index date and generous stockpiling contributed more variability in rates than PS estimation model. Despite the value shifts, significant overlaps in effect estimates suggested consistent findings in relation to the null.

Conclusions: Minor specification changes in baseline inclusion of the index date and stockpiling can alter cohort composition and thus impact risk estimates, especially for rare events or small subgroups. Robust confounding adjustment methods may absorb the differences, but final results should be generalized with caution.

366 | Strategies for selecting start of follow-up in longitudinal studies with multiple eligible index opportunities

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Background: In longitudinal studies, individuals may have multiple eligible index opportunities (eg, exposure episodes). Methods for selecting among these to form analytical cohorts have been informed by concerns about computing power, sample size, and intuition, rather than evidence.

Objectives: Evaluate bias and efficiency of various index selection strategies.

Methods: We simulated 52 weeks of (perfectly classified) data for N = 40 000 people. For each week, we simulated whether a health care visit occurred ($p = 0.125$) and whether exposure was initiated at a visit ($p = 0.15$). We simulated exposure duration by drawing from a normal distribution ($\mu = 8$ weeks, SD = 7 weeks) and weekly mortality ($p = 0.015$) with no exposure effect (null). Eligible index opportunities (visits) had 13 weeks of observed history without the exposure (wash-out). To select among eligible index opportunities, we implemented 5 selection strategies. For each person, we retained (1) all visits, (2) first visit, (3) first visit at each exposure level, (4) a random visit, or (5) a random visit at each exposure level. Across 4000 simulations, we report median risk (by exposure group), risk ratios (RR) for the effect on 1-week mortality with empirical 95% confidence intervals (CIs), and root-mean-squared-error (rMSE).

Results: Estimates were unbiased when selecting all visits (RR = 1.00 [0.86, 1.15]), the first visit (RR = 1.00 [0.75, 1.29]), or the first visit at each exposure level (RR = 1.00 [0.84, 1.18]). rMSE was minimized by selecting all visits (all visits: 0.123; first visit: 0.228; first visit at

each exposure: 0.135). Selecting a random visit ($RR = 0.72$ [0.59, 0.87]) or a random visit at each exposure level ($RR = 0.61$ [0.52, 0.71]) biased estimates downwards. For unbiased approaches (strategies 1-3), risk estimates reflected the true simulated mortality risk (1.5 deaths per 100 people/week). Random selection (strategies 4-5) overestimated risk; eg, selecting random visits produced risk estimates of 2.1 and 2.9 deaths (/100/week) among exposed and unexposed, respectively. In scenarios simulating protective ($RR = 1/3$) or harmful ($RR = 3$) effects, random selection also produced biased estimates, whereas strategies 1-3 remained unbiased.

Conclusions: Selection approaches that are naive to data after index produced unbiased estimates. Evidence that randomly selecting among eligible index opportunities may induce substantial bias suggests further evaluation of cohort selection methods under a range of scenarios is needed.

367 | Implementation of the trend-in-trend study design in a setting with cross-over of preferred treatment choice: An example of second-line antidiabetics

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Background: The trend-in-trend design has been proposed to deal with unmeasured confounding when comparing treated with untreated in the presence of strong calendar time trends. While it might be possible to extend this design to active comparators, it has never before been implemented in this setting.

Objectives: To apply the trend-in-trend design to compare two second-line antidiabetic treatments, thiazolidinediones (TZD) and dipeptidyl peptidase-4 inhibitors (DPP-4i) with respect to risk for congestive heart failure (CHF), ie, in a setting where we know that TZDs lead to a higher risk than DPP-4i.

Methods: Using Medicare claims data 2007-15, we identified 65+-year-old enrollees with 1-year baseline of continuous enrollment, one or more metformin (1st line antidiabetic agent) and no TZD or DPP-4i prescription. We first implemented two separate comparisons: new use of TZD vs none and new use of DPP-4i vs none. For each new user, 9 never users were sampled from all patients with at least the same duration of enrollment without replacement. We used baseline covariates to predict the cumulative incidence of exposure (CPE). We then modeled the number of outcomes as a function of the prevalence of the treatment in each calendar quarter following the index date, stratified by CPE quintiles, using logistic regression.

Results: In the TZD vs none comparison, we identified 38 022 TZD and 332 918 never users. Mean age was 74 for TZD initiators and 75 for never users. TZD users were more likely to develop CHF than non-users (odds ratio, OR: 1.46 (95% confidence interval (CI): 1.45-1.47)). Excluding patients with baseline codes for CHF changed the OR to 0.76 (CI: 0.31-1.89), however. For DPP-4i, we identified 105 232 DPP-4i

initiators and 623 512 never users. Mean age was higher for DPP-4i vs never users (75 vs 74). DPP-4i was associated with a slightly lower CHF risk (OR: 0.76 (CI: 0.31-1.89)). Excluding patients with baseline codes for CHF did not substantially change the OR.

Conclusions: The implementation of the trend-in-trend design in comparative effectiveness research is not straight forward. Treatment effect estimates were imprecise and varied depending on the definition of the cohort. The findings for DPP-4i comparison could have been biased by the time trend of the declining use of TZD over the study period.

368 | Effectiveness of prenatal Tdap in the prevention of infant pertussis in the USA

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Background: It is recommended that all pregnant women in the United States receive tetanus-diphtheria-acellular pertussis (Tdap) immunization to prevent infant pertussis. US recommendations state that immunization during any time of pregnancy is acceptable, although between 27 and 36 weeks was preferable.

Objectives: This study's objective was to examine the clinical effectiveness of prenatal Tdap, and whether effectiveness varies by gestational age at immunization.

Methods: A nationwide cohort study of pregnant women with deliveries in 2010-2014 and their infants was performed. Commercial insurance claims data were analyzed to identify Tdap receipt by the pregnant women, and hospitalizations and outpatient visits for pertussis in their infants until 18 months of age. Pertussis occurrence was compared between infants of mothers who received prenatal Tdap (overall, and stratified by gestational age at administration) and infants of unvaccinated mothers. The duration of protection was evaluated by stratifying the infant's follow-up 0-2, 0-6, and 6-18 months.

Results: There were 675 167 mother-infant pairs in the cohort. Among infants whose mothers received prenatal Tdap, the rate of pertussis was 42% lower (hazard ratio [HR] = 0.58, 95% CI: 0.38, 0.89) than infants whose mothers did not receive prenatal or postpartum Tdap; this reduction was consistent across pertussis definitions (HR for inpatient-only pertussis = 0.50, 95% CI: 0.23, 1.09). Pertussis rates were also lower for infants whose mothers received Tdap during the third trimester. Infants whose mothers received Tdap <27 weeks of gestation did not experience reductions in pertussis rates (HR for pertussis = 1.06, 95% CI: 0.53, 2.15). Protective associations were observed when considering only 0-2 and 0-6 months of follow-up in the infants. No association, positive or negative, was observed between 6 and 18 months of follow-up.

Conclusions: Infants of mothers who received prenatal Tdap experienced half the rate of pertussis as compared with infants of unimmunized mothers, and this reduction is most pronounced in the first few months of life, typically before the infant's recommended receipt of the infant pertussis vaccination series. These results do not provide evidence to support changing the currently recommended timing of Tdap administration in pregnancy.

369 | Advance system testing: feasibility of using a network of health data bases for vaccine safety studies

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Background: The Accelerated Development of Vaccine benefit-risk Collaboration in Europe (ADVANCE) public private collaboration, aims to develop and test a system for rapid benefit-risk monitoring of vaccines using health care databases in Europe.

Objectives: To test the feasibility of the ADVANCE system to generate incidence rates (IRs) of events of interest (EI) associated with whole cell (wP) and acellular- (aP) pertussis vaccines, in children prior to their pre-school-entry booster, using common protocol and analytics.

Methods: The study population were children aged 1 month to <6 years, during 2001-2016, in 5 primary care databases (ie, Italy (Pedianet), Spain (SIDIAP & BIFAP) and UK (THIN & RCGP)) and two Danish hospital databases (AUH & SSI). IR of injection site reactions (ISR), fever, somnolence, persistent crying, febrile or afebrile seizure/convulsion, hypotonic-hyporesponsive episode (HHE) were estimated both in outcome specific risk windows following wP and aP vaccines exposure and in non-risk (baseline) periods (presented below as overall IRs). A self-controlled case series design was used to estimate the dose specific Incidence Rate Ratio (IRR) between aP vs non-risk and

wP vs non-risk in each database, when wP data were available. Heterogeneity of individual database estimates were inspected, and results benchmarked where possible, random-effects meta-analyses were conducted for pooling of the IRR.

Results: In a study population of 5.9 Million the database specific overall (ie, risk and non-risk periods) IR per 1000 PY varied between 0.5 and 3.1 for ISR, 8.5-491.0 for fever, 0.01-0.44 for somnolence, 2.4-22.1 for persistent crying, 2.6-14.2 for febrile convulsion, and between 0.2 and 1.5 for HHE. IRs were similar within the primary care databases, but hospital-based databases could not estimate ISR, somnolence, and persistent crying. The IRR showed higher risks for wP compared with aP for febrile convulsions, fever, ISR, persistent crying, and somnolence for 1st dose, except for somnolence 2nd dose and febrile convulsions 3rd dose. The risk of HHE was higher following wP compared with aP. IRR and IR were consistent with available literature and expert feedback, except for IRR of HHE.

Conclusions: Within ADVANCE we demonstrated the feasibility of generating vaccine safety data in a public private collaboration of a distributed health care database network. This study was for system testing and not to inform regulatory/clinical decisions on pertussis vaccination

370 | Determining which of several concomitantly administered vaccines increase risk of an adverse event

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Background: Childhood immunization schedules involve multiple vaccinations per doctor visit. When increased risk of an adverse event is observed after a visit with concomitant (same day) vaccinations, it can be difficult to ascertain which vaccine(s) triggered the adverse event.

Objectives: We proposed a systematic process to evaluate which concomitantly administered vaccine(s) are most likely to have caused an observed increase in risk. We illustrated the process via simulation and applied it to evaluate risk of seizures the day after vaccination in a real cohort of vaccinated children.

Methods: The process involved univariate, multivariable, and stratified analyses followed by estimation of attributable risk. Each step used a self-controlled interval design with a defined risk (day 1) and reference window (days 15-56). The simulation retained the observed pattern of vaccination in the real cohort. We simulated "true" effects for diphtheria-tetanus-acellular pertussis (DTaP) and pneumococcal conjugate (PCV) vaccines on risk of seizure the day after vaccination. Simulated effects were either multiplicative, only present with joint exposure, or had negative multiplicative interaction. After applying the process

to simulated data, we evaluated risk of seizure 1 day after vaccination in the real cohort.

Results: Although we simulated elevated risk of seizure for only 2 vaccines in the schedule, analyses suggested that risk increased with the number of same day vaccinations ($p < 0.01$). Real cohort results paralleled simulated negative multiplicative interaction; estimated risk with co-administration was less than the product of estimates with separate administration. In real data, we narrowed the association with seizure 1 day post vaccination from all vaccines in the schedule to DTaP, PCV, and/or *Haemophilus influenzae* type B (HIB) ($p < 0.01$) but were not able to further disentangle these relationships in our data. When none of these three vaccines was administered, no elevation in risk was observed.

Conclusions: Most vaccines in early childhood are co-administered with other vaccines, making it challenging to pinpoint which are associated with adverse events. The process outlined in this paper could provide valuable information on the magnitude of potential risk from individual and concomitant vaccinations. Candidate vaccines identified in initial analyses should be further investigated with independent data as well as biologically based, statistically independent hypotheses.

371 | Epilepsy in children following pandemic influenza vaccination

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Background: Influenza vaccination has been associated with an increased risk of febrile seizures in children. There is a link between febrile seizures, particularly complex febrile seizures, and an increased risk of later epilepsy.

Objectives: To determine whether pandemic influenza vaccination was associated with increased risk of epilepsy in children.

Methods: Information from Norwegian registries from 2006 to 2014 on all children under 18 years living in Norway on October 1st, 2009 was used in Cox regression models to estimate hazard ratios (HR) for incident epilepsy after vaccination. Self-Controlled Case Series (SCCS) analysis was used to estimate incidence rate ratios in defined risk periods after pandemic vaccination.

Results: In Norway, the main period of the influenza H1N1 pandemic was from October to December 2009. On October 1st 2009, 1 154 113 children below 18 years of age were registered as residents in Norway. Of these, 572 875 (50.7%) were vaccinated against pandemic influenza. From October 2009 through 2014 there were 3628 new cases of epilepsy (incidence rate 6.09 per 10 000 person-years). The risk of epilepsy was not increased after vaccination: HR 1.07, 95% confidence interval (CI); 0.94-1.23. Results from the SCCS analysis supported the finding of no association between vaccination and subsequent epilepsy.

Conclusions: Pandemic influenza vaccination was not associated with increased risk of epilepsy. Concerns about pandemic vaccination causing epilepsy in children seem to be unwarranted.

372 | Risk factors of zoster vaccine failure among elderly in England

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Background: Herpes zoster (HZ) is a painful skin rash that occurs frequently in older adults and is caused by reactivation of latent varicella zoster virus. Since 2013, England offers zoster vaccination routinely to 70-year-olds and, as part of the catch-up, to 79-year-olds.

Objectives: To investigate 11 pre-identified potential risk factors for zoster vaccine failure.

Methods: This retrospective cohort study included subjects born in 1943-1946 (routine cohort) and in 1934-1937 (catch-up cohort) in England. We used the Clinical Practice Research Datalink (CPRD) and Hospital Episodes Statistics (HES) to identify HZ cases and the pre-identified risk factors. The risk factors were gender, age group, chronic obstructive pulmonary disease, immunocompromised, asthma, type 2 diabetes, smoking status, body mass index categories, ethnicity, co-administration with influenza vaccine and with pneumococcal vaccine. We estimated vaccine effectiveness (VE) for each risk group using a quasi-Poisson regression model including interactions between exposure status and the risk factors to estimate differential VE. Model simplification was performed using F-statistics at 5% significance level. The overall VE and relative increases/reductions were derived from the final model.

Results: The overall VE was 72.5% [95% CI: 67.7%-76.6%]. We identified 2 factors significantly associated with decreased vaccine protection while accounting for differences in HZ baseline risk by gender and other risk factors. Relative decrease in VE was 23.9% [95% CI: 14.2-36%) for type 2 diabetics to healthy subjects and was 20.6% (95%CI; 8.6-36.4%) for current smokers to never-smokers. Relative increase in VE of 24.8% [95%CI; 13.8-34.9%] was found for underweight to normal weight subjects.

Conclusions: Our study suggests that diabetics and current smokers are less protected by the current UK zoster vaccine compared with the general population, while persons with underweight may be better protected. Co-administration with influenza vaccine did not affect the vaccine protection. Contrary to the clinical trial results, age did not seem to affect VE. Further study is required to assess if alternative vaccinations strategies are warranted for the diabetic population, who seem to be least well protected.

373 | HPV vaccines and risk of thyroid disorders in young girls

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Background: A previous study on the risk of autoimmune diseases associated with Gardasil* and Cervarix* based on the French national health insurance reimbursement databases (SNDS) has reported an increased risk of thyroid disorders after Cervarix*. However, only cases of thyroiditis identified during hospitalization or long-term diseases (LTD) reports were considered.

Objectives: This study aims to further explore this signal, by including all incident cases of thyroid disorders, diagnosed either in hospital or outpatient care settings.

Methods: All girls aged 13 to 16 years between 2008 and 2012, covered by the general health insurance scheme, without history of autoimmune diseases, thyroid disorders or intensive thyroid follow-up were included. Thyroid disorders cases were defined by two consecutive refills of marker drugs (ATC: H03A, H03B), combined with at least a diagnosis marker (TSH, FT3 or FT4 tests and either thyroid autoantibodies testing or ultrasound, or ICD-10 thyroid disorder diagnosis (E05 or E06) during hospital stays or in LTD reports). Their incidence was compared between girls exposed to Gardasil or Cervarix vaccination and unexposed girls, using a Cox model using age as timescale, adjusted for inclusion year, geographic area, socio-economic indicators, health care use level and other immunizations.

Results: Among 2 166 961 girls (average age 13.5 yr), 37.3% received HPV vaccine (Gardasil* 93%, Cervarix* 7%) and 4558 thyroid disorders cases occurred during a mean follow-up of 21 months. Gardasil* was associated with a slight but significant increased risk of thyroid disorders (Hazard Ratio, HR: 1.12, CI95% 1.04-1.21), and Cervarix* with a non-significant increased risk (HR: 1.19, CI95% 0.93-1.51). The association with Gardasil* was no longer significant when censoring the first three months after vaccination (HR: 1.07, CI95% 0.99-1.16).

Conclusions: The risk of thyroid disorders appears slightly increased after HPV vaccination. However, censoring the first 3 months after vaccination suggests that this association may be explained by reverse causality, the use of health care system for the first thyroid-related symptoms leading to vaccination.

374 | Maternal use of atypical antipsychotics and gestational weight gain

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Background: Atypical antipsychotic (AAP) use during pregnancy has been increasing, leading to concerns over its metabolic effect. Although evidence suggests AAP treatment induces clinically relevant weight gain, limited data are available on the impact of maternal AAP use on gestational weight gain (GWG).

Objectives: To assess whether AAP continuation vs discontinuation during pregnancy is associated with increased GWG and whether pre-pregnancy body mass index (BMI) modifies the association.

Methods: We conducted a cohort study of pregnant women in Medicaid Analytic eXtract (MAX) files linked to Florida and Texas Birth Certificates (BC) in 2004-2010. The cohort consisted of women with a singleton live birth continuously enrolled from 90 days before conception. We identified pregnant women with ≥ 1 AAP prescription fills during the 90 days prior to the conception, and defined those with ≥ 3 prescription fills during pregnancy as continuers and those with no AAP fills as discontinuers. We measured GWG by subtracting pre-pregnancy weight from weight at delivery on the BC. To assess effect modification of pre-pregnancy BMI (under/normal weight: BMI < 25; overweight: $25 \leq \text{BMI} < 30$; obese: BMI ≥ 30), we fitted a generalized linear model with an interaction term between exposure and BMI categories after inverse probability of treatment weighting (IPTW). To estimate the difference in means of GWG between exposure groups in each BMI category, we fitted generalized linear models after IPTW using robust variance estimates.

Results: Among 88 235 eligible pregnancies, mothers continued AAPs during 377 pregnancies and discontinued AAPs during 812 pregnancies (mean GWG, 27.6 lbs vs 25.9 lbs). The effect of continuation on GWG was different across the BMI categories (P for interaction = 0.03). The crude difference in GWG between continuers vs discontinuers was -1.01 (-3.44, 1.43) lbs among under/normal weight mothers, 0.32 (-3.34, 3.98) lbs among overweight mothers and 1.68 (-2.00, 5.36) lbs among obese mothers. After IPTW, the difference was -1.96 (-4.82, 0.89) lbs among under/normal weight mothers, 0.67 (-3.31, 4.64) lbs among overweight mothers, and 5.62 (1.03, 10.21) lbs among obese mothers.

Conclusions: Our findings suggest that compared with discontinuation, continuing AAPs in pregnancy was associated with increased GWG among obese mothers, while the GWG was comparable between continuers and discontinuers among overweight and slightly decreased among under/normal weight mothers with a confidence interval that includes no difference.

375 | Maternal use of benzodiazepines and z-hypnotics during pregnancy and developmental outcomes in offspring at 5 years of age

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Background: The effects of prenatal exposure to benzodiazepine (BZD) and z-hypnotic on a child's developmental outcomes remain unresolved.

Objectives: To quantify i) time-varying effects of prenatal BZD/z-hypnotic exposure on child's motor and communication development, and attention-deficit/hyperactivity disorder (ADHD) traits by age 5 years; ii) the effect of co-exposure with opioids or antidepressants on these outcomes.

Methods: We used data from the Norwegian Mother and Child Cohort Study and the Medical Birth Registry of Norway, limited to women with depressive/anxiety disorders, sleeping or pain-related conditions. The windows of exposure to BZD/z-hypnotic were early, mid and late pregnancy. Child's motor and communication development, and ADHD traits were assessed via the "Ages and Stages Questionnaire" and the Conners' Parent Rating Scale-Revised, respectively. Mean scores were calculated and standardized. We fit general linear marginal structural models (MSM) to account for time-varying exposure and confounders (depressive/anxiety symptoms, co-medication), and censoring. We stratified the analyses by maternal underlying disorder.

Results: We included 36 086 children born to mothers with depressive/anxiety disorders (n = 4195), sleeping (n = 5260) or pain-related conditions (n = 26 631). There were 283 children prenatally exposed to BZD/z-hypnotics (0.8%). In the weighted analysis, children born to women with depressive/anxiety disorders who took BZD/z-hypnotic in late pregnancy had greater gross motor deficits (β : 0.77, 95% CI: 0.06, 1.49) compared with unexposed children. No such effect was observed in the sleeping (β : -0.00, 95% CI: -0.78, 0.78) and pain-related (β : -0.01, 95% CI: -0.65, 0.64) strata, or on the ADHD trait outcome. Prenatal co-exposure with an opioid or antidepressant did not pose any additional developmental risk on the offspring compared with sole BZD/z-hypnotic exposure.

Conclusions: Children born to women with depressive/anxiety disorders who took BZD/z-hypnotic late in pregnancy presented with greater gross motor deficits compared with the unexposed, but not to the extent that the motor delay was of clinical relevance. This association may be attributable to residual confounding by maternal psychiatric disease, and/or to a higher cumulative dose drug effect. There was no evidence for an association between prenatal BZD/z-hypnotics and risk for ADHD traits, or for an opioid or antidepressant co-exposure effect.

376 | Self-reported postnatal depressive symptom severity after treatment with antidepressants in pregnancy: A cross-sectional study in 12 European countries using the Edinburgh Postnatal Depression Scale

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Background: Whether antidepressant treatment lowers the risk of relapse of maternal depression during or after pregnancy remains an unanswered question.

Objectives: To quantify the association between antidepressant treatment in pregnancy and postnatal depressive symptoms as measured by the Edinburgh Postnatal Depression Scale (EPDS) and the inherent sub-dimensions of anhedonia, anxiety, and non-specific depressive symptoms.

Methods: We used data from the Multinational Medication Use in Pregnancy Study, a web-based study collecting data on more than 8000 pregnancies in 12 European countries via an electronic questionnaire. We limited the sample to mothers of children with less than 1 year of age at the time of questionnaire completion, who reported a psychiatric disorder in pregnancy (n = 173). The main outcome measure was severity of depressive symptoms, as measured by the main EPDS and the three sub-dimensions (z-scores). Antidepressant use in pregnancy constituted the exposure variables. We applied inverse probability of treatment weighting (IPTW) using the propensity score, and then multiplied the IPTW to the sampling weight. The new composite weight was applied to fit generalized linear models.

Results: One in two mothers with psychiatric disorders reported use of antidepressant in pregnancy (86/173). In the weighted model, mothers who had been medicated at any time during pregnancy (adjusted β : -0.34, 95% CI: -0.66, -0.02), or in two or three trimesters, displayed lower postnatal symptom severity compared with the nonmedicated counterpart, and particularly on the anxiety sub-dimension (adjusted β : -0.44, 95% CI: -0.84, -0.03). In the strata by time since childbirth, the association between antidepressant treatment in pregnancy and reduced postnatal depressive symptoms was only

evident in the earliest postnatal period (<25 weeks, adjusted β : -0.74 (-1.24, -0.24); ≥ 25 weeks, adjusted β : -0.03 (-0.44, 0.39)).

Conclusions: Although longitudinal studies are needed to confirm or refute this association, women treated with antidepressant during pregnancy were less likely to report postnatal depressive symptoms, particularly in the early postpartum period, compared with the nonmedicated counterpart. Women should be empowered to develop an evidence-based understanding of the benefits of antidepressant treatment in pregnancy, in order to optimize maternal-child health.

377 | Association of antidepressant continuation in pregnancy with maternal gestational weight gain and gestational diabetes

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Background: Every year, ~300 000 pregnant women in the United States use antidepressants. In non-pregnant women, antidepressant use is associated with weight gain and development of diabetes. Although there is some evidence for higher risk of gestational diabetes (GDM) associated with antidepressant use in pregnancy, most studies failed to account for maternal mental health, possibly leading to confounding by indication.

Objectives: To assess the association of antidepressant continuation into pregnancy with gestational weight gain and GDM among women using antidepressants in the 6 months before pregnancy.

Methods: We conducted a retrospective cohort study of singleton, live births from 2001 to 2014 to women enrolled in Kaiser Permanente Washington, an integrated health care delivery system. We categorized women with an antidepressant fill during pregnancy as exposed ($n = 1638$) and women without as unexposed ($n = 1211$). Data were obtained from electronic health plan databases and linked Washington state birth records. We calculated unadjusted incidence and means of our outcomes in exposed and unexposed women. Generalized estimating equations were used to calculate mean differences (MD), relative risks (RR) and 95% confidence intervals (CI), adjusted for demographics, health indicators, other medication use, mental health care utilization and psychiatric diagnoses. We also conducted analyses using inverse probability of treatment weighting to account for more detailed information about mental health care utilization and psychotropic medication use.

Results: Women had a mean age of 31 years and 86% were non-Hispanic white. Women who continued antidepressants in pregnancy gained approximately 30.5 lbs, as compared with 30.3 lbs in women who discontinued (adjusted MD 1.0 lbs, 95% CI -0.2 to 2.3). 17% of continuers had "inadequate" gestational weight gain, as compared with 18% of discontinuers (adjusted RR 1.00, 95% CI 0.86-1.17). 54% of continuers had "excessive" weight gain, as compared with 51% of discontinuers (adjusted RR 1.04, 95% CI 0.97-1.11). 9% of

continuers developed GDM, as compared with 7% of discontinuers (adjusted RR 1.12, 95% CI 0.86-1.46). Findings were similar after inverse probability of treatment weighting.

Conclusions: We observed no association between continued antidepressant use in pregnancy and gestational weight gain or GDM. Previously reported associations of antidepressant use with GDM may have been due to confounding by indication.

378 | Are associations between prenatal antidepressant exposure and toddler neurodevelopment mediated by gestational age at birth?

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Background: Prenatal selective serotonin reuptake inhibitor (SSRI) exposure has been associated with depressive and anxiety symptoms in childhood as well as reduced gestational age (GA) at birth; however no studies have examined GA as a potential mediator for neurodevelopmental outcomes in children, especially not while using a sibling design to control for shared unmeasured confounders.

Objectives: To estimate direct and indirect effects of prenatal SSRI exposure, using a sibling controlled study design.

Methods: We identified live singleton births in the Norwegian Mother and Child Cohort Study that were part of a sibling group of two or more, and which were present at 18 or 36-month follow-up. SSRI exposure was ascertained through self-report, and anxiety and depressive symptoms were measured using the Child Behavior Checklist (CBCL); GA was ascertained from birth registry linkage. Effect decomposition was used to quantify natural direct (NDE) and natural indirect (NIE) effects of SSRI exposure, adjusting for potential confounders. Effects were obtained by combining estimates from the outcome regression with a regression of the mediator on the exposure and confounders. Results are reported as mean differences in T-scores for exposed versus unexposed children, with 95% confidence intervals estimated via 500 bootstrapped samples, comparing results from the sibling analysis to those obtained without considering siblings.

Results: 21 998 children were present at 18 months follow-up, and 19 007 at 36 months, of which 197 were exposed to SSRIs. Mediation analysis at 18 months showed no association of SSRI on anxiety/depressive symptoms, either through GA [NIE 0.04(-0.03, 0.14)] or through other routes [NDE 0.48(-1.82, 2.40)]; sibling analysis showed a similarly minimal indirect effect [NIE 0.04 (-0.07, 0.18)], but a moderate direct effect [NDE 2.53 (-1.11, 8.12)]. We observed a similar pattern at 36 months follow-up.

Conclusions: Estimates of the direct effect of prenatal SSRI exposure differed substantially between cohort and sibling model approaches, suggesting a probable role of unmeasured shared confounding. All models consistently showed little to no effect of gestational age as a mediator, indicating that observed associations between prenatal SSRI

exposure and anxious/depressed symptoms in children are unlikely attributable to shortened gestational age. Confidence intervals were wide, and these findings should be replicated in a larger sample.

379 | Psychotropic polytherapy among publicly insured pregnant women in the United States

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Background: Psychotropic polytherapy is known to be common in the general population. However, both its frequency in pregnancy, a period when women try to avoid unnecessary medication exposure, and its potential association with adverse pregnancy outcomes are unknown.

Objectives: To explore patterns of use of psychotropic polytherapy in pregnancy and to document the prevalence of maternal and neonatal outcomes in pregnancies exposed to psychotropic polytherapy in a national cohort of publicly insured pregnant women in the United States.

Methods: We defined a cohort of 1 760 450 pregnancies ending in live birth among women enrolled in Medicaid from 3 months before the date of the last menstrual period through 1 month after delivery, between 2000 and 2013. We first described the use of anticonvulsants, antidepressants, antipsychotics, anxiolytics, benzodiazepines, other hypnotics, and stimulants during pregnancy. We then defined the frequency with which these medications were used in combination (ie, psychotropic polypharmacy) and trends in the use of polytherapy over time. We also evaluated the prevalence of preterm birth, small for gestational age, neonatal drug withdrawal, NICU admission, cesarean delivery, preeclampsia, and maternal end-organ injury in pregnancies exposed to psychotropic polypharmacy.

Results: A total of 135 670 (8%) of women took ≥ 1 psychotropic medications during the first trimester. Among those, 29% were exposed to ≥ 2 and 8% to ≥ 3 different psychotropic medication classes. The frequency of psychotropic polytherapy use increased from 1.7% of all pregnancies in 2000 to 3.4% in 2013. Antidepressants and benzodiazepines were the classes most frequently included in the polytherapy regimens. Psychotropic medication use tended to be slightly lower in late pregnancy except for Z-drugs, which was three times more common in late versus early pregnancy. The frequency of adverse pregnancy outcomes increased with co-exposure to increasing numbers of psychotropic medications. For example, the prevalence of NICU admission was 8.2% after pregnancies with monotherapy, and 9.9% and 15.9% with polytherapy involving 2 and 4 different medication classes, respectively.

Conclusions: The number of women using psychotropic polytherapy during pregnancy increased markedly over the past decade. Future studies should explore the impact of simultaneous exposure to multiple psychotropic medication classes, considering specific combinations and adjusting for specific indications and other potential confounders.

380 | Fluoroquinolone use and risk of aortic aneurysm and dissection: Nationwide cohort study in Sweden

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Background: Recent studies have raised concern that fluoroquinolone antibiotics may be associated with an increased risk of aortic aneurysm and dissection. Fluoroquinolones have non-antimicrobial properties that may jeopardize the integrity of the extracellular matrix of the vascular wall.

Objectives: To investigate if oral fluoroquinolone use is associated with increased risk of aortic aneurysm or dissection.

Methods: We conducted a nationwide historical cohort study in Sweden, 2006-2013, using linked register data on patient characteristics, filled prescriptions, and cases of aortic aneurysm or dissection. The cohort included 360 088 treatment episodes of fluoroquinolone use (78% ciprofloxacin) and propensity score-matched comparator episodes of amoxicillin use ($n = 360\,088$). The propensity score included a total of 47 covariates covering demographic information, medical history, prescription drug use, and health care utilization. Cox regression was used to estimate the hazard ratio for the primary outcome of a first diagnosis of aortic aneurysm or dissection, defined as admission to hospital or emergency department for, or death due to, aortic aneurysm or dissection, within a 60-day period from start of treatment.

Results: Within the 60-day risk period, the rate of aortic aneurysm or dissection was 1.2 cases per 1000 person-years among fluoroquinolone users and 0.7 cases per 1000 person-years among amoxicillin users. Fluoroquinolone use was associated with an increased risk of aortic aneurysm or dissection (hazard ratio 1.66; 95% CI, 1.12-2.46), with an estimated absolute difference of 82 (95% CI, 15-181) cases of aortic aneurysm or dissection per 1 million treatment episodes. In a secondary analysis, the hazard ratio for the association with fluoroquinolone use was 1.90 (95% CI, 1.22-2.96) for aortic aneurysm and 0.93 (95% CI, 0.38-2.29) for aortic dissection. Exploring the timing of events, 26 (41%) of the total 64 cases of aortic aneurysm that occurred among fluoroquinolone users were in the first 10 days from start of treatment; the hazard ratio for this period was 2.91 (95% CI, 1.37-6.22).

Conclusions: In this nationwide cohort, fluoroquinolone use was associated with an increased risk of aortic aneurysm or dissection. This association appeared to be largely driven by aortic aneurysm.

381 | Non-vitamin K antagonist oral anticoagulants and risk of liver injury

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Background: Non-vitamin K antagonist oral anticoagulants (NOACs) are relatively new drugs used for stroke prevention in non-valvular atrial fibrillation (NVAf). However, there are concerns that their use may be associated with hepatotoxic effects.

Objectives: To determine whether the use of NOACs is associated with an increased risk of serious liver injury compared with the use of vitamin K antagonists (VKAs) in NVAf patients with and without prior liver disease.

Methods: Using the administrative databases of the Canadian province of Quebec's health insurances, we conducted a cohort study among patients newly diagnosed with NVAf between January 2011 and December 2014. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of serious liver injury (defined as either a hospitalization or related death) were estimated using time-dependent Cox proportional hazards models, comparing current use of NOACs to current use of VKAs, separately among patients with or without prior liver disease. We conducted several sensitivity analyses, including stratification on disease risk score quintiles, adjustment for propensity score quintiles, marginal structural Cox proportional hazards model, and accounting for competing risk due to death.

Results: The cohort comprised 51 887 patients, including 3778 with prior liver disease. During 68 739 person-years of follow-up, 585 patients experienced a serious liver injury. Compared with current use of VKAs, current use of NOACs was not associated with an increased risk of serious liver injury in patients without prior liver disease (crude incidence rates, 3.9 versus 4.5 per 1000/year; adjusted HR, 0.99; 95% CI, 0.68-1.45) or with prior liver disease (crude incidence rates, 24.5 versus 44.8 per 1000/year; adjusted HR, 0.68; 95% CI, 0.33-1.37). The results remained consistent in sensitivity analyses.

Conclusions: Compared with VKAs, NOACs were not associated with an increased risk of serious liver injury irrespective of baseline liver status. Overall, these results provide reassurance regarding the hepatic safety of NOACs.

382 | Does comorbidity interact with acute myocardial infarction to increase mortality?

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Background: Comorbid diseases may increase the mortality of myocardial infarction (MI) patients directly or indirectly by modifying their treatment intensity.

Objectives: We examined whether comorbid diseases and MI interact with one another to increase mortality beyond their independent effects acting alone.

Methods: Using Danish medical databases, we conducted a nationwide cohort study of all patients diagnosed with MI between 1995 and 2013 ($n = 160\,360$) and a comparison cohort of persons without MI from the general population matched on age, sex, and comorbidities in the Charlson comorbidity index. The study outcome was time-to-death and the cohorts were followed from the MI/index date until death, emigration, 5 years of follow-up, or 31 December 2013, whichever came first. Standardized mortality rates with 95% confidence intervals (CIs) were computed using age and sex weights based on the inception MI cohort. The interaction was examined on the additive scale by calculating interaction contrasts, which measure the combined mortality effect of MI and comorbidity that cannot be explained by combining their individual effects. The follow-up period was stratified by the first 30 days, 31 days to 1 year, and >1-5 year after the index date. Analyses were repeated within strata of comorbidity levels (1, 2-3, 4+).

Results: 39% of patients were female, and the median age was 71 (IQR 60, 80) years. Among those with severe comorbidity (level 4+), the mortality rate per 1000 person-years within >1-5 years follow-up was 245 (95% CI 231, 259) for MI patients and 179 (95% CI 174, 184) for comparison cohort members, yielding a rate difference of 66. For patients without comorbidity, the corresponding mortality rates per 1000 person-years were 69 (95% CI 67, 71) in the MI and 50 (95% CI 49, 50) in the comparison cohorts (rate difference = 19). The interaction contrast was thus 47 (95% CI 32, 61), meaning that the interaction accounted for 19% (47/245) of the total mortality rate in MI patients with severe comorbidity. Similar patterns were seen for short-term mortality (30 days and 31-365 days) and for the less severe comorbidity categories.

Conclusions: Comorbidities interact with MI to increase mortality beyond that explained by MI and comorbidities acting alone. This finding highlights the prognostic importance of treating comorbidities in patients with MI.

383 | Risk factors for stroke and choice of oral anticoagulant in atrial fibrillation

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Background: Since 2010, several direct oral anticoagulants (DOACs) have been introduced as alternatives for warfarin for stroke prophylaxis in atrial fibrillation. Information is needed on their use in clinical practice.

Objectives: To study risk factors for stroke in patients initiating oral anticoagulants for atrial fibrillation in Norway and their association with receiving DOACs versus warfarin.

Methods: Individually linked data from the Norwegian Prescription Database and discharge codes from the Norwegian Patient Registry

were used to identify all patients naïve for oral anticoagulants since 2004 initiating treatment with warfarin, dabigatran, rivaroxaban or apixaban for atrial fibrillation from 2010 to 2015 in Norway. We describe temporal changes in their CHA₂DS₂-VAsC score (congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, ischemic stroke/transient ischemic attack/arterial thromboembolism, vascular disease [myocardial infarction, atherosclerosis or peripheral arterial disease], age 65-74, female sex). We used multiple logistic regression to identify CHA₂DS₂-VAsC risk factors associated with receiving DOACs versus warfarin in 2015.

Results: From 2010 to 2015, the yearly number of new oral anticoagulant users increased from 7588 to 13 344. All new users initiated warfarin in 2010, while 86% initiated a DOAC in 2015. The mean CHA₂DS₂-VAsC score decreased from 3.2 (SD 1.7) to 3.1 (SD 1.6) in the same period. Vascular disease (0.56 [0.49-0.63]), heart failure (OR 0.65 [95% CI 0.58-0.72]) and diabetes (0.83 [0.73-0.95]) decreased the odds of receiving DOACs instead of warfarin, and ischemic stroke/transient ischemic attack/arterial thromboembolism (1.31 [1.12-1.54]), age 65-74 (1.23 [1.06-1.43]) and female sex (1.22 [1.10-1.36]) increased it. Age ≥ 75 (reference age < 65) and hypertension had no impact.

Conclusions: The uptake of DOACs was rapid and spurred an increase in new users of oral anticoagulants for atrial fibrillation from 2010 to 2015 in Norway. The mean CHA₂DS₂-VAsC score did not change substantially during this period. Vascular disease, heart failure and diabetes were associated with initiation of warfarin; previous stroke, age 65-74 and female sex with initiation of DOACs.

384 | Effect of migraine on cardiovascular diseases

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Background: Migraine may play role in development of cardiovascular diseases (CVDs).

Objectives: To examine the risks of myocardial infarction, ischaemic stroke, haemorrhagic stroke, peripheral artery disease, venous thromboembolism, atrial fibrillation or flutter and heart failure in patients with migraine and in a general population comparison cohort.

Methods: Using Danish registries, we conducted a nationwide population based cohort study of all incident migraine patients diagnosed between 1995 and 2013 (n = 51 032) and a general population comparison cohort without a history of migraine (510 320) matched, 10 to 1, on age, sex and calendar year of migraine diagnosis (indexdate). All members of the study population were followed from the index date until the specific CVD event, death, emigration, or 30 November 2013, whichever came first, allowing a maximum of 19-year-long follow-up time. After an initial event, we continued to follow patients for subsequent other cardiovascular events. Using Cox proportional

hazards regression, we estimated the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of the CVDs, separately. The hazard ratios were controlled for age and sex by study design and adjusted for further comorbidities. Follow-up was stratified by 0-1, >1-5 and >5-19 years after the indexdate. In a sensitivity analysis, we included also the users of triptans or ergotamine, restricting the study period to 2004-2013, to identify patients in the primary health care sector.

Results: The median age at diagnosis of migraine was 35 (interquartile range 22-47) years, and 71% of the study population were women. After adjustment for the comorbidities, in the 0-19 year window, migraine was associated with myocardial infarction (aHR: 1.49, 95% CI: 1.36 -1.64), ischaemic stroke (2.26, 95% CI: 2.11-2.41), and haemorrhagic stroke (1.94, 95% CI: 1.68-2.23), as well as venous thromboembolism (1.59, 95% CI: 1.45-1.74) and atrial fibrillation or atrial flutter (1.25, 95% CI: 1.16 -1.36). We found no association with peripheral artery disease (1.12, 95% CI: 0.96-1.30) or heart failure (1.04, 95% CI: 0.93-1.16). In the sensitivity analysis, the aHRs in the 0-1 and >1-5 year period were attenuated compared with the corresponding results in the main analysis, and the associations in most cases disappeared.

Conclusions: In this study, migraine was associated with an increased risk of cardiovascular disease. This suggests that migraine should be considered a potent and persistent risk factor for most cardiovascular diseases.

385 | Long-term clinical outcomes following a myocardial infarction among the general population in England

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Background: Myocardial infarction (MI) is associated with high mortality and an increased risk of consequent cardiovascular (CV) events.

Objectives: To describe the incidence of a range of CV outcomes among MI patients in England up to 10 years after their MI and to identify characteristics predictive of these outcomes.

Methods: Patients from the Clinical Practice Research Datalink, linked to Hospital Episode Statistics and the Office for National Statistics death data, who had a diagnosis of MI, no history of intracranial haemorrhage and who survived > 14 days following the date of their index MI event were included. Time to all-cause death, CV death, MI recurrence (≥ 14 days after index) and ischaemic stroke (IS) was estimated using Kaplan-Meier (KM) methodology. Predictive factors were identified using Cox regression with backwards selection. The discriminative ability of the models was assessed using c-statistics.

Results: 37 333 patients were included; the majority were white (93%) men (63%), with a median age of 72 (IQR = 61-82). The KM probability of all-cause death at 10 years was 49% (95% confidence interval

[CI]:48-51) and CV death 25% (95%CI = 23-27). The probability of MI recurrence by 10 years was also high (24%, 95%CI = 23-25), whereas the IS risk was lower (7%, 95%CI = 6-7). The risk of all outcomes increased with age and was higher among individuals who had an MI before index (all $p < 0.001$). History of heart failure was the strongest clinical predictor of all-cause death, CV death and MI recurrence (HR = 1.73, 95%CI = 1.66-1.80; 2.19 [2.06-2.33]; 1.26 [1.18-1.35], respectively), and history of atrial fibrillation the strongest clinical predictor of IS (1.77 [1.50-2.08]). History of stroke/transient ischemic attack (TIA) was associated with an increased risk of all-cause death, CV death and IS (1.32 [1.25-1.37]; 1.45 [1.35-1.54]; 2.17 [1.85-2.50] respectively), but not with MI recurrence after adjustment for clinical/demographic factors. There was reasonable discriminative ability for all outcomes ($c = 0.74-0.80$) apart from MI recurrence ($c = 0.60$).

Conclusions: The estimated 10-year probability of death was high, and nearly 1 in 4 patients experienced an MI recurrence within 10 years. The association between history of stroke/TIA and death/IS underscores a high unmet need, as this is a population contraindicated for a number of antithrombotic medications. The use of data sources containing more in-depth cardiology variables should be considered in order to more accurately predict MI recurrence.

386 | Antidiabetic medication in pregnancy: An international drug utilization study

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Background: Type II diabetes mellitus and gestational diabetes (GDM) are becoming increasingly prevalent as the burden of the obesity epidemic grows worldwide. Consequently, the need for antidiabetic medication (ADM) use in pregnant woman has increased. While insulin has been the ADM of choice in pregnancy, in the last decade, oral hypoglycemic agents have been increasingly recommended. Data on current patterns of use and how they have changed over time are sparse.

Objectives: To assess the prevalence of different classes of ADM use in pregnancy from 2000 to 2015 in the Nordic countries and the United States.

Methods: Data sources included individually linked data from the nationwide health registers in Iceland (2003-2012), Norway (2006-2015), Denmark (2006-2012), Finland (2000-2014), Sweden (2006-2013), and US Medicaid Analytic eXtract (MAX; 2000-2013, public

insurance) and Truven Health MarketScan (2012-2015, private insurance) databases. The prevalence of ADM use in each country was calculated as the proportion of pregnancies in which women filled at least one prescription for an ADM in the 90 days before or within the three trimesters of pregnancy (T1-T3).

Results: A total of 5 666 942 pregnancies were included. ADM use remained stable in Sweden (1.1-1.3%) and in the US-MarketScan (5.2-5.4%), increased in Norway (1.3-2.1%), Denmark (1.4-2.0%), Iceland (1.6-3.2%), Finland (0.8-3.4%), and in US-MAX (2.3-3.9%). Overall, biguanide and sulfonylurea use increased, while insulin use varied by country over time by increasing (Sweden, Norway, Iceland, Finland), decreasing (US-MAX), or remaining constant (Denmark, US-MarketScan). In all countries, use of insulin increased from the period before pregnancy to T1 and continued to increase throughout pregnancy while use of biguanides decreased from T1 to T2. Insulin and sulfonylurea use increased in T3.

Conclusions: Insulin was the most common ADM used in pregnancy, and its preference for treatment of pre-gestational diabetes was demonstrated by an increase in use from before pregnancy to the first trimester. An increase in insulin and sulfonylureas use in the third trimester suggests a preference for these agents in the treatment of GDM. However, the prevalence and patterns of use of the classes of ADM differed between countries and over time. ADM class initiation and switching patterns in pregnancy will be further investigated.

387 | Clinical effectiveness of sitagliptin compared with sulphonylureas for type 2 diabetes

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Background: Comparative effectiveness of adding sitagliptin or sulphonylureas to metformin for type 2 diabetes from a glycaemic-target and treatment-change perspective has not been previously evaluated in the UK.

Objectives: To evaluate clinical effectiveness for sitagliptin vs sulphonylureas as add-on to metformin in adults with type 2 diabetes.

Methods: We identified individuals aged ≥ 18 with type 2 diabetes between 2007 and 2013 who had either sitagliptin or sulphonylureas added to metformin from The Health Improvement Network UK primary care database. We followed them for 30 months, till they left the practice, died or end of 2014. We used multivariable Cox regression to analyse the number of individuals initiated on sitagliptin vs sulphonylurea who 1) recorded an undesirable HbA1c of $>7.5\%$ and 2) underwent treatment-change (addition/replacement) with another anti-diabetic. We adjusted for demographics, comorbidities and prescribed medications at baseline.

Results: We identified 23 601 individuals: 19 477 on sulphonylureas and 4124 on sitagliptin. We found that individuals initiated on sitagliptin were slightly more likely than those on sulphonylureas to record an undesirable HbA1c $>7.5\%$ during follow-up (Hazard Ratio 1.11 95%CI 1.06-1.16). When analysis was restricted to those

individuals who were prescribed continuous prescriptions of either treatment and metformin (no greater than 60 day gaps between successive prescriptions), no significant difference was found in recording a HbA1c >7.5%. We found however, that those on sitagliptin were nearly twice as likely to have their treatment changed during this follow-up period (1.98 HR 95%CI 1.86-2.10). When this analysis was restricted to those with continuous prescriptions, estimates remained similar. Further analysis revealed that 66.4%(n = 1789) of those prescribed sitagliptin that recorded an undesirable HbA1c >7.5% and 83.7%(n = 10 446) of those on sulphonylureas had no treatment change introduced within 3 months of this recording. This was despite all national guidelines advocating change highlighting a significant inertia in UK clinical care.

Conclusions: Though sitagliptin users were only slightly more likely to record an undesirable HbA1c >7.5%, treatment change was nearly twice as likely. Analysis revealed a significant inertia in changing treatment following initiation of both treatments despite identification of poor glycaemic control. Inertia may be greater among those prescribed sulphonylureas and warrants further investigation.

388 | Hepatic safety of vildagliptin: Multi-database, non-interventional safety study

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Background: Vildagliptin is a DPP-4 inhibitor for type 2 diabetes treatment, available as single agent and fixed-dose combination with metformin. In response to an EMA request, vildagliptin safety outcomes including adverse hepatic events (AHEs) were assessed under real-world conditions.

Objectives: To assess if vildagliptin is associated with an increased risk of incident AHEs compared with other non-insulin antidiabetic drugs (NIADs).

Methods: This cohort study used data from 5 European electronic health care databases (DBs) from the UK (CPRD), Germany and France (IMS Disease Analyzer), Denmark (OPED) and Sweden (National Registers). Patients with type 2 diabetes aged ≥18 years with a NIAD prescription from Jan 2005-Jun 2014 were included. The date of first NIAD prescription in the study period defined the index date. Time-dependent exposure (vildagliptin vs other NIADs) was assigned. Patients with cancer, HIV/AIDS or insulin prior to index date were excluded. Patients were followed until the earliest of DB coverage end, transfer out of the DB, death, insulin prescribing, or AHE of interest, defined as "serious AHE" (eg, hepatic failure, cirrhosis, fibrosis, liver transplant) or "ALT/AST increase >3-times upper limit of normal (ULN) and bilirubin >2-times ULN" (only assessed in CPRD). Negative binomial regression was used to

estimate age-/sex- and fully adjusted incidence rate ratios (aIRRs) with 95% confidence intervals (CIs).

Results: Overall, 738 054 patients were included with 20 973 (2.8%) exposed to vildagliptin (mean follow-up: 1.4 years; 28 330 cumulative vildagliptin patient-years). DB-specific aIRRs for serious AHEs did not suggest an increased risk with vildagliptin (range of individual aIRRs: 0.29-0.55), with two data sources having an upper limit of the 95% CI < 1.0 (IMS Germany: 0.65; IMS France: 0.63). The aIRR for ALT/AST >3-times ULN together with bilirubin >2-times ULN was 0.72 (95% CI: 0.42-1.25).

Conclusions: Analyses from 5 European DBs do not show an increased risk of AHEs associated with vildagliptin compared with other NIADs. Due to the limited confounder adjustment, residual confounding may remain.

389 | Incretin-based drugs and the risk of cholangiocarcinoma among patients with type 2 diabetes

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Background: Dipeptidyl peptidase-4 inhibitors (DPP-4Is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are commonly prescribed antidiabetic drugs. Despite their favorable effects, there is some evidence that they may increase the risk of cholangiocarcinoma (CCA), a rare but fatal cancer. To date, no observational study has assessed this potential association in the real-world setting.

Objectives: To determine whether the use of DPP-4Is and GLP-1 RAs is associated with an increased risk of CCA among patients with type 2 diabetes.

Methods: Using the UK Clinical Practice Research Datalink, we identified a cohort of 149 730 patients newly treated with antidiabetic drugs between January 1, 2007 and June 30, 2016, followed until June 30, 2017. Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident CCA associated with use of DPP-4Is and GLP-1 RAs, separately, when compared with use of at least two antidiabetic drug classes, with exposures lagged by 1 year for latency purposes. Secondary analyses assessed whether the association varied by cumulative duration of use and time since initiation. Models were adjusted for age, sex, smoking status, body mass index, alcohol-related disorders, markers of diabetes severity, and comorbidity. Several sensitivity analyses were conducted to assess the robustness of the findings.

Results: During 572 848 person-years of follow-up, there were 85 incident CCA events (incidence rate: 14.8 per 100 000 per year). The use of DPP-4Is was associated with an over two-fold increased hazard of CCA, when compared with use of at least two antidiabetic drug classes (23.8 vs 12.1 per 100 000 per year, respectively; HR:

2.14, 95% CI: 1.18-3.87). HRs increased with longer durations of use, reaching a peak after 1 to 2 years of use (HR: 2.66, 95% CI: 1.22-5.79), and decreasing after more than 2 years of use (HR: 1.42, 95% CI: 0.57-3.57). A similar pattern was observed with time since initiation. The use of GLP-1 RAs generated an elevated association with a wide confidence interval (HR: 2.20, 95% CI: 0.81-6.02). The low number of GLP-1 RA exposed events precluded from assessing possible duration-response relationships. Overall, these findings remained consistent in sensitivity analyses.

Conclusions: The results of this large population-based study indicate that the use of DPP-4Is, and possibly GLP-1 RAs, may be associated with an increased risk of CCA among patients with type 2 diabetes.

390 | Time to treatment intensification in patients on dual pharmacotherapy for type 2 diabetes

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Background: Based on available evidence, it is not clear whether adding a DPP4 inhibitor (DPP4i) to metformin (MET) monotherapy, rather than other second-line non-insulin antidiabetics, can delay the time to further treatment intensification (TI) in patients with type 2 diabetes.

Objectives: To investigate the association between TI and the use of DPP4i vs sulfonylurea (SU) as second-line therapy for type 2 diabetes.

Methods: Administrative data from the Tuscany region in Italy (3.5 million inhabitants) were used. Patients receiving a DPP4i or a SU between 2008 and 2015 were selected. The first dispensing of DPP4i or SU was the index date. At index date patients had to be ≥ 18 years old, have ≥ 1 year of look-back into the database, be already on MET monotherapy since ≥ 60 days, be persistent to MET (no treatment gap ≥ 90 days), have not taken any other antidiabetic drug before. The study cohort was followed up to 31st, December 2016, the occurrence of censoring events (discontinuation of MET, DPP4i or SU, switch, cancer, death, end of data) or TI (insulin use or add-on of a

3rd non-insulin hypoglycaemic), whichever occurred first. Patients experiencing TI within 180 days from index date were censored (primary treatment failure). Patients initiating DPP4i were matched 1:1 to SU initiators by sex, age band and year of index date. The Hazard Ratio (HR) with 95 confidence interval (95CI) of TI occurrence in patients treated with MET + DPP4i vs MET + SU was estimated with a Cox regression model. Matching covariates and MET treatment duration at index date were included into the model.

Results: The matched cohort included 2281 patients in each treatment group. Patients on MET + SU were more frequently censored because of discontinuation of MET (21% vs 13%) or index drug (47% vs 30%). Median and interquartile range (IQ) of follow-up time in years was 1.5 (0.5-3.1) for MET + iDPP4 and 0.5 (0.3-1.6) for MET + SU. The primary outcome occurred in 250 patients in the MET + iDPP4 group and in 119 patients within the MET + SU. Adjusted HR for TI in patients exposed to MET + iDPP4 vs MET + SU was 1.1 (95CI 0.8-1.3).

Conclusions: The analysis of the administrative database of Tuscany showed no difference in time to TI in patients treated with DPP4i + MET vs SU + MET. Higher treatment discontinuation observed in MET + SU had an important impact on the results observed. Sensitivity analysis incorporating determinants of discontinuation, such as socioeconomic status, use of diabetes-specific specialist care and comorbidities, will provide further insight into this finding.

391 | Risk of uroseptic hospitalizations among patients initiating sodium-glucose co-transporter 2 inhibitors: A retrospective cohort study

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Background: Although clinical trials for Sodium-Glucose co-Transporter 2 inhibitors (SGLT2) did not show an elevated risk of life-threatening Urinary Tract Infections (UTIs), the FDA revised the labels for SGLT2 products in 2015 citing several spontaneous post-marketing reports of urosepsis among patients using SGLT2 medications.

Objectives: To compare the risk of uroseptic hospitalizations for patients with type 2 diabetes mellitus (DM) who were prescribed an SGLT2 inhibitor compared with Dipeptidyl peptidase-4 (DPP-4) inhibitors.

Methods: Within 2 commercial insurance data (Optum and MarketScan; Mar 2013-Sep 2015), a 1:1 propensity score matched cohort of patients initiating an SGLT2 inhibitor or a DPP-4 inhibitor was created, where cohort membership required evidence of type 2 DM and age ≥ 18 at the time of drug initiation. The propensity score was constructed using 84 variables, which included surrogates for diabetes severity, risk-factors for UTIs, and other sociodemographic variables. A uroseptic hospitalization was defined as a hospitalization with evidence of both sepsis and an UTI. Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) were estimated for SGLT2 inhibitors versus DPP-4 inhibitors. Results were pooled using meta-analysis.

Results: The 1:1 PS matched cohort was comprised of 139 174 initiators of either an SGLT2 or DPP4 inhibitor. Baseline covariates were well balanced after matching with no standardized difference greater than 10% (mean [SD], age 55 [10]; 55% male). Patients in the SGLT2 group were followed up for a mean of 201 days and had 40 uroseptic hospitalizations corresponding to an incidence of 1.1 cases per 1000 person-years; while the DPP-4 group was followed for a mean of 194 days and had 50 uroseptic hospitalizations corresponding to an incidence of 1.3 cases per 1000 person-years. The adjusted HR for urosepsis among SGLT2 initiators was 0.77 (95% CI, 0.50,1.12).

Conclusions: In a large cohort study, SGLT2 inhibitor use appeared not to be associated with an increase in the risk of uroseptic hospitalizations when compared with a comparable class of anti-diabetic medication.

392 | Estimating the optimal duration of initial opioid analgesic prescriptions in post-surgical populations using FDA's sentinel distributed database

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Background: The US Food and Drug Administration (FDA) has identified prevention of new opioid addiction as a primary goal of the agency for 2018. As part of this strategy, limits on prescribing for acute pain have been proposed, necessitating evidence generation to inform policy.

Objectives: To estimate opioid requirements among opioid-naïve adults in the context of post-surgical pain for 14 common surgical procedures in the FDA's Sentinel Distributed Database (SDD).

Methods: Data from October 5, 2009 to October 5, 2014 from 15 health plans contributing to the SDD were included. We identified patients who filled an opioid prescription of ≤ 30 days duration within 7 days of any of 14 common surgical procedures. Patients were required to be ≥ 18 years of age, with no prior opioid use, surgery, cancer, or substance abuse in the 183 days preceding the index dispensing. Patients were followed for the duration of their index opioid dispensing, plus a 14-day extension period. Patients filling any opioid during follow-up were considered to have "refilled." Descriptive statistics concerning the days supply, number of tablets dispensed, and morphine milligram equivalents (MME) of index dispensings were generated. A generalized additive logistic model (GAM) was used to estimate the probability of refill (PR) as a smooth function of days supply of the index dispensing. This model was used to estimate the number of treatment days required for each condition using a PR threshold of 20%, a threshold consistent with emerging surgical guidelines.

Results: Among opioid initiators identified, cesarean section ($n = 291\ 566$), tooth extraction ($n = 217\ 598$) and laparoscopic cholecystectomy ($n = 131\ 371$) were the most frequent preceding

surgeries. The median initial days, tablets and MME supplied across all 14 surgeries ranged from 3 to 7 days, 20 to 60 tablets, and 113 to 450 MME. Between 9% and 55% of patients refilled following their initial dispensing, with the highest proportions among knee arthroplasty (55%), hip fracture repair (41%) and hip replacement (32%) patients. GAM analysis identified 7 surgical conditions for which 1 day of opioids was sufficient to attain a PR $< 20\%$, 2 conditions where 10 days might be sufficient, and 5 conditions potentially requiring 30+ days.

Conclusions: Varying opioid requirements across post-surgical populations are important to consider when developing regulatory policies that promote adequate treatment of pain while minimizing leftover medications.

393 | Prescription opioid use and concurrent psychotropic drug use during pregnancy: A population-based retrospective cohort study utilizing linked administrative data

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Background: It is important to investigate the use of prescription opioids during pregnancy to gain insight into the potential impact of maternal opioid exposure during pregnancy on children.

Objectives: The objective of this study was to determine the prevalence of prescription opioid use and concurrent psychotropic drug use in a large, Canadian population-based cohort of pregnant women.

Methods: Using population-level linked administrative data from a universal health care system, this study included all women with a live birth in Manitoba from 1996 to 2014. Dispensing of opioids was determined from prescription drug claim data. Patterns of prescription opioids dispensed to pregnant women were investigated by demographic characteristics, region of residence, and socioeconomic status. Concurrent psychotropic therapies were also measured.

Results: In a large population level sample of pregnancies ($N = 245\ 784$), 2.43% of pregnancies were exposed to 2+ dispensations of opioids. An additional 4.95% of pregnancies recorded at a single opioid dispensation. Compared with women who were not dispensed any opioid prescriptions, the proportion of opioid exposed pregnancies who were also prescribed anti-depressants (SSRI/SNRI) was sevenfold higher (22.5% vs 3.05%). The same pattern was found for anxiolytics (37.2% vs 1.5%) and antipsychotics (3.5% vs 0.34%).

Conclusions: High proportions of women were dispensed opioids during pregnancy. Further research should be done on the short term and long term effects of these medications on infants and children. Moreover, these results highlight the need for further investigation into the effects of exposure to multiple psychotropic drugs on the developing fetus.

394 | Identifying off-label pharmaceutical company promotion of opioids for cancer pain management

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Background: State and federal governments have sued manufacturers of fentanyl-based products for engaging in fraudulent marketing activities aimed at increasing sales for non-cancer indications. Such off-label promotion has contributed to opioid addiction, morbidity and mortality.

Objectives: To identify trends in potential off-label promotion and utilization of opioid agonists with indications restricted to the management of breakthrough cancer pain in adults: fentanyl sublingual spray (Subsys[®]), fentanyl buccal tablet (Fentora[®]), fentanyl sublingual tablet (Abstral[®]) and fentanyl nasal spray (Lazanda[®]).

Methods: We used General Payments files (2013-2016) from the Centers for Medicare and Medicaid (CMS) Open Payments Database and Part D Prescriber files (2013-2015) from the CMS Medicare Providers Utilization and Payment Data. We identified health care providers who received a promotional payment or wrote prescriptions (≥ 11) for fentanyl-based products. Providers were categorized as oncologists or non-oncologists based on specialty/sub-specialty and specialties were further collapsed according to Healthcare Provider Taxonomy codes. Descriptive statistics were used to assess payment patterns and utilization trends.

Results: Health care providers received a total of \$23 543 142 (114 573 payments), of which 15% was received by oncologists (\$3 543 831; 18 461 payments) and 85% was received by non-oncologists (\$19 999 311; 96 112 payments). A total of 34 713 Medicare Part D claims were filed, with oncologists writing 3% (970) of prescriptions and non-oncologists writing 97% (33 743) of prescriptions. Four specialties accounted for 76% of all promotional payments and 85% of all Medicare Part D claims—pain management specialists (\$10 553 598; 15 945 claims), physical medicine & rehabilitation (\$3 768 417; 5247 claims), primary care physicians (\$2 403 365; 4542 claims), and other service providers (\$1 606 417; 3785 claims).

Conclusions: Non-oncologists received a larger proportion of promotional payments and prescribed a greater amount of fentanyl-based cancer pain management products, indicating both off-label promotion and use. Although efforts to loosen restrictions on off-label promotion are mounting (eg, state legislation permits off-label communication with payers/providers), regulators and policymakers should reconsider such actions for opioids.

395 | Using trajectory models to assess effect of hydrocodone up-scheduling on chronic opioid users

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Background: In October 2014, the US Drug Enforcement Agency rescheduled hydrocodone combination products (HCP) further restricting their use under the Controlled Substances Act. While the policy change resulted in large declines in aggregate sales, it is unclear how it affected chronic users of the drug specifically its impact on the use of other opioids and non-opioid analgesics.

Objectives: To quantify the effect of hydrocodone's "upscheduling" on the use of opioid and non-opioid analgesics among chronic users of HCPs.

Methods: Using IQVIA LRx LifeLink anonymized pharmacy data between October 2013 and September 2015, we applied interrupted time series analysis and group-based trajectory modeling to characterize the effect of the schedule change on 316 731 long-term HCP users. The main measures were the number of prescriptions, patients, tablets and morphine milligram equivalent units of opioids, muscle relaxants, antidepressants, antipsychotics, and nonsteroidal anti-inflammatory drugs dispensed monthly. Multinomial logistic regression and difference-in-difference analyses were used to assess the relationship between patients' longitudinal response patterns to the policy change and key demographic and health care utilization characteristics.

Results: The schedule change was associated with significant declines in the number of opioid prescriptions (20.9%, from 421 798 to 333 627) dispensed and patients on opioids (11.4% from 307 974 to 272 804). Few patients (16%) used other opioid analgesics while three in four used non-opioid analgesics. Group-based trajectory modelling showed that longitudinal responses to the rescheduling was varied. Majority of the cohort continued to fill HCP prescriptions consistently; notably, 15.4% showed dramatic declines in HCP use and accounted for 64.7% of the total decline in opioid volume use. After the schedule change, the latter group received a higher proportion of their opioids from emergency care providers than the rest of the population (2.8% vs 1.2%). There were no substantive demographic differences between the group with significant declines in HCP use and the rest of the cohort. Up-scheduling of hydrocodone did not result in a shift in the choice of analgesics used.

Conclusions: Group-based trajectory modeling are useful at identifying differential effects of pharmaceutical policies. A small fraction of the population accounted for majority of the declines in opioid use with minimal changes in the use of non-opioid analgesics.

396 | Predictors of opioid tapering success

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Background: Reducing opioid use is a high priority; however, little is known about patient characteristics associated with tapering success

Objectives: To identify predictors of success among patients in a pharmacist-led opioid tapering program

Methods: We assembled a retrospective cohort of adult (>20 yrs) Kaiser Permanente Northwest (KPNW) patients using long-term, high-dose opioids referred to a pharmacist-led opioid tapering service between Feb 1, 2010 and Dec 31, 2016. Time zero was the first contact with the program; patients were required to have continuous membership and drug coverage during the baseline yr and during follow-up. The outcome was the % change in total dispensed morphine equivalents (DME) in the 6 months before time zero compared with the 6 months including and after time zero. Success was defined as (1) 25% reduction and (2) 50% reduction. Candidate predictors were identified a priori (allowing >20 events per variable) based on literature and clinician input and were measured at baseline using KPNW's electronic health record. Predictors included: age; sex; socioeconomic status; smoking; body mass index; DME; long acting opioids; psychotropic medication use; comorbid conditions (mental health, type of pain diagnosis); and health care utilization. Logistic regression was used to estimate the odds of successful tapering associated with each predictor, controlling for other characteristics; we used an alpha of 0.05

Results: We identified 1770 patients who were referred for tapering; 6% were excluded. Patient's average age was 56 yrs with 62% female. Patient's DME was stable at baseline (<8% change). After intervention 940 patients reduced by 25% and 455 by 50%. Patients with more types of prescribed medications at baseline were less likely to successfully taper by 25% (OR 0.96 for each additional med, 95% CI 0.94, 0.99), as were patients with higher baseline quartile of opioid dose (OR 0.84, 95% CI 0.76, 0.93) or who had a baseline pain assessment (0.67, 95% CI 0.51, 0.89). Patients using benzodiazepines were more likely to successfully taper by 50% (OR 1.30, 95% CI 1.00, 1.68) as were those with higher baseline quartile of opioid days supplied (OR 1.17, 95% CI 1.05, 1.31). Patients with anxiety (OR 0.75, 95% CI 0.57, 0.98) or with more unique medications (OR 0.96, 95% CI 0.93, 0.99) were less likely to taper by 50%

Conclusions: These unique data provide valuable insights into opioid tapering and may help in designing tapering interventions, including identifying patients who may require greater resource intensity (eg, mental health consult) to successfully taper

397 | Assessing association between cash payment and potential opioid misuse among patients on chronic opioid therapy

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Background: Prescription opioid misuse and overdose among patients on chronic opioid therapy (COT) has become a serious public health problem in the United States. State-run prescription drug monitoring programs (PDMP) were established or strengthened to monitor potential opioid misuse (POM). PDMP administrators and criminal investigators have cited cash payment as suggestive of POM but there is little evidence to substantiate this claim.

Objectives: To evaluate the association of cash payment with potential opioid misuse among patients on COT.

Methods: De-identified 2015 Rhode Island PDMP data which includes method of payment was used to conduct a cross-sectional study. The method of payment was categorized as no cash, cash only, or both (insurance with at least one cash payment). We defined COT as having received at least 90 days' supply during a 6-month period. A validated opioid misuse index that combines the number of prescribers and pharmacies used and days' supply of short-acting and long-acting opioids was used to define POM. A multivariable logistic regression model was used to examine the association between cash payment and POM, controlling for sex, age group, and type of opioid used. Because the pharmacy benefit design for many Medicare Part D drug plans includes a coverage gap where patients pay cash for a limited period of time the analysis was stratified by age group (patients under 65 years vs patients 65 and over).

Results: A total of 45 332 individuals (23%) met the inclusion criteria for COT, of which 80% paid for all of their opioid prescriptions with third party insurance exclusively, 3% used only cash, and 17% paid at least one opioid prescription in cash. The median age was 57 and 59% were female. Among patients under 65 years old those who had insurance coverage and paid for at least one of their opioid prescriptions in cash were more likely to exhibit a pattern of opioid filling suggestive of opioid misuse as compared with those who paid all opioid prescriptions insurance exclusively, after controlling for potential confounding variables (OR = 2.7; 95% CI: 2.5-2.9). Among patients aged ≥65 years, the association was stronger among women (OR = 3.0; 95% CI: 2.6-3.3) than men (OR = 2.3; 95% CI: 1.9-2.7).

Conclusions: While there may be legitimate reasons to pay for opioid prescriptions in cash, this study suggests that patients on COT who pay for some but not all opioid prescriptions in cash should raise special concerns for potential opioid misuse only when the patient has other health insurance coverage.

398 | Comparative safety and effectiveness of alendronate versus raloxifene in women with osteoporosis

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Background: Prevailing clinical wisdom favors the bisphosphonate alendronate over selective estrogen modulator receptors such as raloxifene as first-line pharmacologic therapy for osteoporosis treatment. However, comparative effectiveness evidence for osteoporosis drugs remain insufficient.

Objectives: To determine the comparative effect of alendronate versus raloxifene on fracture rates and select adverse events associated with long term bisphosphonate use.

Methods: Through the Observational Health Data Sciences and Informatics (OHDSI) community, we conduct an observational network study comprised of nine data sources that include electronic medical records and insurance claims. We compare osteoporotic women over 45 years who are new users of alendronate or raloxifene from 2001 to 2012 in regard to hip fracture, vertebral fracture, and several alendronate-associated adverse events (atypical femoral fracture, esophageal cancer, osteonecrosis of the jaw). We use propensity score stratified survival analysis to estimate comparative hazard ratios (HR). We additionally perform negative control experiments to control for residual unmeasured confounding.

Results: We identify over 320 000 eligible users of alendronate and raloxifene across 9 databases. Alendronate and raloxifene (reference) have similar hip fracture risk (HR 1.03, 95% CI: 0.94-1.13), but alendronate have slightly higher vertebral fracture risk (HR 1.07, 95% CI: 1.01-1.14). Among concerning alendronate adverse events, alendronate has higher risk for atypical femoral fractures (HR 1.51, 95% CI: 1.23-1.84) but similar risk for esophageal cancer (HR 0.95, 95% CI 0.53-1.70) and osteonecrosis of the jaw (HR 1.62, 95% CI 0.78-3.34). We demonstrate substantial control of measured confounding by propensity score adjustment, and low residual systematic bias through negative control experiments, lending credibility to our effect estimates.

Conclusions: In a retrospective, new-user comparative effectiveness study across nine data sources, we find that raloxifene users have a

similar hip fracture risk, slightly decreased vertebral fracture risk, and fewer adverse atypical femoral fractures as compared with alendronate users.

399 | The effect of oral bisphosphonates on acute kidney injury, gastrointestinal events and hypocalcaemia in patients with chronic kidney disease

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Background: Oral bisphosphonates (oBP) are contraindicated in patients with severe chronic kidney disease (CKD), but there is a lack of data on the safety in this area.

Objectives: To study the association between oBP use and risk of acute kidney injury (AKI), gastrointestinal events (GIE) and hypocalcaemia (HC) in patients with moderate-severe CKD.

Methods: Patients with stage 3B+ CKD (eGFR < 45) were identified in two primary care records databases from the United Kingdom (CPRD) and Spain (SIDIAP) linked to hospital inpatient data. Patients with CKD exposed to oBP were identified and matched to up to 5 patients from the same database using propensity score matching. Confounders included a priori defined variables: age, gender, concomitant diseases and medications. Missing data within covariates (creatinine (SIDIAP), BMI, alcohol use, and smoking) were imputed using multiple imputation. First AKI, GIE and HC events were identified for each patient as the outcomes of interest. Analyses were undertaken for each outcome and each database separately. Patients were censored at the event, death, end of study or database, or 210 days after the final prescription whichever came first. Cox regression models were used. Absolute rates were calculated per 10 000 person years.

Results: In CPRD there were 10 701 exposed patients matched to 42 489 unexposed patients. In SIDIAP the numbers were 4143 and 20 165. For AKI there were 1848 events in CPRD and 1456 in SIDIAP; HR (95% CIs) were 0.94 (0.82, 1.08) in CPRD and 1.08 (0.93, 1.25) in

SIDIAP with absolute event rates of 116.9, 113.2, 166.2 and 153.1 for exposed and unexposed in CPRD and SIDIAP respectively. This gave a pooled HR (95% CI) of 1.00 (0.91, 1.11). For GIE there were 891 events in CPRD and 178 events in SIDIAP, with HRs of 1.07 (0.87, 1.30) and 1.53 (1.01, 2.32) respectively with absolute event rates of 62.9, 53.3, 25.2 and 17.3. This gave a pooled HR (95% CI) of 1.14 (0.96, 1.37). Finally, 150 HC events were identified in CPRD, and 6 in SIDIAP; HRs were 0.82 (0.50, 1.34) in CPRD, but not calculated in SIDIAP due to low HC events. Absolute event rates were 8.9, 9.1, 1.4 and 0.5.

Conclusions: oBP use was not associated with increase the risk of AKI in patients with moderate-severe CKD in both datasets. A 50% excess risk of GIE is seen in one of the databases but not in the other. HC was extremely rare and not associated with oBP use.

400 | Risk of age-related macular degeneration and cataract surgery after initiation of denosumab versus zoledronic acid for osteoporosis: A multi-database cohort study

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Background: While ocular side effects have been reported after use of intravenous zoledronic acid (ZA), the risk of age-related macular degeneration (AMD) and cataract in patients using ZA or denosumab, a biologic drug for osteoporosis, is unknown.

Objectives: To evaluate comparative risk of age-related eye disease with denosumab versus ZA in osteoporosis patients.

Methods: We conducted a cohort study using the claims data from Optum Clinformatics™ Datamart (1/1/2010-9/30/2015) and Truven MarketScan (1/1/2010-6/30/2015). We identified individuals aged ≥50 years who had ≥1 diagnosis of osteoporosis. Incident users of denosumab or ZA were identified based on the first date of dispensing (ie, index date) of the study drug after 455 days of continuous enrollment. The primary outcomes were AMD and cataract surgery based on ICD-9-CM diagnosis codes and Current Procedure Terminology codes. Patients were followed from the index to the earliest event of the following: death, disenrollment, outcome occurrence, switching/discontinuing treatment, end of data, or 365th day of follow-up. To account for >50 baseline covariates including demographics, comorbidities, medications, and health care utilization, we performed 1:1 propensity score (PS) matching separately in each database. We calculated incidence rate (IR) and hazard ratio (HR) for each outcome in the PS-

matched cohort. Estimates from the two databases were combined with an inverse variance weighted fixed-effects model.

Results: After PS matching, there were 10 022 pairs of denosumab and ZA initiators from Optum and 28 074 pairs from MarketScan. Mean age was 71 in Optum and 68 in MarketScan. In Optum, the IR of AMD per 1000 person-years was 5.03 (95%CI 3.63-6.80) in the denosumab group and 4.71 (95%CI 3.46-6.28) in the ZA group. The IR of cataract surgery per 1000 person-years was 34.66 (95%CI 32.15-37.31) in the denosumab group and 38.54 (95%CI 36.12-41.08) in the ZA group. IRs of these outcomes were similar in the MarketScan cohort. The combined HR (95%CI) associated with denosumab use versus ZA was 1.09 (95%CI 0.87-1.37) for AMD and 0.90 (95%CI 0.82-0.98) for cataract surgery.

Conclusions: In this multi-database cohort of 76 192 osteoporosis patients, initiation of denosumab versus ZA was associated with a modestly decreased risk of cataract surgery but not with the risk of AMD.

401 | Oral bisphosphonate use and all-cause mortality in patients with advanced (stage IIIB+) chronic kidney disease: A propensity score analysis

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Background: Chronic kidney disease (CKD) is associated with a significantly increased risk of fractures and mortality. Bisphosphonates, which are highly effective in reducing osteoporotic fractures, have been associated with better survival. However, the risks and benefits of oral bisphosphonates (oBP) are unclear in patients with CKD especially in those with stage IV+.

Objectives: To study the association between oBP use and all-cause mortality in stage IIIB+ CKD.

Methods: A population-based cohort study including all subjects with an eGFR < 45/ml/min/1.73 m² aged 40 years or older, with at least 1 year of run-in data available. Previous and current users of anti-osteoporosis drugs other than oBP were excluded. *Setting* The SIDIAP (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) database linked to the Catalan Renal Registry (details on renal replacement therapy), and inpatient records. *Exposure* oBP prescriptions identified from pharmacy dispensations. oBP use was modelled as a time-varying exposure to avoid immortal time bias. Treatment episodes (in BP users) were created by concatenating prescriptions until patients switched or stopped

therapy (refill gap in prescriptions of 180+ days), or were censored (end of study or transfer out) or have died. A washout period of 180 days was added to (date of last prescription +180 days). **Main outcome** All-cause mortality. **STATISTICAL ANALYSES** Interactions with gender, previous fracture and CKD stage were tested for using multiplicative terms. Propensity scores (PS) were calculated using multivariable logistic regression modelling. Pre-specified predictors of mortality were included in the models. Cox regression models were used to perform adjustment for PS before and after PS trimming (at 5th and 95th percentiles) where 10% of subjects whose PS have little or no overlap were removed.

Results: Out of 86 127 non-users and 4146 oBP users, there were 36 513 (42%) and 1330 (32%) recorded deaths, respectively. There were no significant interactions between BP use and gender, history of previous fracture and CKD stage. Adjustment for PS hazard ratio (HR) for all-cause mortality in oBP users was 1.04 (95% CI 0.99–1.1). Adjustment for PS following PS trimming at the 5th and 95th percentiles was 0.95 (95% CI 0.89–1.01).

Conclusions: oBP use is not associated with mortality amongst patients with advanced CKD (stage IIIB+). More data is needed on the risks and benefits of oBP in CKD patients.

402 | Oral bisphosphonate use and latent class trajectories of kidney function: A cohort study

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Background: Oral bisphosphonates (BP) are cautioned or contraindicated in patients with moderate-severe chronic kidney disease (CKD) due to concerns regarding their effects on renal function. There is a scarcity of data on the existing trajectories of variation in estimated glomerular filtration rate (eGFR) over time.

Objectives: To identify clusters of patients with stage 3B+ CKD with different patterns of eGFR over 7 years; and to examine the association between the baseline BP use and the observed eGFR trajectories.

Methods: A cohort of 105 720 people were identified from UK primary care records (CPRD) aged 40+ with baseline (first available or most recent before BP initiation) eGFR < 45 ml/min/m². Patients with <2 eGFR measurements over 7 years or a prescription of anti-

osteoporosis therapy prior to baseline were excluded. Discrete time survival mixture analysis was used to identify clusters of patients with distinct kidney function trajectories over 7 years. This method addresses non-ignorable missing eGFR due to death. Bayesian information criterion and change in log-likelihood were used to select the optimal model. BP use was measured before ascertaining trajectories. Multinomial logistic regression was used to examine the association between the baseline BP use and the identified eGFR trajectories, adjusted for pre-identified baseline confounders.

Results: We identified six clusters representing different trajectories. Two clusters (C1, 2%, C2, 11%) experienced *improving* eGFR but with different accelerating rates (mean(SD) 6.08 ± 2.22 and 3.20 ± 1.60 per year, for C1 and C2 respectively). One (C3, 31%) had *gradually improving* eGFR (1.18 ± 1.32). Patients in C4 (35%) had either fluctuating eGFR, late-improving eGFR or stable stage 3B eGFR. 17% (C5) of patients had a (rapid) *declining* eGFR (−1.23 ± 1.59), and 4% (C6) had *persistent low* eGFR. When compared with C3, patients in the low or declining eGFR clusters (C4, C5 and C6) were more likely to have BP users, with adjusted relative risk ratios (95% CI) of 1.74 (1.60, 1.89), 3.03 (2.78, 3.32) and 3.08 (2.68, 3.55) respectively.

Conclusions: Six distinct trajectories of kidney function progression are identified in 3B+ CKD patients. BP use is almost twice as common in those with fluctuating/late-improving/stable CKD, and 3-fold more prevalent in those with more rapid decline in or persistently low eGFR. Further research is needed, including the validation of the identified clusters and the observed associations with BP use, in external datasets.

403 | Comparative cardiovascular safety of strontium ranelate and bisphosphonates amongst patients with no contraindications: A multi-database study in 5 EU countries by the EU-ADR Alliance

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Background: Newly identified risk of cardiovascular safety associated with the use of strontium ranelate (SR) have led to new contraindications and restricted use in May 2013 by the EMA/PRAC. We present the final results of the Post-Authorization safety Study (PASS) that was requested by the EMA.

Objectives: To evaluate the risk of thromboembolic events and the new risk of cardiac events among new users of SR and oral bisphosphonates (BP) without contra-indications for SR.

Methods: We conducted three multinational, multi-database (Aarhus Denmark, HSD Italy, IPCI Netherlands, SIDIAP Spain, and THIN UK), nested case-control studies. Within a cohort of new users of SR or BP who started index therapy before June 2013 and with no contraindications for SR use, we matched cases of 1) Acute myocardial infarction, AMI, and 2) Venous Thromboembolism, VTE, and 3) cardiovascular death, CVD, up to 10 controls on gender, year of birth, index date, and country. Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals (CIs) according to current vs past SR use, and current SR vs current BP use, adjusting for potential confounders, within each database. Data were pooled using (random effects) meta-analysis. VTE and CVD events were validated in all but Danish data.

Results: For VTE (5614 cases, 56 036 controls), an excess risk was found with current vs past SR use, with adjusted OR (aOR) of 1.30 [95%CI 1.04-1.62], and with current SR compared with current BP use: aOR 1.24 [0.96-1.61]. No excess risk of AMI (5477 cases, 54 674 controls) was found with neither current vs past SR (aOR 0.71 [0.56-0.91]) or current use of SR vs current BP: aOR 0.89 [0.70 to 1.12]. Finally, no increased risk of CVD (3019 cases, 29 871 controls) was seen with current vs past SR use (aOR 0.68 [0.48-0.96]), but risk was higher with current SR vs current BP use: aOR 1.35 [1.02-1.80].

Conclusions: This study found no evidence of an increased risk of AMI but a 25-30% excess risk of VTE in SR users without contra-indications. Despite no excess risk in the comparison of current vs past SR users, a 35% excess risk of CVD was observed when current SR and current BP users were compared. The latter disparity could be partially explained by cessation of such preventative therapies in end-of-life, or by residual confounding by indication.

Questions often remain concerning which patients may benefit most from therapy.

Objectives: To predict and quantify NCB distribution among patients indicated for a new oral antiplatelet drug, vorapaxar, using clinical trial and real-world data.

Methods: The study sample included patients indicated for vorapaxar with a prior myocardial infarction (MI) and no prior stroke, TIA, or severe bleeding, as identified in the Clinical Practice Research Datalink, linked to the Hospital Episode Statistics and Office of National Statistics databases. NCB components were defined as cardiovascular [CV] death excluding fatal bleed, non-fatal MI, non-fatal stroke and severe bleeds to avoid double counting of events. Risk prediction models were developed to estimate the baseline risk of each outcome for each patient over 3-years of follow-up. The drug's hazard ratios (HRs) relative to placebo, as observed in the pivotal RCT, were applied to baseline risk estimates to compute expected attributable risks, which were summed to estimate per-patient NCB. Sensitivity analyses assessed the potential effect of underestimating bleeding risk. NCB was described overall, by highest/lowest deciles of risk and age.

Results: The sample included 31 941 adults, median (IQR) age of 71 (60-81) yrs, 93% white and 64% male. Overall, the median (IQR) reduction in the 3-yr probability of key outcomes (NCB) was 4.3% (4.3-6.9%). Sensitivity analyses showed that 100% of patients would maintain a positive NCB if bleeding risk increased 12-fold. NCB remained favorable by subgroup, likely due to a high correlation of ischemic and bleeding risk (Spearman's rho = 0.82). The relative NCB was consistent for patients within the highest/lowest deciles of risk for each outcome, ranging from 9-12% to 2-3%, respectively (with non-overlapping CIs). NCB was greater for older vs younger patients (5.9% [5.9-8.5%] and 2.6% [2.6-3.2%] for ≥ 65 yrs, 7.2% [7.2-9.8%] and 3.1% [3.1-4.2%] for $\geq < 75$ yrs, respectively).

Conclusions: Individualizing benefits and risks can be used to predict the NCB of new drugs prior to market entry, providing greater assurance to regulators and other stakeholders of favorable benefits for products as used in routine clinical practice. Analyses may be limited by model discriminative ability and HR parameter estimate uncertainty.

404 | Use of real-world evidence in personalized benefit risk assessment: Closing the knowledge gap

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Background: As real-world experience with new drugs takes time to accumulate, little is known soon after launch about the anticipated net clinical benefit (NCB) of a drug as used in routine clinical practice.

405 | Quality of reporting on risk minimization evaluation studies: A systematic review

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Background: The RIMES Statement was recently introduced to improve the reporting on medicinal risk minimization evaluation studies. The statement describes topics that should be included in manuscripts that are categorized into four domains (key information, intervention design, implementation, and evaluation).

Objectives: To characterize the current standard of reporting in published scientific literature for risk minimization evaluation studies and to identify the key gaps in reporting standards.

Methods: Articles published between January 2012 and January 2017 were selected from three online databases (MEDLINE, Pubmed, Embase) to capture articles published after relevant regulatory guidances were issued in the United States and EU. Manuscripts were eligible if they were: (1) available in English, (2) included a regulatory-required risk communication intervention and (3) reported on the effectiveness of initiatives. Two reviewers examined a total of 1584 unique titles meeting search criteria. Of those, 73 abstracts and 35 full articles were reviewed.

Results: Seventeen articles meeting inclusion criteria were identified and reviewed. Many articles commented on key information such as study limitations ($n = 16$) and generalizability of results ($n = 10$); however, fewer addressed sustainability ($n = 5$). In terms of intervention design, most articles included the goals of the risk communication materials ($n = 16$), implementation dates ($n = 15$), the specific tools utilized ($n = 17$) and the tool content ($n = 16$). About half of the articles described how the materials were distributed ($n = 9$). Pretesting materials among stakeholders and piloting studies was described in 18% of articles ($n = 3$). One article described establishing success metrics *a priori*. Among the implementation domain, few studies assessed process metrics ($n = 2$), used a formal implementation protocol ($n = 1$), or described important modifications made to the intervention ($n = 1$). No articles described how intervention implementers were trained. Reporting of evaluation methods (ie, study goals, variables, and sources of data) was described in all articles ($n = 17$).

Conclusions: Most publications adhered to general recommendations of reporting scientific methods. Consistent reporting gaps included the lack of (1) formative pre-testing of messaging, (2) *a priori* definition of successful risk communication, and (3) implementation science considerations (ie, reach, adoption, and maintenance metrics) against which to assess effectiveness.

406 | Impact of schedule IV controlled substance classification on the use of carisoprodol in the United States

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Background: Carisoprodol is a skeletal muscle relaxant with considerable abuse potential. On January 11th, 2012, the Drug Enforcement Agency classified carisoprodol as a schedule IV controlled substance at the US federal level. It is unknown how the prescribing pattern of carisoprodol was affected by this policy.

Objectives: To quantify the effect of federal scheduling on the use of carisoprodol in a commercially insured population.

Methods: This quasi-experimental study included patients with musculoskeletal disorders in the Truven MarketScan Research Database between Dec 2009 and Feb 2014. We performed an interrupted time-series analysis to assess changes in proportions of patients who filled/newly filled carisoprodol each month 2 years before and after the scheduling using segmented linear regression. Results were stratified by whether a state had individually scheduled carisoprodol before the federal policy. As a reference, we examined the use of diazepam, which had schedule IV designation throughout the study period, to evaluate potential effects of other concurrent activities. For example, increasing mandates to review PDMPs for controlled substance prescription may affect prescribing independent of scheduling.

Results: A total of 13.3 million patients were included. Overall, 29 states with no scheduling prior to 2012 federal policy had lower levels of carisoprodol use compared with 16 states with scheduling before 2010 (50.5 vs 83.2 per 1000 patients). Among states adopting federal law, scheduling was associated with an immediate decline in use (level change: -1.5 per 1000 patients, $p < 0.08$; trend change: -0.2 per 1000 per month, $p < 0.01$). During the 1st, 2nd, 3rd, and 4th 6-month after implementation, the relative difference between observed and predicted (without policy) use was 9.3%, 11.6%, 11.3%, and 17.5%. Among states where carisoprodol was already scheduled, the federal policy also decreased the rate of use (level change: -0.4 per 1000 patients, $p < 0.7$; trend change: -0.4 per 1000 per month, $p < 0.01$). The relative difference between observed and predicted use was 2.1%, 3.8%, 9.8%, and 13.5% during the 4 6-month windows. Similar patterns were observed for incident use. Diazepam dispensing remained relatively stable during the study period.

Conclusions: Schedule IV controlled substance classification at the federal level was associated with a moderate decrease in the dispensing of carisoprodol, and this effect was stronger in states with no equivalent state law already in place.

407 | Impact of risk evaluation and mitigation strategies (REMS) on erythropoiesis stimulating agent use

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Background: In 2007, the US Congress authorized the Food and Drug Administration (FDA) to require REMS for drugs with known safety issues. These REMS can include elements to assure safe use (ETASU), such as person, place, and volume restrictions on dispensing, which are typically reserved for drugs with the most serious risks. Although FDA has frequently mandated ETASU REMS, little is known about their effects on drug use.

Objectives: To assess the impact of the ETASU REMS for the erythropoiesis stimulating agents (ESAs) darbepoetin alfa (Aranesp) and epoetin alfa (Epogen/Procrit), which were added several years after the drugs entered the market and instructed against use of the drugs in cancer patients with hemoglobin levels >10 g/dL.

Methods: Using a large commercial claims database with linked laboratory test results, we identified ESA-naïve adult cancer patients 12 months before and after imposition of the ETASU REMS. All patients were required to have continuous enrollment for at least 180 days before their index date—the first day of the month in which initiation occurred—and to have had at least two claims with International Classification of Diseases codes for cancer during this period. Outcomes of interest were initiation and inappropriate initiation, defined as initiation by patients who had linked hemoglobin test results all >10 g/dL in the prior month. Segmented regression models were used to estimate level and slope changes in monthly initiation per 1000 cancer patients following ETASU REMS implementation, and the proportion of initiation that was inappropriate pre- and post-ETASU REMS implementation was compared.

Results: We identified 2993 darbepoetin alfa initiators and 2178 epoetin alfa initiators. Segmented regression modeling yielded level changes of 8.9 (95% confidence interval [CI], 8.3–26.1) for darbepoetin alfa and 2.5 (95% CI, –6.9 to 11.8) for epoetin alfa. Small slope changes were observed: darbepoetin alfa (0.9 [95% CI, 1.5–3.3]), epoetin alfa (–1.6 [95% CI, –2.9 to 0.4]). Among the 155 (5%) darbepoetin alfa initiators and 156 (7%) epoetin alfa initiators for whom test results were available, we observed comparable proportions of inappropriate darbepoetin alfa initiation (0.60 vs 0.53, $p = 0.41$) and inappropriate epoetin alfa initiation (0.53 vs 0.54, $p = 0.88$) pre- and post-ETASU REMS implementation.

Conclusions: Imposition of the ETASU REMS for darbepoetin alfa and epoetin alfa did not have an appreciable impact on overall or inappropriate treatment initiation.

408 | Impact of risk minimisation measures on the use of strontium ranelate: A multi-national cohort study in 5 EU countries by the EU-ADR Alliance

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Background: In May 2013 and March 2014 the European Commission issued two decisions restricting the use of strontium ranelate (SR). These risk minimisation measures (RMM) introduced new contraindications and limited the indications of SR therapy. At the 32nd and 33rd ICPE we presented the interim findings of our study evaluating the effectiveness of these measures; we here report the final study results.

Objectives: To assess the impact of RMMs on SR utilization in three periods: Reference (01JAN2004–31MAY2013), Transition (01JUN2013–31MAR2014) and Assessment (from 01APR2014).

Methods: Design: Multi-national, multi-database cohort study Setting: Routinely collected electronic health care databases: 1 hospital discharge registry (Denmark) and 4 primary care registries (Italy, Spain, the Netherlands, UK). Exposure: In addition to the prior venous thromboembolism contraindication, RMMs included new contraindications (ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, uncontrolled hypertension) and restricted indications (initiation by experienced physician, not as first line anti-osteoporosis therapy, severe osteoporosis). Outcomes and statistical analyses: We conducted population (average monthly prevalence rates per year and annual incidence rates of SR use), prescription (prevalence of contra/indications) and treatment episode level analyses (1-year cessation probability).

Results: Follow-up time comprised more than 143 million person-years (PY) including 76 141 incident episodes of SR treatment. Average monthly prevalence rate of SR use dropped from 62.63/10 000 PY [95% CI: 62.37–62.89] in the Reference to 8.54 [8.45–8.62] in the Assessment period. Similarly, the incidence rate of SR use fell from 7.35/10 000 PY [7.35–7.35] to 0.22 [0.22–0.22] in the same two periods. The prevalence of any contraindication changed from 2.16% [2.06–2.27] to 1.75% [1.03–2.97] in incident SR prescriptions and decreased from 2.28% [2.24–2.31] to 1.61% [1.48–1.76] in prevalent SR prescriptions; the prevalence of restricted indications increased for both incident and prevalent SR prescriptions. The probability of therapy cessation after 1 year changed from 91.3% [91.0–91.5] to 93.6% [91.4–95.3].

Conclusions: These findings confirm a substantial impact of RMMs on SR utilization: SR use decreased overall, and the proportion of patients fulfilling the limited indications and lacking contraindications increased.

409 | FDA's risk evaluation and mitigation strategy (REMS) for transmucosal immediate release fentanyl (TIRFS)

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Background: Transmucosal Immediate Release Fentanyl (TIRFs) are powerful opioids approved by the US Food and Drug Administration (FDA) solely for breakthrough cancer pain in opioid tolerant patients. The FDA mandated a Risk Evaluation and Mitigation Strategy (REMS) for TIRFs in 2011 due to their potential non-medical use, yet the evolution and outcome of the REMS is unclear.

Objectives: To describe the evolution and outcome of the TIRF REMS, including its effectiveness in educating prescribers, pharmacists and patients regarding the appropriate use of these products.

Methods: Document analysis of sponsor and FDA materials obtained through the Freedom of Information Act (FOIA), including sponsor-

submitted assessments of the REMS at 6, 12, 24, 36, 48 and 60 months following TIRF market entry, as well as FDA feedback evaluating the submitted data, recommending REMS modifications and requesting additional data. Measures of interest included sponsor-administrated surveys assessing prescribers', pharmacists', and patients' knowledge of appropriate TIRF prescribing, dispensing, and utilization; analyses of administrative claims data to characterize the appropriateness of TIRF use; and changes to the REMS implementation or assessment over time. Data from 3812 pages of documents are being extracted by two reviewers and the preparation of summary tables for the outcomes of interest across time points is ongoing.

Results: Based on preliminary analyses, 4 years after market entry, 35.2% of prescribers (95% CI: 29.8-40.8) reported prescribing TIRFs for chronic non-cancer pain, while 49.2% of pharmacists (95% CI: 43.4-55.0) and 56.1% of patients (95% CI: 50.4-61.7) erroneously reported that TIRFs are indicated for chronic non-cancer pain. Similarly, at 4 years after market entry, 15.2% of prescribers (95% CI: 11.4-19.6), 14.6% of pharmacists (95% CI: 10.8-19.1) and 56.5% of patients (95% CI: 50.7-62.0) erroneously reported that TIRFs may be used to treat opioid non-tolerant patients. Also at 48 months, approximately one-half of TIRF recipients (49.0%) were opioid non-tolerant based on secondary claims analyses. Analyses of additional sponsor and FDA reports and assessments, including at other time points, are ongoing.

Conclusions: Our preliminary analyses provide an opportunity to assess the REMS program for an important group of opioids that have been associated with widespread non-medical use, addiction and overdose deaths.

410 | Prevalence of systemic sclerosis in Europe and North America: Reducing uncertainty for improving decision making

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Background: Estimations of disease burden often present large uncertainty, especially in cases of rare diseases and when limited evidence is available. As a consequence, decision-making predominantly relies on mean estimates. Poor decisions concerning resource allocation are possible if the likelihood for future information to change this current knowledge is not considered.

Objectives: Using prevalence of Systemic Sclerosis (SSC) as a case study, we illustrate how simulations can be used to support decision makers to judge how existing evidence may change when hypothetical future information becomes available.

Methods: We first conducted a systematic literature review of adult SSC prevalence for Europe and North America, and derived random-effect meta-analysis (MA) summary estimates. We then simulated 1000 hypothetical new prevalence studies of constant size n , and used the predictive distribution from the random-effect MA to capture the added uncertainty due to between-study heterogeneity. Updated prevalence distributions for each region were obtained by iterative

meta-analysis of the prevalence of existing studies with each newly simulated study.

Results: The random-effect meta-analysis prevalence was estimated to be 19.7 per 100 000 (95% confidence interval [95%CI]: 14.7-24.7) for Europe (8 studies) and 35.5 per 100 000 (95%CI: 29.2-44.8) for North America (5 studies). The simulated prevalence of hypothetical new studies could fall between 5.7 and 33.8 per 100 000 in Europe, and between 21.6 and 49.8 per 100 000 in North America, with 95% probability. The resulting updated mean prevalence was found to be between 16.8 and 19.3 per 100 000 in Europe, and between 33.6 and 37.5 per 100 000 in North America, with 95% probability.

Conclusions: Our simulations showed that the updated SSC prevalence for Europe is lower compared with estimates using observed information only. While less evidence is currently available for North America, estimates are more reliable. Simulations can support decision makers by adding knowledge about potential changes of future disease burden.

411 | Moderate and severe systemic lupus erythematosus is associated with greater health care utilization and costs: Analysis of the integrated optum claims data 2011-2015

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Background: Current insights regarding systemic lupus erythematosus (SLE) health care utilization and costs are based mostly on analyses conducted prior to 2011. We quantified health care utilization and costs for US patients with SLE stratified by disease severity.

Objectives: We aimed to quantify recent health care utilization and costs (stratified by disease severity) for US patients with SLE.

Methods: This study utilized integrated Optum administrative claims and electronic health record data of patients with SLE. SLE disease severity was determined using previously published claims-based algorithms. The outcomes examined include health care utilization for patients with SLE from 2011 to 2015, and health care costs for patients with SLE from 2012 to 2015. Analyses of costs were limited to patients enrolled in an Optum-participating health insurance plan for at least 1 year after the index date (the earliest diagnosis date observed in the database). All costs were converted to 2016 US \$.

Results: A total of 29 853 SLE patients were identified in the EHR data, of whom 525 had overlapping claims information. The study population was predominantly female (89.5%), white (68.9%), and middle-aged (mean: 48.5 years). From 2011 to 2015, an average of 13.7% of patients with SLE had ≥ 1 hospitalization annually, 94.4% had ≥ 1 outpatient encounter annually, 25.7% sought emergency care services annually, and 86.3% had ≥ 1 clinic or office visit annually. Average health care utilization was estimated at 1.7 hospitalizations, 2.5 emergency department visits, and 9.9 clinic visits annually. Almost one-fifth of patients (18.8%) used systemic

corticosteroids, 18.3% used antimalarial drugs, and 10.3% used immunosuppressants. Biologic treatment, rituximab or belimumab, was reported for <2% of patients each year. Total annual health care costs for patients with SLE were \$31 800. Increasing disease severity was associated with increased health care costs across all health service types. The total annual cost for severe SLE (\$52 951) was 2.6-fold greater than for mild SLE (\$20 337), and 1.8-fold greater than for moderate SLE (\$28 936).

Conclusions: Patients with SLE, especially those with moderate or severe disease, use considerably more health care services and incur greater costs relative to those with mild disease. SLE remains a significant driver of health care utilization and costs.

412 | Prediction of cardiovascular events in rheumatoid arthritis patients using a multibiomarker of disease activity

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Background: The ACC/AHA recommends preventive strategies for patients with a high predicted risk of atherosclerotic cardiovascular disease (CVD). RA patients are at higher risk for CVD events, yet the role of systemic inflammation and the influence of traditional CVD risk factors is unclear with respect to risk prediction in RA.

Objectives: A simple and accurate algorithm for predicting CVD event risk that includes systemic inflammation might help risk assessment for RA patients and optimize preventive care.

Methods: We derived a US cohort of RA patients with multi-biomarker disease activity (MBDA) test results linked to Medicare claims data. Patients had to have ≥ 1 year baseline with Medicare coverage prior to the first MBDA test. Exclusions were past MI, PCI/CABG, stroke, or cancer. Follow-up ended at the earliest of 1) CVD event; 2) other than CVD cause of death; 3) loss of coverage; or 4) 12/31/2014. The composite CVD event comprised of incident MI, stroke or fatal CVD event, using validated algorithms. MBDA scores were grouped as low (<30), moderate (30-44), and high (>44). Three separate models were developed using Cox regression. Model 1 included age, sex and race. Model 2 included age, sex, race, 9 comorbidities and CVD medication classes, plus interaction terms. Model 3 included age, sex, and race plus categorized MBDA score. We calculated the net reclassification index (NRI) for model 2 and 3 compared with model 1.

Results: A total of 15 757 RA patients were included; mean (SD) age 68.6(10.8) years, 80% female, 80% white. A total 209 CVD events occurred in 14 843 person years (1.41/100 py). The median (IQR) follow up time was 0.84 (0.41, 1.27) year. The maximum event time was at 2.7 years. All models had reasonable discrimination and calibration. The sum of the absolute difference between observed and predicted probability was 0.56, 0.57 and 0.33 for models 1, 2 and 3 respectively. Compared with model 1, model 2 resulted in a positive overall NRI of 0.214 (non-event NRI = 0.173, event NRI = 0.041); model 3 resulted in positive overall NRI of 0.279 (non-event NRI = 0.092, event NRI = 0.187), consistent with more accurate CVD event classification.

Conclusions: Preliminary results from this analysis suggest that a simple algorithm consisting only of age, sex and race plus a MBDA score can provide an accurate method to predict short term CVD risk in RA. Further validation with more extended time frames should improve the utility of this approach.

413 | Propensity score methods: The study of the effect of β -interferon and glatiramer acetate on multiple sclerosis disability

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Background: Multiple sclerosis (MS) is a lifelong disease characterized by a disability progression. The long-term effect of beta-interferon (β -IFN) and glatiramer acetate (GA) on disability remains unclear due to biased observational studies, despite the use of different methods to address indication bias.

Objectives: To explore main propensity score (PS) methods and their impact on the estimation of β -IFN and GA effect on disability progression in Relapsing-Remitting MS (RRMS).

Methods: This retrospective observational study is based on a series of patients from the Rennes MS expert center, France. All RRMS and disease-modifying therapies (DMT) naive patients were included at time of eligibility to β -IFN or GA drugs on the period 01/01/1993-31/12/2015. All patients starting β -IFN (Interferon beta-1b and interferon beta-1a) or GA drugs were included in the exposed group (N = 1328). After treatment start, patients were considered exposed until the end of the study. All DMT naive patients during the relapsing-remitting phase were unexposed (N = 870). The outcome was the need of an unilateral constant assistance to walk about 100 m (measured using the Expanded Disability Status Scale, score 6). Gender, age, MS duration, number of relapses in the last 3 years and period of inclusion were considered as potential baseline confounders. Four PS methods were studied to estimate the average treatment effect in the entire population (ATE) or average treatment effect on the treated (ATT): weighting, matching, stratification and matching with pairwise censoring. Treatment was studied as time-dependent covariate in a Cox model.

Results: Age and clinical characteristics at inclusion were statistically different between the two groups. Among exposed patients, 12% reached the outcome compared with 9% for unexposed ($p = 0.028$). Exposed patients had a mean follow-up duration longer than the one of unexposed (9.43 ± 5.36 vs 6.53 ± 6.02 , $p < 10^{-4}$). Hazard ratios differed according to the PS method used (1) for ATE: weighting: 0.95 [0.5; 1.5], stratification: 0.72 [0.5; 1.1] (2) for ATT: weighting: 0.80 [0.5; 1.2], stratification: 0.77 [0.5; 1.1], matching: 0.89 [0.5; 1.3], matching with pairwise censoring: 0.44 [0.3; 1.0].

Conclusions: Considering only one sub-question explored in the previous studies, we showed that different results could be obtained by

changing only the PS method, thus showing the importance of the choice of PS method to address indication bias.

414 | Herpes zoster in tofacitinib-treated rheumatoid arthritis patients according to concomitant glucocorticoid and methotrexate use

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Background: Tofacitinib is a new janus kinase (JAK) inhibitor and has been shown to increase the rate of herpes zoster (HZ) in patients with rheumatoid arthritis (RA).

Objectives: Based on findings from the tofacitinib clinical development program, we evaluated the potential interaction between tofacitinib, glucocorticoid (GC) use, and methotrexate (MTX) with respect to HZ risk.

Methods: Medicare (2010-2015) and MarketScan data (2010-2016) was used to identify RA patients who initiated tofacitinib, excluding patients with prior HZ or malignancy in a minimum 12-month baseline. Patients were characterized according to concomitant use of methotrexate (MTX), systemic GCs, both, or neither, and contributed exposure time to one or more of these four categories in a time-varying fashion. HZ was identified using ICD9/10 codes plus anti-viral drug use. Patients were censored at first HZ occurrence, cessation of tofacitinib, or 12/31/2016. Cox proportional hazards models were used to compare the age-sex adjusted hazard ratios (HRs) of HZ, comparing the 4 exposure groups.

Results: In MarketScan, 97 HZ events occurred in 2397 person-years in MarketScan (incidence rate = 4.0 per 100 py, 95% CI 3.3-4.9) and 79 events in 2117 patient-years in Medicare (IR = 3.7 per 100 py, 95%CI 3.0-4.7). In MarketScan, crude rates of HZ were highest in RA patients using GCs without MTX (5.8 per 100 py, 95%CI 4.2-8.1), followed by GCs with MTX (3.7 per 100 py, 95%CI 2.0-6.6) and were numerically lower in patients not receiving GCs but not different by MTX use (3.3 per 100 py, 95%CI 2.0-5.6 with MTX; 3.4 per 100 py, 95%CI 2.5-4.8 without MTX). The corresponding IRs in Medicare were 4.3 per 100 py (GC-MTX), 5.7 (GC + MTX), 2.5 (MTX-GC), and 3.2 (-MTX, -GC). After multivariable adjustment and referent to tofacitinib exposure without MTX or GCs, HZ rates were higher only in patients receiving GCs without MTX (HR = 1.66, p = 0.04, MarketScan; HR = 1.42, p = 0.17, Medicare), and GCs with MTX (HR = 1.99, p = 0.03, Medicare).

Conclusions: Absolute rates of HZ were increased in all tofacitinib users compared with historical rates among RA patients using biologics. Concomitant exposure to MTX did not increase HZ risk, but GC exposure did. Mitigating HZ risk among JAK users remains of high importance.

415 | Marginal structure modeling of association between disease activity and hospitalized infection among patients in a rheumatoid arthritis registry

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Background: Higher disease activity might be associated with a higher risk of developing infections among patients with rheumatoid arthritis (RA). However, this association may be confounded due to the effects of other RA treatments or comorbidities.

Objectives: To examine the association between RA disease activity and hospitalized infection using data from the US Corrona RA registry linked to Medicare claims data for outcome ascertainment.

Methods: Using CORRONA RA patients with Medicare coverage in 2006-2014, we identified eligible patients who had at least one visit with moderate disease activity based on the clinical disease activity index (CDAI between 10 and 22). Hospitalized infection was assessed in Medicare data. Follow-up started at the second Corrona visit and ended at the earliest date of: hospitalized infection, high disease activity (CDAI >22), loss to follow-up, or 12/31/2014. We calculated the incidence rate (IR) of hospitalized infection for patients in remission, low and moderate disease activity and hazard ratio (HR) of CDAI categories on hospitalized infection by controlling for time-dependent confounders using marginal structural models (MSM). Each observation was weighted using stabilized inverse-probability-of-treatment weights (IPTW), truncated at the 1st and 99th percentile.

Results: A total of 1618 RA patients were eligible for analysis. We identified 212 hospitalized infections over mean follow-up of 2.2 years. These patients had mean (SD) age of 69.0 (10.0) years and 77.2% were female. The crude IR of hospitalized infection was 4.0 per 100 person years for patients in remission, 7.1 for low disease activity and 7.5 for moderate disease activity. Using MSMs, and referent to being in remission, the HR of hospitalized infection associated with moderate disease activity was 1.19 (95% CI: 0.42-3.42) and for low disease activity was 0.78 (95% CI: 0.37-1.67). Baseline factors that were significantly associated with an increased risk for infection included older age, duration of RA, glucocorticoid use, and history of hospitalized infection.

Conclusions: The crude incidence of hospitalized infection was higher for patients in low or moderate disease activity compared with those in remission among RA patients. However, these differences were greatly attenuated after controlling for confounding using MSMs to account for the interplay of disease activity, RA treatments, treatment switching, and other potential confounders.

416 | Cognitive and other neuropsychological assessments documented in electronic health records prior to or at Alzheimer's disease diagnosis

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Background: Measurement and documentation of cognitive functioning are important to track cognitive decline and help achieve early detection and diagnosis of Alzheimer's disease (AD). Recommendations for the assessment process include recording the name of a suitable test and the patient's score, ideally into the electronic health record (EHR) so that cognitive status is available to all of the patient's health care providers.

Objectives: Our objective was to describe EHR documentation of cognitive assessments and results prior to the AD diagnosis in a large US sample of AD patients.

Methods: We conducted descriptive analyses of cognitive or neuropsychological measures documented in a US EHR database including 49 817 patients aged ≥ 50 y who received the AD diagnosis code between Jan 2012 and March 2016 in an integrated delivery network, with 5 years active history available. Cognitive test names and results were extracted by the database provider using natural language processing.

Results: In the 5 years prior to the coded AD diagnosis, 34.7% ($N = 17\,306$) of patients had documentation of cognitive assessment, with 25.9% ($n = 12\,925$) also having a result and test name recorded. Of the recorded cognitive tests, MMSE was most common (58.1%), followed by a recall test (48.6%), clock drawing (11.4%), Montreal Cognitive Assessment (MOCA, 10.9%), and SLUMS (8.6%), with other tests comprising $< 5\%$. The first provider to record the MMSE was about equally commonly primary care or neurologist, while MOCA was recorded most by neurologists and SLUMS most by primary care. The median time between the first cognitive measure and the first AD diagnosis code was 18.2 months (IQR 6.0–36.0 months). Analysis of the extracted results for first noted MMSE, MOCA or SLUMS showed that 95% were numeric values (median [IQR]: MMSE 23 [18–27]; MOCA 16 [12–20]; SLUMS 14 [9–19], and 5% were qualitative (eg, "normal"). Altogether, 98% of the extracted first cognitive test records were suitable for statistical analysis.

Conclusions: No cognitive or neuropsychological test data was noted in over 65% of medical records prior to the coded AD diagnosis. These real-world data indicate gaps in the assessment and documentation of cognitive impairment, which should be addressed to improve early detection of AD.

417 | Improving claims-based frailty prediction in the medicare population using STOPPFrail drug criteria

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Background: Studies evaluating drug effectiveness and safety in older adults using claims data may be subject to unmeasured confounding by frailty. Faurot et al. developed a claims-based algorithm to predict dependency in activities of daily living (ADL), a proxy for frailty, in the 2006 Medicare Current Beneficiary Survey (MCBS). Recently, the STOPPFrail criteria were published identifying medications that are considered potentially inappropriate in individuals with limited life expectancy and/or severe functional or cognitive impairment. Adding data on STOPPFrail medications may improve frailty prediction in older adults.

Objectives: We evaluated the performance of the original Faurot algorithm for predicting ADL dependency in the 2009 MCBS cohort, and assessed improvements in model performance due to addition of STOPPFrail medications.

Methods: We identified community-dwelling respondents to the fall 2009 MCBS, who were 65+ years old, with Medicare Parts A and B coverage ($n = 5441$) and a subpopulation with continuous Part D coverage in the prior calendar year ($n = 2524$). The original model parameters were used to estimate the c-statistic for ADL dependency in the full cohort and Part D subcohort. Claims for lipid-lowering therapies, theophylline, and 2+ antidiabetic drugs in the 90 days prior to survey were assessed for the Part D subcohort and the c-statistic was recalculated. Lastly, we calculated net reclassification (NRI) and integrated discrimination improvement (IDI) indices to quantify improvements in classification of frail individuals using this medication data.

Results: The original Faurot model performed well in predicting ADL dependency in the 2009 full cohort and subcohort (c-statistics, full: 0.798, Part D: 0.786). Addition of the selected STOPPFrail medications increased the c-statistic to 0.808 in the Part D subcohort; only theophylline was inversely associated with ADL dependency in univariate analysis. The NRI indicated that 18.4% and 11.8% of those who did and did not report ADL dependency, respectively, were correctly reclassified by the model containing drug information (NRI: 0.067, $p = 0.024$). The difference in average predicted probabilities between those who did and did not report ADL dependency was larger for the new model than the original Faurot model (IDI: 0.019, $p = 0.002$).

Conclusions: Adding three STOPPFrail medication criteria to the Faurot ADL dependency model led to meaningful improvements in discrimination and classification of frail individuals.

418 | Anticholinergic safety in US nursing home residents with dementia: Risk of delirium and mortality

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Background: Anticholinergic drugs (ACDs) may increase the risk of delirium and mortality in older patients. Prior studies for ACDs and delirium in older patients did not account for important confounders, eg, cognitive function and functional status, or did not examine the high-risk population of institutionalized older patients with dementia.

Objectives: To investigate whether ACDs increase the risk of delirium and mortality in residents with dementia in skilled nursing facilities (SNFs) after adjusting for confounding by comorbidity and functional status.

Methods: We conducted a new user design cohort study using US Medicare and the Minimum Data Set (MDS) including all residents aged 65 in SNFs enrolled in Medicare Part D (7/2007-12/2013). We assembled a cohort of dementia patients defined as users of anti-dementia drugs [ADDs] (donepezil, galantamine, rivastigmine, and memantine). The exposure was new use of ACDs (e.g., mirtazapine, quetiapine, and risperidone). We further categorized ACD use by the anticholinergic risk scale (ARS) 1-2; and ARS >3. ARS is a categorically ranked list predicting the risk of anticholinergic adverse effects. Primary outcomes included 1) delirium defined using validated algorithms and 2) all cause death. We used Cox proportional hazard regression adjusted for socio-demographics, comorbidities, co-medications, cognitive function, and functional status.

Results: We identified 20 824 subjects with dementia (mean age 85 years old, 72% female). New users of ACDs (n = 5072, 24%) were more likely to have anxiety or depression but had better cognitive function. Incidence of delirium for nonusers, ARS 1-2, and ARS >3 were 75, 206, and 283 per 1000 person-years, respectively. During follow-up, 1052 patients died with mortality rates of 85, 223, and 493 per 1000 person-years, respectively. After confounding adjustment, hazard ratios (HRs) for delirium were 1.6 (95% CI, 1.3-1.9) for ARS 1-2 and 1.5 (95% CI, 0.94-2.23) for ARS >3. The adjusted HRs for mortality were 2.4 (95% CI, 2.0-2.8) for ARS 1-2 and 3.2 (95% CI, 2.4-4.3) for ARS >3.

Conclusions: ACDs were associated with a 1.5-3 fold increased risk of delirium and mortality among SNF residents with dementia treated with ADDs even after adjusting for cognitive and physical function. ACDs with ARS >3 were associated with a more pronounced increase in mortality but not delirium compared with ACDs with ARS 1-2. Clinicians should be aware of these risks when prescribing ACDs in institutionalized patients with dementia.

419 | Can treatments for hypertension be repurposed for the treatment of dementia?

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Background: Evidence suggests midlife hypertension can increase the risk of Alzheimer's disease and vascular dementia in late life. Also, some antihypertensive drugs have been proposed to have cognitive benefits, independent of hypertension.

Objectives: To systematically assess the major antihypertensive drugs as repurposing candidates for dementia.

Methods: We conducted a prospective cohort study using data from the UK Clinical Practice Research Datalink. All patients aged 40 and over who received a first prescription for an antihypertensive drug were extracted from the dataset (~940 000 patients). The drugs were then assessed using instrumental variable (IV) analysis, to address potential confounding by indication, with physicians' prescribing preference as a categorical instrument. Multivariable logistic regression analysis was also conducted to assess the extent of confounding. Beta-adrenoceptor blocking drugs were used as the control throughout and the outcomes tested were Alzheimer's disease, vascular dementia, other dementias and any dementia. For drugs with a suitable genetic proxy, we also performed a two-sample Mendelian randomization analysis with Alzheimer's disease as the outcome. This analysis used data from the UK Biobank to estimate the instrument-exposure association and the International Genomics of Alzheimer's Project to estimate the instrument-outcome association.

Results: Antihypertensive drugs had little effect on risk of Alzheimer's disease, vascular dementia, other dementias and any dementia. These results differ from existing studies—for example, the IV analysis estimated 2.2 per 1000 (95% CI: -3.6 to 8.1) fewer Alzheimer's disease cases among those receiving angiotensin-converting enzyme inhibitors—a much smaller reduction than previously reported. Comparison of our IV and multivariable logistic regression analyses indicates this is likely due to confounding in non-IV studies. For several of the drugs tested, Mendelian randomisation also showed little benefit in reducing risk of Alzheimer's disease, reflecting the results of the IV analysis using physicians' prescribing preference.

Conclusions: This study is the first to systematically assess all the major antihypertensive drugs in relation to dementia. The contrast with previous studies indicates further research into repurposing these treatments is required and highlights the need for additional evidence about the biological and potentially confounding mechanisms linking hypertension and dementia.

420 | Effect of bisphosphonates on nonvertebral fracture among older nursing home residents

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Background: Bisphosphonates and other osteoporosis medications reduce fracture occurrence in older community-dwelling adults. To date, no studies have examined whether bisphosphonates prevent fracture in frail, older nursing home (NH) residents.

Objectives: To evaluate the comparative effectiveness of bisphosphonates versus calcitonin for prevention of nonvertebral fractures in a retrospective cohort of NH residents.

Methods: We used a nationwide sample of 24 571 NH long-stay residents ≥ 65 yrs old who were not taking osteoporosis medications for at least 1 year between 2008 and 2009. New bisphosphonate and calcitonin use was assessed via Medicare Part D, nonvertebral fractures via Part A, and over 100 pretreatment covariates for confounding adjustment via Medicare claims, Minimum Data Set clinical assessment records, and NH facility data. Individuals were followed from the date of the new bisphosphonate or calcitonin dispensing until the first occurrence of nonvertebral fracture, death, Medicare disenrollment, or study end (2013). We used Cox proportional hazards and Fine and Gray competing risk regression models to compare nonvertebral fracture for bisphosphonate and calcitonin new users. Multiple complementary approaches were used to adjust for bias, including propensity score matching, inverse probability of treatment weighting (IPW), multiple imputation, and machine learning.

Results: Mean age of the cohort was 84 yrs (SD 8), 85% were female, and 55% had at least moderate functional impairment. 2036 residents (8.3%) had a nonvertebral fracture and 16 553 (67.4%) died over a mean follow-up of 2.5 years (SD 1.7). After propensity score matching, bisphosphonates were associated with a 9% reduced risk of fracture compared with calcitonin (hazard ratio [HR] 0.91, 95%CI 0.80-1.03). Results varied by method used to minimize bias (HRs ranging from 0.86 for IPW to 0.97 for Fine and Gray models after propensity score matching), and overall, suggested bisphosphonates did not impact or only slightly reduced fracture rates.

Conclusions: These findings suggest that bisphosphonates have, at best, a modest benefit for nonvertebral fracture prevention in NH residents. Multiple complementary approaches to minimize bias produced consistent results. The findings do not rule out the possibility that bisphosphonates prevent vertebral fractures in the NH setting.

421 | Medication appropriateness for elderly nursing home residents with a limited remaining life expectancy: Adjusting the START/STOPP criteria by means of a Delphi consensus study

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Background: Nursing home (NH) residents are generally (very) old and often use a large number of drugs. The Screening Tool to Alert to Right Treatment (START) and Screening Tool of Older Persons' Prescriptions (STOPP) are commonly used to assist physicians with appropriate prescribing, but may not be applicable for frail NH elderly with a limited remaining life expectancy (LRLE).

Objectives: The objective of this study is to adjust the current START/STOPP criteria to elderly NH patients with a LRLE (1.5-2 years).

Methods: This Delphi study was based on the 2015 START/STOPP criteria. Rounds using SurveyMonkey were sent to a panel consisting of 23 international pharmacists/pharmacologists, geriatricians, elderly care physicians, general practitioners and researchers with clinical and/or research expertise on the subject. START/STOPP medication was presented with the indication and treatment goal. The experts considered for each medication(group) whether they would start this and if not, whether they would stop it. They also provided comments. Consensus was defined as $\geq 70\%$ of the participants answering (very) (in)appropriate. Participants were also asked to offer suggestions for additions or adjustments. In subsequent rounds, the panel gave their opinion on criteria for which consensus had not yet been achieved.

Results: After three rounds, 30 START criteria were considered appropriate. Eleven of those criteria were adapted in subsequent rounds, eg, the medicine description and/or indication or treatment goal was changed. Eight criteria were considered inappropriate. Consensus was not achieved for three items. Participants also offered suggestions for alterations and additions to the STOPP criteria, which led to 14 new STOPP criteria and 11 adaptations.

Conclusions: Symptomatic treatment was considered as more appropriate, and preventive treatment as less appropriate. Medication became appropriate for more specific indications. The benefits of medication had to outweigh the risks, adverse effects and time-until-benefit in order to be regarded as appropriate.

For NH patients with a LRLE, preventive medication is regarded less appropriate whereas medication aimed at symptomatic treatment is more appropriate. Appropriate prescribing for these patients remains highly personalized, where the benefits have to be weighed against the risks. The results of this study will be used to develop adjusted START/STOPP criteria.

422 | Association between azathioprine use and risk of acute pancreatitis in pediatric inflammatory bowel disease: A nationwide Swedish cohort study

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Background: Studies have shown an association between use of azathioprine and acute pancreatitis in adult inflammatory bowel disease. However, whether there is an association among pediatric patients is not known.

Objectives: To investigate if there is an association between use of azathioprine and the risk of acute pancreatitis in pediatric inflammatory bowel disease (pIBD) patients.

Methods: We conducted a nationwide Swedish cohort study based on health care register data, 2006-2014. From a cohort of all pediatric patients (<18 years) with IBD (n = 4631), we included 1477 episodes of new azathioprine use and 1477 episodes of no use in propensity score-matched (1:1 ratio) analyses. The propensity score included patient characteristics, comorbidities, previous treatment, indicators of disease severity and health care utilization. Incident cases of acute pancreatitis occurring in the primary risk period of 90 days following treatment initiation were identified through outpatient and inpatient hospital records. A sensitivity analysis was restricted to inpatient cases alone. A secondary risk period of 91-365 days following treatment initiation was also assessed. Cox proportional hazards models were used to estimate hazard ratios (HRs).

Results: Among azathioprine-exposed, mean age was 14.3 (SD 3.2) years, 56.5% were male, and 56.1% had Crohn's disease and 43.9% had ulcerative colitis or IBD-unclassified. During the first 90 days following azathioprine initiation, 23 patients (1.6%) experienced acute pancreatitis compared with 5 patients (0.3%) in the no use group; corresponding incidence rates were 65 and 16 per 1000 person-years. The risk was significantly higher in patients with azathioprine use, HR = 4.21 (95% CI 1.60-11.08). The HR was similar when only considering acute pancreatitis events in inpatient care (4.82 [1.65-14.03]) and there was no increased risk during the period 91-365 days following treatment initiation (0.36 [0.03-4.01]).

Conclusions: Use of azathioprine was associated with an increased risk of acute pancreatitis in pIBD during the first 90 days of use but not later. The finding suggests that the risk of acute pancreatitis needs to be considered when deciding on optimal treatment strategy in pIBD. Additional analyses also including

nationwide Danish data are ongoing and will be presented at the conference.

423 | Cost effectiveness of early treatment in pediatric patients with hepatitis C virus infection

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Background: Hepatitis C virus (HCV) has received significant attention in recent years due to dramatic increases in cases attributed to injection drug use and the availability of highly curative direct acting antiviral (DAA) therapy. Adolescents represent a population that is impacted by HCV but is not routinely considered for therapy.

Objectives: The goal of this study was to evaluate the cost effectiveness of early treatment initiation in adolescent patients with chronic HCV infection compared with previous standard of care of deferring treatment until adulthood.

Methods: We constructed a Markov model to assess the cost effectiveness of treating a hypothetical cohort of patients with chronic HCV aged 12 years with recently approved DAA therapy compared with deferring treatment until adulthood from the societal perspective. HCV transition probabilities, treatment costs, HCV medical care costs, and quality-adjusted life year utility estimates were derived from the literature. Discounted costs per person and total QALYs per person were quantified after 30 Markov cycles. Cost effectiveness was measured as the incremental change in total medical costs per average QALY gained. One-way sensitivity analyses were done by varying scenario parameters for treatment cost, cost of non-HCV related medical care, reinfection rate after treatment, treatment uptake in adults, disease progression in childhood, liver transplant survival, and treatment with recently approved pangenotypic DAAs.

Results: Compared with deferring treatment to adulthood, treatment of adolescents for chronic HCV resulted in an average of 1.96 additional QALYs. In the base case analysis, the incremental cost effectiveness of early compared with deferred treatment was approximately \$30 000 per QALY gained after 30 Markov cycles and within the generally accepted US willingness to pay threshold. In a scenario analysis, hypothetical treatment initiation with currently available pangenotypic agents was also projected to be cost effective ranging from \$6300 to \$21 000 per QALY gained. Cost effectiveness estimates for early treatment initiation were sensitive to variations in DAA costs, reinfection rates in adults, and treatment uptake in adults.

Conclusions: Early treatment initiation in adolescent patients with chronic HCV infection with currently available DAAs appears to be cost effective compared with deferred treatment. Future efforts to control the HCV epidemic should include increasing the number of children treated.

424 | A statistical model of RSV disease in neonates and efficacy prediction for maternal vaccines

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Background: In the United States, RSV is the leading cause of respiratory-related hospitalization in children under 1 year of age, with the bulk of disease occurring in the first six months of life and peaking at 1.5 months of age. Prior studies have demonstrated correlation between maternally derived RSV neutralizing antibody titers in the infant and the reduction of severe RSV disease, with a transplacental transfer ratio close to one, which suggest that maternal vaccination is a plausible strategy to reduce severe disease in infants. Accurate prediction of maternal vaccine efficacy in infants depends on the assumptions that are used to translate vaccine immunogenicity in the mother into infant disease outcomes.

Objectives: Develop statistical models to evaluate maternal RSV vaccine efficacy for infants.

Methods: We established statistical models on severe infant RSV disease based on the following assumptions: 1) maternal titers follow a normal distribution on a log scale; 2) the transplacental transfer ratio of mother to infant is 1:1; 3) the decay of infant neutralizing titers follows an exponential model, and maternal antibody half-life is 28 days; 4) newborn infants are exposed to RSV at a constant rate per day; 5) the probability of an infant developing disease after exposure is a function of the titer and a threshold level; 6) the incubation period between exposure and disease development is 5 days; 7) the probability of developing severe disease is a function of infant airway (bronchiolar) diameter; 8) size of infant airway diameter is a function of age in days.

Results: With the above model, we simulated 10 000 mother-infant pairs and used the simulated datasets to estimate rate of severe RSV disease, independent of the reported epidemiology. The estimated rates of RSV disease by month of age determined from the model are consistent with published epidemiology data, with the peak at 1.5 month of age. The models were further applied to predict the efficacy of maternal vaccines in reducing infant RSV disease by relating a fold rise in maternal neutralizing titers to the month-by-month incidence in infant RSV disease in the first 6 months of life.

Conclusions: The models and simulated datasets can be used to estimate rates of infant RSV disease based on different fold rises of neutralizing titers of mothers, thus predicting vaccine efficacy based on serological data.

425 | Association between oseltamivir and suicide among children: A case-crossover study

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Background: Indicated for the treatment of influenza type A and B, oseltamivir carries a labeled warning for an increased risk of neuropsychiatric adverse events among children. Initially based on case reports, further studies of this association have found mixed results, and been limited by small sample size and potential confounding.

Objectives: To determine the association between oseltamivir exposure and suicide among children, using a case-based design.

Methods: A case-crossover study was conducted using the Truven Marketscan Commercial Claims and Encounters database. We examined five influenza seasons (2009-2013, defined as October 1-April 30 of the following year). In primary analysis, case and control window durations were set to 10 days, with a 10 day washout period between. A case event was defined as the presence of a suicide-related ICD-9-CM code during the influenza season. Subjects were considered exposed during a given window if oseltamivir days supplied overlapped with the window dates. Sensitivity analyses were conducted to examine the potential for within-season time trends (restricting the season to January-March), and to determine the effect of varying window durations. A complementary analysis examining an event of "influenza-only" was done to assess potential confounding by indication. Conditional logistic regression was used to calculate Odds Ratios (OR) and 95% Confidence Intervals (CI). Stratification by hypothesized effect modifiers such as age, gender, history of suicide attempt, and history of mental health diagnosis was conducted.

Results: Over the study period, 251 individuals with both eligible events and oseltamivir exposure during the same season were identified, making up the analytic cohort. Mean age was 14.9 years, 61% were female, and underlying mental health diagnoses were common (65%). We found no association between oseltamivir and suicide (OR: 0.64, CI: 0.39, 1.00), and no significant effect modification. Results of sensitivity analyses examining alternative time windows were similar to primary analysis, as were those from restricting the eligible event period. A complementary analysis of influenza events (OR 0.63, CI: 0.34, 1.08) suggested no confounding by indication.

Conclusions: In contrast with the current labeled warning, we found no association between pediatric exposure to oseltamivir and attempted suicide. Our results are consistent with previous studies and should increase confidence in prescribing oseltamivir in this population.

426 | Gabapentin use for hospitalized neonates

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Background: Despite minimal safety and effectiveness data, some clinicians have advocated for the use of gabapentin to treat neonatal irritability of presumed neurologic origin. The extent of gabapentin administration to hospitalized neonates is unknown.

Objectives: To identify trends in gabapentin utilization among infants hospitalized in neonatal intensive care units (NICUs) at United States (US) children's hospitals and to evaluate the associations between clinical diagnoses and gabapentin treatment.

Methods: We included infants in the 2005-2016 Pediatric Health Information System with a documented NICU admission. To determine the effect of various diagnoses on the probability of receiving gabapentin, we used a modified Poisson regression with a robust between-cluster variance estimator to calculate the adjusted relative risk (aRR) for gabapentin receipt. We also evaluated treatment timing and duration and examined the relationship between birth gestation and treatment.

Results: Of 298 143 infants hospitalized in US NICUs, 381 ever received gabapentin treatment (0.13%). The median age at first administration was 65 days (25th-75th%: 37-125) and median treatment duration was 16 days (25th-75th%: 8-36). Overall gabapentin use steadily increased from 0% in 2005 to 0.1% in 2013 and 0.36% in 2016. Gabapentin was prescribed at 31 of 48 studied hospitals where the proportion of neonates ever receiving gabapentin ranged from 0.01% to 8.07% (median 0.05%; 25th-75th%: 0.02, 0.12). Prescriptions followed a bimodal gestational age distribution with term (0.14%) and less than 29-weeks gestation preterm infants (0.22%) most likely to receive gabapentin. Infants with chromosomal abnormalities (aRR 5.41 [3.21, 9.10]), necrotizing enterocolitis (aRR 2.56 [1.55, 4.22]), periventricular leukomalacia (aRR 2.43 [1.22, 4.84]), congenital brain abnormalities (aRR 2.36 [1.14, 4.88]), and seizures (aRR 2.09 [1.33, 3.29]) had higher probabilities of treatment. The majority of infants receiving gabapentin (88.7%) did not have a seizure diagnosis.

Conclusions: Gabapentin use in US NICUs has increased in recent years and varies markedly between institutions. The majority of gabapentin is prescribed to neonates without a seizure diagnosis. Term infants, <29-weeks gestation preterm infants, and neonates with chronic genetic, neurologic, and gastrointestinal diagnoses have higher probabilities of receiving treatment.

427 | Relational patient-provider continuity of care and the risk of emergency department use among US Medicaid-insured youth with mental health diagnosis

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Background: A consistent patient-provider relationship across multiple health events is an important component of patient care that has been associated with accumulated knowledge of the patient and patient-focused care among youths with non-mental health conditions. However, there is little evidence to support this assertion among patients with mental health conditions, particularly among publicly insured youths who are early initiators of mental health (MH) service utilization.

Objectives: We assessed relational patient-provider continuity of care (CoC) in the 24 months following first mental health diagnosis and compared the risk of emergency MH service utilization across three levels of CoC (low; medium; or high).

Methods: Using Medicaid administrative data, we identified a continuously enrolled cohort of youths with a first mental health diagnosis from 2008 to 2012 (N = 45 271) and followed them longitudinally for 24 months to assess: 1) patient-provider CoC; and 2) the incidence of MH emergency department (ED) visit. We measured CoC using the Alpha Index (W. Lou, 2000), a continuity measure that ranges from 0 to 1, reflecting both the concentration of providers and the sequential continuity in a series of patient visits. We used Cox's proportional hazards models to compute hazard ratios of mental health ED visit in the 24 months following diagnosis, adjusting for sociodemographic and clinical characteristics. Our models compared: 1) youth with low CoC to those with high or medium CoC; and 2) youth with low or medium CoC to those with high CoC. Given its potential to change with each patient visit, CoC was incorporated as a time varying ordinal covariate in the regression models.

Results: In the 24 months following first mental health diagnosis, 50.7% of the cohort had medium CoC (0.50-0.70), 24.9% had low CoC (≤ 0.49), and 24.3% had high CoC (0.71-1.00). Overall, 10.8% of the cohort had a mental health ED visit. Low CoC was associated with a greater hazard of ED visits. Compared with youth with high continuity index, youth with low or medium CoC had a 2.97 (95% CI = 2.7-3.2) fold greater hazard of ED visits. Similarly, youth with low CoC had a 2.20 (95% CI = 1.9-2.5) fold greater hazard of mental health ED visits in comparison with those with medium or high CoC.

Conclusions: Relational patient-provider CoC may be a useful tool in reducing unnecessary, potentially disruptive emergency department services for pediatric mental health conditions.

428 | Breast cancer risk in chronic users of phthalate-containing medications: A Danish nationwide cohort study

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Background: Phthalates are commonly used as pharmaceutical excipients. Preclinical evidence implicates some phthalates in breast cancer progression—particularly dibutyl phthalate (DBP), which potentiates the estrogen receptor (ER).

Objectives:

Estimate the association between medication-borne phthalate exposure and breast cancer risk in a Danish nationwide cohort.

Methods: We queried the Danish Medicines Agency to identify all phthalate-containing oral medications marketed in Denmark. We recorded the product code and the type and mass of phthalate per pill. We enrolled a nationwide cohort of women at risk for a first cancer between 2005 and 2015, and who had no previous exposure to a phthalate-containing drug. Using the National Prescription Registry we characterized time-varying, medication-borne phthalate exposure. We ascertained incident cancers by linking to the Danish Cancer Registry. We fit Cox regression models to estimate associations between cumulative phthalate exposures and breast cancer incidence, updating exposures annually and lagging by 1 year. We adjusted for established risk factors, comorbidity, and co-medications.

Results: We identified 481 products from 24 drug classes containing either DBP, diethyl phthalate (DEP), cellulose acetate phthalate (CAP), hypromellose phthalate (HPMCP), or polyvinyl acetate phthalate (PVAP). Phthalate masses ranged from 3 µg to 1.3 g per pill. We followed 1.12 million women over 9.99 million person-years, over which 27 111 breast cancer cases occurred. Fourteen percent of the cohort ($n = 161\,751$) was prescribed a phthalate-containing drug. CAP, DEP, HPMCP, and PVAP exposure were not associated with breast cancer risk. The highest level of cumulative DBP exposure ($>10\,000$ mg; range: 10 024–71 340 mg; median: 15 390 mg) was associated with an 80% increase in breast cancer risk compared with no exposure ($HR_{adj} = 1.8$; 95% CI: 1.0, 3.1). The association was strongest for ER+ disease ($HR_{adj} = 1.9$; 95% CI: 1.1, 3.5). No published evidence links the drugs represented by DBP-containing products (bisacodyl, budesonide, mesalazine, multienzymes, diclofenac, and lithium) with breast cancer risk.

Conclusions: High DBP exposure was associated with increased breast cancer incidence, particularly ER+ disease. This association merits further investigation. In the meantime, it may be prudent for women taking DBP-containing medications to substitute a phthalate-free version of the same drug, other considerations being equal.

429 | Use of vitamin K antagonists and prostate cancer risk: A Danish nationwide study

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Background: Use of warfarin and other vitamin K antagonists (VKAs) have been suggested to reduce the risk of prostate cancer. Identification of cancer preventive effects of VKAs would have implications for the development of drugs for prevention or treatment of prostate cancer.

Objectives: To examine whether VKA use was associated with a reduced risk of prostate cancer.

Methods: We conducted a nationwide case-control study using Danish demographic and health registry data. As cases, we identified all Danish men with incident, histologically verified prostate cancer between 2005 and 2015. We restricted cases to men aged 40–85 years without previous cancer (except non-melanoma skin cancer). Population controls were age-matched 1:10 to cases using risk-set sampling. The main exposure was defined as three or more years of cumulative VKA use. Additional exposure periods of <1 , 1–3, 3–5, 5–10, and >10 years were examined to evaluate potential dose-response relations. Using conditional logistic regression, we estimated odds ratios (ORs) for prostate cancer associated with VKA use. We adjusted for age and calendar time (by design), comorbid conditions (diabetes, chronic obstructive pulmonary disease, ischemic heart disease, congestive heart failure, and conditions that might contraindicate VKA use), use of drugs with suggested preventive effects against prostate cancer, and highest achieved education.

Results: We included 38 832 prostate cancer cases with a median age of 69 years. Among cases, 1089 (2.8%) had used VKAs for three or more years compared with 10 803 (2.8%) controls yielding a crude OR of 1.01 (95% CI, 0.95–1.08). Multivariable adjustment for covariates had limited influence on the association (OR, 1.03; 95% CI, 0.97–1.10). We observed no dose-response pattern (eg, 5–10 years of VKA use: OR, 1.06 95% CI, 0.97–1.16).

Conclusions: We found no evidence of a reduced risk of prostate cancer associated with VKA use. Several anti-neoplastic mechanisms have been proposed for VKAs in relation to prostate cancer development, however, in view of our findings, it is questionable whether these translate to the clinical setting.

430 | Use of valproic acid and risk of skin cancer

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Background: Valproic acid has been reported to increase cutaneous photosensitivity, however, whether valproic acid use is associated with non-melanoma skin cancer and malignant melanoma is unknown.

Objectives: We conducted a nationwide case-control study using Danish health registry data to examine the association between valproic acid use and risk of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma (MM).

Methods: As cases we identified all Danish residents with incident, histologically verified BCC, SCC, or MM during 2004-2015. Cases were matched by risk-set sampling 1:10 to population controls on calendar time, sex, and age. Using conditional logistic regression, we estimated odds ratios (OR) with 95% confidence intervals (CI) for BCC, SCC, and MM associated with use of valproic acid. We adjusted for age, sex, and calendar time (by design), comorbid conditions, use of other photosensitizing drugs, and highest achieved education. We pragmatically defined our main exposure as a cumulative dose of valproic acid of 750 g or above corresponding to 500 defined daily doses (long-term use). Additional categories of cumulative dose were examined to evaluate dose-response relationship. Further, we examined whether stratifying by sex, age, tumor localization, indication for valproic acid therapy, and history of psoriasis, atopic dermatitis, or actinic keratosis modified the association. In all analyses, we disregarded valproic acid use 2 years prior to the index date to avoid reverse causation bias.

Results: We identified 69 361 BCC cases, 9264 SCC cases, and 16 387 MM cases. We observed similar prevalence of long-term use both for BCC (0.2% vs 0.2%), SCC (0.3% vs 0.2%) and MM (0.2% vs 0.3%) in cases and controls, respectively, with corresponding adjusted ORs of 1.1 (95% CI, 0.9-1.2) for BCC, 1.1 (95% CI, 0.7-1.7) for SCC, and 0.7 (95% CI, 0.5-1.1) for MM. We observed no dose-response relationship (eg, a cumulated dose of 1500-2999 g yielded an OR of 1.2 (95% CI, 0.9-1.6) for BCC, 0.8 (95% CI, 0.3-1.8) for SCC, and 0.6 (95% CI, 0.3-1.4) for MM. Although statistical precision was limited in some strata, the associations were not modified by age, sex, tumor localization, indication for valproic acid therapy, or other skin conditions.

Conclusions: This study provides no evidence of an association between valproic acid use and basal cell carcinoma, squamous cell carcinoma or malignant melanoma.

431 | Testosterone supplementation in relation to prostate cancer in a US commercially insured claims database

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Background: Testosterone supplementation is a common treatment that has more than doubled in use in US men since 2003. There has been concern that testosterone could increase prostate cancer (PC) risk, given the efficacy of androgen deprivation therapy for PC. Initial studies examining associations between testosterone and PC have been inconsistent, and limited in size and duration.

Objectives: To validate a claims algorithm for incident PC and evaluate the relation between testosterone supplementation and incident PC in a large claims database.

Methods: This retrospective cohort and validation study was conducted in the HealthCore Integrated Research Database (HIRD), consisting of commercially insured individuals across the United States from 2006 to 2015. After exclusion of patients who may have had prevalent PC, we identified 76 159 men who initiated testosterone, 721 326 matched unexposed men and 147 620 men initiating phosphodiesterase 5 inhibitors (PDe5i). PC was defined as a PC diagnosis code up to 4 weeks after a prostate biopsy. In a subset of men, PC was validated by electronic linkage to the Georgia cancer registry. PC rates were computed using multivariable Poisson regression and propensity scores using inverse probability of treatment weighting.

Results: The incident PC algorithm had an overall positive predictive value of 83% (95%CI = 79%, 87%) and sensitivity of 88% (95%CI = 85%, 92%), which were comparable across groups. Testosterone was associated with lower rates of PC compared with unexposed men (adjusted incidence rate ratio [aIRR] = 0.77, 95%CI = 0.68, 0.86) and compared with PDe5i exposed men (aIRR = 0.85, 95%CI = 0.79-0.91). Associations were similar within various subgroups including men receiving PC screening or with baseline hypogonadism. In a subset of men with prostate specific antigen (PSA) values, mean PSA was slightly lower among testosterone exposed men than either comparison group both before and after testosterone initiation/follow up. The IRR of 0.77 could be explained by an unmeasured confounder that was positively associated with both testosterone and PC by an IRR of 1.92 each, conditional on the controlled confounders.

Conclusions: Men dispensed testosterone supplementation had a lower rate of PC than unexposed men or men dispensed PDe5i drugs. This finding was not explained by measured confounding or outcome misclassification. Further work is needed given the lack of a strong mechanism.

432 | Use of proton pump inhibitors and risk of pancreatic cancer

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Background: Preclinical studies have suggested that proton pump inhibitors (PPIs) may increase pancreatic cancer risk, however, epidemiological studies are few, and the results are conflicting.

Objectives: This spurred us to evaluate whether PPI use is associated with an increased risk of pancreatic cancer in a large population-based study.

Methods: We conducted a nationwide case-control study using data from Danish demographic and health care registries. All patients (n = 6921) with a first cancer diagnosis of pancreatic cancer between 2000 and 2015 were identified from the Danish Cancer Registry and age-, gender-, and calendar-matched 1:20 to population controls using risk set sampling. Conditional logistic regression was applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer associated with PPI use, adjusting for potential confounders. In secondary analyses, we examined dose-response patterns and associations with individual PPIs as well as with histamine-2-receptor antagonists.

Results: Ever use of PPIs occurred among 27.8% of 6921 pancreatic cancer cases and 25.4% of 34 695 matched controls, yielding a neutral adjusted OR of 1.04 (95% CI 0.97-1.11). ORs were also close to unity in analyses of high-use of PPIs (≥ 1000 DDDs; OR, 0.92 95%CI 0.80-1.07). There was no evidence of a dose response relationship in terms of cumulative use (in defined daily doses), of PPI with ORs close to unity across categories, including for those with the highest cumulative use (>2000 DDDs; OR, 1.03 95%CI 0.84-1.26). Analyses of individual types of PPI, patient characteristics, and of histamine-2-receptor antagonists use also returned neutral associations.

Conclusions: In this large nationwide case-control study, PPI use was not associated with an increased risk of pancreatic cancer.

433 | Development of predictive models to identify advanced-stage cancer patients in a US administrative claims database

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Background: Health care claims databases are a valuable source for real-world evidence in oncology. However, the lack of information on cancer stage is a considerable limitation. Past attempts to identify cancer stage in health care claims have met limited success.

Objectives: To develop predictive models to identify five types of advanced cancer (ovarian cancer [OC], urothelial carcinoma [UC], gastric adenocarcinoma [GC], Merkel cell carcinoma [MCC], and non-small cell lung cancer [NSCLC]) in the HealthCore Integrated Research Database (HIRD), which contains health care claims data from across the United States.

Methods: Individuals with ≥ 1 claim with a diagnosis of a cancer of interest in the HIRD between 2010 and 2016 were linked to one of three US state cancer registries or the HealthCore Integrated Research Environment Oncology. Stage information obtained via linkage was used as the gold standard (ie, dependent variable) for predictive models. For each cancer of interest, a predictive model was developed using claims data to estimate the probability of being a case with a primary tumor in an advanced stage. Predictor variables available in the HIRD were identified by Least Absolute Shrinkage and Selection Operator (LASSO) regression. Cross-validation techniques were used to control overfitting, and classification error rates and Receiver Operating Characteristic curves were used to select a probability threshold for accuracy.

Results: A total of 2723 OC, 6522 UC, 1441 GC, 109 MCC and 12 373 NSCLC cases were used in development of the predictive models. For example, predictors of advanced OC included a diagnosis of secondary malignant neoplasm of the respiratory and digestive systems ($\beta = 1.47$), treatment with bevacizumab ($\beta = 1.01$), and treatment with olaparib ($\beta = 0.67$). C-statistics were >0.85 for all five models indicating high discrimination. At selected predicted probability thresholds, the positive predictive values were high: for OC PPV = 0.95 (95% confidence interval [95% CI]: 0.94-0.96), for UC PPV = 0.78 (95% CI: 0.70-0.86), for GC PPV = 0.86 (95% CI: 0.83-0.88), for MCC PPV = 0.77 (95% CI 0.68-0.89), and for NSCLC PPV = 0.91 (95% CI 0.90-0.92).

Conclusions: Accurate algorithms were developed via predictive modeling in an administrative claims database to identify five types of advanced cancer.

434 | Short-term risk of bleeding, ischemic stroke, and death in patients with atrial fibrillation switching between oral anticoagulants: A case-crossover study

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Background: In clinical trials of atrial fibrillation (AF) patients, switching between non-vitamin K antagonist oral anticoagulants (NOAC) and vitamin K antagonists (VKA) was associated with a markedly increased short-term risk of both bleeding and arterial thromboembolism. While common in clinical practice, the short-term risks

associated with switching in real-life anticoagulant users remain unknown.

Objectives: To assess the association between anticoagulant switching and short-term risk of bleeding events, ischemic stroke, and all-cause mortality in patients with AF.

Methods: We conducted a case-crossover study based on the Danish nationwide health registries. Using all Danish oral anticoagulant users with AF in 2011–2017 as the source population ($n = 246\,143$), we identified all outcomes of interest ($n = 23\,599$) as well as all anticoagulant switches ($n = 19\,805$) during the study period. The case-crossover population consisted of patients with (a) an outcome (ie, bleeding ($n = 359$), ischemic stroke ($n = 137$), or all-cause mortality ($n = 829$)) and (b) an anticoagulant switch during the 180 days preceding the outcome. For each outcome, we used conditional logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CI) comparing the occurrence of switching during the 30-day period immediately preceding an outcome event to that in reference intervals during the period 60–180 days before the outcome. Analyses were performed for switches from VKA to NOAC, NOAC to VKA as well as for single NOACs (ie, dabigatran, rivaroxaban, or apixaban).

Results: Switching from VKA to NOAC was associated with an increased short-term risk of bleeding (OR 2.1, 95% CI 1.6–2.7), ischemic stroke (OR 2.1, 95% CI 1.4–3.3), and all-cause mortality (OR 2.3, 95% CI 2.0–2.7). All risks were increased after switching from NOAC to VKA, although to a lesser extent, with ORs for bleeding, ischemic stroke, and all-cause mortality of 1.4 (95% CI 0.9–2.3), 1.5 (95% CI 0.7–3.3), and 1.6 (95% CI 1.1–2.3), respectively. Stratified analyses showed some variation according to NOAC type, but interpretation was generally limited by low statistical power. Adjustment for trend in exposure with the case-time-control approach yielded similar results.

Conclusions: In patients with AF, switching between oral anticoagulants, and in particular switching from VKA to NOAC, is associated with an increased short-term risk of bleeding, ischemic stroke, and all-cause mortality.

435 | Moving from RECORD to CORD—Guidelines for conducting research using routinely collected health data

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Background: Background/Problem being addressed: In 2015, the RECORD (REporting of studies Conducted using Routinely collected health Data) initiative introduced reporting guidelines for observational studies based on routinely collected health data, in order to reduce research waste. In pharmacoepidemiology, RCD are broadly accepted and widely used to evaluate the “real-world” effectiveness and safety of medicines. However, the methodological complexity of pharmacoepidemiological research means that reporting requirements

fall outside of the scope of existing reporting guidelines including RECORD or STROBE. In a symposium session during the 2018 ICPE conference in Prague, we propose to introduce people to the new RECORD for pharmacoepidemiology guidance (RECORD-PE), an initiative that was funded by ISPE. We anticipate RECORD-PE between 3 and 6 months prior to the ISPE Annual Meeting, and therefore perfectly timed for a “release event” to expose ISPE members to this initiative. We will also introduce the concept of a “CORD (Conduct of Observational research using Routinely collected data) Centre,” a virtual “Methods Centre” for studies using routinely collected health data, in order to not only improve reporting, but also to explore how better reporting can lead to better methods. This CORD Methods Centre will combine transparency and reporting, with educational initiatives, methodological advancement, and knowledge translation of research to the bedside, policy makers, and stakeholders.

Objectives: Learning objective/s: 1. Review the RECORD reporting guidelines for pharmacoepidemiology (RECORD-PE). 2. Discuss existing evidence and publications guiding researchers who conduct research using routinely collected health data. 3. Evaluate the needs of audience members for methodological guidance for research using routinely collected health data. This information will be used to further develop plans for the CORD Methods Centre to support international research conducted using routinely collected health data.

Description: Approach: Focusing on research using health data, speakers will discuss the role and impact of RECORD. We will introduce people to RECORD for pharmacoepidemiology research. We will engage audience members to better understand their needs and priorities, particularly as they relate to better reporting of pharmacoepidemiological research and better methods for routinely collected data research in future.

436 | Pharmacoepidemiology in Eastern Europe—A EuroDURG/SIG-DUR symposium dedicated to the late MUDr. Ludvík Štika

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Background: In the early days of pharmacoepidemiology (long before it was named pharmacoepidemiology) in Europe there were innovative local initiative, one was in Prague (at that time Czechoslovakia). This was done by a practicing neurologist in 6th Prague district for 30 years: the late MUDr. Ludvík Štika. He was a pioneer in implementing pharmacoepidemiology in health care to improve rational use of drugs. At a pharmaceutical conference in Prague 1973 he was able to present incidence and prevalence of prescriptions purchased at pharmacies in defined populations in two districts of Prague. These data were unique at that time.

Objectives: To show how pharmacoepidemiology has developed in Central and Eastern Europe, how it could contribute to better understanding of medication use, thus promoting a safe and effective

prescribing and use of medicines. The symposium is of interest for policymakers and researchers promoting rational use of medicines. Specific groups who would benefit from participating are researchers active in health policy, pharmacoepidemiology and ethics in observational research.

Description: The symposium will begin with the early history of pharmacoepidemiology in Czechoslovakia, subsequently followed by three presentations of current pharmacoepidemiology activities focusing on Central and Eastern Europe, ending with a panel discussion: 1. A tribute to MUDr. Ludvík Stika, a pioneer in Pharmacoepidemiology (15 minutes, Ulf Bergman, Sweden) 2. The historical development of pharmacoepidemiology in the Czech Republic (education and research) (20 min, Jiri Vlcek, Czech Republic) 3. Antibiotics in Central and Eastern Europe (20 min, Vera Vlahovic-Palcevski, Croatia) 4. Electronic Databases and opportunities for record-linkage in Central and Eastern Europe (20 min, Jolanta Gulbinovic, Lithuania) 5. Panel debate with the audience on how pharmacoepidemiology could contribute to a better understanding of medication use in Central and Eastern Europe (15 min, Bjorn Wettermark, Sweden, Chair, Jiri Vlcek, Co-chair, and all presenters above)

437 | Ten years of ENCePP: Time to celebrate and move forward

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Background: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP; www.encepp.eu) was launched by the European Medicines Agency in June 2007 to become an active European research network conducting independent observational studies on medicines based on principles of transparency, scientific independence and common quality standards. Ten years on, ENCePP has changed the landscape of pharmacoepidemiology in Europe by increasing the capacity for pharmacoepidemiology research, introducing public registration of observational studies, defining common methodological standards complementing regulatory guidance and proposing governance principles based on a Code of Conduct. While we celebrate these achievements, ENCePP should not stand still but move forward to further strengthen scientific guidance, collaboration and support to public health. It should involve more centers and data sources from Eastern European countries, seek development of global standards in collaboration with the ISPE-ISPOR Task Force and ISO-P on pharmacovigilance, and meet new methodological challenges rising from new data sources such as social media and big data and by

innovative models for data extraction and analysis from electronic health care databases, their validation and their regulatory applications.

Objectives: To present the achievements of ENCePP after 10 years and discuss future ENCePP dynamic development

Description: Representatives of the ENCePP Steering group and working groups will describe the network, how it supports regulatory medicines evaluation, and some key outcomes: EU-PAS Registry, Code of Conduct, Guide of Methodological Standards, Checklist for Study protocols, Resources database and Multi-database research methods. With this as a background, panelists and audience will discuss future orientations and development of ENCePP, especially the expansion to Eastern European countries, interactions with learned societies, pharmaceutical companies and other stakeholders, new methodological challenges and involvement of additional expertise, datasources and centres. Participation will be encouraged to discuss the next directions for this important initiative for European Pharmacoepidemiology.

438 | When and where to use blinding in pragmatic randomized clinical trials

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Background: Blinding (or masking) of treatment assignment is routinely implemented in randomized controlled trials (RCTs) to minimize the potential for bias that can occur with the reporting, assessment, or management of conditions, particularly when there are pre-conceived notions about the treatments under study. However, the complexity and costs of masking treatments can be non-trivial, and can hinder how generalizable the findings may be to a “real world,” clinical setting. The literature on pragmatic randomized clinical trials (pRCTs), while extensive, fails to address when blinding may be appropriate and how to blind aspects of a pRCT while maintaining the “real-world” nature of the study.

Objectives: Our goal is to advance the thinking around the role of blinding in pRCTs and to challenge the current RCT construct by discussing when and where blinding is most useful. We plan to frame our discussion around 1) why this is an important issue, 2) features of pRCT study design and outcomes which can make blinding unnecessary, and 3) solutions for how blinding may be implemented effectively to maintain generalizability. The symposium will be of interest to those keen to understand issues associated with designing and implementing pRCTs.

Description: There is mounting interest in how medical products perform under conditions of real-world use for regulatory decision making. In the United States, the 21st Century Cures Act mandates that the FDA establish a program to evaluate the potential use of real-world evidence (RWE) to help support approval of new indications or meet post-approval study requirements. As FDA is a strong

proponent of randomized studies, pRCTs have become a popular design for understanding how medical products work in routine clinical practice. Yet, the degree to which pRCTs achieve generalizable findings that inform clinical practice varies considerably, especially when pRCTs blind patients and physicians to treatment assignment. An introduction to the topic (15 min, Christian) will be followed by presentations (15 min each, Brouwer, Girman, Davis), with audience questions interspersed, on why the attributes of various outcomes should influence when blinding is needed, solutions for implementing blinding effectively in pRCTs while maintaining generalizability, and how such considerations might be weighed with the complexities, costs and potential for misclassification for specific pRCT designs. A moderated Q&A with a panel of the presenters will follow (30 min, Dreyer) and audience polling will wrap the session.

439 | Patient-focused benefit risk assessment: Why, when and how should epidemiologists get involved

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Background: Patient groups, industry and health authorities want to better integrate patient preferences concerning risk and harms into the benefit-risk (B-R) assessment of medicines. This process is moving rapidly, aided by momentum from initiatives such as the FDA's 21st Century Cures Act, FDA and EMA pilot projects in patient preferences, and the IMI-PREFER initiative. Awareness of these developments needs to increase across the ISPE community so that epidemiologists are ready to be valuable partners in the collection and use of patient preference data by health authorities.

Objectives:

- 1 To understand the motivation for including patient input into B-R decisions
- 2 To illustrate when and how patient preferences may be important in B-R assessments via four case studies
- 3 To understand regulators' interest in and perspective on patient-focused B-R initiatives
- 4 To describe when and how epidemiologists can participate in patient preference research

Intended audience: Epidemiologists who would like to better understand patient preferences and the epidemiologist's role in patient preference research used in B-R assessments.

Description: This session will be organized as follows:

- The introduction will provide an update on developments in the policy context that motivates the incorporation of patient

preferences in patient-focused B-R, including the increasing number of public-private partnerships, regulatory initiatives, and forthcoming FDA guidances on patient experience data (10 min: RD)

- Four case studies sponsored by or received favorably by regulators will illustrate the use of patient preferences to support B-R decision making. The case studies will highlight the situations in which patient focused B-R assessment are useful, the steps involved in their implementation, the inputs required, and the outputs generated. (40 min: BH, KM)
- Building on the case studies, we will highlight the emerging role of epidemiologists in identifying the need for patient-focused B-R assessment, including how epidemiologic expertise and skills can be used to design, perform, and interpret patient preference studies for B-R assessment. (LR: 10 min)
- Next, a regulator's perspective will be shared: "Patient Preferences in European Drug Regulation—Are We Ready?" (15 min: AC)
- Finally, the audience will be polled to understand their experience with patient focused B-R analysis, their views on when it can add value, and the obstacles to its adoption. This will form the basis of an interactive discussion (15 min: EA)

440 | A novel approach to correlate soft and hard outcomes: Effectiveness of abatacept (Orencia®) patient alert cards in rheumatoid arthritis patients

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Background: Patient Alert Cards (PACs) for intravenous (IV) and subcutaneous (SC) abatacept (ORENCIA®) are designed to inform patients and health care professionals (HCPs) about the risk of infections with the ultimate goal of reducing undesirable outcomes, eg, hospitalisations, or reducing their severity. The effectiveness of the PACs in rheumatoid arthritis patients was evaluated as part of a post-marketing commitment to the European Medicines Agency (EMA).

Objectives: To assess receipt, awareness, utilization, utility, knowledge and behaviour by patients, and correlate responses with clinical/safety outcomes in the same patients. A HCP survey was also conducted, and results are reported elsewhere.

Methods: Cross-sectional survey of patients, and a retrospective chart review, conducted in France, Germany, Spain, Sweden and the UK. Patient questionnaires were completed online or on paper. Clinical retrospective data from patient medical records were abstracted, and entered into a proprietary and validated electronic case report form.

Results: The recruitment rate (completers/eligible) was 67.9%. The patient survey was completed by 190 patients, of whom 181 participated in the retrospective study. The majority of patients had been on Orencia for >1 year (67%) and 66% were administered the SC formulation. Sixty percent of patients were aware of the PAC, of whom 95% had received (mainly through specialist nurses [45%] or via the

medication box [31%]) and 84% had read the material. The PAC was similarly read by most patients in the IV and SC groups. Knowledge about the risk of infections was higher among patients who received the PAC compared with those who had not (64% vs 46%, $p = 0.013$). The mean level of utility of the PAC was 61%. The percentage of patients with infections leading to hospitalisation increased as the global score of understanding and implementation of the PAC (from the patient survey) decreased: 3% for scores $\geq 67\%$, 5% for scores 34–67% and 8% for scores $\leq 33\%$. The correlation was not statistically significant.

Conclusions: The study was a novel design that bridges the gap of linking process indicators with clinical/safety outcomes. The survey results described the differential effectiveness of the Orenzia PAC. Despite already being included inside the Orenzia product packaging, the distribution of the PAC to patients could be improved. The study described how routine clinical practice setting and nurses are the more effective mean of patient education.

441 | The effect of risk evaluation and mitigation strategies on health care provider's awareness of drug risks

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Background: Risk Evaluation and Mitigation Strategies (REMS) are required risk management plans that use risk minimization strategies beyond the professional product labeling to ensure that the benefits of a drug or biological product outweigh its risks. REMS can include one or more elements, which can include a communication plan and elements to assure safe use (ETASU). Communication plan REMS involve information dissemination only. ETASU REMS that are linked to distribution of the drug require health care providers to take additional actions (ie, trainings, knowledge assessments, certification and enrollment) to prescribe the drug. There have been few published studies that have evaluated REMS assessment data across REMS programs to determine the effectiveness of the REMS elements.

Objectives: The objective of this evaluation was to characterize the effectiveness of different types of REMS (communication plan REMS and ETASU REMS) using knowledge rates from health care provider surveys and to examine factors that may contribute to acceptable knowledge rates.

Methods: REMS assessments submitted to the Food and Drug Administration (FDA) from April 2008 until August 2016 that contained health care provider surveys were systematically reviewed. Descriptive analyses were conducted of the aggregate respondent, program and survey design characteristics, and knowledge rates. Associations between factors that may contribute to health care providers' understanding of the REMS risk(s) and acceptable knowledge rates of the REMS risks were explored.

Results: A total of 82 REMS programs were examined. Results show two-thirds of the REMS program (68%, $n = 56$) were meeting the knowledge goal of $\geq 80\%$. Programs that met the knowledge goal were more likely to have the risk the REMS was intending to mitigate in the

boxed warning, to focus the REMS information on a single risk, and to have additional educational materials beyond a letter for health care professionals and REMS website. Current ETASU REMS had a significantly higher mean knowledge score than current communication plan REMS (90% vs 81%, $p = 0.0062$).

Conclusions: This research may have future implications for the design and evaluation of REMS programs. Future research should seek to identify what specific aspects of REMS contribute the most to health care provider knowledge. Attempts should continue to be made to standardize REMS assessment surveys so information is more comparable across REMS programs.

442 | The use of real-world evidence in European medicines regulation

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Background: Given concerns among the public over the use of routinely collected health care data for research, it is important that not only are strict confidentiality requirements met, but in addition that the research conducted is of benefit to patients and the wider public. One area where such benefit may be demonstrated is in the post-marketing evaluation of medicines.

Objectives: To evaluate the use of non-interventional studies and routinely collected health care data in post-marketing safety and efficacy referrals conducted by the European Medicines Agency (EMA).

Methods: We reviewed all EMA referrals made due to post-marketing safety or efficacy concerns that were evaluated by an EMA assessment committee between 1st January 2013 and 30th June 2017. From the referral notification and the assessment report we collected information about the referral, the medicinal product under investigation, the adverse events under study and the types of evidence that were assessed (preclinical, randomised trials, etc). We evaluated how each type of evidence was used and the contribution of non-interventional evidence to decision-making.

Results: In the assessment reports of the 52 eligible referrals many evidence types were cited including pre-clinical studies (29/52, 56%), non-randomised trials (33/52, 63%), randomised trials (48/52, 92%), non-interventional studies (41/52, 79%), spontaneous reports (38/52, 73%), and systematic reviews of randomised trials (27/52, 52%). Of the 41 reports citing non-interventional evidence, 31/41 (77%) referenced non-interventional studies of routinely collected data. Non-interventional studies were frequently relied on for evaluating product safety (31/52, 60%), product usage (14/52, 27%), and product efficacy (18/52, 35%). For the majority of referrals non-interventional evidence contributed to decision-making (30/52, 58%) and in three referrals it was the primary or only type of evidence used to make a decision.

Conclusions: European regulatory decision-making for medicines is based on evidence from a range of different sources. Non-interventional studies have an important role, providing useful information, particularly on product safety and usage, and are frequently required to determine the

effectiveness of regulatory action. Further successful incorporation of non-interventional evidence in decision making will require high quality study design, conduct and reporting, as well as timely and high quality data.

443 | Mapping benefit-risk decision-making processes and identifying decision points with the potential to include patient preference information throughout the medical product lifecycle

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Background: Patient preference information (PPI) has not been effectively integrated in decision-making throughout the medical product lifecycle (MPLC). When conducted, studies have been designed to address a specific need, and there has been no systematic approach to integrating these data in decision-making. A first step requires an understanding of existing processes and decision points to know how to best incorporate these data to improve patient-centric decision making.

Objectives: The aims were to: 1) identify the decision-making processes and decision points throughout the MPLC for stakeholders, and 2) determine which decision points have potential to include PPI.

Methods: A 3- step approach was conducted, including a scoping literature review identifying relevant white and grey literature, validation meetings with stakeholders to confirm decision-making processes, and semi-structured interviews with representatives of 3 stakeholder groups (industry n = 24, regulatory n = 22, HTA/payers n = 24). The literature review was conducted using five scientific databases, and interviews were conducted within seven different European countries and the United States.

Results: Six decision points were identified for *industry decision-making process*: prioritization of targets, studies, assets, or post approval opportunities; and decisions to advance product development, submission, or launch. Four decisions points were identified for *regulatory decision-making process*: submission and validation, scientific opinion, orphan designation and commission decision. Six decision points were identified for *HTA decision-making*: filtration, prioritization, and appraisal for reimbursement decision-making (and repeated if a reassessment is needed). Patient representatives are involved in some decision-making processes within all stakeholder groups. PPI is currently not considered required information to be submitted for decision-making, but there was general agreement by stakeholder groups that it would be of great benefit.

Conclusions: Each of the decision points requires different information and/or data to be submitted, which is assessed by decision-

makers using pre-set criteria. PPI is considered an important component to inform future decision-making across the MPLC.

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444 | Trends in US emergency department visits for zolpidem-related adverse events before and after FDA drug safety communications, 2010-2016

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Background: Based on new data, the Food and Drug Administration (FDA), in two Drug Safety Communications (DSCs) issued in 2013, recommended lowering the bedtime dose of zolpidem, especially when prescribed for women.

Objectives: To describe time trends in emergency department (ED) visits for zolpidem-related adverse events (AEs) in the United States, before and after FDA zolpidem DSCs.

Methods: We used data from an active, nationally representative sample of 59 hospital EDs participating in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project to estimate national ED visits due to zolpidem in 2010-2016. We estimated percentage of zolpidem-related AEs among all ED visits. We calculated ED visit rate per 10 000 prescriptions dispensed from retail and long-term care pharmacies using IMS National Prescription Audit data. We employed piecewise (segmented) regression to calculate average change in estimated 6-month rates of ED visits, and used Joinpoint Regression to identify potential inflection points.

Results: We estimate an annual average of 9578 (95% confidence interval [CI], 7108-12 048) ED visits for zolpidem-related AEs during 2010-2016; approximately 60% were made by females. Prescription-adjusted annual rates of ED visits for males and females were similar. The percentage of zolpidem ED visits among all ED visits was lowest in the second half of 2014 (0.3%). We observed a decrease in prescription-adjusted rates from 3.0 ED visits per 10 000 prescriptions in 2010 (CI, 2.0-3.9) to 1.4 in 2014 (CI, 0.8-2.0); then an increase to 3.2 in 2016 (CI, 2.0-4.5). The best-fit regression model of ED visit rates by 6-month intervals identified a single inflection point in the second half of 2014 ($p = 0.018$) with a significant decrease of 7.7% biannually from 2010 to 2014 and a non-significant increase of 20.7% from the second half of 2014 through 2016. A model with 2 inflection points did not reach statistical significance ($p = 0.07$); the first segment decreased 5.6% biannually (2010 to the first half of 2013), the second segment decreased 12.8% biannually (to the second half of 2014), and the third segment increased 24.5% (to the second half of 2016).

Conclusions: The 2013 zolpidem DSCs might be related to a short-term decline in zolpidem-related AE ED visits in 2014. However,

because the decrease in ED visit rates was not sustained, questions remain concerning the long-term impact of FDA's zolpidem DSCs.

445 | Consistency of drug labels for therapeutically equivalent medications

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Background: A drug product label (DL) is the full description of the drug's indications, administration, warnings, contraindications, and adverse events. A DL is written by a brand manufacturer, and is published when the drug is initially approved and marketed. Since only the holder of a new drug application (NDA) is permitted to update a DL, inconsistencies in drug labeling may exist when branded drug application holders update their product labeling, and the generic drug application holders must wait until FDA approves the change to the brand drug labeling to update generic drug labeling.

Objectives: To evaluate labels of 13 drugs with narrow therapeutic indices (NTI) to assess whether information on drug administration is documented consistently between brand-name and AB-rated generic drugs.

Methods: DLs in XML format were downloaded from the DailyMed website. Twenty-four DL sections were identified as sources for information on drug administration. A semantic natural language processing approach was used to extract this information and subsequently indexed as AB-rated brand-generic DL pairs. We assessed the consistency of information in the generic DL sections as having either "no difference," "minor difference," or "major difference" when compared with the brand-name DL. Differences that do not convey the same information as the brand drug were defined as major. Sections with a "major difference" were further categorized as either "no information," "less information," or "more information."

Results: A total of 150 brand-generic DL pairs representing seven formulations were evaluated. Of these, 48% had inconsistent information (major or minor difference) in one or more 1 label section(s) of the generic DL when compared with the brand-name DL. Of the 51 DL pairs with a "major difference," the generic DL had either no information (43%), less information (20%) or more information (37%) relative to the equivalent brand DL. [INFORMATION FOR PATIENTS SECTION] (11%) and [STORAGE AND HANDLING SECTION] (10%) had the greatest number of brand-generic DLs pairs with a "major difference."

Conclusions: DLs are the primary tool used by FDA to communicate essential information for safe and effective use of NTI drugs. Majority of generic DL sections showed relatively small differences. Despite FDA's mandate that generic DLs are the same as brand DLs, bioequivalent drugs may differ in drug administration information. The combination of proactive monitoring and innovative technologies are needed to enable ongoing label compliance.

446 | Evaluation of physician knowledge of safety and safe use information for aflibercept

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Background: As part of the risk-management plan for aflibercept (an intravitreal antineovascularisation agent with several indications), Bayer developed materials to educate physicians and patients on the key safety and safe use information for aflibercept and distributed them to ophthalmology practices to increase awareness and understanding.

Objectives: To measure whether physicians received the aflibercept prescriber guide (PG) and the injection procedure video and evaluate their knowledge of key safety information.

Methods: An observational, cross-sectional study was conducted in the UK, Germany, France, Spain, and Italy. Ophthalmologists who had prescribed and/or administered aflibercept in the past 6 months were recruited from a web panel to complete a survey. Data analyses were descriptive.

Results: Of 459 eligible physicians, 445 consented and 428 completed the questionnaire and were included in the analysis. Eighty-seven percent reported receipt of the summary of product characteristics (SmPC), 77% the PG, and 50% the intravitreal injection procedure video. Knowledge was high on storage and preparation (74%, 95% CI [70-78%]) to 97%, 95% CI [95-99%] for 5 of 6 items) and injection procedures (83%, 95% CI [80-87%] to 96%, 95% CI [93-97%] on 5 items). Knowledge of dosing requirements was highest for wet age-related macular degeneration (28%, 95% CI [24-33%] to 94%, 95% CI [91-96%] on 4 items) and lower for newer or less commonly prescribed indications. The 28% knowledge level reflected more conservative interpretation of monitoring requirements (eg, 28% correctly responded "true" to there being no monitoring requirements between doses, while 68% responded "false"). Overall, knowledge of preparing patients for treatment was high (63%, 95% CI, [58-68%] to 94%, 95% CI [91-96%] on 3 items). Most physicians (82%, 95% CI [78-85%]) identified all contraindications for use. Knowledge was also high for recognising signs and symptoms of possible side effects (78%, 95% CI [73-81%] to 89%, 95% CI [85-92%] on 4 items).

Conclusions: Physicians' knowledge of most important topics was high (eg, side effects). Knowledge was lower for topics less frequently encountered (eg, use in women of childbearing potential) and for more complex aspects of safe use (eg, dosing and monitoring) for which we assume physicians would consult the label/PG rather than relying on recall. Reported receipt of the SmPC and PG was high, and the high level of knowledge suggests that the key safety information is available to physicians.

447 | Acceptance of uncertainties at marketing authorisation and the fate of medicines in the European Union

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Background: For patients to have timely access to medicines, the European Medicines Agency (EMA) may accept less conclusive clinical evidence at time of marketing authorisation (MA), leading to a higher level of uncertainty. The drug regulatory consequences of (non-) acceptance of uncertainties at MA remain unknown.

Objectives: To characterise the regulatory drug life-cycle of non-approved and approved innovative medicines and specifically for approved medicines to associate post-approval changes to the MA with presence of uncertainties regarding phase III data at MA.

Methods: We performed a retrospective cohort study of innovative medicines for which a MA was requested from the EMA (1 Jan 2009-31 Dec 2010), excluding influenza vaccines. For non-approved medicines, we identified eventual approval after 2010. For approved medicines, we identified revocation, withdrawal, suspension and changes to clinical sections of the product information. Uncertainties regarding phase III data at MA were identified in a previous study. Outcomes were extracted from European Public Assessment Reports. The median number of changes and interquartile ranges (IQRs) were calculated and distribution was compared using the Wilcoxon Rank Sum test.

Results: We identified 62 requests for a MA, of which 40 were approved (23 in the group with uncertainties and 17 in the group without) and 22 were not. Of the latter, 3 were eventually approved after 2010. In both groups of approved medicines, 2 were withdrawn post-approval. No revocations or suspensions occurred. Among all approved medicines, we identified 471 changes to the clinical section of the product information (median 8.5, IQR 4-16), which were similarly distributed over the two groups (median 8, IQR 4-17 for medicines with uncertainties vs median 9, IQR 5-15 for medicines without uncertainties). For medicines with uncertainties, in the upper quartile relatively many changes occurred (median within quartile 26.5 for 6 medicines vs 22.5 for 4 medicines without uncertainties). The most frequently observed changes concerned the sections Undesirable effects (31% of all changes) and Warnings and precautions for use (27% of all changes), which were similar for medicines with and without uncertainties (32% vs 29% and 27% vs 27%, respectively).

Conclusions: Acceptance of uncertainties regarding phase III data at approval does not seem to affect the number of post-approval

changes made to the MA. Further research will evaluate the type, impact and timing of changes in more detail.

448 | Utilization of ICD10 codes indicating weeks of gestation in routine clinical care of pregnant women in the USA

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Background: Administrative claims databases are increasingly being used for research to evaluate the safety and effectiveness of medications used during pregnancy. However, these databases have been criticized for lacking an important data element, the last menstrual period (LMP), and must infer this date using algorithms derived from claims.

Objectives: To assess the pregnancy start date based on the ICD-10 code category (3ZA) that is specifically tied to the pregnancy weeks of gestation.

Methods: The Optum Dynamic Assessment of Pregnancies and Infants (DAPI) is a database of pregnancy episodes derived from the Optum Research Database. We identified pregnancies of women continuously enrolled from at least 6 months prior to the beginning of pregnancy through the end of the pregnancy episode in the 2 years following the transition from ICD-9 to ICD-10 coding in the United States (01 October 2015-01 October, 2017). We randomly selected and assessed claims profiles (25 each) of pregnancies ending in a livebirth, stillbirth, elective abortion or spontaneous abortion. The end of pregnancy and pregnancy outcomes were identified through algorithms that utilize a combination of ICD-10 diagnosis and procedure codes.

Results: From 132 858 pregnancy episodes with a known pregnancy outcome, 2715 (2%) were ectopic and 164 (0.1%) were trophoblastic disease. The remaining pregnancies resulted in 113 326 (85%) livebirths, 697 (0.5%) stillbirths, 6005 (4.5%) elective abortions and 9951 (7.5%) spontaneous abortions. Twenty livebirths and stillbirths, respectively, had at least two 3ZA codes. From the elective abortion profiles, 14 (56%) had at least one 3ZA code; minimum weeks of gestation code across the profiles was less than 8 weeks; maximum weeks of gestation code was 17; 2 profiles had unspecified weeks of gestation. Twenty-two (88%) profiles for elective abortions had at least one 3ZA code. From these, 9 (41%) had maximum weeks of gestation between 10 and 12; 9 (41%) had only a code for less than 8 weeks gestation (Z3A.01); and 4 (18%) had unspecified weeks of gestation (Z3A.00).

Conclusions: The new ICD-10 code category for weeks of gestation was observed in 85 of the 100 profiles assessed, suggesting extensive utilization of the code in routine clinical care of pregnant women. This code category may serve to more accurately estimate beginning and end of pregnancy in administrative claims data. Further assessment of the presence and performance of this code, particularly for pregnancy loss, is warranted.

449 | Linkage of mother and child pairs in the information system for research in primary care (SIDIAP) in Catalonia

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Background: Studies on the benefits and risks of drugs during pregnancy are limited given that pregnant women are usually excluded from clinical trials for ethical reasons. The Information System for Research in Primary Care (SIDIAP) is a potential data source to investigate adverse drug reactions during pregnancy and early life. However, only a very small fraction of mother and child health records are directly linked in SIDIAP.

Objectives: To develop and validate an algorithm to link mother and child pairs in SIDIAP for children born from 2005 to 2016 in Catalonia.

Methods: SIDIAP contains anonymized information recorded in primary care centres of the Catalan Health Institute (CHI) for 5.8 million people since 2005, including clinical diagnoses, laboratory tests, prescribed/dispensed drugs, vaccinations, demographic/lifestyle information. 692,402 subjects born from 2005 to 2016 were included. The CHI has access to personal data and used the following information from women and children to create an algorithm of linkage: national insurance number and the co-insurance status (holder/beneficiary), family name, age (women aged 14–49 years), dates of birth and delivery. Descriptive comparisons of those linked and unlinked mother-child pairs were conducted. Children with direct linkage available in their records ($n = 7,307$) were used as the gold-standard of true matches in order to validate the created algorithm.

Results: The proposed algorithm established mother and child pairs for 67.8% ($n = 241,859$) of all boys and 68.1% ($n = 228,687$) of girls in SIDIAP. Of these, 382,082 (81.2%) pairs were linked using only national insurance number and co-insurance status. The mean of age (6.1 [SD = 3.3] vs 6.7 [SD = 3.5] years) and the MEDEA index of deprivation (22.0% vs 22.6% in the most deprived) was similar, while the proportion of foreigners (10.5% vs 20.8%) was lower in the linked compared with the unlinked children, respectively. The proposed algorithm established linkages for 5,358 children in the validation dataset, and 95.4% of those pairs were confirmed as true matches.

Conclusions: The linkage of mother and child pairs in this large electronic health records data base provides a powerful resource for investigating maternal and child health and a useful tool for studies on pharmacovigilance and drug and vaccine safety among pregnant women. Additionally, the linked population is representative of the total children born from 2005 to 2016 in SIDIAP, although it underrepresents foreigner population.

450 | Impact of validation of major bleeding events diagnosis recorded in a primary care database

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Background: Major bleeding is an important safety endpoint in clinical trials evaluating anticoagulant therapy. In general practice, the risk of major bleeding may be assessed via observational studies using registries, insurance claims databases or primary care databases; however, the validity and completeness of these sources needs to be demonstrated.

Objectives: The purpose of this study was to evaluate the impact of validation on the identification of major bleeding events in patients receiving anticoagulant therapy in The Health Improvement Network (THIN) database.

Methods: Patients aged 2–89 who received a first prescription for an anticoagulant (rivaroxaban or warfarin) between 2012 and 2015 were identified in the THIN database, a large UK primary care database. Data are collected from over 600 general practices throughout the UK. Major bleeding events, defined as a bleeding event necessitating hospitalization or referral to accident and emergency services or a specialist clinic, were identified using a two-step ascertainment process based on Read Codes for bleeding events first and codes for referrals and hospitalization after. Events were then validated using a two-step process requiring manual review of patients' records followed by recoding of additional information in free text comments by the general practitioner.

Results: The positive predictive value for the ascertainment of major intracranial (IC) bleeds using only recorded codes was 96.6%, compared with 70.4% for gastrointestinal (GI) bleeds and 64.1% for urogenital (UG) bleeds. The incidence of major IC bleeding events was therefore similar when calculated prior to and following validation (0.32 per 100 person-years and 0.31 per 100 person-years, respectively). In contrast, the incidence of major GI bleeds identified using codes alone was reduced following validation, from 2.05 to 0.94 per 100 person-years; similarly, that of major UG bleeds decreased from 2.45 per 100 person-years using codes alone to 1.11 per 100 person-years following validation.

Conclusions: Major GI and UG bleeding events ascertained from primary care databases require further validation using any available additional information included in the free text comments to minimise outcome misclassification. Validation against free text therefore increases the reliability of the data obtained; conversely, the absence of validation may lead to overestimations of the incidence of major GI and UG bleeds.

451 | Effect of coding system on the consistency of prevalence estimates in databases

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Background: Capturing disease state in administrative databases is commonly done by applying algorithms based on diagnosis codes, with validation studies demonstrating how different algorithms vary in sensitivity and specificity. While it is expected that prevalence measured with a sensitive algorithm would differ as compared with a specific algorithm, it is unknown whether the difference in prevalence would remain constant as published algorithms are “translated” from the ICD-9 coding system and re-validated in the larger and more detailed ICD-10 code set.

Objectives: To evaluate whether the relative difference in prevalence using sensitive versus specific algorithms remains constant when applied using ICD-9 versus ICD-10 codes.

Methods: We used de-identified data from the Optum Clinformatics® Data Mart database to compare the prevalence of several diseases using codes identified by Quan et al when measured using algorithms with varying levels of specificity and sensitivity. Prevalence was evaluated separately using ICD-9 or ICD-10 diagnosis codes through a sensitive (defined as any inpatient [IP] or any outpatient [OP] diagnosis) and a specific algorithm (any IP diagnosis or two OP diagnoses up to 30 days apart). To compare the effect of ICD version, we estimated prevalence separately within the ICD-9 diagnosis code era (2013-2014; N = 11 222 968 patients) and the ICD-10 code era (2016-2017; N = 12 544 877 patients).

Results: Overall, ICD-10 codes identified more cases than ICD-9 codes, resulting in a 1.2 to 2.2 times higher prevalence when using the sensitive algorithm. With ICD-9, use of the specific compared with the sensitive algorithm resulted in a median relative decrease in prevalence of 49% across diseases (range: 33% to 64%); with ICD-10, the median decrease was 45% (range: 34% to 67%). For example, in ICD-9, myocardial infarction (MI) prevalence was 0.80% using the specific algorithm and 1.60% using the sensitive algorithm, representing a 50% relative decrease. In ICD-10, MI prevalence was 1.10% and 2.10% respectively, with a 52% relative decrease. Similar trends were seen when the specific algorithm was varied by amount of allowed time between OP encounters.

Conclusions: The expected variation in prevalence as measured with algorithms of different specificity can be impacted by the underlying coding system. However, the relative impact of the coding system was modest in the studied diseases and algorithms.

452 | Prognostic impact of various comorbidity measures on 1-year mortality

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Background: To analytically achieve prognostic comparability of contrasted groups, pharmacoepidemiologists use diagnoses-based measures of comorbidity (like Charlson comorbidity index [CCI]) or admission-type based measures. Expanding lookback period involves a tradeoff between identifying more comorbidities and potentially capturing prognostically irrelevant ones.

Objectives: To compare prognostic values of various comorbidity measures and lookback periods with respect to 1 year mortality.

Methods: Using linked registry data, we identified patients with myocardial infarction (MI) in Denmark, in 2009-2011, and obtained hospital data on preceding prognostic measures: admission types, and length of stay (LOS) for all hospitalizations and component diagnoses of the CCI. We examined each measure with lookback periods of 1, 2, 3, 5 and 10 years.

We used logistic regression-generated c-index to estimate the additional discrimination obtained by adding each measure to a reference model containing age alone. The “worse” c-index is 0.5 (model is as good as “a coin toss” in discriminating) and the best is 1.0 (modelling full discrimination). Expressed in percent, 50% is the maximum possible improvement.

Results: We identified 26 160 patients with MI, of whom 24% died within 1 year of diagnosis. The reference model including age alone obtained c-index (95% CI) of 0.76 (0.76-0.77), or an improvement of 26% (26-27). Adding the CCI score with a 10-year lookback period explained an additional 1.7% (1.5-2.0). Admissions count, acute admissions, and LOS each had similar effect, with the best result achieved by adding cumulative LOS with a 1-year lookback period: 2.4% (2.0-2.7). Including each of the 19 CCI-component diseases independently (with same lookback period) produced up to 2.4% (2.1-2.7) model improvement with a 10-year lookback period. A full model adding both short- and long-term contributions of all the measures produced an improvement of 4.5% (4.1-4.9).

Conclusions: Length of hospital stay within the year preceding admission improved the c-index by 2.4% for predicting one-year mortality in patients admitted with MI, and thereby performed slightly better than the other single measures. Combining all available measures produced a 4.5% improvement above the 26% obtained in a model containing age alone.

453 | Development of a dynamic pregnancy database within the optum research database

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Background: Pregnant women are generally excluded from randomized clinical trials. The opportunity to use administrative health care databases to examine the safety of medications that might be used during pregnancy is increasingly common, both in parallel with, or as an alternative to more traditional pregnancy registries.

Objectives: To develop a Pregnancy Database

Methods: We have developed a database of pregnancy episodes, termed the Optum Dynamic Assessment of Pregnancies and Infants (DAPI), using insurance claims and electronic health records (EHR) from the Optum Research Database (ORD). This collection of pregnancies can link maternal exposures with a range of pregnancy outcomes, and can be customized to address research questions regarding utilization, effectiveness and safety of medications used by pregnant women in routine clinical care. Formed using a set of published claims-based algorithms that include ICD9 and ICD10 codes for diagnoses and procedures, along with CPT and HCPCS procedure codes, the database can: (1) identify distinct pregnancy episodes; (2) estimate beginning and end of a pregnancy episode; and (3) identify pregnancy outcomes and infant outcomes. Pregnancies resulting in a livebirth are linked to the infant(s) based on the infant's date of birth, the delivery date, and a family member ID.

Results: 888 150 pregnancies with a known pregnancy outcome are captured in DAPI from January 1, 2007 through October 1, 2017; 12% from the Northeast, 27% Midwest, 44% South, and 17% West. The age distribution (in years) is 13% (18-24); 63% (25-34); 23% (35-44); and 0.4% (≥ 45). Identified pregnancy outcomes include 743 998 (84%) livebirths; 3987 (0.45%) stillbirths; and 126 522 (14%) abortions (spontaneous and elective); other outcomes include ectopic or trophoblastic disease. 635 721 (85%) livebirths have been linked to their mothers. Approximately 6% of pregnancies have both claims and EHR pregnancy-related medical information that include additional supplemental details (not available in claims) such as height, weight, blood pressure measurements, lab tests results, and smoking status.

Conclusions: This large pregnancy database is sourced from claims and EHR, providing a platform for studies of medication exposure during pregnancy, pregnancy outcomes, and infant outcomes. Ongoing development and validation work will further enhance the utility of this resource.

454 | Intravitreal antiVEGF drugs use in Italy in the years 2010-2016: A multi-regional study on claims databases, enriched with prospective data collection

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Background: Anti-vascular endothelial growth factor (anti-VEGF) drugs, as aflibercept, ranibizumab, bevacizumab, and pegaptanib, are intravitreally administered to treat retinal diseases. No data on the pattern of these drugs use in Italy are available.

Objectives: This study aimed at exploring the pattern of anti-VEGF drugs/dexamethasone use in 4 Italian Regions in the years 2010-2016.

Methods: This population-based, drug-utilization study was conducted using administrative databases of 4 Italian Regions in the years 2010-2016. A Case Report Form (CRF) was developed to prospectively collect clinical data from ophthalmologic centers in Sicily and Basilicata. Incident users of anti-VEGF/dexamethasone were

characterized. Prevalence of use, switching pattern and frequency and number of dispensing were calculated. Indications of use were validated for a sample of users from Sicily and Basilicata, through probabilistic linkage to data collected in CRF. The study was conducted in the context of a multi-regional pharmacovigilance project, funded by Italian Medicines Agency (CUP-H56D16000070005).

Results: Among 40 557 patients treated with the study drugs in the study years, 39 539 (97.5%) were incident users, most of whom used ranibizumab (N = 29 646; 75.0%). Most of incident users were females (M/F = 0.8). Around 31% (N = 12 349) patients were judged as affected by diabetic macular edema, the remaining by age-related macular degeneration. Through random sample validation of 1% incident users from Sicily and Basilicata, 75% positive predictive value of indication of use identified in claims database was estimated. The prevalence of use increased over time. During follow-up, two thirds of ranibizumab and aflibercept users received first three administrations within average 35 days lag time. Almost 40% dexamethasone users received consecutive dispensing within 165 days, despite Summary of Product Characteristic (SPC) recommends retreatment to occur after 180 days. Switch among different study drugs was not frequent during the first year (N = 1858, 8.0%).

Conclusions: In 4 Italian Regions, use of intravitreal anti-VEGF drugs/dexamethasone increased 4-fold in the study years, but was not always in line with SPC. Indication of use and clinical parameters may not be satisfactorily identified in claims databases thus requiring enrichment through prospective data collection from ophthalmology centers.

455 | The missing puff: Results of multiple imputation of PPFEV1 in CPRD

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Background: Severity of chronic pulmonary obstructive disease (COPD), with key component percent predicted forced expiratory volume in 1 second (ppFEV1), is an important predictor of COPD outcomes and mortality.

Objectives: To evaluate the effect of missingness in ppFEV1 for the assessment of COPD severity using data on spirometry and symptoms from the Clinical Practice Research Datalink and estimate mortality rates and rate ratios (RRs) adjusting by COPD severity when complete case analysis (CCA) and multiple imputation (MI) are used.

Methods: Cohort study of new users of acclidinium and LABA medications between 2012 and 2015, aged ≥ 40 years with COPD. Severity was classified as GOLD A, B, C, or D according to (1) ppFEV1 (recorded or estimated using expected FEV1 and FEV1, or the Global Lungs Initiative European Respiratory Society Task Force formulas); (2) symptoms from the mMRC dyspnoea grade, the COPD Assessment Test (CAT), or physician-recorded breathlessness; and (3) exacerbation history. The mortality rates and RRs (acclidinium vs LABA) were obtained using a negative binomial regression model adjusting for COPD severity, sex, age, smoking status, and BMI. CCA and MI were employed to account for missing data on ppFEV1. MI was performed using the fully conditional

specification method with 10 imputations. The imputation model included the outcome, exposure, and many a priori relevant variables.

Results: The study included 3555 new users of acclidinium and 4797 new users of LABA. Spirometry results on ppFEV1 (recorded or estimated) were missing for 12.4% of the patients. Approximately 72% of the patients with available data had a ppFEV1 >50%. The distribution of COPD severity among users of acclidinium using CCA vs MI was 24.3% vs 24.7% in category A, 17.2% vs 17.0% in B, 21.7% vs 22.5% in C, and 36.8% vs 35.8% in D. For users of LABA, it was 38.1% vs 38.0% in category A, 19.4% vs 19.2% in B, 22.5% vs 23.0% in C, and 20.0% vs 19.8% in D. The adjusted mortality rates per 1000 person-years when using CCA vs MI were 23.08 vs 25.63 among users of acclidinium and 29.77 vs 33.90 among users of LABA. The adjusted mortality RRs for acclidinium vs LABA were 0.78 (95% CI, 0.58-1.03) with CCA and 0.76 (95% CI, 0.57-1.00) with MI.

Conclusions: Minor differences were observed in the distribution of COPD severity and in the mortality RRs employing CCA vs MI to handle missing data on ppFEV1. Use of MI allowed the inclusion of all the study population in the analyses.

456 | Dispensing of specialist HIV drugs in community pharmacies—Evaluation of effects on access and satisfaction

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Background: The prospect of chronic HIV patients obtaining their ART medication in community settings has considerable interest for health authorities. In Portugal, the Health Ministry promoted a pilot study randomizing the dispensing of ART therapy to hospital pharmacies and to community pharmacies in order to assess the impact of a transfer of dispensing from the current hospital setting. This study “piggy backs” on that pilot and uses data from patients randomized to community pharmacies.

Objectives: To evaluate the impacts of transferring the ART therapy from hospital to community pharmacies.

Methods: Observational, prospective cohort study of the patients in the pilot study randomized to community pharmacies who were invited to participate and followed for 6 months. Data were collected through the pharmacies' software (demographics, drugs dispensed, and pharmacists' interventions) and patients' self-reported questionnaires (QoL, satisfaction, adherence, travel and waiting times). Descriptive statistics characterize the participants, drug exposure, and pharmacist's interventions and the analysis compares QoL, adherence, satisfaction, travel modes, travel times and waiting times between the two dispensing settings.

Results: 29 pharmacies recruited 43 patients with a mean age of 54 (SD 9.85), 72% male and 48% were unemployed. The most frequently dispensed drugs were Abacavir/Lamivudine, Ritonavir, and Emtricitabine/Tenofovir, 49%, 33% and 30% of the times, respectively. Patients reported a significant increase in satisfaction levels regarding waiting time, privacy, business hours and overall satisfaction ($p < 0.05$). Mean travel time decreased 74% from 46 (SD 28) to 12 (SD 16) minutes. 79% of the patients walked to the community pharmacy compared with the 37% that walked to the hospital. Waiting time was 11 minutes lower ($p < 0.05$). There were no impacts on the QoL and on self-reported adherence. The clinical stability of all patients was maintained. A total of 235 pharmacist interventions were reported as a consequence of the identification of health and drug-related problems, the most common being potential drug interactions.

Conclusions: The findings suggest that changing the dispense setting of ART therapy from the hospital to the community pharmacy will not have negative impacts on health gains, measured by QoL, adherence and clinical stability and it will positively impact on patient's satisfaction levels and access times.

457 | Part 2 treatment pathway analysis of incident dementia patients in four electronic health record databases in Europe

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Background: Treatment pathway analyses provides crucial insights into disease management. The European Medical Information Framework (EMIF), an Innovative Medicines Initiative (IMI) project, provides a platform for research using real-world patient health care data from across Europe to evaluate treatment of dementia and physician prescribing behaviours.

Objectives: To evaluate the heterogeneity of real-world treatment pathway in newly diagnosed dementia patients regarding; specific dementia therapy initiation, lines of therapy, duration, switching, add-on and combination therapy, time to discontinuation and patient characteristics.

Methods: We obtained ethical approval to access 4 databases: The Health Improvement Network (THIN, UK), the Integrated Primary Care Information (IPCI, The Netherlands), the Health Search Database (HSD, Italy) and the Aarhus University Hospital database (AUH, Denmark). Dementia patients were identified from registration to database end with their incident diagnosis recorded at age ≥ 55 with at least 1 year registration prior to diagnosis, initiating a therapy within a year

(± 365 days) of diagnosis and with at least 2 years follow-up post dementia therapy initiation. Dementia therapies included donepezil, galantamine, rivastigmine and memantine. We performed descriptive analysis including sunburst plots, Kaplan-Meier curves and boxplots to provide a visual representation of the dementia treatment pathway.

Results: We identified 191 933 incident dementia patients in all 4 databases. 42 552 patients fulfilled our inclusion criteria. The most common first line therapy initiated within a year (± 365 days) of diagnosis was rivastigmine in IPCI, donepezil in HSD and THIN, and memantine in AUH. Memantine was the most common second line therapy across all databases. Galantamine in IPCI and donepezil in AUH, HSD and THIN were the most common third line therapies. In the 2 years follow-up post therapy initiation, the longest median duration of use was galantamine in HSD (84 days), donepezil in AUH (154 days), donepezil and memantine in IPCI (97.5 days) and in THIN all therapies had the same median duration of use (56 days).

Conclusions: We provide a real-world insight into the treatment pathway of dementia patients and the heterogeneous management across Europe.

458 | Prevalence and determinants of ADHD medication use in Quebec children between 1998 and 2015

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Background: An increase in attention deficit hyperactivity disorder (ADHD) medication use has been observed over the last two decades.

Objectives: We aimed to: 1) describe the time trends of ADHD medication use among children aged 18 years and under, stratified by sex, age groups and types of ADHD medication, 2) to determine dosages and switches among ADHD medication users, 3) to identify and quantify determinants of ADHD medication use in children.

Methods: Using the Quebec Pregnancy/Children Cohort, we conducted a longitudinal cohort study to investigate trends in the prevalence of ADHD medication use among singletons liveborn between 1998 and 2015. We excluded children with autism spectrum disorder. Among treated children with ADHD, we assessed dosages and switches of ADHD medications. Logistic regression models were used to estimate crude and adjusted odds ratios (OR) with 95% confidence intervals (CIs) to identify factors associated with ADHD medication use among children.

Results: During the study period, we identified 235 132 singletons. We observed a significant increase in the prevalence of overall ADHD medication use ($p < 0.01$). We found that the prevalence rates of ADHD medication use were significantly increased with a higher prevalence for boys vs girls (67.3% vs 32.1%) and in children 6-11 years old (80.8%). Methylphenidate was the most used (60.5%). We found that 96.7% of ADHD medication prescriptions were at optimal dosage compared with 0.7% and 2.6% at sub-dosage and over-dosage, respectively. We found that 20.4% of children switched to another class of ADHD

medications or had concomitant use of ADHD medications. Factors significantly associated with ADHD medication use were male sex, low birth weight, having ADHD diagnosis at age 6-11 years, having asthma and epilepsy, and having depression/anxiety. Use of antidepressants before the 1st diagnosis of ADHD was strongly associated with ADHD medication use (aOR = 3.06, 95%CI [2.21-4.22]). Younger maternal age, being on welfare, maternal psychiatric disorders and maternal use of antidepressants during 2nd/3rd trimesters of pregnancy were also predictors of ADHD medication use in children.

Conclusions: Our findings indicate that ADHD medication use increased over time, specifically for children aged 6-11 years. Furthermore, overall ADHD medications are prescribed predominantly according to published recommendations.

459 | Seventeen-year nationwide trends in use of long-acting bronchodilators and inhaled corticosteroids among adults: A Danish drug utilization study

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Background: Long-acting bronchodilators and inhaled corticosteroids (ICS) are the cornerstones in treatment of chronic obstructive and inflammatory pulmonary diseases. However, non-adherence to guidelines is widespread. Detailed information on real-life treatment patterns is needed to promote rational use.

Objectives: We aimed to investigate nationwide time trends in individual-level treatment patterns of long-acting bronchodilators and ICS.

Methods: Using nationwide Danish health registries, we identified all Danish adults with a prescription of long-acting bronchodilators and/or ICS from 2000 to 2016. We investigated the total use of long-acting bronchodilators and ICS, the proportion of current users and the rate of new users over time. Finally, we assessed treatment persistence.

Results: We included 23 061 681 prescriptions of long-acting bronchodilators and ICS issued to 805 860 individuals from 2000 to 2016. Over this period, the total annual amount of prescribed long-acting bronchodilators and ICS increased 39%. Similarly, the proportion of adult users increased from 2.6% to 4.5%, mainly driven by the introduction of combination therapy and long-acting muscarinic antagonist (LAMA). Though the rate of new users of fixed dose combination drugs increased substantially over time, the overall rate of new users was stable. In general, the proportion of patients on therapy after 1 year was low (25-53%), especially among young individuals and users of ICS.

Conclusions: We document a pronounced increase in the total use of long-acting bronchodilators and ICS over time, mainly driven by the introduction of combination drugs and LAMA. Special attention should be paid to the low level of persistence, especially among young individuals and users of ICS.

460 | Recent trend of antidiabetic medications use and hypoglycemia among T2DM in the US commercially insured population

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Background: It is not clear how anti-diabetes medication use and hypoglycemia have been influenced by the change in clinical guidelines for diagnosis and treatment of type 2 diabetes (T2DM) and availability of newer anti-diabetes agents in recent years.

Objectives: This study aims to investigate 1) the prevalence and annual trend of use of different types of anti-diabetic medications and combinations from 2008 to 2014 and 2) the incidence and annual trend of hypoglycemia diagnosis in the same period.

Methods: Design: Retrospective, cross-sectional, time series analyses Setting: The study used data from the Marketscan® Commercial Claims and Encounters and Medicare Supplemental Database from 2007 to 2014. T2DM population was defined for each study year in the study period and included patients: (1) receiving at least 1 inpatient or 2 outpatient T2DM diagnosis, (2) aged 18 years of age or older, (3) maintaining continuous enrollment for the entire calendar year. Exposures: Any anti-diabetic medications including oral antidiabetic agents and insulin. Outcomes: (1) the prevalence of different anti-diabetic medication use and (2) incidence of hypoglycemia. Anti-diabetic medications were classified according to the therapeutic class and use was measured by having at least one prescription filled for that drug class. To identify hypoglycemic events, we used inpatient and outpatient claims with primary or secondary diagnosis codes (Ginde, 2008). Statistical Analysis: we calculated annual rates of using different drug classes and incidence of hypoglycemia. All analyses were stratified by sex and by age groups. We conducted linear regression to test trends in the treatment use rates, prevalence of hypoglycemia.

Results: Among up to 1.5 million T2DM patients, 60% to 62% received at least one antidiabetic medication in a given year during the study period from 2008 to 2014. The use of metformin increased from 38% to 44%, insulin from 16% to 22%, DPP-4 inhibitors from 6% to 10%, and SGLT-2 inhibitors from 1% to 10%. The use of TZD decreased from 14% to 4%. No marked changes in the distribution of using multiple antidiabetic medications. Similar patterns across gender and age groups. Incidence of hypoglycemia increased from 4.6% to 5.5%, especially among the 65+ years old.

Conclusions: The change in guideline for T2DM and availability of new antidiabetic agents may impact the pattern of antidiabetic medication use with increasing incidence of hypoglycemia particularly among elderly.

461 | Impact of new drugs and treatment recommendations on drug utilization in multiple sclerosis

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Background: Since 2011, eight disease-modifying treatments (DMTs) for multiple sclerosis (MS) have been approved in Europe. In addition, rituximab, approved for certain types of cancers and rheumatoid arthritis, has been increasingly used in Sweden off-label to treat MS.

Objectives: To describe drug utilization in MS and assess the impact of both the introduction of new drugs and treatment recommendations issued to facilitate rational drug use.

Methods: Interrupted time series analyses were conducted using data on all MS patients treated with DMTs in the Stockholm County, Sweden, from January 2011 until December 2017. Inpatient and outpatient drug utilization data were derived from the regional health care data warehouse (VAL). The interventions were: 1) the introductions of fingolimod (August 2011), alemtuzumab (September 2013), dimethyl fumarate (May 2014), teriflunomide (June 2014), peginterferon beta-1a (May 2015), and daclizumab (February 2017); 2) the local recommendation on rituximab use issued at the largest MS clinic in Stockholm (November 2012); and 3) the regional Drug and Therapeutics Committee (DTC) recommendation on how dimethyl fumarate should be used (October 2015). The study outcome was the count of monthly prevalent DMT users throughout the study period.

Results: There were 4765 individuals diagnosed with MS residing in the Stockholm County from 2011 to 2017. Of these, 2934 (62%) were treated with an MS DMT. Of the drugs introduced since 2011 only fingolimod and dimethyl fumarate significantly impacted MS DMT utilization. In parallel, the use of rituximab off-label increased steadily, reaching 58% of all DMT-treated MS patients by the end of the study period. The local recommendation on rituximab was associated with an increase in rituximab use. The regional DTC recommendation on dimethyl fumarate was associated with a decrease in dimethyl fumarate use.

Conclusions: Three drugs—fingolimod, dimethyl fumarate, and rituximab off-label—impacted MS DMT utilization in the Stockholm County. The associations between the treatment recommendations and subsequent changes in drug utilization indicate that such interventions can influence the uptake and utilization of new drugs used in the specialized care setting.

462 | Post-surgical opioid prescriptions and risk of long-term use in the USA

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Background: In response to the opioid crisis, some have focused on restricting the days supply for initial post-surgical prescriptions to ≤ 7 days. However, there is limited evidence of the effect of limiting days supply on long-term use.

Objectives: To evaluate differences in risk of long-term use following surgery among an opioid naïve population using the 7-day cutoff, compared with cutoffs based on morphine milligram equivalents (MME) and quantity of pills (QTY) dispensed.

Methods: Using the MarketScan Commercial Claims and Encounters and Medicare Supplemental database, we identified all patients undergoing outpatient surgery between 1/1/2006 and 9/30/2015. Patients were required to have ≥ 12 months of prior continuous enrollment with no baseline surgeries or opioid prescriptions, and ≥ 180 days of follow-up. We identified the initial post-surgical opioid prescribed, examining the days supplied, total MME, and QTY dispensed. We used Poisson regression controlling for age, sex, surgical site, year, and baseline health comorbidities (mental health, history of substance abuse, pain-related diagnoses, medications) to estimate adjusted risk differences (RD) per 100, risk ratios and 95% confidence intervals (CI) of long-term opioid use (prescription fill 90-180 days post-surgery) comparing those receiving larger versus smaller amounts of opioids.

Results: We identified 6 866 805 opioid-naïve surgical patients (mean age 46 yrs). Overall, 35% received an opioid for post-operative pain, with median days supply = 4, median total MME = 200, and median QTY = 30. Among those receiving post-op opioids, 13% received prescriptions for > 7 days and 7% had long-term opioid use. Risk of long-term use was 1.22 times (CI: 1.17, 1.29) higher among those receiving > 7 days (RD = 1.5, CI: 1.4, 1.6) compared with those receiving ≤ 7 days. Those receiving > 200 MME were at 1.08 times (CI: 1.04, 1.13) the risk of long-term use compared with those receiving ≤ 200 MME (RD = 0.46, CI: 0.40, 0.53), and patients receiving > 40 pills were at 1.18 times (CI: 1.12, 1.23) the risk of long-term use (RD = 1.1, CI: 1.0, 1.2) compared with those receiving ≤ 40 pills.

Conclusions: Opioid naïve patients receiving > 7 -day supply of opioids for post-op pain were at increased risk of long-term use. While patients receiving > 200 MME or > 40 pills were also at increased risk, the association was stronger among those with > 7 days supplied (number needed to harm ~68). Further work will examine predictors of initial prescriptions above recommended cut points, and risk factors for continued use after 90 days.

463 | Adherence of prescribers to recommendations to reduce medication related hospitalizations

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Background: In the Netherlands a task force assigned by the Dutch government developed 40 recommendations to reduce medication related hospitalizations.

Objectives: The aim of this study was to assess the adherence of prescribers to these recommendations.

Methods: The adherence of prescribers to the recommendations was measured for the years 2009-2014, in the Integrated Primary Care Information database (IPCI: containing data from GP patient record systems) and a community pharmacists (CP) database (SFK: containing medication dispensing data) using pre-specified performance indicators. Measurability of indicators depended on the data available in each database. Potential for improvement of adherence was assessed by two independent reviewers per database. Of the 40 recommendations, 11 were translated into 29 indicators measurable in both databases and 7 into 28 additional indicators measurable only in IPCI.

Results: In IPCI 7 indicators (12%) improved during the study period and 50 indicators (88%) remained the same. For 40% of these indicators no further improvement is expected. Twenty-one indicators (36%) with still a large potential for improvement were related to *gastrointestinal and other bleedings* (4), *electrolyte disturbances*, *renal insufficiency and heart failure* (10), *fractures due to fall incidents* (4), *fractures associated with glucocorticoid steroids* (2), and *bradycardia associated with digoxin and/or sotalolol* (1). Twelve of these indicators originated from recommendations advising laboratory measurements before or after initiation of a new treatment. In SFK only 29 indicators were measurable. For 74% of these indicators no further improvement is expected. Two indicators showed improved adherence during the study period. The two indicators with large potential for improvement were related to *gastrointestinal and other bleedings*. Six indicators were estimated with different potential for improvement between the databases.

Conclusions: As shown in two types of databases, the majority of indicators still have a potential for improvement. These results show that despite efforts by regulatory officials and health care professionals in response to multiple safety reports, adherence of prescribers to these recommendations can still be improved.

464 | Risks of ischemic and bleeding events of drug-eluting stents: A nationwide population-based cohort study

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Background: Percutaneous Coronary Intervention (PCI) with drug-eluting stents (DES) reduce the occurrence of major adverse cardiac events but may lead to bleeding complications notably due to the recommended antiplatelet therapy after implantation. To date, although a large variety of DES are commercialized, comparative data on their relative effectiveness and safety have remained limited.

Objectives: To compare the risks of ischemic and bleeding events between the major types of DES used in France in 2014.

Methods: Data of the French national health insurance reimbursement and hospitalisation databases (SNDIS) were used. All adult patients covered by the general health insurance scheme (ie, about 75% of the French population) and hospitalized for PCI with DES implantation in 2014 were included and followed during 1 year after DES implantation. The risk of ischemic events (revascularization, acute coronary syndrome and/or stroke), major bleeding events and/or death was compared across six types of DES (XIENCE, PROMUS (durable-polymer everolimus-eluting stents), RESOLUTE (durable-polymer zotarolimus-eluting stent), BIOMATRIX, NOBORI (biodegradable-polymer biolimus-eluting stents) and ORSIRO (biodegradable-polymer sirolimus-eluting)), using a multilevel Cox model adjusted for individual comorbidities, cardiovascular risk factors and treatments at baseline and for hospital characteristics.

Results: A total of 52 891 subjects were included: 34.4% were implanted with XIENCE, 27.6% with PROMUS, 24% with RESOLUTE, 8% with BIOMATRIX, 5% with NOBORI and 1% with ORSIRO. The incidence rate of ischemic events, major bleeding events and/or death was 19 per 100 person-years overall, ranging from 15 for ORSIRO to 21 for RESOLUTE. In multivariate analysis, the risk of ischemic events, major bleeding events and/or death did not differ between the various DES (in comparison with XIENCE: adjusted HRs ranging between 0.85 [CI95%: 0.68-1.07] and 1.04 [0.98-1.10]). Results remained unchanged when analysis was restricted to patients at high risk of bleeding or thrombosis at baseline.

Conclusions: Risks of ischemic and bleeding events does not differ across the various types of DES used in real-life in France. This study shows the usefulness of the French medico-administrative databases for health technologies assessment.

465 | Safety evaluation of the levonorgestrel intrauterine device Mirena® from the French nationwide claims and hospitalization database

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Background: Copper and levonorgestrel intrauterine devices (c-IUD and L-IUD) are common and effective reversible methods of contraception. In early 2017, concerns emerged from German users regarding the safety of the L-IUD Mirena. These were largely echoed in social networks and medias in France which led to a tremendous amplification of adverse events reporting for this device in May 2017. In response, the French National Agency for Medicines required a pharmacovigilance national-level study to review the safety profile of Mirena.

Objectives: To assess the Mirena risk in real-life in comparison with c-IUDs use to provide additional information to the pharmacovigilance national-level study.

Methods: This retrospective cohort study used data of the *Echantillon Généraliste de Bénéficiaire* database, a representative 1/97th random sample of the French national health care claims database, and included women aged between 20 and 55 years with a first reimbursement for either Mirena or c-IUD between 1 January 2010 and 31 December 2014. Risks for Mirena compared with c-IUDs use were estimated over up to 6 years of follow-up for the following events: all-cause death, hospitalizations (any cause), ectopic pregnancy, pelvis inflammatory disease or infection, uterine perforation, IUD ablation for potential intolerance (ie, not followed by pregnancy, childbirth or abortion), neuro-psychiatric drugs initiation, or new psychiatric consultation(s). A Cox model adjusted on age was applied in an *intention-to-treat* survival analysis, after matching subjects from both groups (Mirena vs c-IUDs) on a propensity score. In addition, an *as-treated* analysis was conducted in which follow-up of women within a group was censored if they removed their IUD (censoring at date of removal).

Results: Among the women who initiated contraception with IUD between 1 January 2010 and 31 December 2014, 9318 Mirena users (mean age 36.2) could be matched to 10 185 c-IUD (mean age 35.4). After matching and age-adjustment, Mirena users had a slight but significant higher risk of IUD ablation for potential intolerance (HR 1.05, 95%CI 1.01 to 1.10) or anxiolytic drugs initiation (1.08, 1.01 to 1.15) when compared with c-IUD users. The *as treated* analysis confirmed these results.

Conclusions: These results confirm the lack of difference that can be found when comparing Mirena safety with that of other IUD. They also support the safety signal on anxiety that was raised from pharmacovigilance data for this specific L-IUD.

466 | Investigation of psychiatric adverse events following exposure to levonorgestrel containing IUDs

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Background: Intrauterine devices (IUD) are implantable contraceptives of which some brands steadily release levonorgestrel (LNG) over an extended time period. Exposure to LNG-releasing IUD can increase the risk of depression but case reports and on-line discussion suggest wider psychiatric effects.

Objectives: This study investigates a possible association between LNG exposure and anxiety, panic attacks, sleep problems and restlessness.

Methods: A cohort study was performed to compare incidence of psychiatric adverse events between groups of women who were new users of LNG-releasing and non-hormonal intrauterine devices. Women were selected from a UK general practice database (THIN) and maximum follow-up was 5 years. The data are representative of the UK population. To assess effects on the total exposed population, women both with and without prior symptoms were examined in separate analyses. The statistical analysis used a Cox proportional hazards method adjusted for demographic and clinical features observed in the year prior to treatment. The proportional hazards assumption was tested for each explanatory variable. Hazard ratios for first occurrence of psychiatric symptoms or prescriptions of disease specific treatments were calculated on an intention to treat basis. A sensitivity analysis assessed the effect of censorship at cessation of treatment exposure.

Results: Significant associations were found between levonorgestrel exposure and raised hazards of anxiety (HR = 1.20 95% CI (1.09, 1.31)) and sleep problems (HR = 1.22 95% CI (1.08, 1.38)) in women without prior record of these events. Over the 5 years 16% of unexposed women had records of anxiety suggesting an attributable risk of 3.5% for LNG exposure if a causal relationship exists. Significant effects were not found in women with prior symptoms but similar hazard ratio estimates were observed. No significant associations were found for panic attacks or restlessness. Clear baseline differences in clinical characteristics and age between the groups were present. These were included in the model as potential confounding factors.

Conclusions: Associations consistent with a causal effect of levonorgestrel exposure on anxiety and sleep problems were observed. Substantive differences in baseline characteristics of the treated groups make robust conclusions difficult but the results strongly suggest that additional studies are warranted.

467 | Abstract Withdrawn

468 | Utilizing natural language processing to identify intraoperative medical device failures and subsequent surgeon mitigation

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Background: Circular staplers are a critical device when creating gastrointestinal anastomoses. Intraoperative device failures can be mitigated by the surgeon resecting the prior failed anastomosis and creating a new anastomosis with another circular device.

Objectives: The objective of this study was to estimate the frequency of device mitigation with a second device and evaluate automating this process utilizing natural language processing (NLP).

Methods: This study analyzed the United States Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database which houses reportable medical device reportable complaints. A random sample of circular stapler complaints from May 2004 to July 2017 were identified and labelled as whether a second circular device (MULTI) was utilized to mitigate the device failure or some other mitigation method (SINGLE). NLP was performed with pre-processing of the event description text with feature extraction and creation of unigrams. Machine learning classifiers, including linear: support vector classifier (SVC) with a linear kernel, ridge classifier and tree-based: decision tree (DT), random forests (RF) were evaluated. Positive predictive value (PPV), sensitivity, and F1 score (summary score based upon PPV and sensitivity) were calculated. The most informative words and the linear model coefficients for the positive (MULTI) and negative (SINGLE) classes were presented. Python 3.5.3, NLTK toolkit for pre-processing and Scikit-learn machine learning library were utilized.

Results: A total of 1028 complaints were labelled: 35.4% had a of these had a surgeon intervention with a second device. The best performing linear classifier was SVC with (PPV, sensitivity, and F1): MULTI (0.87, 0.76, 0.81), SINGLE (0.88, 0.94, 0.91), and average (0.88, 0.85, 0.86). The most informative words for MULTI: "another" (-4.82), "like" (-3.12), and "new" (-2.92) and SINGLE: "suture" (1.67), "sew" (0.96), and "make" (0.90). The best Tree-based classifier was DT which had a similar performance SVC: MULTI (0.81, 0.82, 0.81), SINGLE (0.90, 0.90, 0.90), and average (0.86, 0.86, 0.86).

Conclusions: Natural language processing models had good prediction for identification of device failures where a second device was utilized. Future applications of NLP include identification of specific device failure modes and mitigations which may be useful for developing novel signal detection methods.

469 | Analysis of the likelihood of hypertension among discharges with IUD removal vs insertion suggests IUD-related risk increase mostly in non-White women

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Background: As part of Translational Epidemiology/Genetics research that is essential for predictive evaluation of real-world performance of medical products, we are developing evidentiary approaches that are aimed at device evaluation in sex/race-stratified subpopulations and identification of biomarkers indicative of device performance.

Objectives: To address safety of intrauterine devices (IUD) and examine the role of Hypertension (HTN) as possible IUD-related adverse outcome, based on its likelihood among race-stratified subpopulations with IUD removal vs insertion.

Methods: National Inpatient Sample from Agency for Healthcare Research & Quality (NIS/AHRQ, 2010-2014) was used for a retrospective analysis of comorbidities in IUD-related discharges, using CCS and ICD9 codes. Using SAS v.9.4 (Proc Logistic: Unadjusted and Adjusted for interactions among age, race, and IUD status), the incidence of HTN (CCS: 98 and 99) was compared among discharges with no IUD codes (no-IUD) and the race-stratified (White, Black, and Rest) discharges with IUD removal (V25.12) and IUD insertion (V25.11).

Results: Compared with no-IUD discharges, HTN was less frequent among IUD discharges with both insertion and removal: OR = 0.11 [95% CI: 0.09; 0.13] and OR = 0.44 [95% CI: 0.37; 0.52], respectively. However, the likelihood of HTN was increased among discharges with IUD removal vs insertion in all race-stratified subpopulations (White, Black, and Rest). Black women had the highest likelihood of HTN, as confirmed by direct comparison between the Black and White women with IUD removals: OR = 3.67 [95% CI: 2.31; 5.83]. Further suggesting the race-related HTN risk increase *after* IUD use, the HTN likelihood was either similar or even lower among non-White vs White women with IUD insertion: OR_{Black} = 0.96 (95% CI: 0.61; 1.50) and OR_{Rest} = 0.33 (95% CI: 0.21; 0.53). Logistic regression models confirmed race and age as potential confounding variables. Consistent with the HTN risk modification by race, our preliminary *in silico* queries identified SNPs that can be considered as putative race-related HTN biomarkers.

Conclusions: Epidemiologic evidence suggests that IUDs may exacerbate the race/age-related risk of HTN, especially in non-White women. Further pharmacogenetic research is needed for identifying biomarkers that can predict and mitigate HTN risk among the race-stratified IUD users.

470 | Analysis of allergic/inflammatory skin conditions among discharges with IUD removals vs insertions suggests IUD-related risk increase which is modified by race

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Background: As part of CDRH's efforts for predictive evaluation of real-world performance, we are developing evidentiary approaches aimed at device evaluation in sex/race-stratified subpopulations.

Objectives: To explore the risk for Allergic/Inflammatory Skin Conditions in race-stratified IUD users.

Methods: National Inpatient Sample from Agency for Healthcare Research & Quality (NIS/AHRQ) was used for a retrospective analysis of Allergic/Inflammatory Skin conditions in IUD-related discharges, identified by CCS and ICD9 codes. Using AHRQ/NIS data (2010-2014) and SAS v.9.4, comorbidities were compared among discharges with no IUD codes (no-IUD) and race-stratified (White, Black, and Rest) discharges with IUD removal (V25.12) or IUD insertion (V25.11).

Results: Compared with no-IUD, women with IUD insertions and removals showed similar frequencies for overall Allergic/Inflammatory Skin conditions. However, their risk was higher in Black vs White women with both IUD removals: OR = 1.66 [95% CI: 1.11; 2.47] and insertions: OR = 1.24 [95% CI: 0.96; 1.59]. Compared with no-IUD, likelihood for Dermatitis Eczema was lower among IUD insertions: OR = 0.55 [95% CI: 0.30; 1.03]; the same trend among IUD removals did not reach statistical significance. Compared with their counterparts with insertions, White and Rest women with IUD removals had higher risk of Dermatitis/Eczema: OR = 1.31 [95% CI: 1.27; 1.34] and OR = 1.89 [95% CI: 1.80; 1.99], respectively. Black women with IUD removals had lower likelihood of Dermatitis/Eczema when compared with Black women with insertions OR = 0.30 [95% CI: 0.27; 0.33] as well as to White women with removals: OR = 0.43 [95% CI: 0.39; 0.46]. An opposite trend for higher Dermatitis/Eczema risk in Black vs White women was found when comparing discharges with IUD insertions: OR = 1.87 [95% CI: 1.82; 1.91]. The small number of Allergic Urticaria cases precluded separate analysis. When this category was combined with Dermatitis/Eczema, Black women with removals vs insertions showed a risk increase: OR = 2.61 [95% CI: 2.50; 2.73], similar to their White and Rest counterparts. The likelihood of Dermatitis/Eczema combined with Allergic Urticaria was also higher in Black vs White women with IUD insertions: OR = 1.78 [95% CI: 1.74; 1.82].

Conclusions: IUD may increase the risk of Allergic/Inflammatory skin conditions; risk modification by possible race-related predisposition suggests the need for putative race-related biomarkers.

471 | Can electronic health records be used to identify medical procedure-related events indicative of difficult insertion of intrauterine devices?

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Background: Procedure-related information is needed to contextualize use of a medical device or drug delivery system, but many procedure-related events are poorly captured in claims data. One way to potentially obtain meaningful procedure-related data is through electronic health record (EHR) review.

Objectives: We assessed the potential to collect procedure-related information on difficult intrauterine device (IUD) insertions within 4 EHR systems, to satisfy a regulatory safety study.

Methods: A stratified random sample of 125 postpartum women receiving IUDs was assessed at each of 4 sites (3 Kaiser Permanente sites—Northern California, Southern California, and Washington—and Regenstrief Institute, Indiana). Structured (National Drug Codes, International Classification of Diseases 9-Clinical Modification, Current Procedural Terminology) and unstructured (chart review of clinical notes) data were used to identify possible indicators of difficult IUD insertion. We assessed use of cervical dilation, ultrasound guidance, misoprostol, paracervical block, clinician note for “difficult insertion” or “complicated procedure,” and insertion of a second IUD within 30 days as possible indicators. Descriptive statistics for prevalence were calculated for each site.

Results: Prevalence of indicators of difficult IUD insertion across sites were cervical dilation, 0.0–1.6%; ultrasound guidance, 0.8–3.2%; misoprostol, 0.0–1.6%; paracervical block, 0.0–1.6%; provider note, 0.1–1.6%; and insertion of a second IUD, 0.8–1.6%. No site consistently reported the highest or lowest proportion across indicators. If all indicator categories were considered mutually exclusive, then difficult insertions would constitute 4.8–8.8% of all insertions across sites.

Conclusions: The overall prevalence of indicators of difficult IUD insertion was slightly lower than has been published (8–9%). The prevalence of some indicators (eg, dilation) was lower than previously published, while the prevalence of other indicators (eg, misoprostol) was similar to previous reports. Substantial effort was needed to capture specific, procedure-related information for occasional events. Although we were able to identify indicators of difficult insertion using structured and unstructured EHR data, we cannot determine the proportion of the possible indicators that represent true difficult insertions.

472 | Hydroxyurea adherence and cumulative dose associated with hospital readmission in sickle cell disease

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Background: Sickle cell disease (SCD) is a congenital hemoglobinopathy characterized by frequent emergency room (ER) visits and hospital admissions. The current knowledge base lacks definitive supporting evidence from large-scale population-based studies on the effects of HU on readmission risks.

Objectives: To assess the effects of HU on acute care utilization and readmission rates by SCD patients in the real-world setting.

Methods: A six-year retrospective cohort study was performed using Truven Health MarketScan® databases, covering >10% total SCD population in the United States. All hospitalizations for SCD-related complications from 1 January 2009, and 31 December 2014 were identified as eligible cases. HU utilization patterns were evaluated using proportion of days covered (PDC) and average daily dose in the 180 days preceding index admission. Multivariable logistic regression was used to assess the association between HU exposure patterns with all-cause 30-day readmission or ER visits. We used generalized estimating equations assuming a first-order autoregressive covariance structure, adjusted for demographics and comorbidities, to estimate odds ratios (OR) with 95% confidence intervals (CI).

Results: Among 6926 patients analyzed, we identified 20 721 SCD-related admissions. HU exposure was found in 4263 of 20 721 SCD-related admission events (20.6%) within 6 months prior to the admission. HU was more likely to be provided to children 10–17 years (957 of 3469 [27.6%]) as well as young adults aged 18–29 years (1733 of 6761 [25.6%]) compared with other age groups. HU exposure was associated with lower 30-day all-cause readmission rates in adults treated with an average daily dose of ≥ 1 g during the six months period prior to index admission (OR, 0.72; 95% CI 0.52–0.99) and an average daily dose of 0.5–1 g (OR, 0.73; 95% CI 0.57–0.93), compared with patient admissions with <0.5 g average daily HU use; adherence to HU as the PDC ≥ 0.80 was associated with lower 30-day all-cause acute care utilization (OR, 0.54; 95% CI 0.43–0.68) and PDC 0.50–0.80 (OR, 0.60; 95% CI 0.50–0.71), compared with patient admissions with <0.50 adherence to HU use.

Conclusions: Adherent use of HU with higher dose is instrumental in reducing 30-day re-admissions among patients with SCD.

473 | Entacapone and prostate cancer in Parkinson's disease patients: A large veterans health administration study

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Background: An increased incidence of prostate cancer was observed in Parkinson's disease patients treated with entacapone during a preapproval randomized clinical trial; the relation has not been robustly investigated in the US ambulatory setting.

Objectives: To investigate whether entacapone is associated with prostate cancer and assess whether the association is correlated with advanced disease at time of cancer diagnosis.

Methods: Using data from the Department of Veterans Affairs health care system, new-user cohorts were created of PD patients treated with add-on entacapone or add-on dopamine agonist/monoamine oxidase B inhibitors between January 2000 and December 2014. Patients were followed on treatment for occurrence of prostate cancer, identified via linkage to the VA cancer registry.

Results: Mean follow-up time was 3.1 and 4.0 years in the entacapone and control cohort, respectively. There were 17 666 subjects meeting study criteria (mean age, 74 (SD 8.6) years); the entacapone-treated group comprised 5257 subjects. Twenty-three prostate cancer cases occurred in the entacapone cohort and ninety-seven in the control cohort. The overall incidence of prostate cancer was 1.8 per 1000 person-years of risk. There was no difference in risk of prostate cancer between the cohorts for increased duration of entacapone intake (adjusted HR: 1.08; 95% confidence interval: 0.46-2.51 for cumulative exposure of 2 or more years). Time since starting drug therapy and cumulative dose (mg) also do not suggest a difference in prostate cancer risk between cohorts.

Conclusions: Prolonged therapy with entacapone was not associated with increased prostate cancer incidence; however, higher severity of prostate cancer was observed.

474 | Viral kinetic correlates of cytomegalovirus disease and death after hematopoietic cell transplant

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Background: Despite significant strides in pre-emptive antiviral treatment of cytomegalovirus (CMV) infection after hematopoietic cell transplantation (HCT) and a corresponding reduction in CMV disease rates, toxicity from these therapies remains unacceptably high. Due to low CMV disease rates, clinical trials for novel therapeutics are not practical to conduct due to the need for large sample sizes to show clinical benefit. CMV viral load (VL) has therefore been proposed as a molecular surrogate endpoint for use in clinical studies given the observed relationship between viral load and the occurrence of disease. However, the exact quantitative and qualitative relationship of viral load measurements and disease risk and death remain to be elucidated.

Objectives: The goal of this study was to quantify the relationship of longitudinal metrics of CMV VL with CMV disease and mortality.

Methods: CMV viral load measures and CMV-associated outcomes were collected using data and samples from a landmark double-blind, placebo-controlled randomized clinical trial (RCT) of ganciclovir (GCV) treatment to prevent CMV in HCT patients (Goodrich et al. NEJM 1991). CMV DNA PCR testing was performed on frozen plasma samples collected during the first 100 days post-HCT in both GCV-treated and placebo patients. Viral kinetic parameters including most recent VL, highest VL measure, duration of VL detection, and the change in VL measure were calculated from CMV DNA PCR values as continuous, time-dependent variables. Cox proportional hazard models assessing associations between viral kinetic markers and time to CMV disease and death events were adjusted for donor CMV serostatus and acute graft-versus-host-disease, counting events to day 100 and day 180 post-HCT.

Results: Among 37 GCV-treated patients, the incidence of CMV disease and mortality were significantly reduced in the first 180 days post-HCT as compared with 35 placebo recipients. The mortality reduction among the GCV-treated patients was sustained through 3 years following study completion. Higher recent VL, highest VL, and longer duration of VL detection were associated with CMV disease alone (HRs and 95% CI: 1.8 (1.4, 2.4), 1.9 (1.4, 2.6), 1.4 (1.1, 1.8), respectively) and CMV disease or death (HRs and 95% CI: 1.6 (1.3, 1.9), 1.5 (1.2, 1.9), 1.2 (1.0, 1.4), respectively) at 180 days.

Conclusions: Our results support VL markers as correlates for CMV disease and death. This may facilitate further study and delivery of potent, non-toxic CMV therapies to HCT recipients.

475 | Demographic characteristics and treatment patterns among patients treated for hereditary angioedema in a US cohort, 2006-2015

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Background: The high disease burden and rarity of hereditary angioedema (HAE) requires a greater understanding of patient characteristics and treatment patterns. New data are presented from a large cohort of HAE patients in the United States.

Objectives: Describe demographic and clinical characteristics as well as treatment patterns among a cohort of patients with claims for HAE-related diagnoses and treatments.

Methods: This retrospective cohort study used PharMetrics Plus, a US administrative claims database, from 2006 to 2015. An algorithm was developed to identify HAE patients of all ages using claims for ICD-9-CM (277.6) or ICD-10-CM (D84.1) codes (typically used for HAE) and HAE-related treatments. Patient characteristics and treatment patterns were analyzed using descriptive statistics.

Results: 1429 treated HAE patients were identified (62% female, mean age at first HAE-related claim = 39 years [SD 16], mean follow-up duration = 1015 days [SD 850]). Across all years, 45% received only C1-esterase inhibitors (C1-INHs), ecallantide, or icatibant (increasing from 29% in 2010 to 71% in 2015), 22% received only androgens (declining from 90% in 2006 to 15% in 2015), 7% received only fresh frozen plasma, tranexamic acid, or aminocaproic acid, and 26% received a combination of treatments. 79% had a claim for swelling/angioedema and 55% received depression/anxiety treatment. An additional 1488 patients received no HAE-related treatment but had claims with ICD-9-CM (277.6) or ICD-10-CM (D84.1) codes.

Conclusions: These data provide evidence of changing treatment patterns among a large US commercially insured HAE population. In recent years, most HAE patients were treated with C1-INHs, ecallantide, or icatibant. Androgen treatment declined; however, 15% were still treated only with androgens in 2015. The disease burden due to comorbid depression or anxiety warrants further investigation, along with those patients without HAE treatment.

476 | Burden of illness in patients with Duchenne muscular dystrophy in the United States

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Background: Duchenne muscular dystrophy (DMD) is a rare muscular dystrophy affecting mostly males. Orthopedic, cardiac, and respiratory conditions are known to impact patients' quality of life and/or are the leading causes of premature death. Due to the rarity of DMD, burden of the disease is not well understood.

Objectives: This study aims to describe the burden of DMD in terms of comorbidities and ambulatory status in patients.

Methods: This is a retrospective, observational study using a large administrative claims database in the United States with patients under commercial and Medicare Supplemental insurance plans. Since there is no specific ICD code for DMD, the following criteria were used to identify potential DMD patients: (1) male, (2) had ≥ 2 claims with ICD-9-CM code for hereditary progressive muscular dystrophy (359.1) or ICD-10-CM code for muscular dystrophy (G71.0) that were

≥ 30 days apart between January 2010 and March 2017, and had ≥ 1 claim before 2014, (3) aged < 18 years at time of first claim, and (4) with complete medical and pharmacy records in 2014. All records in 2014 and before were included in the study.

Results: 691 patients were identified. Of which, 51 patients (7%) aged 2-5 years, 232 patients (34%) aged 6-11 years, 262 patients (38%) aged 12-17 years, and 145 patients (21%) aged 18+ years. Orthopaedic conditions increased from affecting 22% in patients aged 2-5 years, to 72% in patients aged 18+ years. Scoliosis, specifically, while affected 6% of patients aged 2-5 years, was observed in 53% of patients aged 18+ years. Consistently, while only 8% of patients aged 2-5 years had a power wheelchair-related claim, it increased to 56% in patients aged 18+ years.

Among patients aged 2-5 years, 27% developed cardiac conditions, including cardiomyopathies and heart failure. This proportion increased to 63% in patients aged 18+ years. In all age groups, respiratory infections affected at least half of the patients, and there was a general increase in respiratory insufficiency or failure over age.

Conclusions: Burden of patients increased over age, affecting not only the orthopaedic aspects of patient's health, but also heart and respiratory functions. Limited by the lack of specific ICD code for DMD, our sample could have included patients with other types of muscular dystrophies, indicating the need to create a specific ICD code for DMD to facilitate research in this disease.

477 | Acute generalized exanthematous pustulosis: Results of the German registry over a 10-year period

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Background: Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction. The clinical picture shows an acute onset of erythema usually arising in the face and body folds that spreads over large areas of the body. AGEP typically presents with facial edema and dozens to hundreds pinhead-sized non-follicular pustules appear on the erythematous areas. The skin eruption is accompanied by fever and neutrophilia in the peripheral blood. Mucous membranes are sometimes affected and in about 20% of the cases at least one internal organ is involved. Within a few days AGEP resolves with a typical postpustular desquamation.

Objectives: To provide data on demography and drug exposure of AGEP-cases over a period of 10 yrs (2003-12).

Methods: Patients, who were ascertained by the German Registry on severe skin reactions (dZh) between 2003 and 2012 with a validated diagnosis of AGEP, were included for analysis. For drug analysis cases that developed in the hospital were excluded.

Results: 97 cases of AGEP were validated by experts as definite (39/97) or probable (58/97) using a specific score. The median age was 62 years (range 15-89 years). Women (50.5%) and men (49.5%) were equally affected. All patients developed erythema (91% widespread) and 43 patients at least two different skin

lesions, of which maculopapular/morbilliform eruption (58/96) and diffuse erythema (55/96) occurred most frequently. All patients developed pustules and in 95% the typical desquamation was observed. Mucous membranes were involved in 22% of the cases (1 site: 15/97, ≥ 2 sites: 6/97). The most common cause of AGEF was the intake of penicillins (32%), but other highly suspected drugs were also observed, eg, clindamycin (9%), terbinafine (7.4%), hydroxychloroquine (4.4%). No plausible drug cause was found in 7.4% of the cases.

Conclusions: Patients from Germany are older compared with published data on AGEF. This may reflect the aging population in Germany, but could also mean that the disease is rarely identified as a form of SCAR in children and adolescents. In our study we could not confirm the previously described female predominance. More than 50% of the cases can be explained by a drug known to be associated with AGEF (EuroSCAR-study), whereas other drugs, eg, prednisolone or sulfonamides, are less frequent causes.

478 | Efficacy of enzyme replacement therapy for Hunter syndrome

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Background: Mucopolysaccharidosis II (MPS II) or Hunter syndrome is characterized by the absence or deficiency of the iduronate-2-sulfatase enzyme that is involved in the early stages of glycosaminoglycan degradation (GAGs). The only available treatment is high-cost enzyme replacement therapy (ERT) with either idursulfase or idursulfase beta. **Objectives:** The aim of this study was to evaluate the efficacy and effectiveness of ERT for patients with MPS II.

Methods: We conducted a systematic review of observational studies and clinical trials. We searched the databases: MEDLINE (Pubmed), LILACS, Cochrane Library and EMBASE (accessed April 2017), and performed manual search and searched gray literature. The assessment of methodological quality was performed using the Newcastle scale for observational studies and the risk of bias of clinical trials from the Cochrane Collaboration.

Results: Search retrieved 361 publications. After eligibility criteria assessment we included eleven studies (four cohort studies and seven clinical trials), of which six were funded by the drug-producing company. Clinical trial and observational studies presented, respectively, low and high methodological quality. In the clinical trials intravenous ERT with idursulfase was shown to be superior to placebo for urinary GAGs, hepatomegaly, splenomegaly and six-minute walk test (6MWT).

Cohort studies confirmed trials results and showed greater survival for patients treated idursulfase. In a clinical trial intravenous idursulfase beta was superior to idursulfase for urinary GAGs and 6MWT. In the clinical trial of intrathecal idursulfase the treatment showed decrease in GAG levels in the cerebrospinal fluid.

Conclusions: Intravenous ERT with idursulfase showed favorable results for light outcomes, such as 6MWT and urinary GAGs, as well as for survival. Intravenous idursulfase beta was better than idursulfase for light outcomes, suggesting that it may favorably alter survival. Intrathecal idursulfase is still under study for severe MPS II, and the decrease in in GAG levels in the cerebrospinal fluid must be confronted with development and disease progression results.

479 | Safety of enzyme replacement therapy for mucopolysaccharidosis II

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Background: Mucopolysaccharidosis type II (MPS II), also known as Hunter's syndrome, is a lysosomal storage disease - deficiency or non-existence of the iduronate-2-sulfatase (IDS) enzyme. Currently, the main treatment available for MPS II is the IDS enzyme replacement therapy (ERT) with idursulfase or beta-idursulfase.

Objectives: The objective of this study was to evaluate the safety of ERT for patients with MPS II.

Methods: We conducted a systematic review of observational studies and clinical trials. We used the databases MEDLINE (Pubmed), Latin American and Caribbean Literature in Health Sciences (LILACS), Cochrane Library and EMBASE (accessed April 2017), including manual search and gray literature. The methodological quality assessment was performed using the Newcastle scale for observational studies and the risk of bias of clinical trials from the Cochrane Collaboration.

Results: Thirty-six publications were found. After eligibility criteria assessment we included and we included eleven studies (four cohort studies and seven clinical trials), of which six were funded by the drug-producing company. Clinical trial and observational studies presented, respectively, low and high methodological quality. The studies evaluated 1693 subjects (with a minimum of ten and a maximum of 1400). Intravenous ERT with idursulfase or beta-idursulfase was shown to be safe with few adverse reactions related to the two technologies evaluated. The most important events were infusion reactions, with severe adverse reactions reported, such as anaphylaxis. However, safety results are of concern in intrathecal administration, since severe adverse reactions were frequent, including reports of infection in the cerebrospinal fluid.

Conclusions: The major safety concern with intravenous ERT with either idursulfase or beta-idursulfase are infusion reactions, hence the necessity of assisted infusion in most cases. Intrathecal ERT is still under study, and cerebrospinal fluid infection will be a challenge for wider use.

480 | Comparative performance of a modified landmark approach to avoid immortal time bias when no time to treatment data are available within oncological databases

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Background: The Mantel-Byar method (MBM) is a gold-standard analytical approach to avoid immortal time bias (ITB), but requires information on the time between start of follow-up and exposure initiation. Alternatively, a modified landmark approach might be used, which assumes exposure initiation at a pre-defined landmark time.

Objectives: In context of an expected positive association between adjuvant chemotherapy (ACT) and overall survival among resected pancreatic cancer (PaC) patients, this study aims to empirically assess the performance of this modified analytical approach relative to a conventional landmark analysis and the MBM.

Methods: Data from resected PaC patients diagnosed in 2003-2014 and registered in the national cancer registries of Belgium, the Netherlands or Slovenia were used to estimate the association between ACT and overall survival using a Cox proportional hazards model by country and overall. Results derived from ITB (neglecting the time to ACT initiation), MBM, conventional and modified landmark analyses with assumed cut-off times of ACT initiation at 9, 12 and 15 weeks post-diagnosis were compared.

Results: In total, 5668 patients with a total of 10 921 person-years of follow-up were eligible. All analytical approaches showed an expected significant survival benefit for resected PaC patients who received ACT, but ITB analyses led to strong overestimation of ACT benefits compared with MBM (ITB: overall HR [95%CI] 0.68 [0.62-0.75] vs MBM: 0.82 [0.71-0.93]), whereas the conventional landmark approach generally provided rather conservative estimates (0.86 [0.75-1.00] 15 weeks landmark). HRs derived from modified landmark analyses depended on the cut-off time, but were similar compared with the MBM at 15 weeks (0.81 [0.70-0.94]).

Conclusions: A modified landmark approach might be a valid alternative to the MBM if no time to treatment information is available. The performance depends on the chosen cut-off time.

481 | Assumptions about grace period in exposure definition may impact comparative estimates on risk of gastrointestinal bleeding between oral anticoagulants

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Background: With administrative data, a treatment episode is constructed using refill dates, days' supply, and allowing for a grace period between dispensations. In clinical practice, warfarin dosages are frequently adjusted that results in longer refill gaps compared with direct oral anticoagulants (DOACs). Universal application of the same grace period to warfarin and DOACs may lead to differential misclassification of exposure and biased comparative safety estimates.

Objectives: To investigate how the assumption on grace period in exposure definition may impact the estimates of relative risk of gastrointestinal (GI) bleeding between warfarin and DOACs.

Methods: Design: retrospective population-based cohort study with competing risk analyses. Setting: from computerized health care databases of the Régie de l'assurance maladie du Québec (RAMQ) we identified all patients with atrial fibrillation, newly dispensed an oral anticoagulant between 2010 and 2014. Exposure: time-dependent exposure definition to classify each day of follow-up into three mutually exclusive categories: warfarin use, DOAC use, or neither. Treatment episodes were constructed consecutively assigning five different grace periods: fixed (3, 30, 60 and 90 days), and 75percentile of the dispensation duration. Outcome: GI bleeding identified using ICD-9 and ICD-10 codes. Statistical analysis: for each definition of grace period, competing-risk analysis using Fine and Gray modeling was performed to estimate the subhazard ratio with 95%CI of the risk of GI bleeding associated with use of warfarin vs DOACs. The models were adjusted for quintiles of propensity scores, year of cohort entry, and an indicator variable accounting for the number of switches between treatment categories.

Results: We identified 44 492 patients. With 3-day grace period, use of warfarin was associated with significantly lower risk of GI bleeding compared with DOACs (0.86, 95% CI:0.77-0.96). However, when we increased grace periods to 30, 60, and 90 days, the risk was similar between warfarin and DOACs (0.95, 95% CI:0.85-1.06; 0.94, 95% CI:0.84-1.05; and 0.96, 95% CI:0.86-1.07, respectfully). With the 75percentile grace period, the risk was significantly lower for warfarin vs DOACs (0.83, 95%:0.74-0.92).

Conclusions: Universal assignment of the same grace period to warfarin and DOACs may lead to misclassification of exposure and biased estimates on comparative safety.

482 | Defining exposure measures for inferring the association between prescription opioid use and bone fracture

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Background: A variety of study designs and exposure measures have been used to examine the risk of bone fracture associated with prescription opioid utilisation, but a comprehensive critique of their methodological approaches has not yet been undertaken.

Objectives: This systematic review aimed to identify and critique observational studies reporting bone fracture outcomes in which the effect of prescription opioid exposure was reported.

Methods: An electronic literature search of MEDLINE (1946-2017), Embase (1974-2017) and CINAHL Plus (1937-2017) was conducted using structured search strategies. Published observational and open-label studies reporting risk estimates for the association between prescription opioid(s) and bone fracture were included. The study quality was assessed by use of the ROBINS-I tool. Data regarding study objectives, design, and definitions of exposure and comparator were extracted, appraised and reported.

Results: Of the 21 included studies from North America, Europe and Australia, assessing opioid use and bone fracture risk was the primary objective in 8 studies, including nested case-control (n = 3), case-control (n = 1), prospective (n = 1) and retrospective cohort (n = 3) studies. The nested case-control and the case-control studies retrospectively examined for the presence of an opioid prescription within 12-months (n = 3) and 14-days (n = 1) prior to the bone fracture. Only 1 case-control study matched controls based on pain condition, controlling for confounding by indication. Duration of the 4 cohort studies ranged from 1 to 9 years; opioid use was compared with no use (n = 3) or NSAID use (n = 1) and opioid exposure was defined in various ways: ≥ 1 opioid prescription during 5-years (n = 1), participant-reported daily use at each of 3 visits during 9-years follow-up, long-term use (≥ 3 fills in the first 90 days of treatment) (n = 1), and persistent use (< 14 -day gaps between fills) (n = 1). The remaining 13 studies, including case-control (n = 3), case-crossover (n = 1), prospective (n = 4) and retrospective cohort (n = 5) studies did not directly assess the association between opioids and risk of bone fracture.

Conclusions: The relationship between prescription opioids and bone fracture remains contentious due to varying definitions of opioid exposure and potential for confounding. Future studies need account for potential confounders and aim to better understand how different definitions of opioid exposure relates to the risk of bone fracture.

483 | The effect of anti-acid therapy on survival in idiopathic pulmonary fibrosis: A methodological review of observational studies

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Background: International treatment guidelines for idiopathic pulmonary fibrosis (IPF) have given a conditional recommendation for anti-acid therapy in patients with IPF. However, the evidence supporting this recommendation and subsequent observational studies reported conflicting results on the potential beneficial effect of anti-acid therapy on mortality.

Objectives: We reviewed these studies to evaluate whether these discrepant findings could be explained by time-related methodological issues, such as immortal time bias, a bias not previously described in the field of IPF.

Methods: We searched the databases EMBASE AND MEDLINE (from the earliest available online year until July 2017) for observational studies assessing the effectiveness of anti-acid therapy on mortality in IPF. Studies were examined for the presence of immortal time bias. Study-specific hazard ratios were pooled using random-effect models, categorized into studies with or without immortal time bias.

Results: We identified 10 observational studies. Five cohort studies reported highly beneficial effect estimates associated with anti-acid use, with adjusted hazard ratios ranging from 0.23 to 0.58. Four of these five studies were clearly affected by immortal time bias, with a pooled hazard ratio of 0.46 (95% CI 0.30-0.69) while the fifth was unclear. The five studies that avoided immortal time bias reported no significant association between anti-acid use and mortality, with a pooled hazard ratio of 0.94 (95% CI 0.76-1.17).

Conclusions: The apparent highly beneficial effects of anti-acid therapy on mortality in patients with IPF result from observational studies affected by immortal time bias. The effectiveness of anti-acid therapy on mortality in patients with IPF thus remains uncertain and needs to be reassessed with more accurate observational study methods.

484 | Variation of the exposure measures for evaluating long-term opioid utilisation in chronic non-cancer pain

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Background: A variety of measures are found in epidemiological studies to quantify long-term opioid utilisation and inference its associated

outcomes in patients with chronic non-cancer pain (CNCp). However, the systematic appraisal on the selection of exposure measures is lacking.

Objectives: This systematic review aimed to identify and critique opioid utilisation measures used in observational studies on patients with CNCp.

Methods: An electronic search was conducted in PubMed (1975-2017), MEDLINE (1946-2017) and EMBASE (1974-2017) using structured search strategies. Fully published observational studies reporting measures for opioids use in patients with CNCp were included. The study quality was assessed by the Newcastle-Ottawa Scale. Data regarding study objective, design, comparator, exposure and outcome measures were extracted, appraised and reported.

Results: The 28 included studies used various aggregated level or individual patient data for different research purposes. Of the 17 studies measured opioid exposure and relevant outcomes (pain relief, health care service use and cost, abuse, dependence, overdose adverse drug reactions), 4 cross-sectional studies measured occurrence of exposure (≥ 1 prescription, ≥ 70 days/3 months, ≥ 3 quarters/year) during a study period ranged from 10 months to 9 years. Similarly, the remaining 13 retrospective cohort studies measured occurrence of exposure defined as ≥ 1 or ≥ 2 prescriptions or receiving opioid daily for 12 weeks during a study period ranged from 6 months to 5 years. Of the 11 studies that only measured opioid exposure, 6 cross-sectional studies measured Defined Daily Dose (DDD; $n = 4$), Oral Morphine Equivalent (OMEQ) dose ($n = 4$), number of opioid prescriptions ($n = 3$), number of opioid users ($n = 2$) and duration of opioid use ($n = 2$) during a study period ranged from 1 to 11 years. Likewise, the remaining 5 cohort studies also measured the duration of opioid use ($n = 3$), number of opioid prescriptions ($n = 2$), OMEQ dose ($n = 2$), DDD ($n = 1$) and total amount of dose in milligram ($n = 1$) in the study period range from 1 to 15 years.

Conclusions: Although dosage such as OMEQ was the common domain to measure opioid utilisation, the appropriateness of inferencing outcomes with various measures of opioid prescription occurrence over a long-term period is still contentious. Further studies are needed to validate the opioid measures for assessing long-term opioid exposure associated outcomes.

485 | Impact of recruitment approach on response rate to an online survey assessing behavior related to the misuse and abuse of prescription opioids

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Background: Increasing internet availability allows for the use of web-based surveys for epidemiologic studies. However, there is little published research on the effectiveness of different approaches used to

contact and recruit participants for these studies. There is a need to gather data on recruitment strategies for internet studies to maximize online survey response rates.

Objectives: To evaluate the impact of email and letter-based recruitment strategies on the response rate for an online survey assessing behavior related to the misuse and abuse of prescription opioids.

Methods: The study included survey-eligible adult individuals who were enrolled in a commercial insurance plan that contributed administrative claims data to the HealthCore Integrated Research Database (HIRD), had ≥ 2 pharmacy claims for any opioid analgesic on two different dates between July 2015 and December 2016 (study period), continuous medical and pharmacy benefits during the study period and both email and mailing addresses available. Potential participants were identified from claims in the HIRD and invited to participate in a cross-sectional online survey to assess behavior related to the misuse and abuse of prescription opioids. Study participation consisted of completing a one-time internet survey designed to be 20-30 minutes long. Initially, eligible individuals were sent an email that invited them to participate in the study. Individuals who did not respond to the first email were sent two additional email outreach attempts. As a means of further increasing the response rate as measured by the list completion rate (completed surveys/sample used), a mailed letter invitation and follow-up by additional reminder email communications were subsequently added for up to four email contacts and one mailed letter.

Results: Of 1018 completed surveys, 283 were obtained from a list of 9280 individuals following the original email and two additional outreach emails for a list completion rate of 3.0%. Following the addition of the mailed invitation letter, the list completion rate more than doubled to 7.8%. After a final reminder email following the recruitment letter, the list completion rate increased to 10.9%.

Conclusions: The use of multiple types of recruitment strategies offers a means to improve overall internet survey response rates. Use of any single recruitment mode alone may not reach all potential participants.

486 | Application of the prevalent new-user design among commercially insured US patients (MarketScan 2006-2015)

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Background: The active comparator new-user (ACNU) study design is the preferred design in pharmacoepidemiology and comparative effectiveness research because of its theoretical and practical advantages. The ACNU design has been recently criticized because it reduces the cohort size when many new-users have been treated with the older comparator drug and are therefore excluded from the study. The prevalent new-user (PNU) design has been proposed to address this issue, but the design changes the causal interpretation of the treatment effect estimates. Implementation of the PNU design in US commercial claims databases, like MarketScan, has not been evaluated.

Objectives: To determine the change in cohort sizes between the ACNU and PNU designs in MarketScan with a study question comparing users of a more recent antidiabetic drug class, sodium-glucose cotransporter-2 inhibitors (SGLT-2i), with users of an older comparator drug class, dipeptidyl peptidase 4 inhibitors (DPP-4i).

Methods: Using the Truven Health Analytics' MarketScan® Commercial Claims and Encounters Database, we identified all new-users of SGLT-2i and DPP-4i using drug claims from January 1, 2006 to September 30, 2015. New-users were required to have at least 1 year of continuous enrollment prior to index date without any prior SGLT-2i and DPP-4i prescriptions. We then applied the PNU design by including prevalent new-users of SGLT-2i with prior DPP-4i use in the year before the SGLT-2i index date. Patients in both designs were required to have at least two same-drug class prescription claims, be continuously enrolled from the first to second prescription fills, and be under 65 years old at index date.

Results: The ACNU design generated a cohort of 48 911 new-users of SGLT-2i. To this cohort, the PNU design added a maximum gain of 4381 (9%) prevalent new-users of SGLT-2i switching from DPP-4i.

Conclusions: Including prevalent new-users in MarketScan increased the SGLT-2i cohort size by at most 9% of the ACNU cohort size since many of the prevalent new-users entered the database on treatment which excludes them from analysis. This gain may be even less if some of the prevalent new-users cannot be appropriately matched with comparators for analysis. The small gain in sample size does not seem to outweigh the disadvantages of changing the causal interpretation of the treatment effect estimates and the increased potential for selection bias and confounding by indication in this setting.

487 | Evaluation of the quality of interim analyses in observational safety studies—Literature review

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Background: Interim analyses are playing an increasingly important role in observational safety studies of medical products as well-conducted interim analyses may detect safety signals early and sometimes inform regulatory decision-making and clinical practice. Yet the methods for interim analyses are under-studied and the quality of the interim results is largely unknown.

Objectives: This literature review aims to examine the quality of interim analyses in observational safety studies and discuss methods and key considerations for conducting interim analyses in observational studies.

Methods: From PubMed and EMBASE databases, we identified interim analyses of observational studies of medical products published between January 2000 and March 2017. We excluded randomized clinical trials, as well as observational studies that did not pre-define a safety outcome.

Results: Of 206 abstracts screened, 21 eligible publications were selected for full review. Three of the 21 interim analyses presented a

pre-defined objective for the interim analyses. Seven articles specified the timing, and four articles specified the frequency, of conducting the interim analyses. Six publications specified who received access to the interim results, eg, Data Monitoring Board. None of the articles provided a stopping rule for the interim analyses. The majority of the interim analyses were descriptive; only two were hypothesis testing safety studies with a comparison group and a relative risk estimate for the safety outcome(s). Both studies presented safety outcomes by treatment exposure group (referred to as unblinding in observational studies), and none suggested a Type I error adjustment due to the unblinded interim look. The interim results from one of the two studies (Meador et al. 2009) led to a Drug Safety Communication by the Food and Drug Administration for labeling update.

Conclusions: This review of a small number of published interim analyses suggests that methods and key considerations for conducting an interim analysis were largely unspecified in the publications, which prevents us from assessing the quality of the interim results. We call for more complete reporting and examination of the methods used in interim analysis in observational safety studies.

488 | The drug interaction outcomes surveillance study: Simulations comparing self-controlled designs

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Background: There is a growing need for real-world evidence on the clinical impact of drug-drug interactions (DDIs). Self-controlled designs, both the case-crossover and self-controlled case series (SCCS), are particularly promising for investigating DDI outcomes in large health care databases. Their comparative performance in this context, however, is unknown.

Objectives: To use simulated data to compare the robustness of the case-crossover design and the SCCS under violation of assumptions in DDI studies.

Methods: We simulated cohorts of 5000 patients, with a chronic drug affected by the interaction (object drug), a 14-day therapy with the drug causing the interaction (the precipitant), and a binary outcome. We assumed no direct effect of the precipitant on the outcome (odds ratio [OR] 1.0), a direct effect of the object drug (OR 2.5), and a positive interaction (OR 2.0) between the object drug and the precipitant. The following scenarios were evaluated: (1) time-varying confounding; (2) chronic precipitant; (3) a population trend in precipitant drug exposure; and (4) event-dependent object drug discontinuation. Cohorts were analyzed using the SCCS and case-crossover designs evaluating exposure to the precipitant within person-time exposed to the object drug. We generated 1000 cohorts for each scenario and compared mean estimates, mean bias, and mean squared error (MSE) for both designs.

Results: The case-crossover produced the most biased estimates with a chronic precipitant (mean bias 0.40) and with a trend in precipitant

exposure (mean bias 0.28), while SCCS produced unbiased estimates in these scenarios. In the presence of time-varying confounding, both designs yielded biased estimates (mean bias 0.19 for SCCS, 0.18 for case-crossover). When patients discontinued the object drug at the occurrence of an outcome, the SCCS produced biased estimates (mean bias of 0.14 with 90% of patients and 0.04 with 50% of patients discontinuing the therapy), whereas the case-crossover estimates were not affected. The SCCS was more efficient, producing smaller MSEs as compared with the case-crossover across all scenarios.

Conclusions: In settings with independent outcomes, no misclassification, and no substantial event-dependent censoring (<50%), the SCCS may be preferred to the case-crossover design for evaluating outcomes of DDIs. With heavy event-dependent drug discontinuation, the case-crossover design may be preferred provided there are no time-related trends in precipitant drug exposure.

489 | The use of case crossover and self-controlled case series studies in pharmacoepidemiology: A literature review

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Background: Case-only study designs like the case-crossover (CCO) and the self-controlled case series (SCCS) design can assess associations of time-varying exposures on risk of acute health events. They use within-person comparisons and therefore better control for non-time varying confounding than conventional designs that rely on comparisons between individuals. Little recent information exists to what extent case-only designs are used in pharmacoepidemiology.

Objectives: To evaluate the use of the CCO design and the SCCS design in pharmacoepidemiology.

Methods: PubMed was searched from inception to 09 January 2018 for original pharmacoepidemiologic research using the SCCS or CCO design. Eligible studies assessed pharmacologic exposures—studies on medical procedures or devices were excluded. Citations including abstracts were used for analysis. Pharmacological exposures (up to 3 per publication) were classified into 10 groups and outcomes (up to 3 per publication) into 15 groups.

Results: The search identified 1968 citations and 322 studies were eligible for inclusion in the review. Over half of the studies (n = 171, 53.1%) used the CCO design, 145 (45.0%) the SCSS design, and 6 (1.9%) used both designs in a single study. The earliest CCO study was from 1995 and the earliest SCCS study from 2001. The number of articles using either design grew from one in 1995 to 42 in 2015, with no apparent further increase in 2016 (37 publications) and 2017 (42 publications). The most common exposures were vaccines (n = 88, 27.3%—about one-third on influenza) followed by psychoactive agents (n = 68, 20.8%), cardiovascular agents (n = 41, 12.7%) and analgesics (n = 23, 7.1%—most on NSAIDs). The SCCS design was used in all but 5 of the vaccine studies (94.0%), whereas the CCO design was used more for other exposures. Fifteen studies

(4.7%) assessed drug-drug interactions. Of all studies, the most frequently seen outcome was cardiovascular diseases (n = 53, 16.5%), followed by gastrointestinal/digestive tract events (n = 34, 10.6%) and bone fractures (n = 20, 6.2%). About one quarter of the studies (n = 86, 26.7%) used the CCO or SCCS design together with another study design for validation purposes.

Conclusions: CCO and SCCS designs are increasingly used to assess a range of pharmacologic exposures and safety and effectiveness outcomes. Vaccine safety studies almost exclusively use the SCCS design, which can adjust for age and time effects as vaccinations are usually given at certain ages or seasons.

490 | Persistent user bias in unidirectional, not bidirectional, self-controlled crossover observational pharmacoepidemiology (SCOPE) studies

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Background: Relationships among different types of SCOPE studies have not been fully understood even by developers of those designs.

Objectives: An ISPE-funded working group is developing guidance documents for SCOPE studies, and studying commonalities among different designs.

Methods: We created a common language of terms, concepts and illustrations so we could compare designs without terminological confusion. Using random replications of hypothetical data, we compared simultaneous exposure- versus outcome-anchored analyses, with respect to impacts of new persistent (chronic) users of medications, with and without reverse causality (ie, outcomes influence future medication use).

Results: For point exposures and point outcomes, the distribution of induction times in an exposure-anchored design (eg, self-controlled case series [SCSS]) is a mirror image of the distribution in an outcome-anchored design (eg, case-crossover [CCO]). This suggests greater commonality than hitherto appreciated. We know persistent users cause a strong positive bias in CCO odds ratios when reference windows only precede outcomes (a “unidirectional” CCO), but not in a standard SCCS study with reference windows before and after exposure (a “bidirectional” SCCS). Simulations reveal it is the unidirectionality that makes persistent users problematic; a bidirectional CCO study is not necessarily biased by persistent users, if exposure data are accurate and reverse causality is absent or very transient. If impacts of reverse causality persist, ie, if health outcomes have a long-term influence on future medication use, then a bidirectional design (using pre-exposure outcome rates) is inadvisable. Persistent users automatically drop out from estimation of a risk ratio in a unidirectional SCCS analysis because their only unexposed time is prior to exposure, which is excluded to prevent reverse causality. In contrast,

dropping persistent users from unidirectional CCO analyses must be done deliberately by the investigator; estimation is limited to transient exposures. Another commonality between outcome- and exposure-anchored designs, is underestimation of associations when persistent users falsely appear to be intermittent users, because of missing data on some of their dispensings or claims.

Conclusions: Commonalities among SCOPE studies enable lessons from outcome-anchored designs to apply to exposure-anchored designs, and vice versa.

491 | Selection bias in observational studies: Impact of identifying “New Users” with open data sources

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Background: Selection bias in general affects the generalizability of results. New user design, where patients free from previous exposure during wash-out period will be enrolled, is often selected in pharmacoepidemiology studies but data continuity in administrative datasets is not always guaranteed.

Objectives: In this analysis, we descriptively assessed an impact of identifying new users in pharmacy claims by applying different eligibility criteria during the wash-out period.

Methods: This is a secondary analysis of a previously conducted persistence study for overactive bladder (OAB) medications, using a pharmacy claims database covering 2% of dispensing records for Japanese outpatients. For better comparability among the OAB medications, new users of each index medication were selected by excluding patients exposed to the index drug during 1-year of pre-index period. In Cohort A, patients were required to have at least one dispense record for any medication every three months during the pre-index period to surrogate the data continuity. In Cohort B, patients were selected without having this requirement from the same source population. We found that older age and previous use of OAB medication were associated with longer persistence. Patient profiles and persistence between these two cohorts were descriptively compared.

Results: By applying this eligibility criterion, the number of patients reduced by 57% (Cohort A = 16 648 and Cohort B = 38 453). Patients in Cohort A were older (mean [SD] 75.9 [10.4] vs 73.3 [13.1] years) and more experienced with non-index OAB medications (21.1% vs 10.0%). The median persistence to each index medication was longer in the Cohort A compared with Cohort B. For example, median persistence to Mirabegron was 105.0 days [95% confidence interval: 96.0, 113.0] in Cohort A and 77.0 days [73.0, 84.0] in Cohort B.

Conclusions: Persistence to medications largely varied by the eligibility criterion. In Cohort A, by restricting patients with any other dispensing records, true new users were excluded and older and more loyal patients to the pharmacy and/or to the OAB treatment were concentrated, resulting in longer persistence. In Cohort B, patients

dispensed at other pharmacies might be misclassified as new users. Other outcomes in New User Design may also be affected with this selection bias. Sensitivity analyses to evaluate the robustness of the results will help to understand the limitations.

492 | The discover study: Diversity of sites, physicians, and patients

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Background: DISCOVER (NCT02322762) is a 3-year, observational study of 14 122 patients with type 2 diabetes (T2D) initiating a second-line glucose-lowering therapy across 673 sites in 37 countries. Extensive efforts were made to include sites and physicians that would represent the management of T2D in each country.

Objectives: To assess the extent to which DISCOVER sites, physicians and patients represent actual T2D care in each country.

Methods: Characteristics of physicians and practices involved in the management of T2D were assessed in each country using published data and insights from key national T2D experts. Physicians/sites that matched these characteristics as closely as possible were invited to participate. Features of participating sites and physicians were compared with the initial sampling plan. Characteristics of patients were also assessed. Descriptive data are reported overall and according to region as classified by the World Health Organization.

Results: Sites were predominantly primary care centres (44.9%, across-region range [ARR]: 11.8-67.7%) and were mainly located in urban areas (83.3%; ARR: 69.8-100.0%). Physicians were primarily endocrinologists/diabetologists (41.8%; ARR: 18.8-77.6%) or primary care physicians (41.2%; ARR: 2.9-71.8%). Although diverse sites and physicians were included, achieving representativeness was challenging, particularly in some lower-middle income countries where published data on T2D care were not available, the number of included sites was small, or primary care centres were not set up for observational research or were not able to participate. Nevertheless, a diverse population of patients with T2D was included. Men (53.2%) and women (46.8%) from various ethnicities (Asian, 42.7%; Caucasian, 29.1%; Arabic, 16.0%; Hispanic, 7.0%; Black, 2.3%; other, 2.9%) and with various levels of education (no formal education, 3.6%; 1-6 years, 17.7%; 7-13 years, 46.6%; >13 years, 32.1%) were enrolled. Mean age was 56.6 years (range: 18 to >90 years); 47.8% (ARR: 39.4-55.5%) of patients were employed or self-employed, and 74.4% (ARR: 32.2-95.1%) had health insurance.

Conclusions: Representativeness in global observational studies is inherently difficult to achieve, particularly in low- and medium-income countries. Efforts to achieve representativeness in DISCOVER led to the inclusion of a heterogeneous population from diverse clinical settings. Overall, ethnicity, sex and urban/rural distributions were in line with the 2017 International Diabetes Federation Diabetes Atlas.

493 | Estimating influenza vaccine effectiveness using an active comparator reduces bias due to confounding by frailty

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Background: Estimating influenza vaccine effectiveness using an unvaccinated comparison group generally results in biased effect estimates with exaggerated beneficial associations.

Objectives: To quantify the reduction of bias when using an active comparator rather than an unvaccinated comparator to estimate preinfluenza season mortality among patients receiving chronic hemodialysis.

Methods: Using data from Medicare's end-stage renal disease program (2009–2013), we compared the risk of all-cause mortality among adult recipients of high-dose vaccine (HDV) versus standard-dose vaccine (SDV), HDV versus none, and SDV versus none. We required continuous hemodialysis from May 1 to Jul 31 and ascertained insurance status and patient characteristics from Feb 1 to Jul 31. Follow-up began on Aug 1 and ended at the earliest of all-cause mortality, receipt of second influenza vaccine or unknown influenza vaccine type, modality switch, end of Medicare as primary payer, or start of influenza season. To quantify confounding bias, analyses were restricted to the preinfluenza season, when protective effects of vaccination should not yet be observed. We estimated standardized mortality ratio-weighted cumulative incidence functions using Kaplan-Meier methods and calculated risk differences (RD) and risk ratios (RRs) between groups.

Results: Of 350 921 eligible patients contributing 825 642 unique patient preinfluenza seasons, 0.8% received HDV, 70.5% received SDV, and 28.7% remained unvaccinated. Compared with unvaccinated patients, HDV recipients (RR, 0.60; 95% CI, 0.51–0.70) and SDV recipients (RR, 0.72; 95% CI, 0.70–0.75) demonstrated a decreased risk of mortality during the preinfluenza period. The effect estimate was attenuated in the comparison of HDV versus SDV recipients (RR, 0.89; 95% CI, 0.77–1.03). RD estimates were similar.

Conclusions: Using an active comparator yielded less biased results than an unvaccinated comparator, as indicated by attenuated protective effect estimates of the association between influenza vaccination and all-cause mortality prior to influenza season. Future vaccine-effectiveness and safety studies should consider the active comparator design to reduce bias due to differences in underlying health status between vaccinated and unvaccinated individuals.

494 | Medication use during pregnancy in the Netherlands: A population-based study

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Background: The importance of monitoring drug use around pregnancy has been widely recognised and there is a current need for recent population-based data on drug utilisation around pregnancy in the Netherlands in order to facilitate contextualisation and decision making in this field.

Objectives: The objective of this study was to assess medication use during pregnancy in a population-based setting in the Netherlands.

Methods: A cross-sectional analysis was conducted using pharmacy dispensing records linked to pregnancy records. Community pharmacy dispensing records were obtained from the Out-patient Pharmacy Database of the PHARMO Database Network (PHARMO)—a population-based network of electronic health care databases combining data from different health care settings in the Netherlands. Pregnancy records were obtained from the Perinatal Registry of the Netherlands (Perined)—a nationwide registry containing maternal and neonatal characteristics and data on perinatal care. Pregnancies between 1999 and 2015 of women registered in Perined as well as PHARMO were included in the study. Use of unsafe medication was defined according to 5 categories of the Dutch classification of medication in pregnancy: A) medication with pharmacological effects that (A1) should be monitored when used or (A2) should be (temporarily) avoided; B) medication with teratogenic effects that (B1) should be monitored when used or (B2) should be (temporarily) avoided and C) medication with unknown risks due to insufficient experience.

Results: The PHARMO-Perined cohort included 475 332 pregnancies of 343 783 women (mean (±SD) age at delivery 30.3 (±4.8) years, 81% with Dutch ethnicity). A total of 335 017 (70%) pregnancies were identified during which women were dispensed medication at least once. Among all pregnancies, 137 893 (29%) were exposed to unsafe medication with the highest use for medication in category C (79 416 pregnancies, 58%) followed by category A2 (48 584 pregnancies, 35%), category A1 (38 084 pregnancies, 28%), category B2 (13 094 pregnancies, 9%) and category B1 (1952 pregnancies, 1%).

Conclusions: Nearly one third of all pregnancies were exposed to medication not indicated as safe. Future interventions in the Netherlands should focus on the prevention of unsafe medication use during pregnancy.

495 | Evaluation of spontaneous adverse event reports for congenital and neonatal birth problems attributed to ondansetron within the FDA adverse events reporting system (FAERS)

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Background: Although ondansetron is currently classified as category B in pregnancy and has been evaluated for the treatment of nausea and vomiting of pregnancy, current guidelines note data related to fetal safety is conflicting.

Objectives: To describe and evaluate spontaneous adverse event reports of congenital and neonatal birth problems attributed to ondansetron.

Methods: The published database quarterly files starting from the first quarter of 2014 till the third quarter of 2017 were queried for reports listing congenital and neonatal birth problems attributed to ondansetron administration as the primary suspected drug with events dates from 2010 to 2017. congenital and neonatal birth problems were identified using the search terms "congenital," "neonatal," and "stillbirth." Ondansetron was identified using the search terms "ondansetron" and "zofran." We calculated the proportional reporting ratio (PRR) and the reporting odds ratio (ROR).

Results: Among 2 231 318 FAERS reports between January 2014 and September 2017, 1063 (0.05%) reports mentioned ondansetron. There were 4857 (0.22%) congenital and neonatal birth problems reports during the same period of which 69 (1.4%) were attributed to ondansetron administration. The PRR and ROR were as following: PRR: 30.24, 95% CI: 24.03-38.05, ROR: 32.26, 95% CI: 25.24-41.25.

Conclusions: Although FAERS is subject to many limitations such as under reporting, the results suggest that ondansetron is associated with higher risk of congenital and neonatal birth problems which needs further studies to confirm or deny this claim.

496 | Glyburide versus insulin for the treatment of women with gestational diabetes in Kaiser Permanente Northern California

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Background: There is controversy regarding whether insulin or glyburide should be the first line treatment for women with gestational diabetes (GDM) requiring medication treatment. However, few studies to date have been conducted in a real-world clinical setting. In Kaiser Permanente Northern California (KPNC), an integrated health care delivery system, medication is initiated in women with GDM after diet

therapy fails, and the treatment options are glyburide or insulin, or both, if glyburide is initiated but failed to achieve glycemic control.

Objectives: To compare neonatal outcomes (macrosomia, infant size for gestational age and NICU admission) among women GDM requiring medication therapy in KPNC from 2007 to 2014.

Methods: A retrospective cohort study design where treatment groups contrasted were defined by therapy regimens (insulin only, insulin and glyburide, versus glyburide only). Poisson regression estimated risk ratios (RRs). The KPNC pregnant population is representative of the underlying population, except it under represents the extremes of income.

Results: Among 5304 women with GDM who were treated with medication, 4622 women were treated with glyburide only, 401 were treated with insulin only and 281 women were treated with glyburide and insulin. After adjusting for pre-pregnancy BMI, race and age, newborns of women treated with insulin only compared with women treated with glyburide only had no significant increased risk for macrosomia (17.2% versus 14.8%;RR:1.06; 0.83-1.35), large for gestational age (LGA) infant (20.5% versus 17.9%; RR:1.12; 0.90-1.39), small for gestational age (SGA) infant (8.0% versus 6.2% 1.22; 0.83-1.80), hypoglycemia (3.0% versus 3.5% 0.67;0.34-1.35) or NICU admission (15.2% versus 16.6%; 0.93; 0.69-1.25). Newborns of women treated with both insulin and glyburide were at increased risk of LGA (1.49; 1.21-1.83) and NICU admission (1.48; 1.16-1.89), but there were no significant differences in macrosomia 1.17; 0.89-1.54), SGA; 0.82 (0.46-1.49) or hypoglycemia (0.45; 0.17-1.22), compared with newborns of women treated with glyburide only.

Conclusions: This preliminary analysis found no significant differences in neonatal outcomes among newborns of mothers treated with insulin compared with glyburide. While there was some evidence that newborns of women who were treated with both glyburide and insulin were at increased risk of LGA and NICU admission, this could be due to confounding by severity.

497 | Pregnancy trends and antiretroviral exposure during pregnancy among HIV-negative and HIV-positive women in a large United States claims database

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Background: In 2015, approximately 6% of women of child-bearing age gave birth in the United States. An estimated 1% of these were HIV-positive women. Pregnancy prevalence estimates among HIV-positive women are limited.

Objectives: To estimate and compare annual pregnancy prevalence among HIV-positive and HIV-negative women of child-bearing age (15-44 years) in the Truven MarketScan Commercial Claims and Encounters database, and the MarketScan Medicaid database. This analysis also explored the prevalence of exposure to any ARV during pregnancy among these women.

Methods: This was a retrospective database study using data from January 2011 to December 2015. Women aged 15-44 years who had pharmacy benefits in the calendar year of analysis, were enrolled for at least the entire year and had ≥ 1 pregnancy outcome code were included. All analyses were performed using SAS version 9.3, and stratified by calendar year, HIV-status and MarketScan database. For the main analysis, annual pregnancy prevalence and age-standardized prevalence ratios, using publicly available data on pregnancy prevalence in the US general population, were calculated. A χ^2 test was performed to compare the proportions of pregnancies in both groups of women, with $\alpha = 0.05$.

Results: Pregnancy prevalence among ≥ 5 million HIV-negative women was $\sim 6\%$ and $\sim 10\%$ in the Commercial and Medicaid databases, respectively, and $\sim 9\%$ among ≥ 7000 HIV-positive women in the both databases. The prevalence was significantly higher among HIV-positive women ($p \leq 0.01$), except for prevalence in the 2015 ($p = 0.63$) Medicaid data. The age-standardized ratios indicated a similar pregnancy prevalence versus the US general population, except for HIV-negative women in the Commercial database who seemed to have a lower pregnancy prevalence compared with the general US population. Approximately 30% and 70% of HIV-positive women were exposed to ARVs during their pregnancy as recorded in the Commercial and Medicaid databases, respectively.

Conclusions: Pregnancy rates in HIV-negative women were similar to previous reports. Claims data seems to be a reasonable data source for estimating pregnancy prevalence in HIV-positive and negative women. The multiple ARV funding sources in the United States may have led to incomplete capture of ARV exposure during pregnancy among HIV-positive women in claims data.

498 | Paternal exposure to methotrexate and the risk of miscarriage—A registerbased nationwide cohort study

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Background: Methotrexate is used as first-choice treatment for rheumatoid arthritis. Methotrexate is furthermore used to treat several malignant diseases, inflammatory bowel disease, psoriasis as well as to terminate extrauterine pregnancies. Multinational recommendation is to discontinue methotrexate at least 3 months before planned pregnancy for both men and women due to concerns of fetal adverse effects.

Objectives: To study the association between paternal exposure to methotrexate within three month before conception and during the first trimester of pregnancy and the risk of miscarriage.

Methods: We conducted a nationwide cohort study identifying all registered pregnancies in Denmark from 1997 to 2015. All births were identified using the Medical Birth Registry, and all records of induced

abortion and miscarriage were from the National Hospital Register. Data on drug use were from the National Prescription Register. Cox proportional hazard regression models were used to calculate the hazard of miscarriage in women with a partner exposed to methotrexate. The study was approved by the Danish Data Protection Agency (2015-41-4309).

Results: We identified 1 364 063 registered pregnancies with known paternity, of whom 520 of the fathers were exposure to methotrexate within the three month before conception to the end of the first trimester. Among these, 46 (8.9%) experienced a miscarriage compared with 122 926 (9.0%) of the unexposed. There were no increased risk of experiencing a miscarriage in pregnancies to men exposed to methotrexate before pregnancies compared with unexposed (adjusted hazard ratio 0.99 (CI95% 0.67-1.46)). Furthermore, we found no increased risk of experiencing a miscarriage in pregnancies to men exposed to methotrexate during first trimester compared with unexposed (adjusted hazard ratio 0.90 (CI95% 0.61-1.32)).

Conclusions: We found no association between paternal exposure to methotrexate before and during early pregnancy and miscarriage. Available data suggest that paternal methotrexate exposure should not be of major concern. Multinational recommendations could be changed accordingly.

499 | Pregnancy outcome after first trimester exposure to bisoprolol: An observational cohort study

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Background: Beta-blockers are frequently used during pregnancy, with labetalol and metoprolol being considered as beta-blockers of choice. However, congenital anomalies and fetal growth restriction have been discussed in context with both, beta-blockers and maternal hypertension as underlying maternal disease. As yet, there are no prospective pregnancy studies on bisoprolol.

Objectives: Pregnancy outcomes after first trimester exposure to bisoprolol with primary focus on spontaneous abortions and birth defects.

Methods: Prospectively ascertained pregnancies exposed to bisoprolol during the 1st trimester were retrieved from the German Embryotox pharmacovigilance database. Pregnancy outcomes were compared with pregnancies without antihypertensive treatment. Confounding was addressed by directly incorporating the covariates or by using inverse probability of treatment weights (IPTW) for dichotomous outcomes. In addition, all retrospectively reported pregnancies with first trimester bisoprolol exposure from the Embryotox adverse drug reaction database were screened for patterns of birth defects.

Results: Inclusion criteria for the prospective study were met by 339 bisoprolol treated women and 678 patients in the comparison cohort. Neither the risk for spontaneous abortions (adjusted hazard ratio [HR_{adj}] 1.06; 0.66-1.70) nor the risk for major birth defects (adjusted odds ratio [OR_{adj}] 0.77; 0.34-1.75) were increased after first trimester bisoprolol treatment. However, a higher rate of preterm births (OR_{adj} 1.90, 1.17-3.11) and reduced birthweight in singleton pregnancies (adjusted standard deviation score difference -0.48; 95% CI -0.62 to -0.34) were noted. Continued treatment with beta-blockers until birth was found to be associated with a higher risk for growth restriction than treatment limited to the first trimester. A sensitivity analysis did not suggest higher rates for spontaneous abortion, major birth defects, preterm birth or growth restriction in bisoprolol exposed women with chronic hypertension compared with bisoprolol exposed women without hypertension.

Conclusions: Our study supports the hypothesis that first trimester bisoprolol treatment does not increase the risk for spontaneous abortions or major birth defects. However, an influence of prolonged bisoprolol exposure on fetal growth cannot be excluded. Funding: German Ministry of Health (BMG) and the German Federal Institute for Drugs and Medical Devices (BfArM)

500 | The pregnancy rate in women of childbearing age with psoriasis

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Background: Pregnancy rate in women with psoriasis is urgently needed to assess feasibility of a pregnancy registry.

Objectives: To assess the pregnancy rates in psoriasis women of childbearing age.

Methods: A retrospective cohort study was conducted using Optum Clinformatics DataMart. Women (18-49 y) were eligible for the study if they had at least two diagnoses of psoriasis ≥ 7 days apart in 2007-2017 and had ≥ 6 M of continuous health plan enrollment before the index date, defined as the first date of receiving a systemic treatment after the first psoriasis diagnosis for biologics and non-biologic systemic therapy group or the first date of psoriasis diagnosis for non-systemic therapy group. Patients were followed from the index date until the earliest of new pregnancy, disenrollment from health plan, turning 50, death, or end of study. A pregnancy was identified based on diagnosis and procedure codes. The pregnancy rate (number of new pregnancies during the follow-up divided by patient years of follow-up) and its 95% confidence intervals (CI) were calculated for all patients and by treatment.

Results: A total of 35 361 women with psoriasis were included. Among them, 6517 (18.4%), 5294 (15.0%) and 23 550 (66.6%) received biologics, non-biologic systemic therapy, and no systemic therapy respectively. Pregnant women ($n = 1733$) within six months before the index date (4.9%, 95% CI 4.7-5.1%) were excluded from the pregnancy rate analysis. Their comorbidities included anxiety

10.2%, depression 10.2%, hypertension 9.8%, asthma 9.8%, and psoriatic arthritis 5.8%. In those who were not pregnant at baseline ($n = 33\ 628$, age 36.7 ± 8.7), most common comorbidities were hypertension 17.4%, anxiety 14.4%, depression 12.6%, asthma 12.4%, psoriatic arthritis 10%, diabetes 7.8%, and atopic dermatitis 6.7%. There were 3437 new pregnancies during 72 471.4 patient-years of follow-up, resulting in an overall pregnancy rate of 4.7 (95% CI 4.6-4.9) per 100 patient-years. The pregnancy rate (per 100 patient-years) was 3.5 (95% CI 3.1-3.8), 4.3 (3.9-4.8) and 5.1 (4.9-5.3) among those who received biologics, non-biologic systemic, and no systemic therapy, respectively. The pregnancy rate was highest in age 25-34, followed by age 18-24, and age 35-49.

Conclusions: Among psoriasis patients, the pregnancy rate was lower in biologic users than those on a systemic therapy and may partially be attributed to differences in the proportion of older age group in the biologic users. This information will help estimate the population size to inform the design of a pregnancy registry.

501 | The epidemiology of pre-existing chronic kidney disease in a cohort of pregnant women in the USA

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Background: Pregnancies in women with chronic kidney disease (CKD) are reported to have a greater risk of adverse outcomes including preterm birth, cesarean section, and intrauterine growth restriction. However, few studies have described the course and consequences of CKD during pregnancy in population-based longitudinal cohorts of pregnant women.

Objectives: To describe the epidemiology of CKD and changes in kidney function over the course of pregnancy in a nationwide cohort of commercially insured women in the United States.

Methods: From the Optum Clinformatics database (2004-2015) where insurance claims are linked to laboratory results for a subset of patients, we identified a cohort of women aged 12-55 years with a completed pregnancy and ≥ 1 recorded creatinine lab value between 90 days before the last menstrual period (LMP) and the end of trimester 1 (baseline period). Based on the mean baseline glomerular filtration rate (eGFR, CKD-EPI formula) we categorized women into two groups: 1) moderate-severe CKD (mean eGFR < 60 ml/min), and 2) mild CKD (mean eGFR 60-90 ml/min). We captured pre-existing comorbidities during baseline, assessed changes in eGFR over the course of pregnancy, and evaluated the risk of preterm delivery between women with moderate-severe vs mild CKD using a multivariable logistic regression model accounting for risk factors for preterm delivery.

Results: Of 318 436 pregnant women identified, 124 classified as moderate-severe CKD (prevalence = 0.03%, mean age 33 years) and 5895 as mild CKD (prevalence = 1.9%, mean age 33 years). Women with moderate-severe CKD had a mean baseline eGFR of 51.0 ml/min (SD 12.2), which increased to 64.6 ml/min in trimester 2 (SD 26.7) and 59.8 ml/min in trimester 3 (SD 31.2). Among women with mild CKD, the mean baseline eGFR was 80.8 ml/min (SD 7.9), which increased to eGFR 111.6 ml/min (SD 12.9) in trimester 2 and eGFR 109.2 ml/min (SD 15.3) in trimester 3. Comparing women with moderate-severe CKD to women with mild CKD, we observed a crude odds ratio (OR) for preterm birth of 2.69 (95% CI, 1.83-3.96, absolute risk = 30.1% vs 14.6%), which remained elevated after adjusting for age, diabetes, hypertension and obesity (OR 2.37, 95% CI 1.60-3.51).

Conclusions: We observed pregnancy-related increases in eGFR regardless of baseline eGFR in women with CKD. Baseline eGFR < 60 ml/min was associated with a greater risk of preterm birth. Population based cohorts developed from administrative data with laboratory results represent a valuable resource to study CKD in pregnant women.

502 | Abstract Withdrawn

503 | Hospitalization of children after prenatal exposure to methadone and buprenorphine: National registry studies from Czech Republic

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Background: WHO strongly recommends opioid dependent women to continue or commence Opioid Maintenance Treatment (OMT) if they become pregnant despite that the evidence behind the recommendation is very low. Long-term effects for the child are not known.

Objectives: The aim of the study was to examine morbidity in children prenatally exposed to OMT by studying hospitalizations up to the age of three.

Methods: We linked data from nationwide registries in the Czech Republic; The Register of Reproduction Health, The Register of Addiction Treatment and The Register of Inpatient Treatment. Linkage of data between the registries was based on the personal identification code.

The study population included all children born during 2000-2014. Children prenatally exposed to OMT were compared with children born to women from general population and to children born by mothers who had been in OMT before pregnancy, but who were not in OMT during pregnancy.

We collected information on all inpatient contacts, length of stay, and primary and secondary diagnosis. Diagnosis was classified according to

ICD-10. Logistic regression analyses were performed for each diagnoses separately. We calculated unadjusted and adjusted Odds ratio (OR) with 95% confidence interval (CI).

Results: By 3 years of age, 54.1% of OMT children (n = 218) have been hospitalized at least once, compared with 35.8% of children from the general population. Children prenatally exposed to OMT drugs were more likely to get diagnoses for all main disease groups. During the first 3 years of life, the most common reason for hospitalisation of OMT children was diseases of the respiratory system and certain infections and parasitic diseases, with 24.3% and 21.6% of children receiving these diagnoses respectively compared with 16.3% and 8.9% in the general population.

In the adjusted logistic regression analysis there were still differences in infection and parasitic diseases (OR = 2.0 (CI 1.4-2.7); disease of digestive system (OR = 1.7 (1.2-2.6)), and disease of the skin and subcutaneous tissue (OR = 1.9 (1.2-3.2)). Children born by mothers who had been in OMT before, but not during pregnancy, showed similar morbidity as children prenatally exposed to OMT.

Conclusions: This study suggests that children exposed to OMT in utero were hospitalised more frequently during the three first years of life. Beside exposure to OMT, there were apparently other socio-economic and biological factors increasing the risk of morbidity in these children.

504 | Late gestation use of serotonin reuptake inhibitor antidepressants is not associated with an increased risk for low milk supply in mothers of preterm infants

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Background: Serotonin plays an important role in human breast milk volume homeostasis within the mammary gland during lactation. Previous research demonstrates women taking antidepressants have lower rates of breastfeeding intention and initiation and are more likely to experience delayed onset of stage II lactogenesis. Whether use of SRIs during lactation is associated with a reduction in breast milk volume or leads to impaired long-term breastfeeding outcomes is unclear.

Objectives: To examine the association between late pregnancy exposure to serotonin reuptake inhibitor (SRI) antidepressants and difficulties in achieving an adequate breast milk supply in women who gave birth to preterm infants, while accounting for the potential impacts of underlying maternal psychiatric illness.

Methods: Retrospective cohort study of 3024 women delivering liveborn preterm infants (<37 weeks' gestation) between January 2004 and December 2008 at a tertiary teaching hospital in Adelaide, Australia. Exposure and outcome data obtained from linked electronic pharmacy and perinatal records. The primary outcome was postnatal domperidone use, considered a valid proxy for presence and

pharmacological management of low milk supply. Relative risks adjusted for maternal sociodemographics and comorbidities (aRRs) were calculated for low milk supply, comparing women with late pregnancy exposure to SRI antidepressants ($n = 86$), women with a psychiatric illness but no antidepressant use ($n = 126$), and women with neither antenatal exposures ($n = 2\,812$).

Results: Compared with non-exposed women, non-medicated psychiatric illness (aRR 1.67; 95%CI 1.18-2.35) but not late pregnancy SRI use (aRR 0.96; 95%CI 0.54-1.71) was associated with an increased risk of domperidone use, indicative of low milk supply.

Conclusions: These findings do not support the previously observed negative impacts of antidepressant use on breastfeeding, instead suggesting that women with an underlying psychiatric illness appear at greatest risk of experiencing low milk supply and could benefit from additional breastfeeding education and support.

505 | Antiepileptic drugs in pregnancy, and duration of pregnancy, birth weight, length and head circumference

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Background: Antiepileptic drugs (AEDs) have been linked to reduced pregnancy duration, birth weight (BW), length (BL), and head circumference (HC). Dose-response effects have not been well characterized for these outcomes; such effects are known for valproic acid and birth defects.

Objectives: Explore the effect of maternal AED use in pregnancy on pregnancy duration, BW, BL, and HC and dose-response effects on these outcomes.

Methods: We identified all infants born in Sweden to women who used AEDs in pregnancy in 1996-2013 and used linear regression to assess associations of interest, adjusting for age, year, smoking habits, body mass index, epilepsy, etc. The reference was lamotrigine use. In AED-specific dose analyses (2006-), we compared tertiles of mean daily dose during pregnancy; the bottom tertile was the reference.

Results: The study cohort had 6720 AED-exposed infants. AED use in pregnancy increased over the study period. The most common AEDs were lamotrigine (34% of infants), carbamazepine (31%), and valproic acid (17%); 68% of AED-exposed infants had a mother with epilepsy. For lamotrigine-exposed infants, mean pregnancy duration was 39.5 weeks (w); BW, 3471 g; BL, 50.0 cm; and HC, 34.8 cm. Compared with infants in the low-dose tertile (mean, 41 mg/d), those in the high-dose tertile (mean, 454 mg/d) were born 0.3 w earlier (95%

confidence interval, -0.6, 0), 11 g lighter (-95, 73), and 0.1 cm shorter (-0.3, 0.4); HC was similar.

Relative to lamotrigine-exposed infants, infants exposed to carbamazepine were born 0.2 w earlier (-0.3, 0), 69 g lighter (-112, -26), and 0.3 cm shorter (-0.5, -0.1); HC was 0.3 cm smaller (-0.5, -0.2). Compared with infants in the bottom tertile of carbamazepine dose (mean, 186 mg/d), infants exposed to high dose (mean, 905 mg/d) were born 0.8 w earlier (-1.2, -0.3), 170 g lighter (-288, -52), and 0.7 cm shorter (-1.2, -0.1); HC was 0.5 cm smaller (-0.8, -0.1).

Infants exposed to valproic acid were 27 g lighter (-79, 24), 0.1 cm longer (-0.1, 0.4), and HC was 0.2 cm smaller (-0.4 to 0.0) than lamotrigine-exposed infants but pregnancy duration was similar. Dose analyses did not show a clear pattern; confidence intervals were wide. HC was 0.6 cm smaller (-1.1, -0.1) in infants in the top dose tertile of valproic acid (mean, 1349 mg/d) relative to the bottom tertile (mean, 211 mg/d).

Conclusions: Relative to lamotrigine, infants exposed to carbamazepine were born slightly earlier and were slightly smaller. Effects were stronger at higher doses. A dose-response effect on HC was seen for valproic acid.

506 | Use of antiepileptic drugs in pregnancy: A multinational register-based study

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Background: It is important to understand the prevalence and patterns of antiepileptic drug (AED) use in pregnancy to quantify fetal exposure and potential for uncontrolled maternal illness.

Objectives: To describe the utilization of AEDs in pregnancy from 2006 to 2015 across the Nordic countries.

Methods: We studied use of AEDs using linked birth and prescription registers in Norway ($N = 590\,253$), Sweden (-2013, $N = 804\,555$), Iceland (-2012, $N = 32\,267$), Denmark (-2012, $N = 430\,718$), and Finland (-2014, $N = 527\,304$). We defined pregnancy exposure based on drugs in Anatomical Therapeutic Chemical (ATC) group N03A dispensed from 90 days before the date of the last menstrual period (LMP) to birth. We examined the prevalence of exposure to any AED during pregnancy by year of birth, maternal age, and pregnancy outcome. Among those with pregnancy exposure, we assessed patterns of use: early discontinuation (no refill in pregnancy), first trimester exposure, initiation after first trimester, and continuous use (fills in each trimester). Finally, we determined the prevalence of any use before, during, and 90 days after pregnancy. We performed

analyses both separately for each country and pooled across countries.

Results: The pooled prevalence of AED exposure in 2.38 million pregnancies was 7.1 per 1000, ranging from 6.0 in Sweden to 10.7 in Iceland. From 2006 to 2012, use increased from 5.4 to 8.1 per 1000, continuing to rise or stabilize in countries with more years of data. This ultimately represented a 49–72% elevation in use from 2006 in each country. The use of AEDs was similar across maternal age, but slightly higher in the youngest and oldest women. The prevalence of use was higher among pregnancies resulting in stillbirth, 10.0 vs 7.3 per 1000 among livebirths. Examination of patterns of use showed that 22% only filled a prescription before LMP, 66% filled a prescription in the first trimester, 6% only filled prescriptions in second or third trimesters, and 36% filled prescriptions in all three trimesters. Prevalence of use was highest before pregnancy, declined throughout pregnancy reaching 35–70% of pre-pregnancy use in the third trimester, and then rebounded after pregnancy to levels between first and second trimester use. We will present country-specific data, use of individual drugs and polytherapy, and switching patterns.

Conclusions: The increased use of AEDs in pregnancy in recent years suggests the need for further comparative safety studies to inform the balance of risks and benefits for treatment use, modification, or discontinuation.

507 | Antipsychotic drug use in pregnancy: A multinational database study

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Background: Initiation or continued use of antipsychotic medication may be necessary during pregnancy for some women. However, little is known about how such treatment varies between countries and over time.

Objectives: To quantify and compare the prevalence of antipsychotic drug use during pregnancy in eight populations worldwide.

Methods: Individually linked data from the nationwide health registers in Denmark (2000–2012), Iceland (2003–2012), Norway (2005–2015), and Sweden (2006–2013), and from administrative data in Australia (New South Wales, 2004–2012), Italy (Lombardy, 2005–2010), and the United States (Medicaid Analytic eXtract, 2000–2013, and Truven Health MarketScan, 2012–2015, representing

publicly and privately insured women, respectively) were used in this study. The study period for each country varied depending on availability of data. The prevalence of antipsychotic (AP) use was calculated as the proportion of pregnancies in each population in which the woman filled at least one prescription for an AP in the period from three months before pregnancy until birth. Use of first-generation AP and second-generation AP were assessed by country and by trimester.

Results: We included 5 773 574 pregnancies. Both the prevalence of first-generation AP (0.03%) and second-generation AP (0.07%) were lowest in the Italian population, and highest in the US Medicaid population (1.8% and 1.5%, respectively). In most countries, prochlorperazine was the most commonly used first-generation AP and quetiapine the most commonly used second-generation AP. First-generation AP use remained stable or decreased over time in the eight populations. After excluding prochlorperazine, a first-generation AP which is primarily used to treat nausea and vomiting, first-generation AP use was more stable across time in all populations. Second-generation AP use increased markedly over time in all populations except Italy, reaching 2% in both the Australian (2012) and the US Medicaid population (2013). For first-generation AP use, the prevalence was highest in the first trimester in most populations, partly driven by prochlorperazine use in early pregnancy. For second-generation AP, the use was highest in the three months before pregnancy and decreased throughout pregnancy.

Conclusions: Antipsychotic use during pregnancy varied considerably between countries, but explaining factors are yet to be understood. Most countries showed an increased use of second-generation AP use over time.

508 | Patterns and predictors for prescription of psychotropics and mood-stabilizing anti-epileptics during pregnancy in Denmark from 2000 to 2016

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Background: The use of psychopharmacological drugs during pregnancy has been subject to considerable controversy for the last decade. Guidelines on the use of these drugs in pregnancy tend to be trivial and rarely offer treating physicians operative decision support. The extent to which actual prescription practices reflect guidelines and recommendations and the developing knowledge on safety during pregnancy is poorly documented.

Objectives: To analyse the development in prescribing patterns during pregnancy for antipsychotics (AP), antidepressants (AD) and mood-stabilising antiepileptics (AEDs) in Denmark from 2000 to 2016.

Methods: In this nationwide drug utilization study, we included all pregnancies in Denmark from 2000 to 2016. Using a unique identification number assigned to all Danish residents, we linked data from the

Danish Medical Birth Register, the Danish Prescription Register, the Danish Patient Register, and data on income, socioeconomic status, and level of education from Statistics Denmark. We collected data on all filled prescriptions for APs, ADs, and mood-stabilising AEDs for the study population. AEDs were restricted to mood-stabilising indications, defined as prescriptions for AEDs within 120 days before or after a prescription for either an AP or AD drug. Women previously diagnosed with epilepsy were excluded. Exposure was defined as reimbursement of at least one relevant prescription during pregnancy. Start of pregnancy was defined as first day of last period. Annual prevalence was calculated as number of exposed pregnancies per 1000 pregnancies per calendar year.

Results: The use of antipsychotics (AP) increased 2.5-fold from a prevalence proportion (PP) of 1.5 per 1000 pregnancies to 3.7 for pregnancies ending in a delivery. Use of mood-stabilising AEDs increased from a PP of 0.1 to 2.1 during the study period. The PP for AP and mood-stabilising AEDs was nearly twice as high for pregnancies ending in miscarriage or termination compared with pregnancies ending in delivery. A marked increase in the prevalence of AD use during pregnancy was seen from 2000 to 2011 but appears slightly in decline from 2012. Age, smoking and social status were associated with increased use. Distribution of utilization appeared reasonably in accordance with diagnoses.

Conclusions: The use of AP, AD, and mood-stabilising AEDs during pregnancy has increased substantially in Denmark from 2000 to 2016. The use of AD from 2012 appears slightly in decline.

509 | Development and evaluation of health education materials for women with gestational diabetes mellitus

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Background: Written health education materials can improve patients' knowledge, adherence to treatment, prevent disease, and reduce health care costs. The prevalence of gestational diabetes mellitus (GDM) has been increasing worldwide. Pregnant women require accessible, easy-to-understand and evidence-based medical information about GDM.

Objectives: The aim of this study is to create and evaluate health education materials for women with GDM.

Methods: The study included three phases: (1) review of the literature for relevant publications; (2) development of written health education materials for women with GDM; (3) evaluation of created education materials by pregnant women. A seven-item self-administered questionnaire was adopted for evaluation of patient satisfaction after the use of educational materials. The instrument was based on five-point

Likert scale. Descriptive and comparative analysis of the results was conducted.

Results: Educational materials were developed according to the best practice principles in written health education materials design relating to content, structure, language, layout and illustrations. The educational booklet provides comprehensive information about GDM and its management (medical nutrition therapy, exercise, insulin use, self-monitoring of blood glucose). Information about follow-up of GDM and prevention of type 2 diabetes has also been included. The usefulness of the educational materials and patient satisfaction were evaluated by a sample group of 20 pregnant women who represent the target audience. Approximately 95% (mean = 4.75) agreed or strongly agreed that the information in the educational booklet was useful. In regard to illustrations, figures and tables 90% (mean = 4.50) of women are satisfied or very satisfied. Patient evaluation regarding the understanding and readability of the written material showed a satisfaction rate of 85% (mean = 4.25). The overall assessment for the educational materials is very high—excellent (65%), very good (30%) and good (5%).

Conclusions: A very high level of satisfaction was achieved among women participated in the study. The educational materials created and evaluated in this study will help health care providers to improve patients' knowledge about GDM and its management. Providing educational materials can enhance patients' health literacy as well as their personal responsibility, motivation and attitude to their own health.

510 | No increase in serious or opportunistic infections in infants prenatally exposed to biologics

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Background: Biologics for the treatment of autoimmune diseases are used by women who become pregnant. Most of these drugs are not thought to cross the placenta in appreciable amounts until the third trimester. There has been theoretical concern that fetal exposure could lead to risk for infections in the neonate.

Objectives: We examined the risk of serious or opportunistic infections in infants up to 1 year of age born to mothers who had or had not been treated with biologics in pregnancy.

Methods: MotherToBaby Pregnancy Studies enrolled women in a prospective cohort study across the United States and Canada who did or did not have rheumatoid arthritis, Crohn's Disease, ulcerative colitis, ankylosing spondylitis, psoriasis, or psoriatic arthritis, and who were or were not treated with a biologic medication. Data from maternal interviews and medical records were obtained, and live born infants were followed up to 1 year of age regarding the incidence of a predefined list of opportunistic or serious infections requiring hospitalization. Infant outcomes following exposure to biologics by gestational age at discontinuation of the drug were compared with outcomes in infants born to women with the same autoimmune diseases but no

treatment with biologics, and outcomes in infants born to women with no chronic diseases. Inverse probability weighting methods and GEE were used to calculate weighted odds ratios (ORs), and 95% confidence intervals (CIs) were calculated using bootstrap.

Results: Between 2004 and 2018, 1513 live born infants were followed by MotherToBaby Pregnancy Studies; 768 were born to mothers treated with biologics, 311 to mothers with the same conditions but no biologic treatment in pregnancy, and 434 to mothers with no autoimmune disease. Rates of serious or opportunistic infections were 3.8%, 4.2% and 2.3% respectively. Weighted ORs and 95% CIs were 0.80 (0.47, 2.15) and 1.66 (0.80, 3.46) respectively. When exposure to biologics was restricted to continued use in the third trimester, weighted ORs were 0.79 (0.46, 2.28) and 1.61 (0.73, 3.57) respectively. Average dose of prednisone or other systemic corticosteroid use in pregnancy was an independent predictor of infant infection.

Conclusions: There was no evidence that maternal use of biologics was associated with an increased risk of serious or opportunistic infections in the infant. This study did not examine biomarkers of immune function or risk of mild infections. However, results are reassuring for women treated with biologics at anytime in pregnancy.

511 | Medically assisted reproduction and the risk of preterm birth

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Background: Medically assisted reproduction (MAR) includes assisted reproductive technology (ART) (eg, *in vitro* fertilization) and the use of ovarian stimulators (OS). MAR has tripled in Canada in the last decade. MAR is not without risk, as conception through MAR increases obstetrical complications and adverse perinatal outcomes, including multiplicity and perinatal mortality.

Objectives: To quantify the risk of preterm birth (PTB) associated with the use of MAR overall and by method within exposed women.

Methods: *Design and setting:* We conducted a cohort study in the Quebec Pregnancy Cohort (QPC), an ongoing population-based cohort, which includes data on all pregnancies of mothers covered by the provincial prescription drug insurance in Quebec and their children from 01/1998 and 12/2015. We included singleton liveborns between 05/08/2010 and 15/11/2015, whose mothers were covered by the RAMQ drug plan for at least 3 months prior to and during pregnancy. This time-period was used given that the MAR universal reimbursement program (QC) was only fully active at that time. *Exposure:* We first considered MAR dichotomously, using naturally conceived pregnancies as the reference. We then categorized MAR into 3 exposure subgroups: OS alone, ART alone (reference), OS and ART combined. *Outcome:* PTB was defined as <37 wks of gestation. *Statistical analyses:* Crude and adjusted odds ratios (cOR and aOR) and 95% confidence intervals (CI) were obtained using generalized estimation

equation models. Subgroup analyses were performed within those exposed to MARs. Covariates included maternal sociodemographics, history of pregnancy complications, comorbidities, and concomitant medication use, measured in the year before the 1st day of gestation.

Results: A total of 57 624 pregnancies met inclusion criteria and were considered for analyses. During the study period, 2055 women were exposed to MARs, of which 404 to OS alone, 557 to ART alone, and 1094 to a combination of both. MAR users were at increased risk of PTB (cOR [95%CI]: 1.45[1.06-1.97], aOR[95%CI]: 1.55[1.10-2.17]; 182 exposed cases). Among MAR users, those on OS alone had a higher risk of PTB (cOR [95%CI]: 1.23[0.49-3.12]; 42 exposed cases).

Conclusions: Conception through MAR increases the risk of PTB when compared with spontaneous conception.

512 | Individual benzodiazepine exposure during early pregnancy and the risk of spontaneous abortion

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Background: Benzodiazepines are frequently prescribed during pregnancy. Study has shown that early pregnancy benzodiazepine exposure was associated with an increased risk of spontaneous abortion. No study has examined the risk of spontaneous abortion associated with individual benzodiazepine exposures. Data concerning the safety of individual benzodiazepines are of major clinical relevance.

Objectives: We quantified the risk of spontaneous abortion associated with prenatal benzodiazepine use as a class and for individual benzodiazepine.

Methods: We conducted a nested case-control study in a cohort of pregnancies covered by the Quebec Drug Plan from 1998 to 2008. Each case of spontaneous abortion was randomly matched to 5 controls on the index date (date of spontaneous abortion), gestational age and calendar year of pregnancy. Benzodiazepine exposure was identified as 1) use in the year prior to the first day of gestation, and 2) from the first day of gestation until index date. We considered the 10 most frequently prescribed benzodiazepines in the Quebec Pregnancy Cohort 1) long-acting: chlorthalidopoxide, clonazepam, diazepam and flurazepam; 2) intermediate-acting: bromazepam, lorazepam and temazepam; and 3) short-acting: alprazolam, oxazepam and triazolam. Conditional logistic regression were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the risk of spontaneous abortion.

Results: A total of 694 (4.0%) of the 17 180 pregnancies ending with a spontaneous abortion had ≥ 1 filled prescription for benzodiazepine during pregnancy, as compared with 1505 (1.8%) of the 85 562 matched controls. After adjusting for potential confounders, early pregnancy benzodiazepine exposure was associated with an increased risk of spontaneous abortion (aOR 1.55, 95%CI 1.36-1.76), but not pre-pregnancy exposure (aOR 0.99, 95%CI 0.90-1.08). Early pregnancy exposure to clonazepam (aOR 1.29, 95%CI 1.07-1.57; 262

exposed cases), lorazepam (aOR 1.42, 95%CI 1.15-1.75; 223 exposed cases), oxazepam (aOR 1.37, 95%CI 1.01-1.85; 90 exposed cases) and temazepam (aOR 1.70, 95%CI 1.08-2.67; 52 exposed cases) were associated with an increased risk of spontaneous abortion.

Conclusions: Maternal exposure to clonazepam, lorazepam, oxazepam and temazepam during early pregnancy was associated with an increased risk of spontaneous abortion. Benzodiazepine exposure before pregnancy alone was not increasing the risk of spontaneous abortions, indication that findings cannot be explained by indication bias.

513 | First trimester exposure to gadolinium contrast: A utilization study of 4.4 million live-birth pregnancies

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Background: The safety of exposure to gadolinium during pregnancy has not been established and limited data suggest possible fetal harm.

Objectives: To examine the prevalence of gadolinium contrast exposure in a real-world setting among a large sample of pregnant women.

Methods: Using the Sentinel Distributed Database, we identified US pregnancies resulting in live births with a date of delivery between 2006 and 2017. Our main outcome was the prevalence of MRI procedures with and without gadolinium contrast, by anatomical location, among pregnant and matched non-pregnant women and by trimester.

Results: Of 4 457 519 pregnancies resulting in a live birth, we identified 11 650 exposures to gadolinium in 10 286 pregnancies, representing 1 contrast MRI in 433 pregnancies (0.23%). Most contrast MRI were of the head (n = 5972), although pelvic and abdominal MRI constituted 21.3% (n = 2189) of all contrast MRI in pregnancy. Gadolinium exposure during the first trimester (n = 6661, 0.15%) represented 64.8% of all exposures during pregnancy and was approximately 6.4-fold greater than exposure in the second trimester (n = 1041, 0.02%) and 2.4-fold greater than exposure in the third trimester (n = 2755, 0.07%).

Conclusions: The rate of exposure to MRI with gadolinium contrast during pregnancy in our US population (0.23%) was approximately 8-fold higher than in a recent population-based study in Ontario (0.03%). The large proportion of gadolinium exposures during the first trimester suggests under-recognition of early pregnancy that may occur among females of reproductive potential. Physicians should consider the possibility of pregnancy before the MRI procedure, and gadolinium should only be used during pregnancy when it is essential and cannot be delayed.

514 | Opioid dispensing patterns after oocyte retrieval

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Background: In the field of reproductive endocrinology and infertility, opioids are commonly used for in the treatment of post-procedure pain. However, the type and quantity being prescribed are largely unknown and leftover prescription opioids are associated with opioid misuse.

Objectives: To describe opioid dispensing patterns following oocyte retrieval among a national cohort of commercially insured women.

Methods: We used Truven MarketScan to identify women undergoing oocyte retrieval (CPT: 58970) 2003-2015, with a maximum of 1 opioid prescription in the 12 weeks pre-procedure, without an opioid use or substance use disorder. We measured the i) proportion dispensed an opioid within 3 days of retrieval, ii) most common opioid dispensed and iii) median oral morphine milligram equivalents (MME) quantity dispensed (interquartile range, IQR, and 10th-90th percentile ranges). We used multivariable logistic regression to calculate adjusted odds ratios (aOR) to describe the association between patient characteristics and opioid dispensing.

Results: Among the 61 463 women with an oocyte retrieval, 3.0% had a diagnosis of anxiety, 3.4% of mood disorder, 4.9% of endometriosis, and 8.6% used SSRI/TCA's. An opioid was dispensed 11.9% of women, most commonly hydrocodone (48.5%), codeine (23.0%), and oxycodone (17.7%). The median oral MME dispensed after retrieval was 90 (IQR, 50-125; 10th-90th percentile, 50-207). Women with mood disorders (aOR 1.17, 95% CI 1.00-1.36), smoking history (aOR 1.68, 95% CI 1.19-2.37), or anti-depressant use (aOR 1.63, 95% CI 1.48-1.81) were more likely to fill an opioid, compared with those without these diagnoses.

Conclusions: Whereas only a small proportion of women fill a prescription for opioids after oocyte retrieval, those who do receive a large quantity of opioids. Patients with a concurrent mood disorder or those taking anti-depressants were more likely to fill an opioid.

515 | Asthma associated with infertility—but not among women taking regular asthma preventers: Evidence from the international scope study

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Background: Asthma is a common chronic disease affecting the lives of reproductive age women and is associated with 8-13% of pregnancies. While maternal asthma has been consistently associated with significant perinatal morbidities and mortality, impacts on fertility are conflicting.

Objectives: To investigate the association between asthma treatment status and time to pregnancy in a large pregnancy-based cohort study.

Methods: Women participating in the multi-centre Screening for Pregnancy Endpoints (SCOPE) study (n = 5 373) completed questionnaires at 15 weeks' gestation regarding asthma diagnosis and medication use (ie, use of short-acting beta-agonist only [SABA], or use of inhaled corticosteroid with or without long-acting beta-agonist [ICS ± LABA]), as well as time to pregnancy. Differences in fecundability (ie, average per-cycle probability of conception) and infertility (>12 months to conceive) were examined using regression analysis.

Results: Of 5617 women in the study, 1106 (19.7%) reported doctor-diagnosed asthma. Among women with asthma, 656 (11.7%) were identified as current asthmatics, and 450 (8.0%) were former asthmatics. Compared with non-asthmatics, reduced fecundability was observed among women using SABAs (adjusted Fecundability Odds Ratio [aFOR] 0.83; 95%CI 0.73-0.94) but not women reporting use of ICS ± LABA (aFOR 1.02; 95%CI 0.87-1.20). Similarly, women using SABAs had an increased risk of infertility (adjusted Odds Ratio [aOR] 1.40; 95%CI 0.97-2.01), but not those using ICS ± LABAs (aOR 1.00; 95%CI 0.59-1.70).

Conclusions: Asthmatic women using intermittent reliever therapy only (ie, SABA's) experience reduced fertility. Lack of association with use of preventer medication (ie, ICS ± LABAs) suggests such treatments could play a protective role in improving asthma control and reducing associated systematic inflammation that compromises fertility.

516 | Abstract Withdrawn

517 | Using supervised machine learning methods to develop a list of medications of greatest concern during pregnancy

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Background: Women and health care providers lack adequate information on medication safety during pregnancy.

Objectives: Our objective was to develop a list of medications of greatest concern during pregnancy to help health care providers counsel reproductive-aged and pregnant women about medication use.

Methods: Prescription drug labels submitted to the US Food and Drug Administration with information in the Teratogen Information System (TERIS) database and/or the 10th edition of *Drugs in Pregnancy and Lactation* by Briggs and Freeman were included (N = 1089). Each data source (drug labels, TERIS, or Briggs and Freeman) provided its own categorization and narrative summary of fetal risk. We applied two types of supervised machine learning (SML) models, support vector machine and sentiment analysis, to the narrative summaries in each data source. These methods create prediction models from the text to classify medications as "high" or "not high" fetal risk. Our final list of medications of greatest concern during pregnancy included those medications categorized as "high" risk in at least three of four prediction models (if two data sources were used) or at least four of six prediction models (if all three data sources were used).

Results: We identified ~ 80 (7%) medications that warrant careful consideration before use in pregnant women and women of reproductive age due to their associations with birth defects, pregnancy loss, or other adverse fetal effects. Most medications were antineoplastic agents, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonist, and anticonvulsants.

Conclusions: This evidence-based list could be a useful tool for health care providers in counselling reproductive-aged and pregnant women about prescription medication use. However, providers and patients should weigh the specific risks and benefits of any pharmacologic treatment to manage medical conditions before and during pregnancy.

518 | The impact of technology on the prevalence of congenital malformations

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Background: As technology improves and becomes more widely accessible, more subclinical malformations are detected. This has both clinical implications—more neonates may require follow-up and interventions—and research implications since inclusion of these malformations in studies evaluating safety of drug exposure during pregnancy could affect the identification of teratogens.

Objectives: To study time trends of technology induced malformations—ie, malformations that are clinically asymptomatic and would therefore remain undiagnosed without screening.

Methods: Our cohort consisted of 1 823 820 pregnant women and their liveborn infants nested in the 2000-2013 US Medicaid Analytic eXtract. Based on inpatient and outpatient claims during the first 3 months of life, we contrasted time trends in 5 cardiac and 2 non-cardiac malformations with a presumably high proportion of technology induced cases (Patent ductus arteriosus (PDA), secundum atrial septal defect (ASD), ventricular septal defect (VSD), pulmonary artery anomalies, pulmonary valve stenosis, hydronephrosis, hydrocephalus) with trends of 4 cardiac and 2 non-cardiac defects unlikely to escape clinical diagnosis (Tetralogy of Fallot, coarctation of the aorta, transposition of the great vessels, hypoplastic left heart syndrome, oral

cleft, abdominal wall defect). We used logistic regression models to account for factors potentially associated with trends in incidence (eg, obesity, age) or detection (eg, screening) of congenital malformations.

Results: The prevalence of secundum ASD rose from 0.45% in 2000 to 1.40% in 2013, of PDA from 0.58% to 0.94%, and of VSD from 0.35% to 0.48%. Time trends were not explained by trends in risk factors. Screening coverage increased over time, and the trend persisted within screened pregnancies. Upon restriction to severe secundum ASD, PDA and VSD (defined as diagnosis in term infant that persisted ≥ 6 weeks after birth or had clinical cardiovascular symptoms), the overall prevalence dramatically decreased (eg, secundum ASD: from 0.83% to 0.10%) and was stable over time. None of the other malformations evaluated showed any temporal variations.

Conclusions: Improvements in the sensitivity of technology to detect subclinical cases play a significant role in the increasing diagnosis of certain common congenital malformations. The trends attenuated when restricting to severe cases, underscoring the importance of the case definition in etiologic studies of birth defects.

519 | Evaluating pregnancy registries: Opportunities for improving post marketing surveillance methods in pregnancy

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Background: Pregnancy registries are amongst the most commonly applied study methods for collecting information on the health of offspring exposed to medicines in utero. It is acknowledged however, they have limitations.

Objectives: For all pregnancy registries we had been made aware of by the year 2016, we set out to evaluate what insights pregnancy registries have provided the European Medicines Agency (EMA) regarding safety of medicine use in pregnancy.

Methods: We identified all pregnancy registries listed in Risk Management Plans (RMPs) for centrally authorised products and in the ENCePP overview of data sources for evaluating drug safety in pregnancy. From their protocols and reports, we evaluated their in- and exclusion criteria, whether it was a product- or a disease registry, the rates of recruitment and loss-to-follow-up, characteristics of those enrolled, and information obtained from the registry regarding medicine safety in pregnancy.

Results: Seventy product registries were listed as commitments in RMPs; we also identified 11 disease registries. Of the 70 product registries, 38 were uninformative either because they had enrolled far fewer patients than planned or even after 5 years or more, no protocol or report had been submitted to EMA. A further 8 turned out to be evaluating success of pregnancy prevention programmes instead of safety. The remaining 24 had important limitations in terms of 30% or more loss to follow-up, mid-study changes in recruitment

strategy leading to uninterpretable results, and clear failures to recruit despite spontaneous reports being available of pregnancies occurring. None of these 24 registries highlighted a safety concern; however, none were designed to ensure comprehensive, non-selective capture of pregnancies and their outcomes. Pregnancy loss or terminations were not systematically captured, if at all. Of the 11 disease registries, 6 had provided some information in the medical literature regarding product safety; recently updated study reports are not routinely submitted to EMA.

Conclusions: Registries are not delivering what they are aimed to achieve and we need to reconsider when and why they are useful, when to opt for a disease rather than a product registry, and if a registry is being embarked upon, then how to improve the duration of and loss to follow up. We also need to consider different, more innovative approaches, in close collaboration between stakeholders globally.

520 | In utero SSRI and SNRI exposure and the risk of neurodevelopmental outcomes in children: A population-based retrospective cohort study utilizing linked administrative data

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Background: Studies have demonstrated an association between the risk of neurodevelopmental disorders in children and exposure in utero to serotonergic antidepressants. However, these studies are limited by confounding by history of maternal depression, disease severity, and use of limited populations. We overcome previous limitations by conducting a population-level analysis of women diagnosed with mood/anxiety disorder, restricting our analysis to patients for whom pharmacotherapy is clearly indicated

Objectives: To investigate risk of neurodevelopmental disorders in children exposed in utero to SSRIs/SNRIs, including: autism spectrum disorder, attention-Deficit hyperactivity disorder and epilepsy.

Methods: Using linked population-based administrative data, we identified all mother-newborn pairs in Manitoba (born 1996 to 2009, with follow-up through 2014). High dimensional propensity scores and inverse probability treatment weighting were used to address confounding by indication and disease severity. The final trimmed cohort consisted of mothers who were diagnosed with a mood/anxiety disorder from 90 days prior to conception until delivery ($n = 4995$). We used Cox Proportional Hazard Regression models to estimate risk of Autism Spectrum Disorder, epilepsy and attention deficit hyperactivity disorder (ADHD) in their offspring.

Results: Among the cohort of mothers diagnosed with a mood/anxiety disorder during pregnancy or up to 90 days before, 16.8% received at least two dispensations of an SSRI or SNRI during pregnancy. We did not observe an association between use of SSRIs/

SNRIs during pregnancy and increased risk of Autism Spectrum Disorder (hazard ratio 0.92; 95% CI 0.42 to 2.03), epilepsy (hazard ratio 1.21; 95% CI 0.48 to 3.05), or ADHD (hazard ratio 1.13, 95% CI 0.78 to 1.64) among offspring.

Conclusions: In a large population level sample, in utero exposure to serotonergic antidepressants compared with no exposure does not increase risk of ASD, epilepsy or ADHD among children of women who have prenatal mood/anxiety disorder.

521 | Opioid prescribing after vaginal and cesarean delivery and risk of persistent use

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Background: Cesarean and vaginal delivery are common procedures for which opioids are prescribed. The persistence on opioids after these procedures is unclear.

Objectives: To describe opioid prescribing patterns and estimate the incidence of persistent opioid use 365 days after cesarean or vaginal delivery.

Methods: We conducted a retrospective cohort study of women age 15-44 enrolled in Tennessee Medicaid (TennCare) who had a delivery between 1/1/2007 and 12/31/2015. All women had TennCare coverage from 180 days prior to delivery through 365 days after delivery. Prescriptions filled between 3 days prior to and 7 days after delivery were considered discharge prescriptions. We considered women with no filled opioid prescriptions during baseline (180 to 3 days prior to delivery) as opioid naïve, and women with baseline prescriptions as opioid-exposed. The postpartum period was defined as up to 42 days after delivery. Women with at least one filled opioid prescription every 45 days through 365 days after delivery were considered persistent users.

Results: There were 169 765 deliveries among eligible women during the study period of which 31.4% were cesareans. Overall, 22.8% (n = 38 658) had baseline exposure to opioids, and 64.2% (n = 108 996) received a discharge opioid prescription. Among opioid-naïve women, 87.5% with a cesarean and 50.0% with a vaginal delivery received a discharge prescription. Filling a second opioid prescription in the post-partum period was more common for cesarean (19.7%) than vaginal (12.9%) deliveries (RR 1.55, 95% CI 1.48-1.58). Persistent opioid use at 365 days after delivery was similar in women with a cesarean versus vaginal delivery (0.64% vs 0.62%, RR 1.05, 95% CI 0.86-1.27). In comparison, opioid-exposed women with a cesarean were more likely than women with a vaginal delivery to receive a discharge prescription (90.5% vs 64.5%, RR 1.40, 95% CI 1.39-1.42), a second opioid prescription postpartum (42.7% vs 34.7%, RR 1.23, 95% CI 1.19-1.26), and to have persistent opioid use at 365 days (8.1% vs 7.4%, RR 1.10, 95% CI 1.01-1.21).

Conclusions: Among opioid-naïve women, 50.0% and 87.5% of those with vaginal and cesarean deliveries, respectively, received an opioid prescription at discharge. About 6 per 1000 were persistent opioid

users at 1 year. However, among women with opioid use during pregnancy, persistent opioid use at 1 year was 81 and 74 per 1000 women with cesarean and vaginal deliveries, respectively

522 | Do ICPE pregnancy abstracts make it to term?

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Background: Conference presentations are a valuable means of early dissemination of research findings. However, a complete understanding of the study methods, results, and implications is achieved only with publication of a full-text article in a scientific journal.

Objectives: To explore the characteristics and publication outcome (ie, full-text article in a scientific journal) of abstracts on pregnancy-related topics presented at the International Society for Pharmacoepidemiology (ISPE) annual conferences (ICPE).

Methods: Abstracts presented at the ICPE in 2014 and 2015 were identified through the conference program and book of abstracts. Workshops and symposia were excluded. Publications were identified from PubMed (year of abstract presentation through 31 December 2017); letters to the editor were excluded. Abstract characteristics (first author's affiliation, countries of authors' affiliations, type of presentation, methods, results, and conclusions), publication outcome, time of first publication, journal category, and impact factor (IF) were evaluated. Kaplan-Meier analysis was used to estimate time to first publication, and multivariable logistic regression was used to identify factors associated with publication.

Results: A total of 119 abstracts were presented (28.6% oral, 71.4% poster), 68% with academic affiliation of first author, 30.3% with authors' affiliation from >1 country (17.6% with intercontinental author's affiliations). Drug safety (57.1%) and drug utilization (16.0%) were the most frequent study types. Of all abstracts, 84.0% used secondary data, 18.5% used multiple data sources, and 63.9% used analytical methods. The primary focus, in 82.4% of abstracts, was medications, most frequently, nervous system medications (30.3%). Outcomes or complications of pregnancy, fetus, or infant, or combinations thereof, were evaluated in 58.8%. A total of 65 abstracts (54.6%) led to publications during the follow-up period. Median time to publication was 1.5 years (95% CI, 1.3-1.7 years), and mean (SD) of the journal IF was 6.3 (8.9). A strong association with publication was observed for international collaborations (OR = 3.0; 95% CI, 1.2-7.3), and marginal associations were observed for type of presentation, medications as a focus of study, and year of abstract presentation.

Conclusions: More than half of the abstracts on pregnancy-related topics presented at the ISPE annual conferences resulted in published papers within 2 years. The factor most strongly associated with publication was international collaboration.

523 | Medication use during pregnancy and lactation in Mainland China: Based on a national health insurance database in 2015

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Background: Medication use during pregnancy and lactation has been globally on the rise in recent years, however, the current status in China remains unknown.

Objectives: This study aimed to explore the status quo of medication use among pregnant and breastfeeding women in mainland China.

Methods: A retrospective drug utilization research was conducted based on China's National Survey of Medical Service Utilization for Basic Medical Insurance Beneficiaries in 2015. Individual's Year-round records of medical service utilization were extracted. International Classification of Diseases 10th Revision was applied to identify women aged 12-54 with a singleton delivery in 2015. We assumed a gestational duration of 270 days with three 90-day trimesters, and 180 days postpartum for lactation. Individuals with full records throughout a studied period were considered sample composition in that period.

Overall period prevalence was defined as the proportion of women who used at least one medicine during each period. Most commonly used drugs was ranked by the percentage of women exposed to each drug. Chi-square test was used for the temporal comparison of prevalence.

Results: Samples in each of the three trimesters ($n = 2896$, $n = 5377$, $n = 7946$), the entire pregnancy ($n = 2896$), and lactation ($n = 6193$) was obtained. In general, 11.0% and 8.7% of women during the entire pregnancy and lactation used at least one drug, and the median number of drugs used were both 3.0. Period prevalence in gestational trimesters was lower than the entire pregnancy, with 5.8% in the first trimester, a significant decrease in the second trimester (4.7%), then a recover to 5.5% in the third trimester. Similar trends can be observed in the use of western drugs and traditional Chinese medicines (TCM), respectively. However, a different pattern was shown in the combination use of western drugs and TCM, from which a sustained decline can be observed from the first trimester (4.0%) through lactation (1.1%). The most commonly used drug excluding diet supplements in pregnancy was progesterone (25.9%), followed by dydrogesterone (13.8%), both indicated to support early pregnancy. Antibiotics, blood-enriching TCM, and analgesics was commonly consumed by breastfeeding women.

Conclusions: This study reveals a conservative state of prenatal drug use in China. Further research on the safety profile of drug use during pregnancy and lactation is still in great need to facilitate clinical practice and reduce risk both for the mother and the fetus.

524 | Pharmacological treatment utilization and discontinuation before and during pregnancy in women with inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD) affects patients in their reproductive years, and no guideline has comprehensively addressed the management of IBD during pregnancy. Limited data is available for medication use before and during pregnancy in the real-world setting.

Objectives: This study aimed to characterize pharmacological treatment of IBD during preconception and pregnancy in a privately insured population.

Methods: We identified pregnant women aged 12 to 55 years with completed pregnancies and linked to their live born infants in the Truven Health Analytics MarketScan Commercial Claims and Encounters database from 2005 to 2015. We included pregnant women who had continuous enrollment in health plans between 6 months before and during pregnancy. Pharmacological treatment was classified into biologics (adalimumab, certolizumab pegol, golimumab, infliximab, natalizumab, vedolizumab), and non-biologics (azathioprine, balsalazide, mercaptopurine, mesalamine, methotrexate, olsalazine, sulfasalazine). We calculated the prevalence of biological and non-biologic treatment during the preconception period and pregnancy. We further described the prevalence of discontinuation, continuation, and initiation of pharmacological treatment during pregnancy.

Results: We identified a cohort of 5290 pregnant women with IBD linked to their liveborn newborns. Before pregnancy, the exposure prevalence was 8.7% for biologics, 24.0% for non-biologics and 3.1% for both. During pregnancy, the prevalence was 9.3% for biologics, 29.5% for non-biologics, and 2.7% for both. During pregnancy, 5.8% IBD patients discontinued any pharmacological treatment, 29.9% continued to be treated, and 11.5% initiated pharmacological treatment. Adalimumab and infliximab were the most commonly used biologics and mesalamine were the most commonly used non-biologics during both the prepregnancy period and pregnancy.

Conclusions: IBD treatment is as common as during the preconception period and highlights the need for more studies that allow a better understanding of risks and benefits of pharmacological treatment options considering effects on both fetal and maternal health.

525 | The top 10 most commonly dispensed medications during pregnancy from 2005 to 2015

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Background: Multiple national and state programs focus on mitigating risk associated with medication exposure during pregnancy but limited up-to-date data are available that describe utilization pattern in the real-world setting.

Objectives: This study aimed to characterize drug utilization pattern and related secular trends during pregnancy and each trimester.

Methods: We identified pregnant women age 12-55 years with a live birth linked to their newborns in the Truven Health Analytics MarketScan Commercial Claims and Encounters database. We required eligible women to have continuous enrollment during pregnancy and utilized prescription drug files to identify outpatient medication dispensings. For each year, we calculated and ranked the proportion of deliveries with ≥ 1 dispensing of individual medications during pregnancy and in each trimester, and examined pattern across study years.

Results: We included a cohort of 1 223 054 pregnant women linked to their newborns. Over the study period, 828 857 (67.8%) new mothers had a dispensing for ≥ 1 prescription medication. The top 10 most commonly dispensed medications during pregnancy were ondansetron (12.6%), azithromycin (11.8%), amoxicillin (10.4%), acetaminophen (8.5%), nitrofurantoin (8.1%), promethazine (6.82%), progesterone (6.01%), docusate sodium (4.45%), levothyroxine (4.15%), and hydrocodone (4.15%). The top 3 most commonly dispensed medications were ondansetron, progesterone, and promethazine in the first trimester; azithromycin, amoxicillin, and ondansetron in the second trimester; and azithromycin, acetaminophen and levothyroxine in the third semester. In the years before 2009, treatment for infections were most prevalent, but were surpassed by ondansetron in 2010.

Conclusions: Medications used to treat vomiting and infections were the most commonly dispensed prescriptions during pregnancy. An increase in ondansetron use was seen in recent years.

526 | A multiphase claims-based algorithm for live pregnancy outcomes research

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Background: Safety studies on outcomes of medication exposure during pregnancy are critical. Administrative claims data could be used; however, these studies are often unfeasible due to the difficulty in identifying pregnancies, estimating gestational age (GA), estimating exposure during pregnancy and linking mothers to infants using only claims data.

Objectives: To develop a multiphase claims-based algorithm that identifies pregnancy outcomes (Phase [Ph]1), estimates GA (Ph2), estimates medication exposure (Ph3) and links mothers to infants (Ph4).

Methods: A multiphase algorithm was developed for use in women aged ≥ 15 and ≤ 50 years with ≥ 1 end of pregnancy (EOP) ICD-9 code

and enrolment and prescription coverage 340 days prior to EOP in the Henry Ford Health System in the United States between 1 January 2013 and 30 September 2015. Algorithms were developed, applied to claims data and validated against electronic medical records. Positive predictive value (PPV), sensitivity (Sens) and 95% CI were calculated. The best-performing algorithm in each phase was used in the next phase. Ph1 results were presented at ICPE 2017 (abstract 154). Two Ph2 algorithms estimated GA at live birth as pre-term (245 days), term (273 days) or post-term (294 days) using EOP ICD-9 code dates adjusted with the dates of obstetric procedure codes. Three Ph3 algorithms evaluated exposure to long-term (eg, antidepressants) and short-term (antibiotics) medications overall and by trimester (using Ph2 estimated GA) using fill date and one of the following: days' supply (DS), DS plus a 14-day grace period or DS plus medication-specific grace periods. Three Ph4 algorithms assessed mother/infant linkage using combinations of birth/delivery dates, 3-digit ZIP codes, caesarean birth codes, delivery status (eg, singleton) and a screening hierarchy.

Results: Ph2 algorithms performed identically for term births (PPV: 94% [95% CI: 91, 96]; Sens: 81% [76, 84]) and post-term births (PPV: 40% [32, 49]; Sens: 90% [79, 96]). Algorithm 2 performed better for pre-term births (PPV: 94% [79, 99]; Sens: 68% [52, 81]). Using Ph2 Algorithm 2, all Ph3 algorithms performed identically overall (PPV: 100% [98, 100]; Sens: 100% [98, 100]). The lowest PPV for long- or short-term drug exposure by trimester was 91% (77, 98) (Sens: 100% [89, 100]). Ph4 algorithms had approximately 60% PPV. Work is ongoing to improve Ph4 algorithm performance.

Conclusions: A multiphase algorithm can be used with claims data to estimate GA at live birth and exposure to medications during pregnancy.

527 | A comparison of pregnancy and lactation product labeling based on FDA and EMA requirements

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Background: The FDA's Pregnancy and Lactation Labeling Rule (PLLR) published in 2014 requires manufacturers to summarize maternal-fetal risk in specific sections in US prescribing information (USPI), replacing Pregnancy Categories A, B, C, D and X. The EMA Guideline (2008) requires similar content in the Summary of Product Characteristics (SmPC).

Objectives: To compare the reproductive risk summaries in the USPI and SmPC for 2 products: Combivir (lamivudine/zidovudine) an antiretroviral prescribed to prevent mother to child HIV transmission, and warfarin, an anticoagulant prescribed to pregnant women for systemic embolism.

Methods: The most recent USPI and SmPC for Combivir (03/2017 and 10/2017, respectively) and warfarin [Cadila Healthcare Limited] (11/2017 and 09/2016, respectively) were obtained. Relevant

information was extracted from USPI sections 8.1-8.3 (Pregnancy, Lactation, and Females/Males of Reproductive Potential) and SmPC section 4.6 (Pregnancy, Lactation, and Fertility).

Results: For Combivir, much of the information was identical between the 2 labels. Both labels recommend avoiding breastfeeding, as both products are present in breast milk. Both state that there are no human female fertility data available. The SmPC states that male fertility is not affected while the USPI does not. The SmPC cautions pregnant women co-infected of the possibility of hepatitis recurrence upon lamivudine discontinuation. For warfarin, both labels indicate an associated increased risk for birth defects and fetal death. In the USPI, warfarin is contraindicated in pregnancy. In the SmPC, warfarin is contraindicated in the 1st and 3rd trimesters. The SmPC states that warfarin can be used during breastfeeding; however, the USPI warns of potential adverse reactions (e.g, bleeding in breastfed infant) and advises consideration of risks vs benefits of breastfeeding. Both labels recommend female contraception during treatment; the USPI extends this caution to at least 1 month after treatment.

Conclusions: For Combivir and warfarin, varying levels of detail related to pregnancy, lactation, and fertility were seen in the USPI compared with the SmPC. Detail was not consistently greater in the USPI vs SmPC. These discrepancies can result in inappropriate prescribing in pregnant and breastfeeding women and unnecessary risk to their fetuses and breastfed children.

528 | Health care provider counseling about prescription medication use during pregnancy among women of reproductive age

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Background: About 7 in 10 pregnant women report taking a prescription medication; however, not all medications are safe to take during pregnancy. It is important for women and their health care providers to discuss the risks and benefits of using specific medications during pregnancy.

Objectives: To estimate the proportion of reproductive-aged women who received counseling by a health care provider about prescription medication use during their last pregnancy, assess when the counseling occurred, and describe demographic factors associated with receipt and timing of counseling.

Methods: We analyzed 2015 *FallStyles* national online survey data, weighted to represent the US population. Participants were included in this analysis if they were women of reproductive age (18-44 years) and if they reported ever being pregnant. Chi-square tests were used to determine if there were significant differences in receipt of and the timing of counseling (ie, before pregnancy only, during pregnancy only, both before and during pregnancy, or not at all) by respondent demographic factors, including age, ethnicity, income, and education.

Results: A total of 3529 adults completed the survey; a response rate of 79.6%. Of the 561 female survey respondents who were of reproductive age, 262 women were excluded because they had never been pregnant and four women refused to answer the survey question. Of the remaining 295 women, the majority (61.1%) received counseling by a health care provider before and/or during pregnancy: 5.1% received counseling before pregnancy only, 21.1% during pregnancy only, and 34.9% received counseling both before and during pregnancy. All demographic factors, with the exception of education, were significantly associated with the timing of counseling ($p < 0.05$). Women aged 30-34 years (42.4%), non-Hispanic white women (38.9%), and women with a household income from \$25 000-\$49 999 (42.2%) were most likely to report receiving counseling by a health care provider both before and during pregnancy.

Conclusions: In our analysis, only one-third of women received counseling by a health care provider about prescription medication use both before and during pregnancy. Given that use of some medications during pregnancy, including early pregnancy, may be associated with adverse outcomes, it is important for health care providers to discuss the risks and benefits of medication use both before and during pregnancy with women who are considering becoming or are already pregnant.

529 | Generation of a New Zealand pregnancy cohort for medicine utilisation and safety studies

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Background: Retrospective cohort studies using cohorts generated from administrative databases are an effective method for assessing medicine use and safety during pregnancy. In New Zealand the Ministry of Health administers several population-level health databases which could be used to generate such a cohort.

Objectives: To assemble a pregnancy cohort for undertaking medicine utilisation and safety studies in New Zealand using four national health databases.

Methods: Delivery records for live and stillborn infants were sourced from the National Maternity Collection. Hospital admission records with a pregnancy-specific ICD-10 code were sourced from the National Minimum Dataset (hospital database). Stillbirths and maternal death records were identified in the Mortality Collection. Antenatal blood tests were identified in Laboratory Claims Collection. A last menstrual period (LMP) date and a pregnancy end date were assigned to identified pregnancies where possible. These dates, in conjunction with a mother's unique National Health Index (NHI) number, were used to merge the pregnancies into a cohort with a single record of an individual pregnancy. Cohort inclusion criteria included a LMP date between 1 January 2005 and 15 March 2015, a pregnancy end date, and a maternal age of 15-49 years. All eligible pregnancies for an individual woman during the study timeframe were included. Records of

live and stillborn infants in the Maternity and Mortality databases linkable to cohort members formed the baby cohort.

Results: The pregnancy cohort contains 942 487 pregnancies to 491 682 women. The baby cohort consists of 632 750 live or stillborn infants. One third (312 542) of the cohort pregnancies were sourced from collections other than National Maternity Collection. 66.3% of the pregnancies resulted in a live birth, 0.2% in a stillbirth, 9.3% in a termination, 5.4% in a miscarriage and 0.5% in other early losses. A pregnancy outcome was unrecorded for 18.3% of pregnancies, the majority of which were identified solely from an early antenatal blood test and presumed to be early pregnancy losses.

Conclusions: The New Zealand Pregnancy Cohort includes the majority of pregnancies in New Zealand over the past decade, including early pregnancy losses as well as deliveries of live and stillborn infants. This cohort will be valuable for investigating patterns of medicine use during pregnancy in New Zealand and developing a fuller understanding of potential impacts of foetal exposure to medicines in early pregnancy.

530 | Awareness strategies, referral sources, and impact on enrollment in pregnancy and lactation studies

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Background: Recruitment is a major challenge for pregnancy and lactation studies. A robust awareness plan is critical. Yet, little data exists on effective awareness strategies.

Objectives: To examine impact of awareness activities on referral sources and enrollment in pregnancy and lactation studies.

Methods: We descriptively examined awareness activities, referral sources, and enrollment in six ongoing pregnancy and lactation studies. Awareness activities were categorized and assessed 3 ways: 1) by primary target audience—patients or health care providers (HCPs), 2) by modality—internet, mailings, scientific conferences, and sponsor referrals; 3) by intensity—persistent or sporadic. Referral source was assessed by asking participants how they heard about the study. Enrollment was assessed by examining overall enrollment metrics.

Results: Three of the 6 studies relied heavily on persistent, direct-to-patient internet and social media initiatives. Internet recruitment initiatives included a study website, banner ads on popular “high traffic” websites directed at patients and google ad word searches. Social media initiatives included implementing Facebook ads and posting study information on Facebook pages of study sites and advocacy groups. For these 3 studies, referrals came primarily from the internet (58.5%) compared with 32.1% from HCPs and 9.4% from various other sources. Two of these 3 studies met their enrollment targets early or on-time. The other 3 studies relied mainly on sporadic awareness strategies targeting HCPs, including mailings and scientific conferences. All 3 have a website and links on other websites (sponsor, FDA, clinicaltrials.gov, etc). One study implemented a banner ad campaign briefly. For these 3 studies, referrals came primarily from HCPs

(72.8%), with only 12% from the internet, 4.8% from the sponsor, 2.5% from study brochures, and 7.9% from various other sources. All 3 studies struggled meeting enrollment targets.

Conclusions: While this study is purely descriptive and not a rigorous evaluation of the effectiveness of awareness strategies, the findings suggest that internet and social media are important awareness strategies in pregnancy and lactation studies. These findings are not surprising given the patient population, young women, who are known to be frequent users of internet and social media. It is important to note that awareness activities are not the only drivers of enrollment. Enrollment is also dependent on uptake of the drug of interest.

531 | Trends in FDA post-marketing commitment requirements for pregnancy registries

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Background: With passage of the Food and Drug Administration Amendments Act (FDAAA) in 2007, the responsibilities of FDA increased and they were granted the authority to mandate pregnancy registries. In a previous study we noted an increase of 30% from 2008 to 2012 in post-marketing commitments (PMCs) to implement pregnancy registries. With implementation of FDA's Pregnancy and Lactation Labeling Rule (PLLR) in June 2015, product labels are required to provide human data on safety of product use during pregnancy, including data collected in pregnancy registries.

Objectives: While this study continues to examine trends in PMCs to implement pregnancy registries, it goes beyond trends and examines specific requirements for those PMCs in the 5 years pre-and post PLLR implementation.

Methods: We searched FDA website to identify approvals of all new molecular entities and biologic therapies from 2013 to 2017. Approval letters were reviewed to identify PMCs for pregnancy registries and data were abstracted on the requirements specified in the letters. Data were evaluated descriptively. This study was limited to new molecular entities and biologic therapies; vaccines and devices were not included.

Results: Of 319 new drugs approved between 2013 and 2017, there were 29 (9.1%) PMCs for pregnancy registries including 8.0% in 2013, 10.2% in 2014, 8.9% in 2015, 9.1% in 2016, and 8.8% in 2017. All products were biologics in 2017-2016 versus half in 2015-2014 and none in 2013. After PLLR implementation, all 3 drugs in 2017 and 1 of 2 in 2016 required a retrospective pregnancy study in addition to a prospective registry. All 5 (100%) product approval letters in the years following PLLR implementation specifically required use of an unexposed comparator, specific outcomes to be collected, and length of infant follow-up. These requirements were only specified in 8.3% of approval letters pre-PLLR.

Conclusions: Unlike the 5-year period post FDAAA that showed a 30% increase in pregnancy registry PMCs, in the 5-year period pre-and post PLLR implementation, there was little variation in the

percentage of drugs that required a PMC for pregnancy registries. However, there were changes in requirements. A noticeable change in the 2 years after PLLR implementation was the additional requirement for both prospective and retrospective pregnancy monitoring studies and the specificity of requirements regarding comparator group, outcomes monitored, and length of follow-up compared with the period prior to PLLR implementation.

532 | Maternal use of thyroid hormone replacement therapy: Group-based trajectory modelling of adherence and agreement between self-reporting and prescription records during pregnancy

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Background: Valid definition of exposure, and knowledge about long-term medication pattern is important for drug safety studies during pregnancy. Few studies have investigated these measures for thyroid hormone replacement therapy (THRT).

Objectives: To i) calculate agreement between self-report and dispensed prescriptions of THRT, and ii) cluster trajectories of women with similar adherence pattern to THRT.

Methods: The study is based on the Norwegian Mother and Child Cohort Study (MoBa), a prospective population-based cohort study. MoBa was linked to prescription records from the Norwegian Prescription Database (NorPD). We estimated Cohen's Kappa coefficients (K) and approximate 95% confidence intervals (CI) for agreement between self-report and prescription records for the six-month period prior to pregnancy and by trimester. Using group-based-trajectory-modelling (GBTM), we estimated adherence trajectories among 1171 women who self-reported and had a prescription of THRT.

Results: There were 56 148 women that participated in MoBa, had a record in NorPD, and available prescription history up to 1 year prior to pregnancy. Of these, 2885 (5.1%) self-reported and/or received a prescription for THRT.

Agreement was perfect six-months prior to pregnancy, $K = 0.86$; CI 0.85-0.88, in the first, $K = 0.83$; CI 0.82-0.85, and second trimester, $K = 0.89$; CI 0.87-0.90. In the third trimester, agreement was moderate, $K = 0.57$; CI 0.54-0.59. Among 1171 women, we identified four GBTM adherence groups: *Constant-High* (50.2%), *Constant-Medium* (32.9%), *Increasing-Medium* (11.0%) and *Decreasing-Low* (5.8%).

Conclusions: Agreement between data-sources was high except for the third trimester. Based on GBTM, about one in two women had adequate adherence throughout pregnancy. Low adherence was nevertheless evident in 6% of pregnant women, raising concerns about adequate thyroid hormone level in pregnancy.

533 | Exposure to mycophenolate before and during pregnancy in France: A nationwide cohort study

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Background: Mycophenolic acid (MPA) is a known teratogenic immunosuppressive substance, widely used after organ transplantation and to treat various autoimmune diseases (AID). The respect of contraindication during pregnancy has not been previously evaluated in France.

Objectives: To describe MPA utilization in the year prior to and during pregnancy in France, according to clinical context of prescription.

Methods: This study was based on the French national health data system (SNDS), a nationwide reimbursement and hospitalization database. Among all female aged 13-49 and ever exposed to MPA between 01/01/2009 and 31/12/2015, those with MPA reimbursement in the year before or during pregnancy were selected. Only the first pregnancy in the study period was considered. Pregnancy start date was calculated using gestational age and date of delivery, abortion, or hospital admission for extra-uterine pregnancy. Frequencies of reimbursements of MPA and azathioprine (AZA), an alternative immunosuppressant, were estimated by trimester, from 12 months before pregnancy start date until the end of pregnancy. Descriptive analyses were conducted according to clinical context (transplantation or other).

Results: Among 14 593 women of childbearing age ever exposed to MPA, 664 first pregnancies occurred (mean age at pregnancy: 28.3 (5.3) years). Among them, 210 (32%) were interrupted before the third trimester. MPA exposure markedly decreased between the fourth and first trimesters before pregnancy, overall (from 76.1% to 25.9%) and regardless of clinical context. The lowest frequency was observed during the second trimester of pregnancy (2.8%). In parallel, AZA exposure significantly raised up during the year before pregnancy from 2.7% up to 32.7%. Conversely to MPA, AZA exposure increase was more marked in transplanted patients, reaching 74.3% during the second trimester of pregnancy (vs 35.1% in non-transplanted). In transplanted patients, during the third trimester of pregnancy, AZA exposure dropped to 45.2%, together with a slight raise of MPA (13%).

Conclusions: This first national study describing MPA use before and during pregnancy shows a net decrease in MPA exposure associated with an inverse trend in AZA use, in the year before conception. This suggests that MPA teratogenicity risk is mostly managed by the pregnancy prevention measures, even if some cases of exposure during pregnancy subsisted until 2015. The impact of the DHPC released late 2015 needs to be assessed later on.

534 | Identifying adverse drug effects from granular longitudinal inpatient data

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Background: Confounding by indication, missing data, and other sources of bias limit the usefulness of observational studies. These issues may be ameliorated in settings where repeated-measures outcomes with time-varying exposures can be used to reduce the impact of baseline confounders.

Objectives: First, to assess the performance of simple longitudinal analysis of observational data in identifying known causal associations between glucocorticoids and hypoglycemic agents on blood glucose level. Second, to use the best-performing simple longitudinal model to assess for potentially causal associations between commonly used drugs and glucose levels.

Methods: Patients admitted to an inpatient cancer center for 1 week or longer during 2015 contributed person-time to the study during their inpatient stay. Drug exposures were defined as time-varying covariates using electronic dispensing records and the outcome (average daily blood glucose in mg/dL) was identified based on electronically captured lab results. For the first objective, varied definitions of exposure period and model specifications were used to assess the association between corticosteroids, insulin, and blood glucose. The exposure definition and model specification that most consistently provided results in accord with known causal effects was chosen for objective two. For objective two, this model was used to assess the association of the 200 most commonly used drugs with blood glucose levels.

Results: Only models that included glucose prior to exposure as a baseline covariate showed directionally correct associations between glucocorticoids and insulin and glucose levels. When the final model was used to screen 200 candidate drugs for an association with blood glucose, 7 statistically significant relationships were demonstrated. Of these, 4 were known causal effects and one (an association between levofloxacin and hypoglycemia) had been widely proposed in the case-report literature.

Conclusions: Simple longitudinal models that examined change in glucose from baseline overcame significant confounding by indication in assessing the effect of insulin and corticosteroids on blood glucose. Used to screen a large number of drugs, such methods identified a set of drug-outcome associations enriched with known causal effects and plausible novel effects.

535 | Characteristics of medical information database network (MID-NET[®]) of 23 hospitals on drug safety assessment

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Background: MID-NET[®] is the Japanese Electronic Medical Record (EMR) database which is a distributed- and closed-network system established by Ministry of Health, Labor and Welfare and Pharmaceuticals and Medical Devices Agency (PMDA) for drug safety assessment in cooperation with 10 medical organizations (23 hospitals). MID-NET[®] includes various types of data including order entry data (prescription, lab results, disease classifications etc) and other medical procedures and its full scale implementation is planned in 2018.

Objectives: To examine characteristics of MID-NET[®] on pharmacoepidemiological assessment of drug safety.

Methods: Characteristics of MID-NET[®] were examined in the following steps: 1) System validation, 2) Data quality management, 3) pilot pharmacoepidemiological studies.

Results: Reliability of the system was verified by assessing error messages and validating application tools with different independent methods. High data quality in terms of consistency between original data and data stored in MID-NET[®] was confirmed by implementing quality management system. Pilot studies revealed that data from patients with broader backgrounds (age, gender, medical history, etc) are available for analysis and risks of adverse events induced by a drug can be objectively examined, especially for the events defined with a laboratory test result.

Conclusions: MID-NET[®] is the highly reliable EMR database which is utilized for pharmacoepidemiological safety assessment of a drug. In 2018, MID-NET[®] will be made available to various users including pharmaceutical companies and academia in addition to PMDA and cooperative hospitals. Data corresponding to approximately 4 million patients are expected to be available in early 2018. Further efforts including continuous quality management and more pharmacoepidemiological studies are needed to fully understand characteristics of this database.

536 | Drug-drug interactions in nursing homes: A systematic review and meta-analysis of 136 357 residents

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Background: Drug-drug interactions (DDIs) are common causes of adverse drug reactions which could lead to clinically important adverse health outcomes. Residents dwelling in nursing homes (NHs) are highly susceptible to expose DDIs due to their advanced age and multiple medications. While systematic reviews have been conducted on DDI prevalence in hospitals and primary care settings, no critical review has been undertaken in the nursing home setting.

Objectives: This study aimed to examine the prevalence and nature of DDIs in NH residents

Methods: The MEDLINE, SCOPUS, the Cochrane Library and CINAHL were searched for relevant studies published from 2001 to January 2018 without language restriction. Observational studies that examined the prevalence of DDIs among NH residents were included in the review and meta-analysis. The risk of bias of eligible studies was assessed using the US National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-sectional Studies. Pooled estimates were obtained using a random-effect model.

Results: Overall, 21 studies were identified that included 136 357 NH residents, of whom 8185 were exposed to potential DDIs. Prevalence rates of patients exposed to at least one potential DDI varied between 0.01% and 87.1%. Across these studies, the median prevalence rate of DDIs among NH residents was 18.3% (interquartile range [IQR]: 4.8-36.8%), with high heterogeneity (χ^2 13 013; d.f. 20; $p < 0.001$; I^2 99.8%). Treatment by potassium-sparing diuretics with either potassium, or with angiotensin-converting enzyme inhibitors were most commonly associated with severe DDIs. Poly-pharmacy was an important risk factor for DDIs in NH residents. Eighteen studies (85.7%) were of good quality as judged by the NIH quality assessment.

Conclusions: This systematic review found that potential DDIs are common amongst NH residents and effective surveillance systems are needed. The drug categories identified in this systematic review provide important targets for improvement of medication safety in NH settings.

537 | The association between potentially inappropriate medication use and health-related outcomes among nursing home residents: A systematic review and meta-analysis

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Background: Several studies reported the prevalence of potentially inappropriate medication (PIM) use among nursing home (NH) residents. However, there is no clear association between negative health outcomes and PIM use.

Objectives: This systematic review and meta-analysis aimed to assess the relationship between PIMs and their consequences for health-related outcomes in NH residents.

Methods: Observational studies that examined the association between health-related outcomes and PIM use among NH residents were identified from the Cochrane library, CINAHL, SCOPUS, and PUBMED until 6th October, 2017. Quality assessment was performed using the National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-sectional Studies. Pooled estimates were obtained by using a random-effect model.

Results: Eleven studies were included in the systematic review and 8/11 studies in the meta-analysis. The prevalence rate of PIMs among nursing home residents ranged from 11.9% to 77.2% with a median of 46.5% (Interquartile range; IQR = 32.2-50.3%). Our meta-analysis demonstrated that PIM users had a significant association with mortality compared with PIM non-users (OR = 1.46, 95% CI: 1.24 to 1.72, I^2 51.8%). In the United States, PIM users were more likely to be hospitalized than non-users (OR = 1.27, 95% CI 1.15 to 1.41, I^2 0%). For health-related quality of life (HRQoL), no significant changes were observed in EQ-5D score ($p = 0.07$) and E-VAS score ($p = 0.34$). However, in terms of 15D and PWB scale, quality of life was better for residents who were not PIM users after adjustment for age and gender. The cost of pharmaceutical care services was positively correlated with the number of medications that inappropriately prescribed.

Conclusions: The use of PIM was significant and associated with a higher risk of mortality among nursing home residents. But the results on HRQoL remained inconclusive. Further studies with prospective long-term follow up are needed to establish the association with mortality.

538 | Signals in types of adverse event reporting of concurrent use of botanical dietary supplements and anticancer prescriptions in the US Food and Drug Administration adverse event reporting system (FAERS)

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Background: Approximately 1 in 5 cancer patients in the US use botanical dietary supplements (BDS) as complementary and alternative medicine. Existing evidence has shown potential risk of adverse events (AE) among cancer patients treated with anticancer drugs and BDS. But, the nature of potential BDS-anticancer drug interactions remains unclear.

Objectives: To examine signals in types of AE reporting of concurrent use of BDS and anticancer treatments in the US Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: Using the FAERS database from 2004 to 2015, we focused on 6 commonly used BDS (acai, fiber, garlic, ginger, green tea, cranberry) and 26 individual anticancer prescriptions representing both IV and oral dosage forms against a wide spectrum of cancers. AEs reported with targeted BDS (by type) and anticancer prescriptions were identified and further aggregated with MedDRA preferred terms (PT) by System Organ Class (SOC). Disproportionality analyses using the reporting odds ratio (ROR) assessed the relative rates of reporting of any AEs with concurrent use of BDS and anticancer prescriptions compared with anticancer prescriptions only for the most common types of SOC. An $ROR \geq 2$ was used as threshold for signal detection.

Results: A total of 8490 unique AEs were reported over the 12-year period involving concurrent use of BDS and anticancer drugs. Differences in the RORs were observed across SOCs with specific BDS and anticancer combinations compared with anticancer drugs alone. Specifically, compared with anticancer drugs without concomitant BDS use, the ROR for vascular AEs was higher ($ROR = 13.9$; 95% CI = 8.6, 22.4) than other types of AEs for acai and anticancer drugs; the ROR for gastrointestinal AEs was higher ($ROR = 3.5$; 95% CI = 2.9, 4.3) for green tea and anticancer drugs; and the RORs for muscular AEs were higher for ginger ($ROR = 3.4$; 95% CI = 2.5, 4.4) and garlic ($ROR = 2.2$; 95% CI = 1.9, 2.5) used concomitantly with anticancer drugs.

Conclusions: We detected signals indicating potential risks for specific types of AEs with concurrent use of BDS and cancer treatment compared with cancer treatment alone. Findings need to be confirmed through additional population-based observational studies. The differences in types of AEs reported by individual BDS inform research investigating potential interactions between BDS and cancer treatment.

539 | Development and pilot testing of a process for postmarketing surveillance to comparatively assess and monitor for brand vs generic safety and effectiveness

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Background: Generic and brand drugs are tested for pharmaceutical and bioequivalence, but comparative clinical outcomes are rarely evaluated for drug approval.

Objectives: This study depicts development and pilot testing of a process for post-marketing surveillance to comparatively assess and monitor for brand vs generic safety and effectiveness.

Methods: The approach is based on drug-specific new user retrospective cohort studies of insurance claims and electronic health records. As a use case for development, pre-defined adverse event rates were compared among brands, authorized generics (AG), and generics using amlodipine, gabapentin, metoprolol ER, and sertraline as example drugs over a time period of 1999 to 2015. AG drugs were included as brand proxies to control for generic drug perception bias since these drugs are identical to brand but marketed as generic. The primary analyses used multivariable Cox proportional hazards, with an *a priori* defined series of sensitivity analyses of different model and cohort specifications.

Results: The modular design allowed for drug- and event-specific adjustments in measurement and analyses. In primary analyses, comparison of AG vs brand resulted in similar event rates. Comparison of brand and AG with generic commonly resulted in statistically significant differences. For example, flushing was less common with brand and AG amlodipine and metoprolol ER compared with the generic versions. Models appeared to be robust to sensitivity analyses.

Conclusions: This pilot approach provides promise for surveillance of brand vs generic safety signals in real-world settings. Further testing and replication in alternative data sources is needed to support widespread adoption.

540 | A comparison of two algorithms to identify sudden cardiac deaths

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Background: Algorithms to identify sudden cardiac death (SCD) in administrative databases have been developed and validated for use in pharmacoepidemiologic studies. However, the agreement between different algorithms for SCD has not been evaluated.

Objectives: To assess the agreement between two previously validated algorithms for SCD among subjects enrolled in Tennessee Medicaid.

Methods: We conducted a cross-sectional study using Tennessee Medicaid data, structured under the US Food and Drug Administration's Sentinel Common Data Model, from 2007 to 2014. The source population included all deceased patients aged 18–64 years with a date of death and ≥ 6 months of baseline observation prior to death. Algorithm 1 (positive predictive value [PPV] 92.3%) used hospital or emergency department (ED) discharge diagnosis codes to identify SCD. Algorithm 2 (PPV 86.8%) used death certificate underlying cause of death codes to identify SCD and excluded patients who were institutionalized, had a terminal procedure inconsistent with SCD (thrombolysis, radiology, general anesthetic) or had serious non-cardiac illnesses. We identified SCD by each algorithm and estimated the agreement between algorithms.

Results: There were 34 107 all-cause deaths in the source population over the study period. Of these deaths, the two algorithms identified 4372 SCD events: 3117 (71.3%) met Algorithm 1, and 1715 (39.2%) met Algorithm 2. The estimated percent agreement in SCD identification was 10.5%, with 460 patients identified through both algorithms. For Algorithm 1, terminal hospitalization discharge diagnosis codes identified 117 SCDs, and ED discharge diagnosis codes identified an additional 3000 SCDs. For Algorithm 2, there were 5204 deaths with one of the underlying cause of death codes; 1715 deaths met criteria for SCD after excluding 1841 with a recent nursing home or hospital stay, 295 with a terminal procedure inconsistent with SCD, and 1353 with non-cardiac serious illnesses.

Conclusions: This preliminary evaluation shows low agreement between two algorithms for identification of SCD.

541 | Outpatient adverse drug reactions as reason of emergency department visit

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Background: Adverse Drug Reactions (ADRs) are a significant public health issue. Serious ADRs are responsible for emergency department (ED) visits. Limited data of the burden of serious ADRs.

Objectives: To describe the frequency and characteristics of ED visits caused by serious ADRs.

Methods: We conducted a cross-sectional study in a random sample of patients in a teaching hospital in Chile. Each patient was interviewed and their clinical information were collected by pharmacists using a standardized form, which were designed for the study. Sociodemographic characteristics, clinical and pharmacotherapy profile were analyzed. We identified factors associated with ADR using logistic regression.

Results: One thousand patients were recruited, with an average age of 50 ± 19 , women were 61% (611) of the sample. A total of 40 (4%)

visits were caused by an ADR. An 85% (34) was due to unwanted effect and the 15% (6) were allergic reactions. The most common groups of drugs that lead to an ED visit were alimentary tract and metabolism drugs with a 22.5% (9) and anti-infectives for systemic use with a 22.5% (9) of visits due to ADR, a 50% of allergic reactions were due to an anti-infectives for systemic use. Polypharmacy (5 or more medications) was observed in the 20.7% of the sample and 45% of patients with an ADR. The strongest predictor of ED visit caused by a serious ADRs was polypharmacy (OR 2.3; 95% CI: 1.1–4.7). **Conclusions:** ADRs was a cause for consultation to an ED in 4 of 100 patients in our sample. Patients with polypharmacy were more likely to present an ED visit due to an ADR. Our findings could help to determine what patients have more risk of ADRs and prevent them.

542 | Understanding the views of patients using health unlocked, a social network for health, about the monitoring of the safety of medicines

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Background: Adverse drug reactions (ADRs) in the United Kingdom are monitored via the Yellow Card Scheme, however uptake of the scheme is low. Data mining software techniques are now capable of monitoring adverse drug reactions on social media and might prove a way of improving uptake of the Yellow Card Scheme in future.

Objectives: To understand current awareness on Health Unlocked of the Yellow Card scheme and to assess the acceptability of using data mining software to monitor for ADRs and submit these via the Yellow Card Scheme.

Methods: A survey was uploaded to HealthUnlocked asking users questions about the Yellow Card Scheme and the Medicines and Healthcare products Regulatory Authority (MHRA). The survey also asked how acceptable they would find monitoring of the platform by Health Care Professionals, the MHRA and submitting yellow cards via the platform and what would make this process easier. Participants were recruited via a pop up asking them to complete the survey when they logged into the platform.

Results: 1349 Surveys were completed out of 1791 responses over three months. All respondents took regular medication. 87% of people had experienced a side-effect from their medication. Of these, 58% had reported the side effect to a doctor, 10% to a pharmacist, and 9% had not reported their side effect. When asked to rate understanding on a scale of 1–5 (one being no understanding and five being complex understanding), 40% of people rated one for understanding of pharmacovigilance regulation, and 53% of people rated one for understanding of the MHRA. 61% of people rated one for understanding of the Yellow Card Scheme, and 73% rated one for understanding of how to complete a Yellow Card. 94% of people were happy for the MHRA to

use social media posts to monitor ADRs, and 71% of people thought this should be done via a link to an online form on HealthUnlocked. 36% of people thought that pre-filled Yellow Card form based on their HealthUnlocked post was the easiest way to complete a Yellow Card.

Conclusions: Awareness of pharmacovigilance, the MHRA and the Yellow Card scheme is low amongst users of HealthUnlocked. Most users who took regular medication had reported an ADR to a doctor or a pharmacist but very few had completed a Yellow Card form. Most users would be happy for MHRA and health professionals to use data posted online to monitor ADRs and the majority thought that a link to complete a Yellow Card the easiest way to submit an ADR to MHRA.

543 | Use of patient-reported data to detect medication errors

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Background: US Food and Drug Administration (FDA) continuously explores new data sources to support regulatory research. FDA entered into a research collaboration with PatientsLikeMe (PLM) to explore potential uses of patient-generated health data (PGHD) to support regulatory decisions. PLM is an online network where patients report, track and share their health information, which PLM captures in free-text entries and structured data fields. FDA and PLM sought to explore the use of PGHD to detect medication errors.

Objectives: To determine whether medication errors are posted in PGHD on the PLM platform, examine the types of errors frequently described and determine whether the data contained sufficient information for analysis. We also searched the data for a subset of known medication errors.

Methods: Two approaches were used to explore over 4 million entries on the PLM platform of free-text data posted between April 2006 and August 2016 by US PLM members aged 18 and older with any medical condition. For the first approach, we conducted a broad search of free text data using 44 relevant search terms suggestive of a possible medication error. For any free-text post that included both a drug name and one or more relevant search terms, we reviewed the post to determine if a medication error was present and sufficiently documented. The second approach was a targeted search strategy focused on a subset of three drugs: teriflunomide, vortioxetine, ticagrelor. We searched for posts mentioning these drugs and reviewed each post to determine whether it described a known medication error and when the error was posted.

Results: The first approach yielded 206 posts that contained one or more of the 44 search terms: 16 described medication errors. Potential wrong drug error was most commonly identified ($n = 9$), however, the posts did not contain sufficient information for analysis ($n = 7$), or described root causes (eg, similar white tablet appearance) that wouldn't warrant regulatory action ($n = 2$). The second approach did not identify any posts with the known medication errors of interest.

Conclusions: This study demonstrated that a PGHD platform such as PLM may capture medication error information. However, medication errors described in the posts may not be sufficiently documented or warrant regulatory action. These findings underscore the challenges of using data which have not been created specifically for regulatory purposes.

544 | Signal detection in VAERS and EudraVigilance using disproportionality and time to onset method and their combination

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Background: Adverse events following immunization (AEFIs) may be monitored in spontaneous reporting systems using signal detection algorithms which compare the frequency with which a vaccine-AEFI combination is reported as compared with all reports in the database. Alternatively, a recently developed method uses distribution test of reported time-to-onset (TTO) to detect vaccine safety signals with unexpected reported temporal relationship.

Objectives: To compare performance of the Empirical Bayes Geometric Mean (EBGM), the TTO method, and their combination in pediatric vaccine reports in the databases (DBs) of the US Vaccine Adverse Event Reporting System (VAERS) and EU EudraVigilance (EV) as part of the Global Research in Pediatrics project.

Methods: Following DB conversion to a common data model, EBGM and TTO methods were applied to all pediatric vaccine reports and in subgroups of infants (age < 2 yr), children (2-11 yr), and adolescents (12-17 yr) in VAERS, EV, and their combination. Performance of each method was assessed using a previously published vaccine reference set comprising 18 true positive and 113 true negative associations to calculate area under the receiver operating characteristic curve (AUC). The method of Pepe & Thompson (2000) was used to determine the linear combination of EBGM and TTO which maximized the AUC in the VAERS database.

Results: VAERS contained 1.85 million pediatric vaccine reports, in which TTO data was missing in 8%, with highest missing percentage in adolescents (10%). EV contained 251 770 pediatric vaccine reports, 57% of which were missing TTO data (74% missing in adolescents). In VAERS, the TTO method AUCs in the full pediatric population, infants, children, and adolescents were 0.89, 0.88, 0.89, and 0.73 while EBGM AUCs for the same age groups were 0.73, 0.67, 0.72, and 0.69. Performance in EV was similar with the exception that EBGM performed better (AUC = 0.80) than TTO (AUC = 0.70) in adolescents. The combination of TTO and EBGM in pediatrics in VAERS increased AUC to 0.91 from AUCs of 0.89 and 0.73 for the TTO and EBGM components, respectively.

Conclusions: The TTO method performed better than EBGM in both VAERS and EV in pediatric age groups with the exception of

adolescents in EV. Lower performance of the TTO method in adolescents could be related to a higher percentage of missing values in that age group. The combination of EBGM and TTO methods only marginally improved performance compared with TTO method alone.

545 | Pilot of a pharmacoepidemiology capacity building electronic survey for the Latin American and African regions

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Background: The ISPE Global Development Committee in collaboration with the Educational Committee and ISPE Board of Directors aims to build-up pharmacoepidemiology (PE) research capacity in the Latin America (LatAm) and African regions. An electronic survey was developed to identify current status, needs, gaps and priorities in pharmacoepidemiology to support capacity building in these regions.

Objectives: To describe preliminary results from the survey pilot conducted in the LatAm and African regions.

Methods: We conducted a literature review to identify international and local publications, and validated questionnaires focused on capacity building. From this review, the Potter systemic capacity building model was used to establish the hierarchy of needs. The questionnaires were developed considering the following domains: policy, law and regulations;

existing PE systems, structures and skills; existing PE centers and training; data sources and management; risk management and communication. The questionnaire was developed and refined in collaboration with PE international experts, including those from the LatAm and African regions. Two questionnaires were developed: 1. Screening questionnaire to identify target population, 2. In-depth questionnaire to characterize opportunities for capacity building. Both surveys were translated from English to Spanish, French and Portuguese by native speakers who were also PE researchers, and validated by a second set of translators. We used an online survey builder to develop the electronic survey.

Results: Thirty researchers participated in the pilot, 25 (83.3%) accepted to take the interview and 25 completed it. Sixteen (64%) were from LatAm and nine (36%) from Africa. English was the preferred language (N = 12 English, 9 Spanish, 2 French, 2 Portuguese). Fifteen (60%) of pilot participants would be eligible for the in-depth questionnaire. Most participants (N = 20, 80%) work in pharmacoepidemiology, pharmacovigilance or both, and over half (N = 15, 56%) had formal training in the field. More than half (N = 18, 72%) were researchers, and 60% were involved in teaching. Most responders wanted to receive study results (N = 23, 92%). Pilot participants provided a few suggestions on wording or expansion of response options.

Conclusions: The high response rate and overall eligibility rate set a positive stage to pilot the in-depth questionnaire. Leveraging the regional networks will be key to increasing the number of participants in both regions.

546 | Patient reporting of adverse drug events in rural Uganda—What do they know, their attitude and practices toward reporting

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Background: A possibility of patients monitoring and reporting adverse drug events (ADE) can be potentially understood through knowledge, attitudes and practices (KAP) studies.

Objectives: The objective was to investigate the patients' understanding of potential ADEs, and cause, reporting avenues, and practices to inform the regulator efforts of improving patient reporting of ADEs.

Methods: The study was undertaken in a health and demographic surveillance site (IMHDSS) covering rural communities in Eastern Uganda. A structured questionnaire was administered through health facilities and household visits.

Results: We randomly selected 1037 respondents. More than half (59%) get treatment from private drug shops and 37% get from public facilities while the rest get from herbalists/friends/family. More than half (582/1043: 56%) of the respondents knew the potential of drugs to cause an ADE with the rest expressed ignorance about the matter. Fifty five (55%) could tell that a negative effect was due the drug they took and not a disease. Forty four percent (452/1034) had a family member that experienced an ADE. Only 34% have reported an ADE in their life, 23% ignored it and 10% treated themselves. More than

a half of respondent (57%) prefer reporting the ADE to the health worker, 23% ignored it, 10% tried to treat themselves, 9% stopped the drug while only 1% didn't know what to do. Majority (80%) expressed interest in reporting an ADE and 92% consider reporting necessary. Of those that never reported, 38% could not tell if it was an ADE while 33% felt it was not necessary to report, 12% thought it will disappear shortly, 11% feared being victimized while 6% assume that health worker may not have time.

Conclusions: Despite fair understanding of ADEs, there is desire by patients to report an ADE and they prefer reporting to health care workers. There is need for affordable and innovative ways that make it easy for patients to report. Behavioral change strategies to encourage reporting of ADE and drug monitoring are needed

547 | Pharmacovigilance analysis of product confusion errors and issues

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Background: Product confusion errors and issues (related to drug names, dosage, duration, indication, label, packaging) are a common cause of medication errors, which are preventable and may lead to inappropriate medication use or patient harm. The types of confusion errors that occur most frequently and their consequences, have not been extensively documented to date.

Objectives: 1) To describe the types of product confusions errors that have been observed worldwide; 2) To assess the consequences of confusion errors (serious or non-serious adverse events [AE], lack of effectiveness); 3) To characterize the populations affected by these errors.

Methods: Study involved two phases: 1) A literature review on product confusion errors, covering the period 01 January 2013 to 17 November 2017; 2) A descriptive analysis of a spontaneous reporting database (VigiBase™) 2007-2016. All relevant AE reports were identified using the MedDRA Preferred Terms related to product confusion errors.

Results: A total of 42 sources were identified in the literature review, corresponding to 82 cases of product confusion errors. Errors occurred most frequently in vulnerable populations (children <18 years, and elderly age 65+), mainly made by nurses (54.3%) or pharmacists (22.9%), in the hospital setting (63.4%). Name and packaging confusion were the most frequent errors (36.6% and 28.0%, respectively). A total of 1769 individual case safety reports of product confusion errors were found in VigiBase™. Product label confusion was the most common error reported (54.1%), followed by product name confusion (26.3%). Patients and consumers accounted for the most frequent reporting source (39.3%), and the number of reports has been increasing dramatically over time. Of the reported confusion errors, 76.5% resulted in non-serious AEs, 22.0% in serious AEs and 2.4% had no effect. Antithrombotic agents were often involved in the serious AEs related to packaging confusion. Insulins were the most frequently involved in name or label confusions, followed by drugs for peptic ulcer and gastro-oesophageal reflux disease.

Conclusions: Although regulatory agencies have issued guidelines to avoid look-alike/sound-alike drug names, confusion errors still occur, with some leading to severe AEs. Study showed that errors are made principally by health care providers and are reported mainly by patients or their families. These findings highlight that patient engagement is important to prevent product confusion errors from occurring, to respond to errors, and improve care safety.

548 | Adverse drug events: Validating post marketed safety signals with pooled clinical trial results

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Background: Reported adverse drug events (ADEs) lead to 700 000 annual emergency room visits and are the fourth leading cause of death in the United States. While post market signal detection can reduce these burdens, validating those safety signals is time consuming and expensive.

Objectives: To determine whether automated analysis of aggregated pre-approval clinical trial safety outcomes data can assist in validating safety signals arising from surveillance of spontaneous reporting datasets.

Methods: We examined the 295 drug safety labeling changes announced by the US Food and Drug Administration (FDA) during the 1 year period of 1/26/2017 to 1/25/2018. For each ADE that was added to a drug's label post approval, we used Advera Health's Evidex® data and analytics platform to compare: i) a pooled analysis using the Cochran-Mantel-Haenszel (CMH) methods to provide odds ratio (OR) estimates of fixed effect for dichotomous outcomes (ADE vs Not-ADE) between control and treatment groups for clinical trials listed in ClinicalTrials.gov, and ii) the drug-ADE disproportionality calculation using reporting odds ratio (ROR) for ADEs reported in FDA's Adverse Event Reporting database (FAERS). An ROR score above 1.0 was considered elevated in the FAERS data and an OR above 1.0 was considered elevated in the clinical trial data set. Focus was limited to new ADEs which appeared in the Warnings and Precautions section or Adverse Reactions—Post-Marketing section of the label and was limited to FAERS case reports where the drug in question was the primary suspect.

Results: In 71% of the label changes examined, the specific drug-ADE pair with an elevated ROR above 1.0 in the FAERS data at the time of the label change also had an odds ratio (OR) greater than 1.0 in the clinical trial data. Statistical significance of the OR was not considered in this analysis.

Conclusions: Validating safety signals from FAERS data using pooled analyses of clinical trial data is critical to early detection and management of emerging drug safety issues. By comparing signals detected in post-approval ADEs from FAERS that have resulted in label changes by FDA against the same ADEs in prior controlled clinical trials, we demonstrated a methodology for automated validation of post-marketed safety signals with safety outcomes data from controlled

clinical trials. Based on these results, future research covering an expanded breadth of drugs and label changes should be launched to better study and refine the validation attributes and statistical relevance.

549 | Medication errors, impact of work-shifts, and associated contributing factors: A cross-sectional study in a developing country scenario

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Background: Iatrogenesis is an inevitable reality under the current complex health care framework. Medication errors (ME) jeopardises patient safety. It is important to understand how often and why these errors are occurring, and contributing factors. It is essential to reduce their occurrence in the limited resources scenario.

Objectives: To determine the impact of the work-shift and associated contributing factors of medication errors (MEs) occurred in a teaching hospital.

Methods: The ME reporting system was established using the principles based on prospective, voluntary, open, anonymous and stand-alone surveillance in a tertiary care teaching hospital located in a developing country. MEs involving patients of either sex were included in the study, and the reporters were given the choice to remain anonymous. The analysis was carried out to determine the work shift impact, associated causes and outcomes of the reported errors and was discussed with health care professionals (HCPs) to minimise the recurrence of MEs.

Results: A new system of detecting and reporting of MEs was established. Five specialties were focused on to assess the MEs. 1310 MEs were reported. To which 2560 medication errors contributing factors identified. Overall, Shift 1 {[08:00-14:00 hrs] (n = 1165)} recorded the highest contributing factors of error reports, followed by second shift {[14:00-20:00 hrs] (n = 781)} and shift 3 {[20:00-8:00] (n = 614)}. Most errors occurred due to distractions 473 (18.47%), followed by workload 422 (16.48%), communication gaps 341(13.32%), failure to identify the right patients 288 (11.25%), peak hours 233 (9.10%). These errors causing factors occurred during shift 1 234 (20.08%), 157 (13.47%), 172 (13.12%), 104 (8.92%) respectively. Inadequate monitoring 25 (0.97%), took place during shift 2 [12 (1.53%)] leading to 407 (31%), 413 (31.5%) and 425 (32.4%) errors in the first, second and third shifts respectively.

Conclusions: Although the number of errors reported in the 3rd shift was slighter higher with fewer contributing factors there could be more events went unnoticed due to lack of staffing. 24-hour vigilance system should be enforced to reduce the medication errors underreporting. Clinical pharmacist-initiated medication error reporting system has received a tepid response from other HCPs. Predictors are needed to be further analysed. Focusing on what caused an error rather than who; might reduce MEs.

550 | Assessing the quality of the individual case safety reports received at the pharmacovigilance center of Peru using vigiGrade

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Background: The completeness and quality and of the reports of suspected adverse drug reactions are essential criteria in pharmacovigilance in order to detect safety signals. VigiGrade is a tool developed by UPPSALA MONITORING CENTRE to identify well-documented individual case safety reports (ICSR)

Objectives: The purpose of the present research was to explore the completeness and quality of the ICSR of suspected adverse drugs sent to the Pharmacovigilance Center of Peru (DIGEMID) from pharmaceutical manufacturers.

Methods: A cross-sectional study was developed at DIGEMID. Around 5000 individual case safety reports were submitted to Vigiflow since april 2016 to march 2017. The completeness was evaluated using the four parameters of good pharmacovigilance practices established by who and the quality was assessed according to vigiGrade.

Results: There were 2074 reports from manufacturers and only 11% (228) were fully completed. Around 90% of ICSR lack of sufficient information to develop an adequate analysis of the causal relationship between the suspected reaction medication and the adverse reaction. The average score of quality by using vigiGrade was 0.47. The number of well-documented ICRS (>0.80) was 381 (18.4%) and 60% of this were related to serious adverse reactions.

Conclusions: The lack and the poor quality of information included in ICSR from pharmaceutical manufacturers do not allow the identification of potential safety signals to prevent risks. Pharmacovigilance interventions must be implemented to enhance the quality of the ICSR.

551 | Adverse drug events in hospital settings: Reporting & fate at a tertiary academic hospital: Cross-sectional study

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Background: Adverse drug events (ADEs) are deemed global dilemma as they are linked to increased morbidity and mortality. ADEs Reporting has shown to be a key player to mitigate their consequences, especially when followed by appropriate actions to prevent further occurrences.

Objectives: The aim of this study was to investigate the actions that have been taken by various health care providers (HCPs) after each

incident of an ADE including medication errors (MEs) or adverse drug reactions (ADRs).

Methods: A cross-sectional study was launched based on 5453 ADEs reports retrospectively retrieved for nine-month time frame between January and September 2017 at a tertiary academic hospital. Descriptive analyses were used to determine the prevalence of ADRs and medication errors. The most frequent medications that were linked to in reported ADEs were figured out

Results: Of 5453 ADEs reports, 99% represented medication errors cases and as few as 34 cases (1%) were found treating one kind or more of ADRs. It has been found that 68% of the medication errors were classified as prescribing errors, and nearly one-third (35%) of prescribing error cases were reported as dose and frequency related. Antibiotics and anticoagulants were the most classes of drugs involved in ADEs (33% and 13.6%, respectively). Regarding the actions that have been taken after the ADEs, we found that dose adjustment (30%), medication restriction (15.6%) and medication discontinuation (11.7%) were the most frequent types of actions to either quit or alleviate ADEs cases. Only 5% of the included ADEs reports were not clearly described.

Conclusions: The study findings indicate that all ADEs reports were analyzed and verified by medication safety officers and effective risk-mitigation actions were carried out in the vast majority of ADEs cases. As the reporting rate of ADRs are relatively low compared with MEs cases, a necessity for more intensified training and educational sessions to raise the awareness and knowledge toward the importance of ADR reporting is the key element to enhance reporting culture among concerned HCPs.

552 | Subset disproportionality analysis within a global database to uncover adverse drug reactions in risk groups

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Background: There is growing recognition of the variability between patients in both the benefits and harms from medicinal products. In pharmacovigilance, currently used statistical methods to screen large data sets are sensitive to associations at the population-level but can fail to highlight suspected adverse drug reactions in sub-populations at risk.

Objectives: To explore if disproportionality analysis across subsets of individual case reports within a global database can uncover signals of suspected adverse drug reactions in certain risk groups.

Methods: We considered 15.4 million reports up to 2017-08-28 in VigiBase, the WHO global database of individual case safety reports. Disproportionality analyses for drug-adverse event (AE) pairs were performed (1) in the entire database, and (2) across a range of data subsets defined by the following covariates: age, sex, body mass index (BMI), pregnancy status, country/continent of origin, indication for treatment. Drug-AE pairs disproportionally reported in such subsets but not in the database as a whole were considered for review. To reduce the chance of highlighting spurious associations, higher confidence levels were used in the subset analyses; these were specified

through permutation analysis. A restriction was made to drug-AE-subset associations with at least one report after 2012-01-01 for which the observed-to-expected ratio in the subset was at least twice that in the database as a whole. The associations were ordered using *vigiRank*, a statistical signal detection algorithm that accounts for multiple aspects of strength of evidence. Top-ranked associations were subjected to a manual review of the reports and a consultation of the literature in search for support for the possible risk group, to identify potential signals valid for further review.

Results: Out of 281 assessed associations, 13 (4.6%) were classified as potential signals. The highest yield was for patient sex with 5 potential signals (15.6% of all assessed associations in that covariate), followed by BMI with 4 (10.5%), continent with 2 (4.2%), and country and patient age, each with 1 (3.0%, 2.4%). Pregnancy and indication yielded no potential signals.

Conclusions: Potential signals of suspected adverse drug reactions in risk groups can be identified through subset disproportionality analysis within a global database. Further development of such methods could usher in a new era of "precision pharmacovigilance."

553 | Drug shortages may compromise patient safety: Results of a survey of the reference pharmacies of the drug commission of German pharmacists

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Background: Drug shortages are a complex and growing issue. Possible negative consequences for patients pose challenges for health care professionals. Data is limited for specific measures taken by pharmacists to counteract current and imminent drug shortages to ensure patient safety.

Objectives: To shed light on the implications of drug shortages in terms of outpatient and inpatient safety from the perspective of community and hospital pharmacies in Germany.

Methods: We surveyed the Drug Commission of German Pharmacists' two nationwide networks of reference pharmacies: 865 community and 54 hospital pharmacies of various sizes (staff and turnover) and geographical locations. Using the SurveyMonkey[®] online tool, participants were asked to complete a six-question survey, focussing on different topics: occurrence and frequency of drug shortages with and without available therapeutic alternatives, consequences for patient safety, countermeasures taken by pharmacists and examples of a drug prone to shortages. Answers were requested in the context of the last three months prior to the survey and were collected between October 24 and December 5, 2016. Data were resumed into two sets for community and hospital pharmacies. Microsoft Excel[®] was used for calculation.

Results: A total of 482 community and 36 hospital pharmacies participated (response rates of 56% and 67%, respectively). 88.6% (n = 427) of community and 80.6% (n = 29) of hospital pharmacies confirmed

occurrence of drug shortages. A substitute was dispensed ($n = 236$, 60.7% of community and $n = 13$, 44.8% of hospital pharmacies) or the prescribing physician was consulted ($n = 167$, 42.6% of community and $n = 12$, 42.9% of hospital pharmacies) more than 15 times within three months. Adverse effects on patients' medication adherence ($n = 241$, 60.4%) and discontinuation of treatment ($n = 103$, 25.8%) were mainly confirmed by community pharmacists, a delay or deny of a life-saving treatment ($n = 13$, 39.4%) was largely reported by hospital pharmacists. Medication errors ($n = 80$, 20.1% of community and $n = 7$, 21.2% of hospital pharmacies) occurred likewise.

Conclusions: This survey provides insights into the challenges of drug shortages from the perspective of both, community and hospital pharmacies in Germany. Comparing data from hospital and community pharmacies, differences in the incidence and severity of negative effects on patient safety were apparent, possibly stimulating and specifying best coping practices in future.

554 | Gender differences in drug–Adverse drug reaction combinations reported to the national pharmacovigilance centre in the Netherlands

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Background: In general, women have a higher risk for adverse drug reactions (ADRs) than men. Knowledge about gender differences for specific drug-ADR combinations is incomplete.

Objectives: To assess whether there are gender differences in drug-ADR combinations reported to a pharmacovigilance centre, corrected for differences in the number of drug users.

Methods: We included drug-ADR combinations from spontaneous reports to the Netherlands Pharmacovigilance Centre Lareb occurring at least 10 times in the years 2003–2016 for drugs that were used by $\geq 10\,000$ women and men in that period. Data from the Drug Information System of the National Health Care Institute were used for the number of users per drug. Gender-specific ADRs were excluded. For the outcome, ie, specific drug-ADR combinations, we classified drugs on the chemical subgroup level of the Anatomical Therapeutic Chemical system (ATC). ADRs were classified on the preferred term level of the medical dictionary for regulatory activities. Gender differences in specific drug-ADR combinations were tested using bivariate logistic regression analyses, adjusted for the number of drug users per gender.

Results: Gender differences were tested for 2482 drug-ADR combinations. Statistically significant differences were shown in 363 combinations (15%). For most drug-ADR combinations, women had higher

odds than men (321 combinations). This included: thyroid hormones (ATC group H03AA; 32 combinations), HMG-CoA reductase inhibitors (C10AA; 20), centrally acting sympathomimetics (N06BA; 17), other antidepressants (N06AX; 14), tumor necrosis factor alpha (TNF- α) inhibitors (L04AB; 14), and selective serotonin reuptake inhibitors (N06AB; 13). The most common ADRs with a higher odds for women were: nausea (32 combinations), alopecia (28), headache (20), palpitations (18), and dizziness (17). Men had a higher odds for: selective serotonin reuptake inhibitors (N06AB; 10 combinations), and HMG-CoA reductase inhibitors (C10AA; 5). Aggression, death, pyrexia, sexual dysfunction, tendon rupture, and tinnitus were the most common ADRs with a higher odds for men (all in 2 combinations).

Conclusions: We identified gender differences in 363 drug-ADR combinations, with often a higher odds for women. Further studies are needed to assess underlying reasons, including pharmacological and behavioral factors. The results may ultimately lead to gender-specific prescribing recommendations.

555 | Assessment of medication errors in the surgery department in a developing country's tertiary care teaching hospital

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Background: Iatrogenesis is an inevitable reality in the current health care framework. Medication errors (ME) jeopardises patient safety. It is important to understand how often and why these errors are occurring to develop interventions and to prevent their occurrence in a developing nation. Establishing a medication error reporting and monitoring centre is the need of the hour.

Objectives: To determine the incidence, causes, patterns and outcomes of medication errors in the Surgery wards

Methods: The ME reporting system was established using the principles based on prospective, voluntary, open, anonymous and stand-alone surveillance in a tertiary care teaching hospital located in southern India. MEs involving patients of either sex were included in the study, and the reporters were given the choice to remain anonymous. The analysis was carried out to determine the patterns, causes and outcomes of the reported errors and was discussed with health care professionals (HCPs) to minimise the recurrence of MEs.

Results: A total of 304 MEs were reported voluntarily among 7093 admitted patients and the incidence of MEs was 4.2%. The clinical pharmacist has reported 71 (23.3%) medication errors followed by nurses 148 (48.6%) and doctors 85 (27.9%). Administration errors ($n = 130$, 43%) were the most common type of MEs followed by transcriptional errors ($n = 59$, 19%) and prescription errors ($n = 46$, 15%). Reported administration errors were wrong time 45 (15%), incomplete documentation 45 (15%), and dose miss errors 23 (7%). Factors responsible for MEs were due to excessive workload, fatigue, unclear inter-personnel communications and patient-related factors accounted for 78 (12%), 85 (13%), 113 (17.4%) and 64 (9.8%) respectively. The majority of the reported MEs had an outcome of category C and D, based on the National Coordinating Council for ME

Reporting and Prevention (NCC MERP) outcome scale, amounted to 106 (34.8%) and 98 (32.2%), respectively.

Conclusions: Clinical Pharmacist-initiated patient safety programme was tepidly welcomed and then accepted by HCPs upon continuous education and awareness on MEs and patient safety. Although the majority of MEs that reached the patients did not cause any harm. Minimising the workrelated factors that contribute to MEs may improve overall patient safety. Emphasising that ME reporting is not fault finding is essential for heightened acceptance.

556 | Interest in a mobile app for two-way risk communication—A survey study among European health care professionals and patients

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Background: Previously, an app has been developed for health care professionals (HCPs) and patients to report adverse drug reactions (ADRs) to national medicines agencies and to receive drug safety information.

Objectives: To assess 1) European HCPs' and patients' interest in an app for this two-way risk communication, 2) their preferences and perceptions towards specific app characteristics, and 3) which HCPs and patients are particularly interested in the app. In addition, these aspects were studied specifically for the countries where such an app was already available, ie, Croatia (HR), the Netherlands (NL), and the United Kingdom (UK).

Methods: European HCPs and patients were asked to complete a web-based survey developed in the context of the Web-Recognizing Adverse Drug Reactions (Web-RADR) project. Data on app interest and preferences and perceptions towards app characteristics were analysed descriptively. Logistic regression analyses were conducted to assess the association of HCP characteristics (ie, age, gender, use of health apps, reporting an ADR to the agency) and patient characteristics (ie, age, gender, educational level, number of prescribed medicines, use of health apps, ever experienced an ADR, awareness of ADR reporting to agency) on the level of interest in the app (ie, very interested versus not/somewhat interested).

Results: In total, 399 HCPs and 656 patients completed the survey. About half (48%) of the patients; ranging from 38% (NL) to 54% (UK), and 61% of the HCPs; ranging from 42% (NL) 54% (UK), were very interested in the app. A faster means of reporting ADRs and easier access to the reporting form were the main perceived benefits. HCPs and patients who already use a health app were particularly interested in the app (HCPs: OR 3.52; 95% CI 1.96-6.30, patients: OR 1.64; 95% CI 1.19-2.27).

Conclusions: An app is positively perceived by HCPs and patients for reporting ADRs quickly and for receiving drug safety information from national medicines agencies. In particular, HCPs and patients who already use other health apps were interested in the app.

557 | Assessment of patient-initiated adverse event reports received by the Food and Drug Administration from patients like me

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Background: US Food and Drug Administration (FDA) postmarketing drug safety surveillance program staff continuously explores new data sources to advance regulatory science and to support its drug application review mission. One such potential data source is patient-generated health data (PGHD). FDA entered into a Research Collaboration Agreement (RCA) with PatientsLikeMe (PLM) to explore PGHD in the context of a regulatory setting. PLM is an online network where patients report, track, share, and discuss their health information, which PLM captures in free-text entries and structured data fields. FDA has received patient-Initiated Adverse Event Reports generated by PLM.

Objectives: To determine whether the AE reports generated through the PLM platform and submitted to FAERS through the MedWatch program were sufficiently well-documented and could contribute to pharmacovigilance activities.

Methods: We searched the FAERS database for patient-initiated AE reports submitted by PLM from March 1, 2009 through February 8, 2016. Retrieved reports were assessed individually and in aggregate, both for completeness of data and for relevance of data to the reported AE. Additionally, we calculated a vigiGrade completeness score for the subset of direct PLM reports and for comparable subsets of non-PLM reports in FAERS, to compare the level of provided information.

Results: We identified 40 unique patient-initiated AE reports submitted directly by PLM through the MedWatch program. They contained sufficient documentation, such as patient details, succinct information about the course of events and symptoms that the patient experienced, and structured information about the suspect drug. The mean vigiGrade completeness score for this set of 40 PLM direct reports was higher than those calculated for any of the 3 other specified sets of non-PLM reports.

We also identified and reviewed 111 AE reports submitted to FAERS by pharmaceutical manufacturers with PLM documented as the originating reporter. This subset of cases varied with respect to completeness and relevance of data to the reported AE, comparable in general to the usual FAERS reports that FDA receives.

Conclusions: AE reports that are initiated by patients through a platform such as PLM that are screened for completeness and then submitted to the FAERS database contain sufficient case details to meet the FDA requirements for inclusion in the FAERS database and potentially contribute to pharmacovigilance activities.

558 | Current practices of pharmacovigilance in Middle East: A quantitative study among Arab countries

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Background: Pharmacovigilance is getting more popular in Middle East countries than ever before. Most of the Arabic nations realized the vitality of having well-established pharmacovigilance system and its impact towards patient safety

Objectives: To assess the current practices of pharmacovigilance in Arab countries and to explore the gaps and areas for improvement for each program to be considered by concerned policy makers

Methods: A quantitative cross-sectional study was conducted using an adopted questionnaire that was developed by Uppsala Monitoring Center to assess the functional status of pharmacovigilance program in each Arab territory. The study was conducted in the period between December 2017 and January 2018. The questionnaire was answered by a member from each one of pharmacovigilance centers in these countries through direct contact by one of the researchers. There were 42 questions in the questionnaire assessing most of the pharmacovigilance functions. Descriptive analyses of all questions was carried out using SAS, 9.3

Results: A total of 16 countries responded to the questionnaires with a 100% response rate. Out of sixteen countries, approximately 85% of respondents have a stand-alone national pharmacovigilance program and 67% are members in the WHO drug monitoring program. However, 42% don't have access to Vigibase®. Around 30% of countries have both national and regional centers. In 2017, the total number of reported cases were ranging from as few as three reports in Lebanon to over 7000 case reports submitted to Algerian reporting center. It was found that the manufacturers are the major driver for the rise in the rate of reporting followed by physicians and pharmacists, then patients. Interestingly, nurses were found to unexpectedly be the least reporters. The source of the majority of reported cases were from human medicinal products, followed by traditional remedies, medical devices, and cosmetics. Email (93%), web-based forms (67%), and fax (52%) were the means of receiving ADE reports. The majority of respondents denied existence of an independent national committee that advises regulators on drug safety issues. Detailed information on all pharmacovigilance activities in the participated countries will be presented as tables and figures

Conclusions: The study findings showed big variance in pharmacovigilance practices among Arab countries. Generally, there is a necessity for more emphasis from the regulatory authorities and ministries of health on pharmacovigilance tasks

559 | Detecting adverse drug events in spontaneous reporting data: A systematic comparison

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Background: Spontaneous reporting systems (SRSs) are in active use to identify drugs that cause previously undetected adverse drug events (ADEs). A plethora of statistical methods have been proposed

to efficiently sift through the reports and shortlist those drug-ADE pairs that require further scrutiny.

Previous comparison studies compared (an often small number of) methods on real data (which is problematic, since the truth is unknown) or use simulated data that, without exception, assume independence between drugs and ADEs themselves, silently favoring methods that rely on that same assumption.

Objectives: First, to compare 27 methods ranging from simple disproportionality measures (eg, the proportional reporting ratio—PRR), hypothesis tests, Bayesian shrinkage (eg, the information component—IC) to sparse regression. Second, to explore—for the first time—the strength of the innocent-bystander effect (ie, confounding due to other exposures) on their performance.

Methods: We simulate 50 SRSs for each of 21 parameter settings (1050 in total). Each SRS contains 100 000 reports on 500 drugs and 500 ADEs; 100 drug-ADE pairs exhibit either a weak (1/16), medium (1/8) or strong (1/4) correlation. For each of these settings, we assume either no correlations between the drugs and ADEs themselves, or we randomly select drug-drug and ADE-ADE pairs to have a weak, medium or strong correlation.

We apply each method to each SRS. We use the mean area under the receiver operating curves to rank the methods.

Results: The versions of the IC perform overall best. The PRR performs uniformly worst; simply ordering drug-ADE pairs to the number of reports mentioning them would even yield better results. Correlations between drugs and ADEs themselves do not significantly affect the methods' ranking.

Conclusions: The IC should be the method of choice, while the use of the PRR should be shunned. This simulation study suggests that the innocent-bystander effect is small and can be safely ignored.

560 | First year results of using a new prediction model-based algorithm for computer-assisted database screening of adverse drug reactions in the Netherlands

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Background: In 2015-2016 a logistic regression-based prediction model containing 5 predictors (number of reports, disproportionality, reports from health care professionals, reports from marketing authorization holders, Naranjo score) was developed and internally validated using the Summary of Product Characteristics as the gold standard for the outcome. Previous analysis suggested that this model performed better than disproportionality combined with number of reports alone.¹

Objectives: The purpose of the present analysis was to evaluate the real-world performance of this new model in the first year of use.

Methods: In 2017 the new model was used to create priority-based listings for signal detection in the Lareb database, with n reports >3. The

associations on this list received a short assessment in order of descending score. After short assessments, based on internal criteria, drug-ADR associations can be selected for more detailed analysis and potentially lead to Signals.² We tested the performance of the new model on the proportion of initial assessments that were selected for detailed analysis by trained pharmacovigilance assessors. As comparator the proportion selected during use of the old screening model in 2014–2016 was used. A 2-sided Pearson χ^2 -test was used to test the difference in proportion of associations selected for detailed analyses.

Results: 626 initial assessments suggested by the new model were performed, resulted in 53 more detailed analyses (8.5%). In 2016 the proportion was 6.6% (79 detailed/1203 initial), in 2015 2.5% (14 detailed/520 initial), in 2014 4.2% (13 detailed/312 initial). For the new model (2017) vs old method (2014–2016) χ^2 -test $p = .003$.

Conclusions: The real-world performance of the model in its first year of use and the comparison with the old method during three earlier years showed that the prediction model-based approach leads to a better pre-selection of associations and thus more detailed analysis. Literature 1. Scholl JHG, van Hunsel FPAM, Hak E, van Puijenbroek EP. A prediction model-based algorithm for computer-assisted database screening of adverse drug reactions in the Netherlands. *Pharmacoepidemiol Drug Saf.* 2018 Feb;27(2):199–205. 2. van Hunsel F, Ekhart C. Experiences with a computer-assisted database screening tool at The Netherlands Pharmacovigilance Centre Lareb. *Pharmacoepidemiol Drug Saf.* 2015;24(S1):442.

561 | A model for data monitoring committees for retrospective study designs in the real-world setting

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Background: Non-interventional post-authorisation safety studies (NI PASS) are increasingly performed for assessing post-marketing drug safety. They are an important tool for detecting rare risks that are hard to measure during drug development programmes. Regulatory Authorities encourage sponsors with marketing authorisations within the same drug class to collaborate in NI PASS. Data monitoring committees (DMCs) are traditionally set up for randomised clinical trials (RCTs), but may have a central role in the validation and ongoing interpretation of the large amount of data emerging from NI PASS. To our knowledge, DMC guidelines for NI PASS are non-existent.

Objectives: To share our experience with target audience (pharma, academia, regulatory authorities) in view of the expected increase in such joint pharma NI PASS.

Methods: Medullary thyroid cancer (MTC) is an important potential risk for long acting glucagon like peptide 1 receptor agonists (LA GLP-1 RAs). Since MTC is rare, RCTs cannot easily characterise this potential risk. FDA imposed a joint pharma-sponsored, 15-year case-series NI PASS investigating the incidence of MTC across the US state cancer registries in relation to exposure to LA GLP-1 RAs. Because of the study's anticipated long duration and large amount of safety data, sponsors jointly established a DMC. We performed descriptive analysis (hypothesis testing and power calculations were not applicable) of existing literature on safety data monitoring in RCTs, and assessed their applicability and needed modifications, for ongoing interpretation and validation of data from retrospective NI PASS.

Results: We highlight features identified in the literature for data monitoring in RCTs and their applicability to NI PASS, and how we incorporated/adjusted these into a DMC model. Challenges are described in collaborating with multiple sponsors to reach a common DMC model that would balance the individual sponsors' high level of confidentiality and the requirement for all participating sponsors to be alerted of safety concerns raised by the DMC, triggered by any of the participating sponsors' products.

We present an effective DMC meeting structure and communication flow between sponsors, the DMC, other study specific committees and the FDA. Sponsors and DMC members have signed a DMC charter; a kick-off and 3 successful DMC meetings have been held.

Conclusions: This DMC model may be of interest to others involved in this evolving real-world pharmacovigilance area.

562 | Factors distinguishing identified risks from potential risks: Analysis of safety specification of Japan and EU risk management plan

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Background: Based on ICH-E2E agreed in 2004, European Medicines Agency and Japan Pharmaceuticals and Medical Devices Agency (PMDA) introduced Risk Management Plan (RMP) in 2005 and 2013, respectively. Safety specification, the core component of RMP, is divided into 3 categories: identified risk, potential risk, and missing information, but it is unknown what factor is emphasized when deciding categories of safety specification in Japan and EU.

Objectives: To compare the safety specification between Japan and EU, and to identify the factors which strongly affect decision-making to categorize safety specification as identified risk.

Methods: This study included non-orphan drugs approved both in Japan and EU as of Dec 31, 2016 with available RMP. Initial safety specifications and clinical trial data were obtained from RMP, review report, European Public Assessment Report, and Common Technical Document. We analyzed contributing factors to the categorization of identified risk using mixed-effects logistic regression model, taking random effects for drug into account. Outcome was defined dichotomously as (1) listed as

identified risk or (2) listed as potential risk. The model was adjusted for the following covariates: AE rate (%), serious case in clinical trials (Y/N), listed as identified risk in foreign RMP (Y/N), clinically significant ADR known in similar drugs (Y/N). Statistical analysis was conducted using JMP Pro 13.1.0 and SAS 9.4.

Results: A total of 262 and 462 safety specifications were pooled from Japan-RMP (J-RMP) and EU-RMP of 33 sample drugs, respectively. Number of safety specifications per drug was significantly lower in Japan, compared with that in EU (median, 7 [IQR, 3 to 13] vs 14 [11 to 17]; $p < 0.001$). In Japan, AE rate (%) (OR, 1.04; 95%CI, 1.01-1.07), ADR listed as identified risk in EU-RMP (OR, 11.8; 95%CI, 4.01-34.5), and clinically significant ADR known in similar drugs (OR, 6.15; 95%CI, 2.66-14.2) were associated with a higher probability of being listed as identified risk. In EU, on the other hand, AE rate (%) was the only covariate which was associated with a higher probability of being listed as identified risk (OR, 1.04; 95%CI, 1.01-1.07).

Conclusions: AE occurring at high rate had greater probability of being listed as identified risk in both Japan and EU. Additionally, in Japan, clinically significant ADR known in similar drugs and ADR listed as identified risks in EU-RMP were likely to be listed as identified risk.

563 | A comparative analysis of safety advisories in Australia, Canada, the United States, and the United Kingdom

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Background: National regulatory agencies use safety advisories to communicate emergent risks of medicines to clinicians and the public. These advisories can provide guidance to better inform prescribing and decisions, supporting safer medicines use.

Objectives: To determine the frequency and characteristics of safety advisories issued by regulatory agencies in Australia, Canada, the United States, and the United Kingdom, and concordance between regulators over a ten-year period.

Methods: This retrospective study analysed safety advisories from the US Food and Drug Administration (FDA), Health Canada, the Australian Therapeutic Goods Administration (TGA) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA) from 1 January 2007 to 31 December 2016. A database of advisories obtained from regulatory agencies' websites was developed and classified by communication type, drugs or drug classes, and safety concerns, using ATC and MedDRA coding for the latter. These advisories were combined into "drug-risk" groups focusing on the same drug/drug class and safety concern. Key outcomes were the frequency of advisories per country per year and of discordancy per country (failure to issue an advisory on an approved drug).

Results: Over this 10-year period, 1443 advisories were identified (US = 382 CA = 371 UK = 469 AU = 221). Most focussed on a single drug ($n = 1013$) and were alerts ($n = 738$) posted on the regulators' website. Of 677 "drug-risk" groups, 607 (89.7%) were classified as

discordant (≥ 1 regulator did not issue an advisory for an available drug/class). However, 354 "drug-risk" groups (52.3%) contained only a single advisory from one regulator. Among the remaining 323 groups, 260 (80.5%) were discordant. All four countries issued a similar advisory in only 40 cases (5.9%). The TGA was the least likely to issue an advisory compared with other regulators; with no advisory for 438/617 safety concerns (71.0%) for approved drugs, $p \leq 0.00001$. Advisories were missing for approved drugs in the United States for 380/644 (59.0%), in Canada for 316/632 (50.0%) and in the UK for 310/653 (47.5%) safety concerns addressed in ≥ 1 other country.

Conclusions: We found a large degree of difference between regulators in the use of advisories, with Australia less likely to issue alerts than the other countries. These differences between countries in the safety information available to clinicians and the public could lead to adverse public health outcomes.

564 | Is signal detection method based on time-to-onset useful for drugs other than vaccines?

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Background: The disproportionality analysis (DPA) has been widely used for detecting safety signals from spontaneous reports on suspected adverse drug reactions (ADRs). Recently, a new signal detection method based on time-to-onset (TTO; the time between the start of the drug and the onset of the adverse event) has been shown to be useful in detecting a signal for several vaccines.

Objectives: In order to examine whether a TTO-based method is useful for detecting signals from spontaneous reports for drugs other than vaccines, we analyzed spontaneous reports using Japanese Adverse Drug Event Report database (JADER).

Methods: We identified 515 707 spontaneous reports including 133 142 drug-event pairs between April 2004 and December 2014 from JADER. Out of the 133 142 pairs, we analyzed 7966 pairs that [1] reported one of the top 50 events (in terms of the number of reports per event) and [2] had 3 or more reports with information on TTO per drug-event pair. As a disproportionality measure, reporting odds ratio (ROR) was used to detect a DPA-based signal when the lower limit of 95% confidence interval of ROR was >1 . The distribution of TTO of a drug-event pair was compared with that of all other pairs using Kolmogorov-Smirnov two-sample test to detect a TTO-based signal when $p < 0.05$.

Results: Out of the 7966 drug-event pairs analyzed, 1071 (13.4%) were detected as a signal only by the TTO-based method but not by the DPA-based method (defined as TTO-only pairs). Among those TTO-only pairs, the event was listed as an ADR in the drug labeling for 920 pairs (85.9% of the 1071 TTO-only pairs and 11.5% of the 7966 pairs analyzed). The TTO of the TTO-only pairs varied according to the drug class. For example, in 142 (97.3%) of the 146 TTO-only pairs for antimicrobial agents, the median of TTO was shorter, while in 141 (90.4%) of the 156 TTO-only

pairs for immunostimulants or immunosuppressants, the median was longer than the median of all other pairs analyzed.

Conclusions: The TTO-based method may efficiently detect a signal not detected by the DPA-based method, and therefore, further investigation is warranted.

565 | Web-based signal detect ION using medical forums world wide from 2005 to 2015

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Background: While traditional signal detection methods in pharmacovigilance are based on spontaneous reports, the use of social media (SM) has emerged among regulators, industry, and academia. One of the strengths of web-based data is their real-time availability allowing for an early signal detection.

Objectives: This study aimed at assessing (1) the consistency of signals of disproportionate reporting (SDRs) detected from patient's medical forums worldwide compared with traditional reporting systems and (2) the ability of identifying SDRs earlier than the traditional reporting systems. The study focused on 2 products (insulin glargine and zolpidem) over the period 2005 to 2015.

Methods: This was a retrospective study. Messages containing drug-event pairs posted in more than 1000 English-language web forums worldwide were extracted and processed using Natural Language Processing and Machine Learning techniques. The WHO adverse events reporting system (VigiBase[®]) was used as a reference. Several metrics were used to define SDRs (PRR, ROR, EBGM, Lift). Comparison of SDRs detected in patient's forums to SDRs detected in VigiBase[®] was done by describing the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and the area under the curve (AUC). Time difference in months between the detection dates of SDRs from the patient's forums and from VigiBase[®] were analyzed.

Results: The numbers of drug-event pairs identified in patient's forums over the 2005-2015 period for the two products were 57 and 86, respectively. Comparison analysis showed that the sensitivity ranged from 55 to 75.4%, the specificity from 31.7 to 84%, the PPV from 50 to 68.3%, the NPV from 47.6 to 80.4%, and the accuracy from 53 to 72.7%. The AUC reached 0.73 when using the metric EBGM. Up to 32.1% of the SDRs were detected earlier in the patient's forums than in VigiBase[®].

Conclusions: The overall performance of data from web patient's medical forums was good, and it may be a valuable source for signal detection. In total, up to 32.1% of the SDRs could have been detected earlier, thus facilitating increased safety of the patients. These results were in line with results from a previous pilot study using the same methods but focusing on data from the French medical forums only. Further enhancements are needed to investigate the reliability and

validity of patients' medical forums worldwide for signal detection for other drugs by extending the analysis to all possible drugs or at least to a wider selection of drugs.

566 | Impact of the intensified reporting requirements on reporting of suspected side effects of new pharmacological products in Denmark

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Background: The Law of Intensified Reporting Requirement (IRR) has been implemented in Denmark since 2003; the law requires all health care professional (HCP), with prescription rights, to report all suspected adverse drug reactions (ADRs) in the first 2 years after marked authorisation. After this period, the HCPs are required to report suspected serious and unexpected ADRs.

Objectives: The aim of the study was to compare ADR reporting for products while they are under IRR to the period after, for products under intensified reporting between 2003 and 2010 as well as to evaluate Danish physicians' awareness of the IRR. The goal was to assess whether the IRR has an impact on HCPs ADR reporting patterns.

Methods: Danish spontaneous ADR reports for medicines under IRR in the period between 2003 and 2010, with a total consumption above 100 000 DDD, were extracted for the period where they were under IRR and the following four-year period. Mean reports per consumption (1000 DDD) in the two periods were calculated, and t-tests were used to determine difference in reporting frequency. Chi² tests were used to determine difference in distribution of serious and non-serious reports between the two periods. A survey among physicians taking a course organized by the Danish Health Authorities between May 2017 and June 2017 was used to assess physicians' awareness of the IRR.

Results: For the 79 drugs marketed in Denmark between 2003 and 2010, a total of 973 spontaneous ADRs were reported during the IRR period and 2833 after. A significant difference between the distribution of non-serious and serious reports for the two periods was found during (551 vs 422) and after (1463 vs 1370) ($p < .01$). Mean reports per 1000 DDD consumed for the two periods were not statistically different. Of the 74 physicians included in the survey study, 59% had knowledge about the IRR.

Conclusions: Reporting of ADRs while drugs are under IRR was not higher than the period after, even when adjusting for consumed DDDs. However, there was a difference in the seriousness of the ADRs between the two periods. The lack of knowledge of IRR among physicians might contribute to our results.

567 | Validation of algorithms to identify pancreatic cancer and thyroid neoplasms from health insurance claims data in a 10-year follow-up study

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Background: Identification of cancer events in health insurance claims data can be challenging and subject to misclassification. Given the low incidence of certain cancers, robust performance evaluation requires a large sample size with long-term follow-up.

Objectives: To validate algorithms that identified potential incident pancreatic cancer and thyroid neoplasms in a 10-year follow-up study in health insurance claims data.

Methods: This validation study was performed in the context of a cohort study of antidiabetic drug use and incidence of pancreatic cancer and thyroid neoplasms. Among initiators of antidiabetic agents with type 2 diabetes in 2005-2015, potential cases of pancreatic cancer and thyroid neoplasms (including both malignant and benign neoplasms) were identified from a commercial health insurance claims database using "restricted" algorithms that incorporated combinations of ICD-9 diagnosis codes, diagnostic procedure codes (eg, biopsy), and codes for treatments (eg, surgery, chemotherapy, and radiotherapy). Medical records of potential cases occurring at least 1 year after drug initiation were sought. Each record was reviewed by 2 oncologists, and discrepancies were resolved by consensus. Positive predictive values (PPVs) and conditional sensitivity were estimated to evaluate the algorithm performance. The conditional sensitivity was estimated in relation to potential cases identified from a more inclusive "relaxed" algorithm that required only the presence of ICD-9 diagnosis codes.

Results: We identified 558 potential cases with the "relaxed" algorithm and received medical records for 422 (173 for pancreatic cancer, 144 for thyroid cancer, and 105 for benign thyroid neoplasm), for an abstraction proportion of 76%. With the "restricted" algorithm, we identified 97 potential pancreatic cancers, 103 potential thyroid cancers, and 32 potential benign thyroid neoplasms. The PPV was 0.78 (0.69-0.86) for pancreatic cancer, 0.88 (0.81-0.94) for thyroid cancer, and 0.97 (0.84-1.00) for benign thyroid neoplasm. The conditional sensitivity was 0.68 (0.58-0.76) for pancreatic cancer, 0.81 (0.73-0.88) for thyroid cancer, and 0.36 (0.26-0.48) for benign thyroid neoplasm.

Conclusions: The restricted algorithms accurately identified cases of pancreatic cancer and thyroid neoplasms from health insurance claims with high PPV. The conditional sensitivity was lower for benign thyroid neoplasm than for pancreatic and thyroid cancer.

568 | Validity of hospital ICD-10-GM codes to identify acute liver injury

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Background: Acute liver injury (ALI) is a potential adverse drug reaction that often leads to regulatory action. A postauthorization safety study (PASS) conducted in five European data sources used combinations of ICD codes to identify ALI as a safety endpoint among antidepressant users. Validation of potential cases was not possible in the GePaRD, so this external validation study was conducted.

Objectives: Estimate the positive predictive value (PPV) of ICD-10-GM discharge and outpatient hospital codes used to identify ALI. Compare the PPV estimated with or without applying exclusion criteria used in the PASS.

Methods: A cross-sectional study of routine data from a single academic hospital was used. Adult (≥ 18 years) potential ALI cases reported in the hospital information system between 01 Jan 2007 and 31 Dec 2016 were included. Case definitions from the PASS were applied to extract potential cases from the hospital information system. **Specific endpoint:** Discharge diagnosis of ICD-10-GM toxic liver disease codes (K71.0, K71.1, K71.2, K71.6, K71.9, K72.0, K72.9, K75.9, K76.2). **Less specific endpoint:** as above but adding outpatient diagnoses and nonspecific codes suggestive of liver injury (K76.8, K76.9, R16, R16.2, R17, R74.0, Z94.4). True cases were defined based on liver enzymes from electronic medical records and the hospital laboratory database. All clinical data were assessed using double extraction by trained personnel. Exclusion criteria, applied for the secondary objective, were cancer, chronic liver and pancreatic disease, congestive heart failure, and alcohol-related disorders. PPVs (95% confidence intervals [CI]) were estimated with the exact method.

Results: Overall, 154 (485) potential cases were identified for the specific endpoint (less specific endpoint). Sufficient information for analysis was available for 143 [93%] (357 [74%]) cases. Based on liver enzymes and clinical information, 71 (100) cases were classified as true ALI. This resulted in PPVs (95% CI) of 49.7% (41.2-58.1%) for the specific endpoint and 28.0% (23.4-33.0%) for the less specific endpoint. After applying the PASS exclusion criteria, PPVs (95% CI) increased to 62.7% (50.0-74.2%) for the specific endpoint and 45.7% (37.2-54.3%) for the less specific endpoint.

Conclusions: Substantial misclassification must be considered when studying acute liver injury based on routine data using ICD-10-GM discharge codes. PPV increased when using only specific ALI codes with inpatient cases and following exclusion of competing diagnoses.

569 | A prospective cross-sectional study of prescribing errors prevalence and nature in emergency department

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Background: Prescribing errors (PEs) are common threat to patient safety; however, limited data are available on the prevalence of PEs and potential factors that increase PEs among patients treated in the emergency department (ED).

Objectives: To explore the prevalence and nature of PEs in ED and factors associated with increased risk of PE.

Methods: A prospective observational cross-sectional study at ambulatory ED in a tertiary teaching hospital, Riyadh, Saudi Arabia, between July and December 2017 was conducted. Data were collected using a reporting tool customized to suit the purpose of this study. The type of PEs was categorized, and the prescriptions encountered with identified PEs were identified from the data. Potential PEs were discussed with the prescriber for further confirmation of PE. This study has included patients of all age groups who were discharged from ED with a prescription.

Results: Among 504 prescriptions included in this study, 13.5% ($n = 68$) PEs were identified and categorized according to their types as 22% wrong dose, 19.8% wrong frequency, and 14% wrong strength. It was found that 36.8% of PEs were identified from a pediatric unit, followed by 26.5% from acute care unit, and 20.6% from triage unit. Several PEs causative factors were identified; the leading human-related causes for PEs were lack of knowledge (40.9%) and improper selection from a list by computer operator (31.8%). The leading PEs' systems-related factors were pre-printed medication orders (50%), lack of training (31.5%), and noise level (13.0%). The most commonly involved medications with PEs were antibiotics, analgesics, and gastrointestinal medications. This study found the PEs were most commonly done by residents (39.4%) followed by specialists (30.3%) and general practitioners (24.4%). Of the identified PEs, 88.0% were resolved by the pharmacist and have been recorded as accepted interventions, while 12.0% of them have been rejected by the physician as per their clinical judgment.

Conclusions: PEs are common in the ED setting and many human and systems related factors contributed to the development of PEs. This study highlights the need of future research to explore the role of educational programs and strategies to minimize PEs in the ED setting.

570 | Analysis of Drug Information Centre enquires between 1994 and 2016

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Background: Drug Information Centre (DIC) of the Faculty of Pharmacy in Hradec Kralove (established in 1994) is the only university-related DIC in the Czech Republic (CR). So far, DIC has been providing free-of-charge drug information services, namely, answering medicines-related enquiries received from health care professionals (HP) in the CR or from abroad.

Objectives: The aim of the original study was to analyse the patterns of medicines-related enquiries of DIC in the period of 1994-2016.

Methods: Retrospective analysis of the DIC database (MS Excel®) including all enquiries sent by HP to DIC and processed therein between 1994 and 2016. Demographic data received from HP, the type of each medicines-related enquiry (eg, indications, adverse drug reactions, and drug interactions), ATC code, the special population group targeted in the enquiries, as well as the patterns of professional information resources used for answering during the two decades, were evaluated. All data were processed using descriptive statistics.

Results: In total, 2221 enquiries were reported, in average 97 enquiries per year. More than half of the enquiries had been received from pharmacists (1117; 50.3%) all over the CR. The most frequent ATC groups targeted in the enquiries were antitrombotic agents (warfarin and aspirin with highest rate), serotonin selective reuptake inhibitors (sertraline), and beta-blockers (metoprolol). In general, the enquiries were focused mainly on adverse drug reactions (442; 19.5%); second, on indications or contraindications (433; 19.9%); and finally on properties of active substances (353; 15.9%). However, in the first years, mostly adverse drug reactions, properties, and availability of drugs had been dealt with, while nowadays, on the contrary, indications and interactions have been more of interest. In total, only 196 (8.8%) enquiries were related to pregnancy and lactation. During the whole period, factographic printed resources have been used, whereas online as well as bibliographic databases have been more preferred in recent years.

Conclusions: DIC services were used mainly by pharmacists, and a wide range of medicines enquiries were discussed in the investigated period; however, a major shift in requested medicine information was detected.

571 | Cyclooxygenase selectivity and chemical subgroup of non-steroidal anti-inflammatory drugs and frequency of spontaneous reporting of hypersensitivity reactions: A case/non-case study in Vigibase

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Background: Use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with many adverse events, including hypersensitivity reactions (HSRs), such as angioedema and urticaria. However, no studies have investigated whether cyclooxygenase (COX) enzyme selectivity and/or chemical subgroups are associated with a difference in HSRs.

Objectives: To describe and compare the frequency of HSRs among NSAIDs based on cyclooxygenase selectivity and chemical subgroups.

Methods: A case/non-case study was performed using data from the World Health Organization global database of Individual Case Safety Report (ICSR), VigiBase, containing over 13 million ICSRs submitted by the participating member states enrolled under WHO's international drug monitoring program by June 2016. This study was nested among ICSRs where NSAIDs were a suspected drug. Cases were ICSRs mentioning HSRs (urticaria, angioedema, anaphylactic shock, anaphylactic reaction, anaphylactoid shock, and anaphylactoid reaction), whereas non-cases were all ICSRs without HSRs. Based on the ratio of inhibitory concentration 80% of COX-1/COX-2, NSAIDs were categorized into coxibs, non-coxib NSAIDs with COX-2 preference, NSAIDs with poor selectivity, and NSAIDs with unknown selectivity. Only ICSRs with complete information on age and sex, and NSAIDs with first market authorization from 1978 onward were included. RORs and 95% confidence intervals (95% CIs) to assess the association between NSAIDs and the reporting of HSRs were calculated using logistic regression analysis.

Results: We identified 16 289 HSR cases and 160 319 non-cases among ICSRs involving NSAIDs. Non-coxib NSAIDs with COX-2 preference, NSAIDs with poor selectivity, and NSAIDs with unknown selectivity were all associated with an increased reporting of HSRs (age- and sex-adjusted ROR 1.70, 95% CI: 1.61-1.79; age- and sex-adjusted 2.19, 95% CI: 2.11-2.77; and age- and sex-adjusted 1.26, 95% CI: 1.03-1.54, respectively) compared with coxibs.

Conclusions: HSRs were more often reported for NSAIDs with poor selectivity, non-coxib NSAID with COX-2 preference, and NSAIDs with unknown selectivity compared with coxibs.

572 | Eperisone-related adverse drug reactions including anaphylaxis: A study on 242 Korean patients

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Background: Eperisone is an oral muscle relaxant used in musculoskeletal disorders with muscle spasm. Eperisone is often prescribed with NSAIDs. In that reason, eperisone-related adverse drug reaction (ADR) has been overlooked. There are only a few case reports of anaphylaxis.

Objectives: The purpose of this study was to analyze the nationwide ADRs reported in Korea and suggest diagnostic approach of eperisone-induced ADR including anaphylaxis.

Methods: We reviewed eperisone-related pharmacovigilance data reported in Korea from 2010 to 2015. ADRs with causal relationship were selected. Clinical manifestations, severity, outcomes, and re-exposure information were analyzed. For further investigation, 7 years of ADR data reported in a single center was also reviewed. Oral provocation test, skin prick test, and basophil activation test were performed in this center.

Results: During the study period, 207 patients suffered adverse reactions to eperisone in Korea. Mean age was 55.4 years old and 67.1% of the patients were female. The most common ADRs were cutaneous manifestations including urticaria, rash, and angioedema (30.4%). Gastrointestinal symptoms (nausea, vomit, abdominal discomfort, constipation, and diarrhea) were second common ADRs (25.1%). Out of these, 32 (15.5%) patients were reported to have serious ADR, 35 (16.9%) patients were re-exposed and symptoms were reproduced. There were 35 patients with anaphylaxis, representing 16.9% of the patients. In a single center study, 35 patients were selected to analysis. Among them, 12 patients were agreed and underwent oral provocation test. All the provoked patients showed positive reaction. There were 9 patients of eperisone-induced anaphylaxis. Two anaphylactic patients were also underwent skin prick test and basophil activation test, and those were all negative.

Conclusions: Eperisone can cause diverse ADRs, including anaphylaxis. We reported 44 patients with eperisone-induced anaphylaxis. Eperisone is thought to induce non-IgE mediated immediate hypersensitivity based on the small number of mechanism studies.

573 | Abstract Withdrawn

574 | Signals of increased risk of serotonin syndrome associated with drug interaction with tramadol in spontaneous adverse event reporting database

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Background: Tramadol, a potent analgesic agent is commonly used in various pain conditions. Widespread use of tramadol may trigger coincidence of a potential adverse event serotonin syndrome due to drug interaction with other drugs with serotonergic effect.

Objectives: To assess signal of increased risk of serotonin syndrome associated with combined use of tramadol and drugs with anticholinergic burden including antidepressants and antihistamines, compared with tramadol only, in a spontaneous adverse event reporting database.

Methods: We applied case-non-case approach using all reports that includes tramadol in Korean Adverse Event Reporting System Database from 2012 to 2016. Serotonin syndrome cases were defined as reports with "serotonin syndrome" as the adverse event, and reports with neuromuscular, neurovegetative, mental, and digestive symptoms using WHO-ART terminology. Non-cases were all other reports. Among antidepressants and antihistamines, drugs with higher anticholinergic effect were defined as study drugs. Odds ratios (ORs) and their 95% confidence intervals (CIs) associated with combined use of antidepressants or antihistamines with tramadol were calculated using logistic regression model adjusting for age, sex, source, and year of reporting, use of antimigraine, antiemetic agents, and use of other study drugs.

Results: Among individual case reports involving tramadol, 4345 were identified as cases, and 55 680 were non-cases. Compared with tramadol-only group, the adjusted ORs of combined use of antidepressant was 1.36 (95% CI, 1.05-1.76) for serotonin receptor inhibitors, and 0.79 (95% CI, 0.59-1.07) for tricyclic antidepressants. Compared with tramadol-only group, the adjusted ORs of combined use of antihistamines was 1.76 (95% CI, 1.47-2.10) for first generation, and 1.56 (95% CI, 1.22-1.98) for second generation agents.

Conclusions: A tendency of increased number of spontaneous reporting with serotonin syndrome associated with combined use of antidepressants or antihistamines with tramadol were observed. When tramadol users have to use antidepressants or antihistamines with high anticholinergic burden in combination, careful monitoring is needed.

575 | Hypocalcemia and denosumab: A comparative study with hypocalcemic drugs

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Background: Denosumab is a human monoclonal antibody working through inhibition of RANK-ligand osteoclast mediated bone resorption. Denosumab is approved in osteoporosis and in the bone metastases from solid tumors. Denosumab is associated with a risk of hypocalcemia.

Objectives: The aim of this study is to compare the reporting rate of denosumab-associated hypocalcemia with other hypocalcemic drug (furosemide and zoledronic acid) in two pharmacovigilance database.

Methods: Comparative studies were performed: A comparative study in the French Pharmacovigilance database where notifications of hypocalcemia with denosumab, zoledronate, and furosemide were selected and another in Vigibase, the WHO pharmacovigilance database. The association between reported cases and the use of the drug was associated using reporting odds ratio (ROR). The ROR is the ratio of reporting of one specific event versus all other events for a given drug compound. The 95% confidence intervals (CIs) were calculated

using the Woolf method. All analyses were performed using SAS software version 9.1.

Results: In the French Pharmacovigilance database, a total of 584 hypocalcemia cases were reported of which 60 with denosumab 27 with zoledronate and 22 with furosemide. Denosumab was highly significantly associated with hypocalcemia (ROR 165.58, 95% CI [125-219.3]) comparatively with zoledronate (ROR 45.2, [30.5-66.9]) and furosemide (ROR 3.04, [2-4.6]). In Vigibase, a total of 8821 hypocalcemia cases were reported of which 2086 with denosumab, 838 with zoledronate, and 666 with furosemide. In Vigibase, denosumab was highly significantly associated with hypocalcemia (ROR 91.9, 95% CI [87.5-96.6]) comparatively with zoledronate (ROR 38.11, 95% CI [35.4-40.9]) and furosemide (ROR 4.13, 95% CI [3.8-4.5]).

Conclusions: Denosumab is the drug with the higher risk of hypocalcemia in two pharmacovigilance database, national and international. The risk of hypocalcemia was underevaluated, in particular, in clinical trials (Bone et al, 2013; Sugimoto et al, 2015). This is the first study comparing the hypocalcemic activity of denosumab with other hypocalcemic agents. Monitoring serum calcium level before and after denosumab administration is a critical issue. The risk of hypocalcemia should not be underestimated. References: Bone et al, *J Endocrinol Met* 2013, 98:4496-02 Sugimoto et al, *Osteoporosis Int* 2015, 26:765-774

576 | Use of parenteral glucocorticoids and the risk of new onset type 2 diabetes mellitus: A case-control study

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Background: Use of oral glucocorticoids (GCs) has been associated with hyperglycaemia and type 2 diabetes mellitus (T2DM). However, unlike oral GCs, there is minimal or no data on the effect of parenteral GC use on T2DM.

Objectives: To assess the association between use of parenteral GCs and the risk of receiving a first prescription of a non-insulin antihyperglycaemic drug (NIAD) as a proxy for new onset of T2DM.

Methods: A population-based case-control study was performed using the Clinical Practice Research Datalink (CPRD). Cases (n = 177 154) were defined as patients >18 years of age who had their first ever NIAD prescription between January 1987 and October 2013. Controls were matched by age, gender, and general practitioner practice. Conditional logistic regression analyses were used to estimate the risk of NIAD prescription and use of parenteral GCs. Our analyses were statistically adjusted for lifestyle factors, comorbidities, and concomitant drug use.

Results: Although this study confirmed that oral GCs increases the risk of receiving a first prescription of a NIAD (OR 2.63 [95% CI, 2.53-2.73]), there was no association between the use of parenterally administered GCs and the risk of receiving a first prescription of a NIAD (OR 0.88 [95% CI, 0.76-1.02]). The number of GC prescriptions

was not associated with risk of new onset T2DM compared with no parenteral GCs use; neither the type of GC.

Conclusions: Our study does not demonstrate an association between the use of parenteral GCs and the risk of new onset of T2DM.

577 | Risk of diabetes mellitus among rheumatoid arthritis patients taking non-biologic DMARDs: A population-based study

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Background: Rheumatoid arthritis (RA) is associated with an increased diabetes risk, while the traditional disease modifying antirheumatic drug (DMARD), hydroxychloroquine, is associated with a decreased risk.

Objectives: To assess the risk of diabetes among RA patients receiving DMARDs with or without corticosteroids using Quebec health services administrative data.

Methods: We constructed an RA cohort in 2002-2012. Index date was the first date of a methotrexate, hydroxychloroquine, or sulfasalazine prescription (other DMARDs were not considered because of small numbers). We excluded users of corticosteroids, DMARDs (biologic or traditional), antidiabetics, and those with a diagnosis for diabetes in the prior 2 years. Follow-up ended at the first date of death, antidiabetic medication use, or December 2012.

Results: The cohort included 2680 hydroxychloroquine, 1672 methotrexate, and 280 sulfasalazine users. The mean age in years (standard deviation) was hydroxychloroquine 64 (14), methotrexate 67 (12), and sulfasalazine 59 (15), and 73%, 71%, and 64% of hydroxychloroquine, methotrexate, and sulfasalazine users, respectively, were women. In time-dependent Cox regression models, the adjusted hazard ratios (aHR) (95% confidence interval) of diabetes (vs hydroxychloroquine) were methotrexate 2.21 (1.36, 3.59) and sulfasalazine 1.03 (0.24, 4.37). Adjusting for corticosteroid use in time-dependent analyses, aHRs (vs hydroxychloroquine without corticosteroid) were hydroxychloroquine + corticosteroid 4.40 (2.08, 9.34); methotrexate + corticosteroid 12.40 (5.48, 28.08); methotrexate 2.90 (1.60, 5.28); sulfasalazine was not evaluated because of the small sample size.

Conclusions: The risk of diabetes was higher in methotrexate versus hydroxychloroquine users. Corticosteroid use increased the risk by 4 folds in both hydroxychloroquine and methotrexate users.

578 | Risk of diabetes mellitus among rheumatoid arthritis patients taking TNF inhibitors with or without non-biologic DMARDs and corticosteroid: A population-based cohort study

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Background: Rheumatoid arthritis (RA) is associated with an increased diabetes risk, while RA treatments with Tumor Necrosis Factor inhibitor (TNFi) and the non-biologic disease-modifying antirheumatic drug (nbDMARD), hydroxychloroquine, are associated with decreased risks.

Objectives: To assess the risk of diabetes in RA patients using TNFi with or without nbDMARD and with or without corticosteroids using Quebec health services administrative data.

Methods: We constructed an RA cohort of TNFi users in 2002-2012. The index date was the first date of a TNFi prescription. Patients with antidiabetics or a diagnosis for diabetes in the prior 2 years were excluded. Follow-up ended at the first date of death, antidiabetic use, or December 2012.

Results: The cohort included 3286 TNFi users (1599 etanercept, 874 adalimumab, 587 infliximab, and 226 golimumab). The mean age (standard deviation) was 62 years (12) and 73% were women. In Cox regression models, the adjusted hazard ratios (aHR) (95% confidence interval) (vs TNFi only) were TNFi + hydroxychloroquine 0.45 (0.24, 0.86); TNFi + methotrexate 0.60 (0.31, 1.16); and TNFi + other nbDMARD 0.53 (0.29, 0.97). Adjusting for corticosteroid use in time-dependent Cox models, the aHR (95% confidence interval) vs TNFi alone were TNFi + corticosteroid 2.66 (1.38, 5.11), TNFi + hydroxychloroquine + corticosteroid 1.08 (0.45, 2.61), TNFi + hydroxychloroquine 0.49 (0.21, 1.13), TNFi + methotrexate + corticosteroid 1.09 (0.35, 3.36), TNFi + methotrexate 0.84 (0.38, 1.85), TNFi + other nbDMARDs + corticosteroid 0.73 (0.29, 1.84), and TNFi + other nbDMARDs 0.80 (0.40, 1.67).

Conclusions: The risk of diabetes was higher in those using TNFi without nbDMARD in combination with corticosteroid, but similar in those using TNFi with nbDMARD and corticosteroid compared with those using TNFi only.

579 | Comparative safety of flavocoxid (Limbrel) versus NSAIDs among osteoarthritis patients

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Background: Flavocoxid (Limbrel) is a medical food formulated to assist in the management of patients with osteoarthritis (OA). Safety concerns have been raised based on case reports of severe acute liver injury and hypersensitivity pneumonitis (HP). However, the absolute risk of these events is unclear.

Objectives: To determine the incidence rate (IR) of severe acute liver injury and HP in a cohort of OA patients who are new users of flavocoxid and explore feasibility of comparison with a similar cohort of patients initiating prescription NSAIDs for these and other outcomes.

Methods: MarketScan claims data (2006-2016) was used to identify patients initiating flavocoxid or prescription NSAIDs for OA or back pain, with 6 months coverage before initiation with no use, ≥ 50 years age. We excluded patients with prior events or malignancy. We defined exposure by days of supply + 30-day extension. Outcomes included hospitalization for: HP, liver injury, and GI bleed. Poisson regression was used for calculating incidence rates (IRs) and 95% confidence interval (CI). Cox regression was used for calculating age-sex adjusted hazard ratio (aHR) for any exposure/outcome with ≥ 5 events.

Results: A total of 4476 (flavocoxid) and 2 129 727 (NSAID) new users met eligibility criteria. Mean age for flavocoxid was 63, NSAIDs was 61. Flavocoxid users had higher prevalence of comorbidities and more health care utilization. The crude IRs for HP was 1.8 (95% CI 0.6-5.5) [flavocoxid, 3 cases] vs 0.1 (0.1-0.1)[NSAID] per 1000py. The IR for hospitalized liver injury was higher for flavocoxid (4.8, 95% CI 2.4-9.6) vs NSAIDs (2.3, 95% CI 2.2-2.4), aHR = 2.1 (1.1-4.3). IRs for hospitalized GI bleeding were lower for flavocoxid (5.0, 95% CI 2.5-10.0) compared with NSAIDs (9.4, 95% CI 9.1-9.6), aHR = 0.48 (95% CI 0.24-0.96). Ongoing work is evaluating additional outcomes and controlling for potentially confounding factors.

Conclusions: These preliminary results suggests that the absolute IR associated with flavocoxid of HP and hospitalization for serious liver injury are low (2-4/1000py) but higher than in NSAID users (rate difference $\sim 2/1000$ py). The risk-benefit profile of flavocoxid needs to be considered in light of its efficacy and broad safety profile including lower rates of hospitalized GI bleeding.

580 | Analyzing factors influencing the risk of falls—Pilot project results

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Background: In hospitalized patients, the risk of falling is increased due to the changes of environmental factors and very often by modification or changes in pharmacotherapy.

Objectives: The study aimed to analyze the influence of pharmacotherapy and other factors associated with falls in patients, hospitalized

in selected 16 departments in South Bohemian Hospitals during the first 6 months in 2017.

Methods: The results of this case-control study were collected through a web application containing data about patients with falls. The data obtained from patient's medical records (eg, drug and personal anamnesis, selected laboratory results) were completed with other information (eg, associated risk factors). Each fall was matched with max. Ten control patients who did not experience falls during hospitalization, yet showed similarities in some defined parameters (department, sex, age, length of stay, and number of drugs). The analysis was mainly aimed to identify risk drugs, risk diagnosis, and other potential risk factors responsible for falls. The analysis of risk diagnosis was conducted upon literature review and considered 30 risk diagnoses. Potential and individual risks were determined for each patient who experienced falls. The potential risk represented all drugs that showed an increased risk of falls described in current literature or in case it was possible to assume risk according to its mechanism of action (347 ATC codes). If a clinical pharmacist could not exclude the drug influence on fall probability, then the drug was marked as individual risk. The overall influence of pharmacotherapy on falls was classified by using Likert scale. For results evaluation, the Hungarian algorithm for matching cases with controls and descriptive statistics were used.

Results: 135 falls were analyzed with the representation of 50% men, while the median age reached 80.5 years (range 27-94). The total number of drugs was 1083 for all patients, the potential risk was reported in 45%. The highest potential risk was demonstrated by drugs affecting the cardiovascular, or the central nervous system. Clinical pharmacists marked the individual risk in 43% of all potential risk drugs with the most frequented tiapride (11.2%) and furosemide (5.8%).

Conclusions: The influence of administered drugs and other factors on the fall probability was detected in the study. *The study was supported by a grant of Charles University (SVV 260 417). Supported by Ministry of Health of the Czech Republic, grant nr. 16-33463A. All rights reserved.*

581 | Abstract Withdrawn

582 | Neuroleptic drug use and neurodegeneration

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Background: Neuroleptic drugs as a class are well known to cause parkinsonian characteristics among some users. However, how use is related to the spectrum of parkinsonian conditions is now well known.

Objectives: To determine the differences in the use of neuroleptic drugs by neurodegeneration status with a focus on parkinsonism, Parkinson's disease (PD) and Parkinsons Plus variants (PPV) (eg, multiple system atrophy [MSA] and progressive supranuclear palsy [PCP]) and Lewy Body dementia (LBD).

Methods: We used a retrospective cohort design within the Kaiser Permanente Northern California (KPNC) membership. KPNC is an integrated health delivery system with a current membership of over 4 million members where care and documentation across all clinical care is done within a unified system. Parkinsonian conditions were determined for 2008–2014 and neuroleptic drug use was ascertained from electronic pharmacy data back to 1997. The ascertainment and classification of parkinsonian conditions was made on the combined information on diagnoses (and number), pharmacy (eg, antiparkinsonian drugs), and provider type (eg, primary care, neurologist, and movement disorder specialist) examined over time for a minimum of 24 months after initial parkinsonian diagnosis. We analyzed the prevalence and distribution of neuroleptic drug use by type of parkinsonian condition.

Results: We found that among 26 105 individuals with a parkinsonian condition in the study period, 49.7% had received a neuroleptic drug prior to the initial clinical indication of the condition. The proportion of neuroleptic drug use was highest among those with LBD (57.9%), followed by parkinsonism (52.3%), PD (51.9%), and PPV (50.4%) ($p < 0.05$). It was lowest for indeterminate parkinsonian patients (41.2%).

Conclusions: We found neuroleptic drug use was prevalent prior to diagnosis and varied by type of parkinsonian condition.

583 | A novel approach for active surveillance of pregnancy safety in multiple sclerosis

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Background: Pregnancy safety studies aim to reduce uncertainty around the risk of adverse outcomes associated with a new medication. The study size required for timely exclusion of the relative risk (RR) of various outcomes is of interest.

Objectives: To estimate the enrolment required to exclude specific levels of risk in a pregnant population over the first 3–6 years of drug approval using a dual-surveillance approach.

Methods: This case study is based on ocrelizumab (OCR), a newly approved drug for multiple sclerosis (MS), and two key outcomes: major congenital malformations and preterm births (baseline risk 3% and 10%, respectively). Two studies have been designed to assess these and other outcomes in women exposed to OCR: (1) a

prospective pregnancy registry; (2) a multi-database pregnancy outcomes study. Drug-specific pregnancy registries can enrol patients soon after approval and provide detailed case information, but recruitment is generally slow. Existing health care databases accumulate large amounts of data, but limitations include time to data accrual and lack of detailed information on individual cases. We projected the expected number of exposed pregnancies in both studies and estimated the levels of risk this approach would be able to rule out over time, assuming a 1:3 exposed-unexposed ratio in the multi-database study (1:1 in the pregnancy registry study) and a true RR of 1.

Results: The OCR pregnancy registry will collect data in the United States and Germany. Approximately 8, 46, and 55 pregnancies with live births are expected to be enrolled at years 1, 5, and 6. These sample sizes provide 80% power to exclude RRs of 2880, 28, and 21 for major congenital malformations, and 67, 6, and 5 for preterm births. The OCR multi-database study will use US health care claims databases and Danish nationwide registries. An estimated 300 exposed pregnancies will be captured at 5 years after approval. Assuming 215 live births with successful mother-child linkage, the study will have 80% power to exclude RRs of 3.5 for major congenital malformations and 2 for preterm births.

Conclusions: Combined, the registry, which will provide early reassurance regarding substantial risks, and the multi-database study, which will provide narrower safety margins after 5 years, will progressively reduce uncertainty regarding potential risks of adverse outcomes, overcome the limitations of each individual study design, and provide timely and meaningful safety information for women with MS and their physicians.

584 | Association of ischaemic colitis with triptans treatment—A nested case control study in the United Kingdom using the health improvement network primary care data

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Background: Ischaemic colitis (IC) is the most common form of intestinal ischaemia and may be caused by medicines such as alosetron. Triptans are selective serotonergic receptor agonists and are approved for acute treatment of migraine. Although triptans are highly selective for vascular receptors in the nervous system, they may also cause vascular constriction outside the cerebral vascular bed. An association between use of triptans and IC has been investigated, with conflicting results.

Objectives: To estimate the relation between IC and triptans use in a population-based cohort with migraine.

Methods: We conducted a nested case-control study in The Health Improvement Network, a primary care database in the United Kingdom, in a cohort of patients aged 18 and over with a diagnosis of migraine or cluster headache between January 1, 2003, and December 31, 2015, with at least 1 year of valid data prior to cohort entry. Cases

of incident IC were identified through READ codes and matched by age and sex to a maximum of 100 controls using the density sampling method. Drug exposure was assessed using prescription data in the 24 months before the index date. Odds ratios were estimated through conditional logistic regression, adjusted for known confounders from literature which, in univariable models, changed the risk estimate for drug exposure more than 10%.

Results: The migraine cohort consisted of 293 037 patients. Mean age at entry was 43.6 years (interquartile range 31-54), 74.3% were females, and 32% used triptans during the study period. We identified 41 incident cases of IC during the study period (incidence rate of 2.3/100 000 person-years), who were matched to 4005 controls. Covariates were balanced between cases and controls except for opioid use, which was higher in cases than in controls (66% vs 42%, $p = 0.001$). Use of triptans in the 12 months prior to the index date compared with no use was significantly related to IC (OR = 2.29, 95% CI 1.02-5.15). When most recent use was between 12 and 24 months prior to index date, no significant relation was found (OR = 1.90, 95% CI 0.44-8.13).

Conclusions: In a cohort of migraine patients, cases of IC had significantly more triptan use in the previous year than controls. Considering the limited number of cases, this finding should be replicated in a better powered study.

585 | The risk of brain hemorrhage with the use of antidepressant drugs

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Background: The use of antidepressants has been steadily increasing nationwide. However SSRI and non-SSRI may have an impact on hemostasis and thus may increase the risk of hemorrhages related to antidepressive psychopharmacotherapy. A number of serious cases of gastrointestinal bleeding and cerebral hemorrhage has been reported, raising concerns about the safety of these drugs. These agents increase the risk of gastrointestinal bleeding; however, study results have not been consistent on their association with brain hemorrhage.

Objectives: To investigate causality between the risk of brain hemorrhage and use of antidepressant drugs by therapeutic class in Korean patients.

Methods: The patients receiving at least one antidepressant prescription between January 2003 and December 2013 were identified using the National Health Insurance Service-National Sample Cohort (NHIS-NCS) database. The patients diagnosed brain hemorrhage in 2002, any head injury before event date, and had antidepressants prescriptions same or after event date were excluded. Antidepressant drugs were classified as TCAs, SSRIs, SNRIs, and Others. Hazard period and control period were matched by 1:4. Characteristics of this study subjects were analyzed by age group, gender, and class. Statistical analysis was done by using the chi-square test. Odds ratios for brain hemorrhage associated with the use of antidepressants and their 95% confidence

intervals were calculated by conditional logistic regression with adjusting for confounders including antithrombotic agents, antihypertensive drugs, and cerebrovascular disease.

Results: A total of 1173 patients with brain hemorrhage, who received antidepressant drugs were included in this study (34.3% male, 65.7% female). The greatest number of these patients were 60 to 79 years old group (52.8%), followed by 40 to 59 years old group (32.3%). Compared with control periods, adjusted ORs were 2.16 (95% CI, 1.76-2.65) in total antidepressant groups, 2.22 (95% CI, 1.71-2.88) in TCA, 1.72 (95% CI, 1.14-2.60) in SSRI, 1.65 (95% CI, 0.62-4.38) in SNRI, and 1.60 (95% CI, 1.08-2.25) in Others group.

Conclusions: Antidepressants therapy is associated with a the risk of brain hemorrhage due to inhibiting serotonin reuptake which prolonged bleeding time and reduced platelet aggregability and activity. The risk of brain hemorrhage in SNRI group was not significant because of low statistical power.

586 | Reported adverse drug reactions in children and adolescents using antipsychotics: Data from VigiBase

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Background: Antipsychotics are frequently used in children and adolescents to treat psychiatric disorders, but limited evidence is available about their tolerability and safety.

Objectives: To characterize the most frequently reported adverse drug reactions (ADRs) in children and adolescents where antipsychotics are suspected drugs and to determine differences in relative reporting frequency between boys and girls and different age classes.

Methods: All reported ADRs within VigiBase, the WHO global database of Individual Case Safety Reports, concerning children aged 1-17 years and with an antipsychotic as the suspected or interacting drug between 1968 until March 2017 were identified. ADRs were grouped based on available Standardized MedDRA Queries (SMQs), as well as on frequency and clinical knowledge, and stratified by gender and age. Descriptive statistics were used and proportional reporting ratios (PRRs) were calculated.

Results: Overall, 45 201 ADRs were included, of which 27 536 (60.9%) ADRs concerned males and 16 654 (36.8%) females. Most ADRs were reported in adolescents between 12-17 years old ($n = 30 673$; 67.9%). Overall, most reported ADRs were included in the System Organ Classes of nervous system ($n = 10 791$; 23.9%) and psychiatric disorders ($n = 7076$; 15.7%), none of the PRRs were <0.7 or >1.5. Within the grouped ADRs, most related to extrapyramidal syndrome ($n = 6630$; 14.7%), breast disorders and blood prolactin ($n = 2131$; 4.7%), and cardiac arrhythmias ($n = 2080$; 4.6%). ADRs related to breast disorders and blood prolactin were more frequently reported in children 12-17 compared with children 1-5 years old

(PRR = 3.3) and ADRs related to cardiac arrhythmias in children 12-17 compared with 6-11 years old (PRR = 1.6).

Conclusions: Although most reported ADRs were related to extrapyramidal syndrome, there was high variability in reported ADRs where antipsychotics were the suspected drug in children and adolescents and this particularly varied between different age classes.

587 | Use of pharmacoepidemiological approach in evaluating drug effect on driving impairment: A systematic literature review

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Background: While the risks of alcohol-induced driving impairment are well known, there is increased interest in the consequences of driving under the influence of prescription drugs. Recently finalized FDA guidance recommends using "tiered approaches," including epidemiological data, to evaluate the effects of CNS-active drugs on the ability to operate a motor vehicle.

Objectives: To summarize published pharmacoepidemiological studies that investigate the association of prescription medications with driving impairment.

Methods: A search was conducted to identify all approved drugs with driving study results described in the Clinical Studies section of the US prescribing information (USPI). Additionally, the search was expanded to recently approved CNS drugs limited to neurology/psychiatry (Jan 2014-Aug 2017) with Warnings/Precautions related to cognitive/motor impairment and/or precautionary statements related to operating a motor vehicle. PubMed was searched for research papers related to motor vehicle accidents (MVAs) and the usage of these identified drugs via generic name, trade name, and drug synonyms.

Results: Based on label search, 12 drugs were identified with relevant information regarding driving impairment in the USPI with or without detailing driving studies. Subsequently, 37 articles were identified in PubMed containing information regarding MVAs and the 12 above-mentioned drugs. Zolpidem tartrate was the most frequent drug evaluated. Seven studies relied on epidemiological approaches. After full article review, six articles were retained. Rather than primary data collection (ie, survey), 4 of 6 articles used an integrated health care system approach, eg, medical records linked to police reports. Study characteristics (study design, exposure/outcome, statistics, and strength/limitations) are summarized.

Conclusions: In light of the new FDA guidance, developers of drugs with CNS impact must evaluate the potential risk of driving impairment. Pharmacoepidemiologic approaches can be used as a component of these evaluations, enhancing the ability to understand the potential driving risks of drugs with CNS impact in real-world settings.

588 | Do antipsychotics increase the risk of fractures?

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Background: Multiple safety issues have been reported with first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs). Increasing evidence suggests a higher risk of fractures among antipsychotic users compared with non-users, especially in the elderly population.

Objectives: To evaluate the types of fractures reported with antipsychotic use in the FDA Adverse Event Reporting System (FAERS) database and the risk of fractures reported in published literature.

Methods: We searched FAERS for all US cases reporting fractures as of July 7, 2015, using the Medical Dictionary for Regulatory Activities (MedDRA) High Level Group Term fractures. We included cases reporting fractures after the initiation of currently marketed antipsychotics. We also performed a PubMed search of studies examining the association between antipsychotics and fractures published between January 1, 1966, and October 30, 2015.

Results: We identified 229 serious adverse event cases in FAERS reporting fractures with antipsychotic use. Most cases reported the use of SGAs (83.8%), followed by both generations of antipsychotics (11.3%), and FGAs (4.8%). About 59% of cases reported an injury consistent with a fall. The epidemiological evidence from two meta-analyses and 18 other primary studies not included in either meta-analysis suggested an approximately 50% higher risk of fractures among antipsychotic users compared with non-users; the results did not appreciably differ for FGAs versus SGAs. Current users had a higher risk of fractures than past users. Fracture risk peaked within 1 year and then declined with long-term treatment, but it remained significantly increased with continuous exposure. In addition, the FAERS cases noted multiple complications following a fall-related fracture, including surgical management, concussion, head trauma with intracranial hemorrhage (ICH), and death.

Conclusions: Post-marketing evidence supported an association between antipsychotics, possibly through their side effects, and fracture risk. Well-known side effects of these medications include central nervous system and blood pressure effects, which can increase the risk of falls and, in turn, fractures. This work provided the basis for a class labeling change to the "Warning and Precautions" section of all antipsychotics.

589 | Initial patterns of prescription opioid use and risk of mortality among adult patients with non-cancer pain conditions in the United States

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Background: Patients seen for pain in the office are often prescribed opioids. An initial opioid prescription intended for short-term treatment of acute pain may result in chronic opioid use among opioid-naïve patients, increasing the risk of fatal overdose and death.

Objectives: To examine the association between the initial patterns of prescription opioid use for non-cancer pain and risk of all-cause mortality among insured opioid-naïve patients in the United States.

Methods: This was a retrospective cohort study using de-identified administrative claims database (Optum Clinformatics Data Mart; OptumInsight, Eden Prairie, Minnesota). Opioid prescriptions filled between January 1, 2010, and December 31, 2015, were identified among opioid-naïve patients (in last 6 months) who were 18 years or older, not receiving cancer, palliative care, or opioid use disorder treatment. Initial pattern of opioid use (6 months after first prescription) was categorized either as chronic (daily) opioid users if they had more than 90 days' supply of opioids or as non-daily users. Multivariable Cox regression models were used to estimate the association of the initial pattern of opioid use with all-cause mortality, adjusting for baseline covariates to control for confounding.

Results: A total of 3 226 265 patients were included in the study, of which 3% were daily opioid users; 55% were female; median age was 51 years; median Charlson comorbidity index was 0.0; and mean daily morphine milligram equivalent was 34.20 (95% CI: 34.17-34.21). Patients were followed for up to 5 years (median of 2 years) with a total of 7 146 831 person-years during which 32 550 (1%) died. The crude death rate was 455 deaths per 100 000 person-years. After adjusting for potential confounders, patients who were initial daily users had an increased risk of mortality compared with non-daily users (HR = 2.5; 95% CI: 2.3-2.7). The hazard of death was slightly attenuated over time (HR = 1.8; 95% CI: 1.7-1.9 at 5 years).

Conclusions: Over 3% of opioid-naïve patients became chronic opioid users within the first 6 months of initial therapy. Incident chronic opioid use was associated with an increased risk of mortality that persisted for up to 5 years after the initiation of opioid therapy. Our findings are consistent with current CDC recommendations to use the lowest effective opioid dose for the shortest expected duration of pain among opioid-naïve patients.

590 | Trends in carbamazepine use, severe cutaneous adverse reactions, and HLA-B*15:02 screening: A nationwide study in Taiwan

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Background: Carbamazepine was notorious for its potential risk of severe cutaneous adverse reactions (SCARs). After discovering the association between HLA-B*15:02 allele and carbamazepine related SCARs, particularly in the Southeastern Asian population, clinical strategies to prevent carbamazepine related SCARs have changed. However, real-world data are scarce regarding the implementation of HLA-B*15:02 screening in routine clinical practice.

Objectives: We aimed to investigate the trends in carbamazepine use and carbamazepine-related SCARs and to examine the patterns and determinants of HLA-B*15:02 screening in Taiwan.

Methods: A nationwide study was performed using Taiwan's National Health Insurance Research Database. In the first part, new users of carbamazepine received their first carbamazepine prescriptions between January 2005 and December 2014 were included, and those experienced SCAR-related admissions were identified using previously validated ICD-9-CM codes. In the second part, recipients of HLA-B*15:02 screening (reimbursed by Taiwan's National Health Insurance since June 2010) between June 2010 and December 2014 were included and multivariate logistic regression was used to explore factors associated with the use of screening.

Results: We identified 419 900 new users of carbamazepine and 664 cases of carbamazepine-related SCARs between 2005 and 2014. The number of new users and SCAR cases remarkably decreased during the 10-year period (−82.6% and −87.1%, respectively), and the incidence rates of SCARs showed a downward trend after 2011. The screening rates of HLA-B*15:02 allele in outpatient setting increased to 24.9% in 2014. Neurologists (odds ratio 12.33, 95% confidence interval [9.30-16.35]), psychiatrists (9.97 [7.31-13.61]), and neurosurgeons (3.23 [2.42-4.32]) were more likely to performed screening tests than other specialties. Physicians practicing in medical centers (6.00 [5.51-6.54]) and regional hospitals (1.95 [1.80-2.12]) were more likely to perform screening tests than those practicing in district hospitals, while the screening rates in clinics remained 0.0% throughout the study period.

Conclusions: In recent years, new users and SCAR cases of carbamazepine substantially decreased. However, only a quarter of new users were screened for HLA-B*15:02 allele before receiving their first prescriptions, and there were considerable disparities in screening rates across medical specialties and hospital accreditation levels.

591 | Guideline adherence for laboratory monitoring of ambulatory patients treated with lithium: a retrospective follow-up study in the Netherlands

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Background: Laboratory monitoring of patients using lithium is important to prevent harm and to increase effectiveness.

Objectives: The aim of this study was to determine guideline adherence overall and within subgroups for laboratory monitoring of patients using lithium.

Methods: All patients having at least one dispensing for lithium for 6 months from January 2010 to December 2015 were identified retrospectively using data from the Dutch PHARMO Database Network. Monitoring was defined as adherent to the Dutch Multidisciplinary Clinical Guideline Bipolar Disorders if lithium serum levels and creatinine were measured at least every 6 months, and thyroid stimulating hormone (TSH) at least annually during lithium use.

Results: Data were analyzed of 1583 patients with a median duration of seven 6-month periods of lithium use. Patients were monitored for lithium serum levels in 65% of the time in 6-month periods and in 73% for creatinine. TSH was monitored in 73% of years of lithium use. Little over one-third (36%) of patients were monitored adherent to the guideline for all three parameters during total follow-up. Especially males, middle-aged patients, patients using <5 medications, patients receiving prescriptions solely from general practitioners, patients without interacting co-medication, and patients without other days with laboratory measurements were less often monitored adherent to the guideline.

Conclusions: A considerable number of patients were not monitored adherent to the guideline. To ensure patient safety and effectiveness of lithium treatment, it is important to understand why this is the case.

592 | Utilisation and safety of asenapine in primary care in England: Results from a PASS

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Background: Asenapine is approved in the EU for the treatment of manic episodes associated with bipolar I disorder in adults. A PASS was carried out to monitor the use and safety of asenapine using real-world primary care data in England; targeted safety outcomes were oral hypoaesthesia, oropharyngeal swelling, somnolence and sedation, acute allergic reactions, and weight gain (defined as weight [kg] and/or BMI [kg/m²] increase of $\geq 7\%$ at end of study vs index).

Objectives: To describe the utilisation and safety of asenapine in primary care in England.

Methods: A cohort study identified patients (pts) from dispensed prescriptions of asenapine in England from Jan 2012-June 2016. Pt characteristics, drug utilisation, and outcome data were collected from prescribing general practitioners via questionnaires sent at ≥ 3 and ≥ 12 months after the first prescription issued for each pt. Summary descriptive statistics were calculated.

Results: The cohort consisted of 122 pts with 3-month data of whom 56 pts had corresponding 12-month data (median age 44 years [IQR 35-55]; 66.4% female). The most frequent indication was bipolar disorder ($n = 81$, 66.4%); for 10 pts (12.3%), the indication was specifically reported as bipolar I disorder. There were also a number of off-label indications, eg, schizophrenia ($n = 21$, 17.2%). Asenapine was prescribed in accordance with the product label for 61 pts (50.0%) who were started on 5 mg bd; 19 pts (15.6%) were prescribed 10 mg bd. For the 3-month cohort, incidence of targeted events was oral hypoaesthesia $n = 0$ (0.0%), oropharyngeal swelling $n = 1$ (0.8%), sedation/somnolence $n = 5$ (4.1%), and acute allergic reactions $n = 0$ (0.0%). For the 12-month cohort, incidence of targeted events was oral hypoaesthesia $n = 0$ (0.0%), oropharyngeal swelling $n = 1$ (1.8%), sedation/somnolence $n = 6$ (10.7%), acute allergic reactions $n = 0$ (0.0%), and weight gain $n = 10$ (17.9%). In addition to the targeted outcomes, other events of interest included four deaths, one of which was a completed suicide, and a case of foetal spina bifida diagnosed in a pregnant patient taking multiple psychiatric medications.

Conclusions: Asenapine was largely prescribed in accordance with prescribing recommendations. Event counts were small, and no new safety signals were identified. This study design allowed for the timely collection of drug utilisation and safety data directly from prescribing GPs. However, as a result of the small cohort size, any conclusions from this study should be put into context with results from other post-marketing studies.

593 | Utilisation and safety of asenapine in secondary care in the United Kingdom: Results from the observational safety evaluation of asenapine (OBSERVA) study

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Background: The OBSERVA specialist cohort event monitoring (SCEM) study, conducted in secondary care in the United Kingdom, formed part of an EU risk management plan to monitor the use and

short-term safety of asenapine, licensed for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. Targeted safety outcomes were oral hypoaesthesia, oropharyngeal swelling, somnolence and sedation, acute allergic reactions, and weight gain (defined as weight [kg] and/or BMI [kg/m²] increase of $\geq 7\%$ at end of study vs index).

Objectives: To describe the utilisation and safety of asenapine prescribed in secondary care in the United Kingdom.

Methods: An observational cohort study identified patients (pts) via a network of psychiatrists in collaboration with the Mental Health Research Network from Nov 2012–Sept 2016. Pt characteristics, drug utilisation, and outcome data were collected via questionnaires completed by specialists sent at baseline and after 12 weeks of observation. Summary descriptive statistics were calculated.

Results: The final cohort consisted of 125 pts; the median age was 44 years [IQR 35–52]; 63 (50.4%) were male. Asenapine was most frequently prescribed for bipolar disorder ($n = 81$, 64.8%); 15 of these patients (18.5%) had bipolar I disorder reported. There were also a number of off-label indications, eg, schizophrenia ($n = 18$, 14.4%). Asenapine was largely prescribed in accordance with the product label; 56 pts (44.8%) were started on 5 mg bd, and at 12 weeks, 34 pts (27.2%) were taking 10 mg bd. The incidence of targeted events was as follows: oral hypoaesthesia $n = 9$ (7.2%), oropharyngeal swelling $n = 0$ (0.0%), sedation $n = 13$ (10.4%), somnolence $n = 11$ (8.8%), acute allergic reactions $n = 0$ (0.0%), and weight gain $n = 1$ (0.8%). No deaths or pregnancies were reported in the OBSERVA study.

Conclusions: Asenapine was largely prescribed in accordance with prescribing recommendations; the majority of pts were taking asenapine for bipolar disorder at the recommended dose. Event counts were small and no new safety signals were identified. This study provides valuable real-world data to support the post marketing risk-benefit profile of asenapine; however, as a result of the small cohort size, any conclusions from this study should be put into context with results from other research evidence.

594 | Antiepileptic drug use and the risk of stroke among community-dwelling persons with Alzheimer's disease: A matched cohort study

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Background: Persons with Alzheimer's Disease (AD) are more predisposed to seizures than older people in general, and use of antiepileptic drugs (AEDs) is more frequent. AED use has been linked to higher risk of vascular events in general population; however, it is not evident whether the same association is in persons with AD.

Objectives: The aim of the study was to assess the risk of stroke associated with incident AED use among persons with AD.

Methods: The MEDALZ cohort includes all Finnish persons who received a clinically verified AD diagnosis ($N = 70718$) in 2005–2011. Persons with previous strokes were excluded. For each incident AED user ($n = 5617$), one non-user was matched according to sex, age,

and time since AD diagnosis. Analyses were conducted with Cox proportional hazards models and inverse probability of treatment weighting (IPTW).

Results: Compared with non-use, AED use was associated with an increased risk of stroke (IPTW hazard ratio (HR): 1.37; 95% CI: 1.07–1.74). The risk was strongest during the first 90 days (Adjusted HR: 2.36, 95% CI: 1.25–4.47) of AED use. The association was more evident with ischemic strokes (IPTW HR: 1.34, 95% CI: 1.00–1.79) than hemorrhagic ones (IPTW HR: 1.44, 95% CI: 0.86–2.43). Use of older AED was associated with similar risk of stroke as newer AED use.

Conclusions: AED use was related to an increased risk of stroke, regardless of AED type. AED use for other indications than epilepsy should be limited to those without other pharmacotherapy options.

595 | Self-harm in people with epilepsy: Population-based cohort and nested case-control studies

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Background: Self-harm risk in people with epilepsy has not been estimated in a primary care patient cohort, and no published studies have reported on factors contributing to self-harm risk linked with epilepsy.

Objectives: Estimate self-harm risk in people with epilepsy and identify factors that influence this risk.

Methods: We identified primary care patients with incident epilepsy in the Clinical Practice Research Datalink linked to hospitalization episodes and mortality data in England (01/01/1998–03/31/2014). In Phase 1, we conducted a matched cohort study. We matched individuals with incident epilepsy to up to 20 individuals without epilepsy and compared self-harm risk between these two groups using a stratified-Cox proportional hazards model. In Phase 2, we delineated a nested case-control study within the incident epilepsy cohort. People who had self-harmed were matched with up to 20 controls. We identified self-harm recorded in primary care using ReadV2 codes and from hospital and death data using ICD-10 codes. From conditional logistic regression models, we estimated relative risk of self-harm associated with mental and physical illness comorbidity, contact with health care services and antiepileptic drug (AED) use.

Results: Phase 1 included 11 690 people with epilepsy and 215 569 individuals without. We estimated a deprivation-adjusted hazard ratio of 5.31 (95% CI 4.08–6.89) for self-harm in the first year following epilepsy diagnosis and 3.31 (95% CI 2.85–3.84) in subsequent years. In Phase 2, there were 273 self-harm cases and 3790 controls. Elevated self-harm risk was associated with mental illness (OR 4.08, 95% CI 3.06–5.42), treatment with two AEDs vs monotherapy (OR 1.84, 95% CI 1.33–2.55), and AED treatment augmentation (OR 2.12, 95% CI 1.38–3.26).

Conclusions: People with epilepsy have elevated self-harm risk, especially in the first year following diagnosis. Clinicians should adequately monitor these individuals and be especially vigilant for elevated risk in people with epilepsy and comorbid mental illness, those taking multiple AEDs and during treatment augmentation.

596 | Use of high H1 receptor affinity antidepressants and risk of type 2 diabetes mellitus

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Background: Several studies reported an association between antidepressant use and risk of type 2 diabetes mellitus (T2DM). However, it is still not clear whether the association is causal or due to the unhealthy lifestyles associated with depression and consequently antidepressant use. Moreover, it is still not clear whether all antidepressants have the same potential to induce diabetes. Recent studies suggest that the potential of different antidepressants to induce diabetes could be related to their anti-histaminergic activity.

Objectives: To evaluate the possible association between use of antidepressants with different affinity to the H1 receptor (H1-R) of histamine and the risk of developing diabetes.

Methods: The study was conducted using the drug prescription database of Piedmont, an Italian region with a population of about 4.4 million inhabitants. A cohort of 93 331 subjects who were newly treated with antidepressants during 2008-2010 was followed until 2014. During this period, patients who began therapy with an antidiabetic agent were identified. This event was considered as a proxy of the development of T2DM and constitutes the main outcome of the study. Antidepressants were classified as high and low H1R affinity antidepressants according to a previously published method. To avoid misclassification, we only included patients who did not switch from one affinity class to the other during the follow-up period. Risk of T2DM in the two groups was evaluated using non-parametric survival analyses and Cox regression models.

Results: During the follow-up, we identified 4654 subjects who started an antidiabetic medication. Compared with subjects taking low H1R affinity antidepressants, subjects taking high H1R affinity antidepressants had an increased risk of starting an antidiabetic medication (Hazard Ratio [HR]: 1.50; 95% CI: 1.30-1.70; $p < 0.001$). When we restricted the analysis to subjects with high (>80%) adherence to the antidepressant treatment the association was stronger (HR: 1.96; 95% CI: 1.59-2.42; $p < 0.001$).

Conclusions: We observed for the first time that a classification of antidepressants based on their receptor affinity may be useful to

predict diabetes risk. Given the high prevalence of both diabetes and antidepressant use in the general population, these findings can be relevant for public health.

597 | Safety and tolerability of antipsychotic medication use in individuals with autism spectrum disorder: A systematic review and meta-analysis

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Background: Antipsychotic medication is a commonly prescribed drug class in individuals with autism spectrum disorder (ASD). However, the safety and tolerability of these agents have not been fully assessed, with only limited long-term safety studies in the ASD population.

Objectives: To review the safety and tolerability profile of antipsychotic medication in individuals with ASD.

Methods: This study is a systematic review of randomised controlled trials (RCTs) and observational studies on the safety of antipsychotic medication in patients diagnosed with ASD. The Cochrane Library, Medline, Embase, and PsycINFO databases were searched up to January 2018, using appropriate MeSH terms and keywords. Studies included patients of any age, taking any antipsychotic medication (first or second generation) and that reported any adverse events (AEs) in individuals with ASD. The primary outcome of this review was AEs of any severity reported with antipsychotics. Meta-analysis was performed to estimate the pooled prevalence of the overall adverse events using a random effect model.

Results: 2805 records were identified. 53 citations fulfilled the inclusion criteria, of which 39 were RCTs and 14 were observational studies. Most of the studies were based on second generation antipsychotics, specifically risperidone and aripiprazole. Seven observational studies were included in the meta-analysis to estimate the pooled prevalence of AEs which was 50.5% (95% CI: 33-67). Antipsychotic treatment increased the risk of developing AEs by 22% compared with placebo (RR = 1.22, 95% CI: 1.11-1.34, $I^2 = 30.6\%$, $p = 0.184$). A wide range of AEs was identified. The most commonly reported AEs were increased appetite and weight gain, which were associated with discontinuation in many participants. Other AEs that were reported included extrapyramidal side effects, prolonged QT interval, seizures, and hyperprolactinemia.

Conclusions: Antipsychotic-related AEs among patients with ASD were common. Further studies to investigate the implications of antipsychotic-related AEs on health and medication adherence are warranted.

598 | Antiepileptic drug use is associated with an increased risk of pneumonia among community-dwelling persons with Alzheimer's disease: A nationwide matched cohort study

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Background: Besides epilepsy, antiepileptic drugs (AEDs) may also be used for neuropathic pain and behavioral symptoms of dementia. AEDs have sedative properties which may lead to an increased risk of pneumonia.

Objectives: Our objective was to investigate whether antiepileptic drug use is associated with an increased risk of pneumonia among community-dwelling persons with Alzheimer's disease (AD). In addition, we determined the risk according to duration of AED use and sedative potential of AEDs.

Methods: Persons with AD were identified from the MEDALZ dataset which includes all community-dwelling persons who received a clinically verified diagnosis of AD during 2005-2011 in Finland (N = 70 718). New AED users (without active cancer) after diagnosis of AD were identified with 1-year washout period. A matched cohort was formed by matching a nonuser (N = 5769) for each AED user (N = 5769), at the time of AED initiation, by age, gender, and time since AD diagnoses. Data from nationwide registers included dispensed medications which were modeled with PRE2DUP method, hospitalizations, and causes of death. The association between AED use and hospital admission or death due to pneumonia was analyzed with Cox proportional hazard models.

Results: AED use was associated with an increased risk of pneumonia (adjusted HR 1.92, 95% CI 1.63-2.26; incidence rate per 100 person-years 12.58, 95% CI 12.49-12.66 during AED use and 6.41, 95% CI 6.37-6.45 during no use). The highest risk was observed during the first month of use (aHR 3.59, 95% CI 2.29-5.61) and the risk remained elevated until 2 years of use. The risk associated with AED use remained similar when persons with epilepsy were excluded from analyses. AEDs with high sedative potential were associated with higher risk of pneumonia (aHR 2.14, 95% CI 1.88-2.44) than AEDs with less pronounced sedative potential (aHR 1.38, 95% CI 1.21-1.59).

Conclusions: During antiepileptic use, especially use of sedating AEDs, the risk of pneumonia was considerably higher which is concerning as persons with AD are at increased risk of having pneumonia.

599 | Use of antipsychotics and risk of acute respiratory failure among adults: A population-based nested case-control study

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Background: The risk of acute respiratory failure (ARF) from the use of antipsychotics had been overlooked due to limited cases reports. The public has aroused their concern of this drug safety issue after a recently published population-based study of chronic obstructive pulmonary disease (COPD). However, it remains unclear whether this adverse drug reaction could occur among a population of adults who take antipsychotics.

Objectives: To investigate associations between various conditions of antipsychotic usage and the risk of ARF among a general adult population.

Methods: This nested case-control study analyzed 716 493 adults aged ≥ 20 years as the study cohort, retrieved from the Taiwan nationwide health care claims records between January 1, 2000, and December 31, 2013. Cases with any diagnosis of acute respiratory failure, necessitating intubation, and/or mechanical ventilation were matched with up to two randomly selected controls within risk sets by age, sex, cohort entry date, disease risk score of ARF, and presence or absence of heart failure, pneumonia, and COPD. Logistic regression models were fitted to estimate adjusted odds ratios (ORs) of ARF with various conditions of antipsychotic use.

Results: A total of 7084 cases and 12 785 disease risk score-matched controls were identified for analysis. Current, recent, and recent past use of antipsychotics was associated with a 2.33-fold (95% CI, 2.06-2.64), 1.79-fold (95% CI, 1.43-2.25), and 1.41-fold (95% CI, 1.20-1.66) increased the risk of ARF, respectively, while there was no increased risk for antipsychotics discontinued >90 days. There existed a dose-dependent risk of ARF under current therapy with antipsychotics (test for trend, $p < 0.001$), in which antipsychotic use at >1 defined daily dose yielded the highest risk of 6.53-fold (95% CI, 3.33-12.79). The adjusted OR for current oral and any injection administration of antipsychotics was 2.14 (95% CI, 1.87-2.46) and 3.13 (95% CI, 2.41-4.05), respectively.

Conclusions: Use of antipsychotics was associated with an increased risk of ARF in a population of adults. The risk was particularly elevated for those currently receiving high daily dose level or injection of antipsychotic agents.

600 | Neurological adverse events with baclofen among clinical sub-populations with and without alcohol use disorders, HIV, and HCV

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Background: Baclofen has efficacy for the treatment of unhealthy alcohol use but can cause neurological adverse events. Patients with alcohol use disorders (AUD), human immunodeficiency virus (HIV), or hepatitis C virus (HCV) may be at increased risk.

Objectives: To determine the impact of AUD, HIV, and HCV on the incidence and risk for neurological adverse events and related sequelae associated with baclofen exposure.

Methods: We conducted a retrospective cohort study in the Veterans Aging Cohort Study (VACS), a US national cohort of all HIV+ patients, and 1:2 matched uninfected controls receiving care in the Veterans Health Administration (VA). Patients who first received baclofen (BACLO+), for any indication, between 2002 and 2015, were compared with propensity-score matched, baclofen unexposed (BACLO-) patients. Index date was defined as prescription release date for BACLO+ patients and a randomly selected outpatient visit date from a prescribing station for BACLO-. We used ICD-9 outpatient diagnoses to determine 6-month incidence of a combined outcome of falls or fractures, seizures, or altered mental status, excluding those who had an outcome within 1 year prior to baseline. We used Poisson regression models to calculate incidence rates (IR) and rate ratios (RR) stratified by AUD, HIV, and HCV status and baclofen dose. Models were adjusted for age, total medication count, and VACS Index (a measure of physiologic injury).

Results: There were no demographic or clinical differences between 7798 BACLO+ and 27 637 BACLO- PS-matched patients (all $p > 0.07$). Patients in the PS-matched sample had median age of 53 years, were mostly male (96%), 49% were black, 40% were white, 25% had a lifetime AUD, 22% had a current AUD, 9% were HIV-/HCV+, 19% were HIV+/HCV-, and 7% were HIV+/HCV+. The crude IR for the combined outcome per 100 person-years (PY) was 7.35 (95% CI 6.20-8.71) among BACLO+ and 4.66 (95% CI 4.16-5.22) among BACLO- patients. BACLO+ patients with a current AUD or HIV/HCV co-infection were at highest risk. In adjusted analyses, BACLO+ patients were 49% more likely to experience an adverse event than BACLO- patients (95% CI 1.21-1.83). BACLO+ patients with HIV or an average daily dose >30 mg were 85% and three times,

respectively, more likely to experience an adverse event than their BACLO- counterparts.

Conclusions: Patients who received baclofen, particularly those with HIV infection or prescribed higher doses, are at increased risk for neurological adverse events and their sequelae.

601 | The efficacy and safety of psychotropic drug treatment in adolescents with anorexia nervosa: A systematic review

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Background: Anorexia nervosa (AN) is a mental disorder that onsets in adolescents. Treatment of anorexia nervosa is mainly carried out through a multidisciplinary approach, with psychological interventions given as first line treatment. However, psychotropic medications are sometimes prescribed if initial psychotherapy does not provide an optimal treatment response.

Objectives: This systematic review aims to review the existing literature on the safety and efficacy of psychotropic medications treatment in adolescents with anorexia nervosa.

Methods: The PubMed, EMBASE, PsychINFO, and Cochrane Review databases were searched for relevant studies published up to October 2017 investigating psychotropic medications and their safety and efficacy in adolescents with AN. Randomised controlled trials (RCTs) and observational studies were included with no restrictions on study design or psychotropic medication therapeutic class. The primary outcome was defined as weight change as a measurement of drug efficacy, while secondary outcomes included safety of psychotropic medications with regards to adverse events, side effects, safety measurements, and death.

Results: A total of 824 citations were identified of which 10 studies were included in our narrative review. These comprised of three RCTs and seven observational studies, covering a total of 1032 individuals ranging from 10 to 21 years of age. All studies did not find a significant association between the use of psychotropic medications for adolescents with AN and weight change. 70% of the studies (7 out of 10) confirmed safety issues among users of psychotropic medications; however, the safety outcomes varied even between medications from the same therapeutic class, thus prevented us from aggregating the results.

Conclusions: The findings of this review fails to provide strong evidence for the efficacy of the use of psychotropic medications treatment in adolescents with anorexia nervosa. These preliminary results demonstrate a need to characterise the behaviours that lead clinicians to prescribe psychotropic medications and to explore their effects on those specific behaviours. In turn, it will enable us to conduct studies establishing the therapeutic efficacy and safety of psychotropics in the treatment of adolescents with anorexia nervosa.

602 | Prevalence of CYP3A4 inhibitor use in patients with dementia: A cross-sectional study in the United States

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Background: Cholinesterase inhibitors such as donepezil are used to treat some dementias. Since donepezil is partly metabolized by the Cytochrome P450 3A4 (CYP3A4) enzyme, concurrent use of CYP3A4 inhibitors may increase the concentration of donepezil leading to higher risk of adverse events in patients.

Objectives: To assess the prevalence of use of moderate/strong CYP3A4 inhibitors inpatients with dementia with Lewy bodies, Alzheimer's Disease, donepezil users, and those aged 65 years and over.

Methods: This was a cross-sectional study using the US Truven Health Analytics MarketScan Commercial Claims and Encounters and Medicare Supplemental databases. Four cohorts were identified: (1) patients with a diagnosis for dementia with Lewy bodies at any time in their history, (2) patients with a diagnosis for Alzheimer's disease at any time in their history, (3) patients prescribed donepezil in the past year, and (4) patients aged 65 years and over. The most recent 1 year of data available for each patient was utilized as the study period. Patients who did not have a full year of data were excluded. The main outcome measure was use of moderate/strong CYP3A4 inhibitors in the past year. The age and sex distribution (N and %) of patients in cohorts (1) to (4) was calculated. Age was calculated based on age mid-year in the index year (most recent year of data for each patient). The numbers and percentages of patients in cohorts (1) to (4) who were prescribed a moderate or strong CYP3A4 inhibitor in the past year was calculated overall, and by sex and age-group.

Results: The moderate and strong CYP3A4 inhibitors comprised a broad range of drug groups including antibiotics, antifungals, calcium channel blockers, antiarrhythmic drugs, antidepressants, and antiretroviral protease inhibitors, among others. The overall prevalence of moderate/strong CYP3A4 inhibitor use was 18% (n = 4797/26 744), 17% (n = 56 245/326 930), 20% (n = 56 449/278 933), and 15% (n = 1 099 503/7 194 713), respectively, for dementia with Lewy bodies patients, Alzheimer's Disease patients, donepezil users, and patients aged 65 years and over. Prevalence of use of moderate/strong CYP3A4 inhibitors did not differ by age-group and sex.

Conclusions: The one-year prevalence of use of moderate and strong CYP3A4 inhibitors in the dementia with Lewy bodies and Alzheimer's Disease populations ranged from 17% to 18% in this US population.

603 | Risk of self-harm associated with individual antiepileptic drugs: A propensity score analysis

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Background: Despite the associated warnings for suicidality assigned to antiepileptic drugs (AEDs), findings from published observational studies are inconclusive as to whether AEDs elevate risk versus non-use. As epilepsy is almost exclusively treated with AEDs, it is clinically important to know if any particular AED is associated with an increased self-harm risk.

Objectives: To estimate self-harm risks specific to carbamazepine and lamotrigine compared with valproate.

Methods: We used the Clinical Practice Research Datalink (CPRD) in England, 01/01/1998-03/31/2014, and the Secure Anonymised Information Linkage (SAIL) Databank in Wales, 01/01/2001-12/31/2014. In each dataset, we delineated cohorts of individuals with incident epilepsy, aged 10 or over with no history of AED use or self-harm and who initiated treatment with carbamazepine, lamotrigine, or valproate. We assigned propensity scores and applied Inverse Probability of Treatment Weighting (IPTW). We estimated hazard ratios for self-harm in new-users of carbamazepine and lamotrigine versus valproate using weighted Cox-proportional hazards models in each dataset, and meta-analysed estimates using DerSimonian and Laird Random Effects Model. Self-harm was identified from primary care records using ReadV2 codes and from hospital or death records using ICD-10 codes.

Results: 5004 of 5107 new users of valproate, carbamazepine, or lamotrigine in the CPRD and 2617 of 2654 in the SAIL Databank were included in the IPTW analysis. Following IPTW assignment, the previously noted imbalances of covariates—age, gender, antipsychotic use, and alcohol misuse—were no longer statistically significant. There were 60 first self-harm events in the CPRD and 31 in the SAIL Databank. Estimates for risk of self-harm corroborated between datasets. The meta-analysed hazard ratios for self-harm compared with valproate were 1.53 (95% CI 0.89-2.64) for carbamazepine and 1.35 (95% CI 0.79-2.29) for lamotrigine.

Conclusions: There was no evidence of increased or decreased risk of self-harm associated with carbamazepine or lamotrigine, compared with valproate, in people with epilepsy. Clinicians therefore should take a holistic approach when assessing risk of self-harm in this population, giving consideration to other potential risk factors.

604 | Assessment of risk of variant Creutzfeldt-Jakob disease (vCJD) from use of bovine heparin

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Background: Heparin is the primary drug to prevent and treat thromboembolism. Following the outbreak of Bovine Spongiform Encephalopathy (BSE) in Europe, bovine heparin was withdrawn from the US market. The supply of the drug has become stressed, because porcine intestine is now the only source of raw material to produce heparin for the US market. The recent decline in the BSE epidemic prompts the FDA to reevaluate vCJD risk from bovine heparin.

Objectives: We developed a computational model to estimate the potential vCJD risk to patients receiving bovine heparin for treatment.

Methods: The model inputs included BSE prevalence among cattle, infectivity in the intestines of infected cattle, manufacture pool size, infectivity reduction by purification steps, and dosage of heparin. The dose-response relationship was derived from a FDA dose-response model previously developed to estimate the risk of transfusion-transmitted vCJD. The model was adjusted to account for the bovine-human species barrier in human vCJD infection from exposure to BSE agent in bovine heparin.

Results: BSE prevalence among US cattle was estimated to be around 1 per 10 million (USDA 2006). The current BSE prevalence is likely lower than it was in 2006. BSE infectivity in cow intestines varies in a range of 6-13 bovine ID₅₀ per bovine (European Food Safety Authority 2014). A laboratory study resembling heparin purification process demonstrated 3.4-3.6 log₁₀ reduction in scrapie agent (as surrogate of BSE agent). Based on above assumptions, the model estimated the risk of vCJD infection from a single intravenous (IV) injection of one dose (10 000 units) of heparin made from US-sourced bovine materials to be about 1 in every 1 to 10 billion injections. A patient with venous thromboembolism is typically given heparin infusion daily for 1 week with 20 000-40 000 units of heparin per day. Our model estimates the risk to be approximately 1 case of vCJD per 10 million to 1 billion among these patients. These risk estimates likely represent the worst-case scenario as we made conservative assumptions for some model inputs due to limited data.

Conclusions: This case study demonstrates how computational modeling can be used as a tool to incorporate epidemiological information in assessment of therapeutic risk and to help inform regulatory decisions. To reconsider bovine heparin as a potential option for treating thromboembolism, the overall benefits and risks of bovine heparin must be considered; the established benefits should outweigh the potential risks.

605 | Risk of tympanic membrane perforation after quinolone ear drops for acute otitis externa: A retrospective cohort study

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Background: Quinolone ear drops have been shown to impair tympanic membrane healing post-myringotomy. We aimed to examine whether use of quinolone ear drops increases the risk of perforation with intact tympanic membranes in patients with acute otitis externa (AOE).

Objectives: To investigate whether quinolone ear drops use increase the risk of eardrum perforations in children and adults with uncomplicated AOE.

Methods: This was a retrospective cohort study using Medicaid medical encounter and pharmacy billing records from 1999-2010. Children and adults had to have 24 months of continuous enrollment in Medicaid prior to the first antibiotic ear drop dispensing (index date), and they had to maintain their Medicaid enrollment for at least 18 months thereafter. Included ear drops were quinolones (ofloxacin, ciprofloxacin plus hydrocortisone, or ciprofloxacin plus dexamethasone) or neomycin plus hydrocortisone. Occurrence of tympanic membrane perforation (TMP) was identified as the presence of an inpatient or outpatient encounter associated with TMP diagnosis. A Cox regression model, adjusted for patients' demographics, calendar year, and number of ear drop prescriptions was used to compare TMP incidence rate between quinolone and neomycin-exposed patients. We performed several sensitivity analyses by varying the age, TMP definition, and switching between exposure status during the follow-up period.

Results: A total of 112 806 patients entered the study cohort. Unadjusted TMP incidence rates were 75 and 129 cases per 10 000 patient-years following exposure to neomycin and quinolone ear drops, respectively. The adjusted hazard ratio of TMP for quinolone vs neomycin was 1.99 (95% CI, 1.50-2.65). The sensitivity analyses findings were consistent with the primary analysis.

Conclusions: Use of quinolone ear drops for AOE is associated with an increased risk of developing tympanic membrane perforations.

606 | Medication-related adverse events among older adults: A nationwide readmission study

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Background: Polypharmacy and inappropriate prescribing is common among older adults and increases their risk of medication-related

adverse events (MRAEs). Hospitalization represents an opportunity to increase or decrease the risk of MRAEs. Currently, there are limited data on post-discharge MRAEs leading to readmission.

Objectives: The objectives of our study were (1) to describe MRAEs responsible for readmission within 30 and 184 days of hospital discharge among older adults in the United States and (2) to examine whether demographic, clinical, and hospital characteristics were associated with MRAE readmission.

Methods: We used the 2014 Nationwide Readmission Database to examine hospitalizations of persons 65 years of age and older. Survey weighting methods were used to generate national estimates of hospitalization, 30- and 184-day readmission, and 30- and 184-day readmission for MRAEs. Readmissions linked to illicit drug use or intentional harm were excluded from analyses. Odds of MRAE readmission by patient and index hospitalization characteristics were assessed using unconditional logistic regression.

Results: We identified 4 299 147 qualifying hospitalizations of older adults in the United States in 2014. The 184-day readmission rate was 23.2%. A total of 2530 readmissions within 184 days were attributed to MRAEs. The most frequent causes of MRAE readmission were "poisoning by opiates and related narcotics" (18.6%), "dermatitis due to medicines" (12.1%), "poisoning by antidiabetic agents" (10.8%), and "poisoning by benzodiazepines" (7.3%). Factors identified as being associated with MRAE readmission included age >84 years (adjusted odds ratio [AOR], 0.42; 95% CI: 0.34-0.53), length of stay >7 days (AOR, 0.80; 95% CI: 0.67-0.96), and being discharged to home health care (AOR, 1.37; 95% CI: 1.17-1.61). Similar findings were observed for readmissions occurring within 30 days of discharge.

Conclusions: Opiate poisonings are the most frequent cause of MRAE readmission among older adults, and several examined factors may serve to characterize overall risk of MRAE readmission. Future studies should determine if MRAE readmissions are avoidable.

607 | Assessment of transfusion-related acute lung injury (TRALI) after blood transfusion

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Background: TRALI, an adverse event occurring during or within 6 hours of transfusion, is a leading cause of transfusion associated fatalities reported to the US Food and Drug Administration. We examined TRALI occurrence with an FDA Sentinel Systems assessment.

Objectives: To assess TRALI occurrence among patients transfused in an inpatient setting.

Methods: We conducted a retrospective cohort study among patients diagnosed within a large hospital system between 2013-2015. Potential TRALI cases were identified with ICD-9-CM codes and transfusions with ISBT-128 and Codabar codes. TRALI was validated with medical records. We calculated unadjusted TRALI occurrence rates (OC) per 100 000 inpatient stays with transfusions and 95% confidence intervals (CI) overall, by year, age, discharge disposition, mechanical ventilation use, blood components, and number of units transfused.

Results: There were 353 749 transfusion stays during the study period; 208 potential TRALI stays were identified; 118 had a TRALI specific ICD-9-CM code (518.7). When TRALI was defined by its specific ICD-9-CM code, the OC was 30.8 (CI 25.0-36.6) per 100 000 transfusion stays. Annual TRALI OCs (CI) 2013-2015 were 33.7 (17.2-50.1), 28.1 (20.4-35.9), and 33.6 (23.5-43.8), respectively. Patients over 65 years had lower OCs (age category: 0-19 = 44.3 (8.9-79.8), 20-34 = 45.7 (20.9-70.5), 35-49 = 44.5 (23.4-65.7), 50-64 = 35.8 (22.8-48.9), 65-79 = 23.5 (14.6-32.4), 80+ = 21.9 (11.5-32.3). OCs were highest in patients discharged expired (117.4 [73.1-161.6] vs 24.8 [19.4-30.2]) or requiring mechanical ventilation (123.8 [94.0-153.7] vs 14.3[10.0-18.6]). OCs increased as units increased (1 unit = 8.4 [2.2-14.7], 2-4 units = 19.2 [13.2-25.1], 5-9 units = 56.8 [34.1-79.5], and >9 units = 191.9 [130.9-252.9]). Patients exposed to multiple components had higher OCs (RBCs only 18.6 [13.3-23.9], PLT only 25.8 [3.4-55.0], Plasma only 12.3 [4.8-29.4], RBCs and plasma 49.9 [17.3-82.5], RBCs and PLT 74.8 [36.9-112.6], PLT and plasma 103.5 [34.0-247.0], RBCs and PLT and plasma 130.2 [56.5-203.8], and other transfusion combination 241.2 [126.6-355.9]).

When TRALI was defined with medical records, the OC was 19.2 (CI 14.7-23.8) per 100 000 transfusion stays.

Conclusions: TRALI OCs increased as transfused units increased and were highest in patients exposed to PLTs and multiple components. Further investigation of results within validated TRALI cases is warranted.

608 | Reports of adverse events with levonorgestrel IUD Mirena in France before and after the 2017 media intense coverage

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Background: Intra-Uterine Device (IUD), among which levonorgestrel Mirena, is the second most used contraception method in France. In 2017, concerns on adverse events (AEs) associated with Mirena were echoed in French media, first in social networks, then in traditional medias. The media coverage peak occurred in May 2017, which resulted in a tremendous wave of reporting of AEs from patient to French Pharmacovigilance Centres. Noticeably, this reporting mainly used the newly launched web-portal for the reporting of AEs whatever the cause.

Objectives: To describe AEs reported for Mirena, before and after the media coverage peak.

Methods: All reports involving Mirena (marketed in France: July 1995) recorded in the French national pharmacovigilance database were extracted on August 4, 2017. Reports were analyzed according to two periods: before and after the media coverage peak of May 2017. All AEs were analyzed by System Organ Classes (SOC), and Preferred Term (PT) according to the MedDRA classification. Disproportionality analyses were performed on reporting that preceded the media peak.

Results: Among 3224 included cases, 510 (16%) were recorded before and 2714 (84%) after the media peak. Patients median age was similar between both periods (37 vs 36 years). Most of the cases were serious: 53% before and 66% after the peak. Before the peak, 77% were reported by health professionals and 55% were considered serious because of "Caused/Prolonged hospitalization." After it, 93% were reported by patients and 55% were considered serious because of "Other serious medical situation." The number of PT and SOC by case increased between the two periods, with a mean of, respectively, 2.4 and 1.9 before vs 7.2 and 5.0 after the peak. Before the peak, ectopic pregnancy and drug lack of efficacy were among the most frequently reported AEs. After the peak, most frequent AEs were depression (38% vs 10% before), anxiety (31% vs 5%), migraine (22% vs 5%), alopecia (29% vs 9%), or loss of libido (47% vs 7%). Disproportionality identified 15 new signal, notably asthenia (20 cases), arthralgia (9 cases), and erythema nodosum (6 cases).

Conclusions: This study highlighted many differences of AE reports involving IUD Mirena before and after the peculiar media peak that occurred in May 2017 in France for this health product: nature and number of reported AEs, type of reporter, and seriousness criteria of reports. Disproportionality analyses performed in the first period led to identify 15 potential safety signals.

609 | Insertion- and removal-related events associated with the Nexplanon contraceptive implant: Results from the Nexplanon observational risk assessment (NORA) study

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Background: Nexplanon is a subdermal contraceptive implant containing the progestogen etonogestrel. In contrast to Implanon, it contains barium sulfate to facilitate its localization and a new applicator to aid correct insertion. Issues involving Nexplanon have not previously been adequately assessed.

Objectives: To characterize the frequency of insertion- and removal-related events among NEXPLANON users in the United States during standard clinical practice.

Methods: This large, prospective, non-interventional cohort study followed 7369 patients with a newly inserted Nexplanon (IMPLANON NXT) implant. First-ever implant users and repeat/consecutive implant users were recruited by health care professionals (HCPs) between December 2011 and March 2014. Questionnaires were completed by patients at 6-month intervals (beginning on the day of insertion and ending 6 months after implant removal) and by HCPs who inserted or removed the implant. Data analysis characterized the frequency of procedure-related events.

Results: During 7369 implant insertions, HCPs reported 208 events involving 189 patients (2.6% of the study population). HCPs most commonly reported device-handling issues such as difficulty removing the needle protection cap (93 insertions). In total, 49 patients (0.7% of the study population) reported an event in the implant arm at the time of insertion. The most common event was pins/needles/numbness in the arm/hand/fingers (17 patients; 2.3 per 1000 insertions; 95% CI, 1.3-3.7). Follow-up data through July 2017 show that 349 patients reported 606 events in the arm in which the implant was inserted: pins/needles/numbness (192 patients), severe pain (166 patients), altered strength (67 patients), and other events (eg, bruising) (100 patients). Of 4044 successful removal procedures, 54 (1.3%) involved at least one challenge: encasement in fibrotic tissue (28), multiple removal attempts (12), local migration (4), deep implant (8), and other challenges (eg, fragmented implants) (13). One other removal procedure was unsuccessful due to the location of the implant in deep muscle tissue. Three patients were hospitalized for the removal procedure (1 patient had a localized infection in the arm and 2 patients had implants located deep in the arm). In all 3 cases, the implant was successfully removed. Final study results will be available at ICPE.

Conclusions: Insertion- and removal-related events associated with Nexplanon are rare.

610 | Risk of hypertension in patients treated with mirabegron compared with tolterodine: A nationwide cohort study

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Background: Mirabegron is a new selective β_3 -adrenoreceptor agonist approved for the treatment of overactive bladder (OAB). The presence of β -adrenoreceptors in cardiac and vascular tissue could possibly lead to adverse cardiovascular events. Hypertension is a recognized, but less common adverse effect found in placebo-controlled studies. No real life studies compared the risk of hypertension between mirabegron and tolterodine, which is the most commonly used antimuscarinic treatment for OAB in Sweden.

Objectives: To assess the risk of hypertension in patients treated with mirabegron compared with those treated with tolterodine.

Methods: Nationwide population-based cohort study using data from Swedish national registers (dispensed drugs, hospitalization, and death) was conducted. Patients exposed to tolterodine or mirabegron, 18 years of age or older, with no recorded diagnosis of hypertension before treatment initiation were identified between July 2007 and December 2014. The outcome was hypertension identified by diagnostic codes in the health care registers or dispensing of antihypertensive drugs. The cohorts were followed until December 2015. Cox proportional hazard model (counting process approach) was used to compare the risk of hypertension between study cohorts. Hazard ratio (HR) with 95% confidence interval (CI) was adjusted for clinical and sociodemographic factors.

Results: A total of 35 843 patients were identified, of which 5816 (16%) patients receiving mirabegron. Overall, 6661 subjects developed hypertension during the 75 548 person-years of follow-up (6029 on tolterodine and 632 on mirabegron). The IR for mirabegron was 95.2 and for tolterodine 87.5, both per 1000 patient-years. Compared with subjects treated with tolterodine, those receiving mirabegron had an increased risk of hypertension (HR = 1.43, 95% CI [1.38, 1.47], $P < 0.0001$). The results were confirmed in analyses stratified by sex, age, and previous cardiovascular disease.

Conclusions: In line with the placebo controlled trials, there was a moderately increased risk of hypertension in patients treated with mirabegron as compared with those treated with tolterodine.

611 | Opioid-related factors affecting mortality in Indiana, USA

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Background: Opioid abuse and overdose in the United States is a public health emergency. This crisis has largely been fueled by the widespread use of prescription opioids for chronic nonmalignant pain.

Objectives: To determine opioid-related factors affecting mortality of patients in the Indiana Network for Patient Care (INPC).

Methods: INPC is a 30-year health information exchange data that are captured and stored from Indiana's health systems including 17.2 million patients. This study used patient, pharmacy, and mortality data between 01/01/2012-12/30/2016. Subjects were ≥ 18 years old with first opioid prescriptions (index) within study period and did not receive opioid in the past 12 months. Exclusion criteria included diagnoses of cancer, dementia, and/or liver diseases. Outcomes included death and number of days from index to death. Survival analyses were performed to determine differences of survival function between male and female, two age groups (<60 vs ≥ 60 years), and race. Kaplan-Meier plots were used to graph time to death. A Cox-proportional hazards model used death as the dependent variable controlling for sex, age, race, number of opioid prescriptions, number of day supply, and dose (morphine milligram equivalents; MME). SAS 9.4 was used for statistical analysis and $p < 0.05$ was considered statistically significant.

Results: Total 914 834 opioid prescriptions were identified for 202 984 subjects. Mean age was 55.2 years (SD ± 18.0) with majority female (60.4%) and white race (75.8%). Mean number of opioid prescriptions was 2 prescriptions/person, median daily MME was 32.1 mg (range: 22.5, 45.0), and median day supply was 5.5 days/prescription/person (range: 4.0, 10.2). Hydrocodone was mostly prescribed (59.0%). At the end of study period, 746 patients (0.37%) died. Compared with African Americans, risk of death was higher for white patients (1.32 [95% CI: 1.06, 1.65, $p = 0.0122$]). Other significant factors included age (HR = 1.006 [95% CI: 1.001, 1.011], $p = 0.0287$), number of opioid prescriptions (HR = 0.971 [95% CI: 0.962, 0.981], $p = <0.0001$), and average MME dose (HR = 1.023 [95% CI: 1.014, 1.033], $p < 0.0001$).

Conclusions: Using a statewide health information exchange data, we found that race, age, number of opioid prescriptions, and MME are associated with mortality.

612 | Association between persistent opioid prescribing and opioid-related deaths in the United Kingdom

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Background: In the United States, opioid-overdose deaths are related mainly to unintentional opioid poisoning. By contrast, opioid-related deaths in the United Kingdom (UK) tend to involve substance misuse, sedatives, and persistent opioid utilisation, but the association has not been explored.

Objectives: This study aimed to evaluate the association between persistent opioid utilisation and opioid-related deaths in the United Kingdom.

Methods: Design: This nested case-control study used the UK Clinical Practice Research Datalink from 1987 to 2015 with linkage to the Office for National Statistics death certificate. **Setting:** Adults (≥ 18 years) who were prescribed opioids with more than one follow-up year from opioid initiation were selected as study cohort. **Exposures or interventions:** Opioid-related deaths identified by the International Classification of Diseases 10th Revision and mortality dates were defined as cases and index dates. Four controls were matched to each case on the disease risk score, the probability of opioid-related death based on patient characteristics in 1 year before index date. **Main outcome measures:** Persistent opioid utilisation (opioid prescriptions ≥ 3 quarters and ≥ 4500 mg oral morphine equivalent dose) was identified annually from the index date up to three patient-years. Concurrent sedatives (sedatives prescribed from 30 days before each opioid prescription to 30 days after opioid prescription exhausted) were also measured during the three patient-years. **Statistical analysis:** The association between persistent opioid utilisation and opioid-related deaths was assessed by a conditional logistic regression adjusting for concurrent sedatives and reported as adjusted odds ratios (aOR) and 95% confidence intervals (95% CI).

Results: Overall, 230 opioid-related deaths were matched to 920 controls. Persistent opioid use in any of the three patient-years (aOR: 2.0; 95% CI: 1.3, 3.1), especially in the final patient-year (aOR: 3.6; 95% CI: 1.6, 8.0) was significantly associated with an increased risk of opioid-related deaths. Concurrent use of higher dose (0-1 or >1 Defined Daily Dose) of benzodiazepines (aOR range: 3.7, 7.5; $p < 0.0001$) and gabapentin/pregabalin (aOR range: 2.0, 8.8; $p < 0.0001$) were associated with an increased risk of opioid-related death.

Conclusions: Persistent opioid utilisation was associated with a higher risk of opioid-related deaths in the United Kingdom. Health care providers should be aware of risk of persistent opioid utilisation rather than opioid daily dose alone.

613 | Identifying opioid overdose deaths and all-cause mortality in administrative claims data and the National Death Index

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Background: Due to the current opioid public health crisis in the United States, the evaluation of opioid overdose rates has gained increased relevance. However, the sensitivity and accuracy of opioid overdose and opioid overdose death ascertainment using administrative claims databases is uncertain and needs to be validated.

Objectives: To compare opioid overdose deaths and overall mortality in a claims database with the National Death Index (NDI) in a cohort of Extended Release/Long Acting (ER/LA) opioid users.

Methods: We used the HealthCore Integrated Research Database (HIRD) to identify US patients with ≥ 1 ER/LA opioid dispensing and at least 6 months of eligibility prior to the first dispensing of an ER/LA opioid between July 1, 2010 and September 30, 2016. We identified deaths in the HIRD using discharge status/diagnosis codes for death during an emergency/inpatient stay and overdose deaths based on the presence of an opioid overdose diagnosis during these stays. Overall mortality and opioid overdose deaths were identified in the NDI for patients ending their eligibility prior to the end of the study period using probabilistic matching.

Results: We identified 195 350 ER/LA opioid users from the HIRD. Among 150 opioid overdose deaths identified by NDI, only 1 was identified in claims (sensitivity = 0.7%), and only 5 had an opioid overdose code within 3 days of the NDI's opioid overdose death date (sensitivity = 3.3%). For total mortality, claims identified 5375 of the 27 754 total deaths identified by the NDI (sensitivity = 19.4%).

Conclusions: Opioid overdose death and overall mortality were poorly ascertained using claims data. These outcomes often occur outside of the hospital setting and have no associated insurance claim. Claims alone are insufficient for assessing all-cause mortality and fatal opioid overdoses.

614 | Analysis of the risks associated with using dietary supplements by patients in the pre-operative period

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Background: Complementary and alternative medicine (CAM) use by pre-surgical patients is quite common and reaches up to 40% in some countries. Some dietary supplements (DS), mostly herbal remedies, may lead to an increase in adverse drug effects during or after surgery.

Objectives: The aim of this study was to analyse potential risks connected with DS use prior to surgery. A secondary aim was to determine the prevalence rate of DS use by pre-surgical patients, reasons for DS use, and awareness of DS risks.

Methods: 1. Design: An observational, cross-sectional study was conducted using a questionnaire survey. A self-administered questionnaire was distributed among 180 pre-surgical patients at the University Hospital Hradec Kralove from July 2017 to January 2018. The questionnaire included questions focused on demography, use of DS, reasons for DS use, and patient awareness of the risks related to DS use in the pre-operative period. 2. Setting: The departments of surgery, cardiac surgery, neurosurgery, urology, gynaecology, otorhinolaryngology, orthopaedics, ophthalmology, and dentistry of the University Hospital Hradec Kralove. 3. Exposures or interventions: There were no exposures or interventions in this study. 4. Main outcome measures: The percentage of patients using DS potentially causing perioperative or postoperative complications, prevalence of DS use in patients in the pre-operative period, reasons for DS use, and awareness of DS risks. 5. Statistical analysis: Descriptive statistics was used.

Results: Out of 180 respondents, 108 participated in the study (a response rate of 60%). Fifty-five percent of respondents had used some form of CAM less than 30 days before surgery, and 89.8% of them had taken at least one DS. The most commonly used DS were herbals (64.4%), non-herbal DS (49.2%), and vitamins and minerals (37.3%). The top five DS were omega fatty acids, ginkgo, garlic, echinacea, and ginger. The most common reason to use DS was disease prevention (58%). Nearly 27% of patients had used a DS with a potential to cause peri-/post-surgery complications. Almost 31% of patients were aware of risks connected with using DS.

Conclusions: The preliminary results suggest there is a relatively high prevalence rate of DS use in pre-surgical patients in the Czech Republic in comparison with other countries, which could lead to perioperative or postoperative complications. A larger study is needed to confirm these results as well as to identify health-care professional awareness of such risks.

615 | Occurrence of safety outcomes among golimumab initiators in routine care

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Background: Golimumab (Simponi) is a monoclonal antibody against tumor necrosis factor alpha (TNF) that is efficacious in treating rheumatic disease among other indications. First available in the United States in 2009, golimumab is labeled for the treatment of adult patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

Objectives: This study aimed to determine if users of golimumab were at higher risk of select outcomes than users of non-biologic systemic medications for rheumatic disease (rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis) in settings of routine care in the United States.

Methods: This study employed the Optum research database, reflecting reimbursement claims for health care provided to patients in health plans affiliated with Optum. A cohort study of golimumab initiators along with initiators of tumor necrosis factor (TNF) inhibitors and non-biologic therapies was conducted. Patients initiating one of the study medications with a baseline diagnosis of rheumatic disease were accrued between September 2009 and May 2015 and followed until December 2015. Propensity score matching was used to form cohorts that were similar with respect to numerous characteristics simultaneously.

Results: Among 1337 golimumab initiators matched to 4227 non-biologic initiators, there were 40 cases of serious infection among 1880 current golimumab exposure person-years relative to 172 cases among 7226 current non-biologic exposure person-years (adjusted IRR = 0.91, 95% CI: 0.65-1.27). For malignancy, there were 48 events among golimumab users compared with 280 among non-users (adjusted IRR = 0.65, 95% CI 0.48-89). There were 3 cases of

lymphoma among golimumab users relative to 16 among non-users (adjusted IRR = 0.74, 95% CI 0.21-2.66). For the outcome of hepatotoxicity, there were 29 cases among 1888 current golimumab exposure person-years relative to 94 cases among 7293 current exposure person-years (adjusted IRR = 1.02, 95% CI 0.68-1.52). For the outcome of depression, the IRR was 1.45 (95% CI 1.31-1.61), and for total mortality, the IRR was 0.27 (95% CI 0.06-1.10).

Conclusions: Golimumab initiators did not demonstrate any increased signal of serious infection, malignancy including lymphoma, hepatotoxicity, or mortality compared with those who initiated non-biologic therapies. These results from across the first 6 years of golimumab availability provide real-world evidence that golimumab is not associated with increased risk of these outcomes.

616 | Occurrence of safety outcomes among ustekinumab initiators in routine care

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Background: Ustekinumab (Stelara) is a monoclonal antibody against interleukin-12/23 that has efficacy in treating psoriasis.

Objectives: This study aimed to determine if users of ustekinumab were at higher risk of select outcomes than users of non-biologic medications for psoriasis in settings of routine care in the United States.

Methods: This study employed the Optum research claims database. A cohort study of ustekinumab initiators along with initiators of tumor necrosis factor (TNF) inhibitors and non-biologic therapies was conducted. Patients initiating one of the study medications with a baseline diagnosis of psoriasis were accrued between September 2009 and December 2014, and propensity score matching was used to form cohorts that were similar with respect to numerous characteristics simultaneously.

Results: Among 440 ustekinumab initiators (667 person-years) matched to 1054 non-biologic initiators (934 person-years), there were 27 and 62 cases of serious infection (adjusted IRR = 0.81, 95% CI: 0.53-1.26), respectively. For malignancy (including nonmelanoma skin cancer), there were 27 cases among ustekinumab initiators (796 person-years) compared with 64 cases among non-biologic initiators (16 077 person-years; adjusted IRR = 0.89, 95% CI: 0.55-1.44). There was one case of lymphoma among ustekinumab-exposed patients relative to 5 cases among non-biologic-exposed patients (adjusted IRR = 0.53, 95% CI: 0.05-5.23). For the outcome of psychiatric disorder, there were 150 cases among ustekinumab patients (511 person-years) relative to 244 cases among non-biologic patients (752 person-years; adjusted IRR = 1.49, 95% CI: 1.22-1.82). For the outcome of cardiovascular disease, there were 31 cases among ustekinumab patients and 63 cases among non-biologic comparators (adjusted IRR = 1.27, 95% CI: 0.80-2.03). For mortality, the adjusted IRR was 0.80 (95% CI: 0.09-7.16).

Conclusions: These results using claims data from the first 5 years of ustekinumab availability provide real-world evidence suggesting that

ustekinumab is not associated with increased risk of serious infection, cardiovascular disease, malignancy, lymphoma, or mortality compared with matched initiators of non-biologic therapies. The finding of a potentially higher risk of "psychiatric disorder" among ustekinumab initiators deserves further characterization by applying more specific definitions of outcomes. Moreover, the current analysis does not adjust for medical history of this outcome in this population of patients prone to depressive disorders.

617 | Differences in diagnostic and treatment of endometriosis in Europe: Comparative data from the VIPOS study

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Background: The International Visanne Post-approval Observational Study (VIPOS) is designed for the assessment of safety and efficacy of dienogest (DNG) 2 mg for endometriosis therapy in comparison with other hormonal treatments for endometriosis. It provides real-world data on hormonal management of endometriosis in Middle and Eastern Europe.

Objectives: To describe country-specific patterns in diagnosis and treatment of endometriosis using the data from the VIPOS study reflecting country-specific guidelines for endometriosis treatment.

Methods: More than 27 000 patients across six European countries—Germany, Hungary, Poland, Russia, Switzerland, and Ukraine—were enrolled for this prospective, non-interventional cohort study between 2010 and 2016.

Women starting a new hormonal therapy regimen for endometriosis were recruited via gynecologists or specialized endometriosis centers. Data on treatment as well as characteristics of the endometriosis diagnosis were collected with the help of the physicians, whereas the women provided data on their medical and gynecological history, endometriosis-related symptoms, and demographics via questionnaire at baseline.

Results: In total, most of the study participants received a combined oral contraceptive for endometriosis treatment, varying from 79.6% in Hungary to 30.1% in Ukraine with regard to the study population of the given country. Progestins (other than DNG) were mainly prescribed in Germany (12.6%) and Russia (13.7%), whereas danazol is still used in Ukraine (21.0%) and Poland (9.4%). The proportion of women with a surgically confirmed diagnosis was higher in Germany (37.3%) and Poland (32.5%) compared with 11.9% in Hungary or 5.6% in Russia.

Marked differences were seen between the participating countries with regard to the user status (first time user, switcher, and re-starter of hormonal medication for the treatment of endometriosis) as well as in other aspects such as perception of endometriosis-associated pain.

Conclusions: The VIPOS study extends the understanding of endometriosis management in clinical practice and provides valuable data on the type of diagnosis and pharmacological treatment patterns in different European countries.

618 | Drug exposure and risk of acute liver failure leading to registration for liver transplantation (ALFT): Results of the SALT III Study in adults in France

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Background: Acute liver failure leading to liver transplantation (ALFT) indication is largely related to drugs (DILI), as shown by our previous SALT-I 2005-2007 and SALT-II 2008-2013 retrospective multicentre studies and the American DILI network.

Objectives: To estimate the evolution of the risk of DILI-induced ALFT in France in 2015-2016.

Methods: Multicentre, prospective and retrospective, case-population study focused on adults patients registered on transplant list for ALF over 2 years (2015-2016). Data are collected in 17 liver transplant centres. Cases are classified in 2 groups: ALFT "with identified non-DILI cause" (viral, autoimmune hepatitis) and ALFT with well-identified DILI cause, cases with drug exposed ALFT and undetermined ALFT. Drug exposure within 30 days prior to index date (initial symptoms of liver disease) is investigated for all cases, whatever the cause of ALFT. The risk of drug-exposed ALFT, expressed as rate per million treatment-years (tt-yrs), will be calculated using reimbursement data of EGB (permanent random sample of the national health care insurance system database). This incidence rate will be compared with that of ALFT "with identified non-DILI cause" in order to identify drugs increasing the risk of ALF.

Results: To date, 119 of 148 cases ALFT cases have been adjudicated by a hepatologist group in the 17 liver transplant participating centres. Among them, 53 cases (44.5% of ALFT) have been classified as ALFT with non-DILI cause (autoimmune hepatitis $n = 17$ (14.3%); vascular liver injury $n = 10$ (8.4%); hepatitis B $n = 8$ (6.7%); other viruses $n = 4$ (3.4%); alcoholic ALF $n = 6$ (5.0%); mushroom intoxication $n = 4$ (3.4%); other causes $n = 4$ (3.4%) and 50 cases (42% of ALFT) related to paracetamol including 30 cases (25%) with voluntary over-dosage and 21 cases (17.6%) of accidental paracetamol-DILI; 10 cases (8.4%) exposed to drugs 30 days prior to liver injury including 4 DILI with probable causality: amoxicillin (1 case), antituberculous (1 case), antiepileptics (1 case), chemotherapy (1 case), and 6 cases with possible other DILI (several concomitant drugs) and 5 cases (4.2%) not exposed to drugs 30 days prior to liver injury.

Conclusions: In France, over the years 2015-2016, the role of paracetamol in ALFT is further increasing, with a significant proportion of accidental counterpart. Other drugs account for 8.4% of ALFT. Non-identified causes is significantly reduced. The results for the whole 143 patients will be available for April 2018.

619 | Comparative risk of respiratory depression in patients treated with opioids for non-malignant pain

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Background: Opioid use for non-cancer pain has increased considerably and has been associated with fatal overdoses, the majority being unintentional. The most serious opioid-related adverse event is respiratory depression (RD).

Objectives: To assess the comparative risk of RD in new users of opioids for non-malignant pain using routinely-collected hospital electronic patient records (EPR).

Methods: Opioid users from Salford hospital EPR were identified (2014-2017). Patients with prior malignancy were excluded using ICD-10 codes. Electronic National Early Warning Scores were used to define an RD event as any one of the following: respiratory rate (RR) ≤ 8 /min, RR ≤ 10 /min and O₂ saturations $< 94\%$, RR ≤ 10 /min and altered consciousness, or dispensed naloxone use. Administered medication was categorised as opioid monotherapy or combination of opioids. Primary analysis attributed RD to opioids during a risk window of "on drug+1 day," unless patients switched to another opioid. Patients contributed follow-up time from dispensed drug start date until day after discontinuation, first RD event, death or end of hospital admission. Crude rates/1000 person-years (pyrs) and Cox proportional hazards models were used to examine comparative risk of administered opioids and RD, adjusted using propensity scores derived using inverse probability of treatment weights. Daily dose converted to MME was entered as an interaction term.

Results: 33 341 opioid users were included: 18 325 female (55%); mean age (SD) 53(20) years. There were 515 RD events on treatment. The highest crude rates (95% CI) were on fentanyl (222 [106, 465]), oxycodone (221 [182, 270]) and combination opioids (260 [224, 300]). Compared with codeine the highest unadjusted risk was observed in combination opioid (HR 3.1 [95% CI 2.4, 4.0]) and fentanyl groups (HR 3.5 [95% CI 1.6, 7.7]). Patients experienced RD on opioid doses as low as codeine 30 mg PRN; fentanyl patch 50 mcg/hr per 72 hours; oxycodone 1.25 mg QDS; tramadol 50 mg PRN. In the adjusted model using MME, compared with codeine, the adjusted HR of other opioids did not reach statistical significance.

Conclusions: Fentanyl, oxycodone, and combination opioids have the highest risk of RD; following adjustment the risk no longer remained significant. The study's strengths include physiological parameters to define RD and dispensed medications to define exposure. Access to this rich, novel data source for pharmacoepidemiological research will deliver an improved understanding of how opioids can affect patient safety.

620 | Prevalence of hospital admissions related to medication in the Netherlands between 2008 and 2013

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Background: The significant impact of hospital admissions related to medication (HARMs) in the Netherlands was shown by the HARM study. A Dutch consensus guideline containing recommendations to reduce HARMs was published in 2009.

Objectives: The aim of this study was to examine time-trends of potential HARMs and its potential preventability in the Netherlands between 2008 and 2013.

Methods: A population-based cohort study was conducted using the Dutch PHARMO Database Network. The QUADRAT computerized pre-selection was used to make a crude identification of admissions with possible HARMs in four samples (2008, 2009, 2011, and 2013). A physician and a pharmacist independently assessed these admissions with respect to causality and preventability using discharge hospital letters and drug dispensing data. Consensus was reached in case of disagreement. The net percentage of potentially preventable medication related hospital admissions for the years 2008 to 2013 was calculated. Results were stratified by age: 18-65 years (age-group 1) and 65 years and older (age-group 2).

Results: Four samples of 467 (2008), 447 (2009), 446 (2011), and 408 (2013) hospital admissions were assessed. The mean prevalence of HARMs in age-group 1 was 2.7% (95% confidence interval [CI]: 2.4-3.0%), which was approximately four times lower than in age group 2 with a mean prevalence of 10.2% (95% CI: 9.7-10.7%). The associated preventability was also lower in age-group 1 with 25.1% (18.4-31.8%) and 48.3% (95% CI: 44.8-51.8%) in age-group 2. The majority of these preventable admissions were related to fractures (29.1%), syncope's (17.0%), and gastro-intestinal (GI) complications (13.6%). The prevalence of HARMs in both groups showed a non-significant increase between 2008 and 2013 of 2.4% (95% CI: 1.9-3.0%) and 10.0% (95% CI: 9.0-11.0%) in 2008 to 3.1% (2.7-3.5%) and 10.4% (95% CI: 9.4-11.4%) in 2013.

Conclusions: The number of HARMs in the Netherlands did not decrease between 2008 and 2013 despite efforts to reduce it. Especially in the elderly population, additional measures focusing on the prevention of fractures, syncope's and GI complications are necessary.

621 | Trends in US Emergency Department visits for zolpidem-related adverse events before and after FDA Drug Safety Communications, 2010-2016

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Background: Zolpidem is a prescription medication used to treat insomnia. Based on new data, the Food and Drug Administration (FDA), in two Drug Safety Communications (DSCs) issued in 2013, recommended lowering the bedtime dose of zolpidem, especially when prescribed for women.

Objectives: To describe time trends in emergency department (ED) visits for zolpidem-related adverse events (AEs) in the United States, before and after FDA zolpidem DSCs.

Methods: We used data from an active, nationally representative sample of 59 hospital EDs participating in the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project to estimate national ED visits due to zolpidem in 2010-2016. We estimated the rates of ED visits using IMS National Prescription Audit data (2010-2016). We employed piecewise (segmented) regression to calculate average change in estimated 6-month rates of ED visits from zolpidem per 10 000 prescriptions dispensed from retail and long-term care pharmacies and used Joinpoint Regression (National Cancer Institute, Bethesda MD) to identify potential inflection points.

Results: We estimate an annual average of 9578 (95% confidence interval [CI], 7108-12 048) ED visits for zolpidem-related AEs during 2010-2016. We observed a decrease in prescription-adjusted estimated rates from 3.0 ED visits per 10 000 prescriptions in 2010 (CI, 2.0-3.9) to 1.4 per 10 000 prescriptions in 2014 (CI, 0.8-2.0); then an increase to 3.2 per 10 000 prescriptions in 2016 (CI, 2.0-4.5). The bestfit regression model of ED visits by 6-month intervals identified a single inflection point in the second half of 2014 ($p = 0.018$) with a significant decrease of 7.7% biannually from 2010 to 2014 and a non-significant increase of 20.7% biannually from the second half of 2014 through 2016. A model with 2 inflection points did not reach statistical significance ($p = 0.07$); the first segment decreased 5.6% biannually (2010 to the first half of 2013), the second segment decreased 12.8% biannually (to the second half of 2014), and the third segment increased 24.5% (to the second half of 2016). Females accounted for approximately 60% of zolpidem-related ED visits. Estimated annual rates of ED visits for males and females were similar.

Conclusions: The 2013 zolpidem DSCs and changes in prescribing practices may have either led or contributed to a short-term decline in zolpidem-related AE ED visits in 2014. However, because the

decrease in ED visit rates was not sustained, questions remain concerning the long-term impact of the FDA zolpidem DSCs.

622 | Predisposing factors, incidence, and severity assessment of antibiotic-induced hypersensitivity reactions in inpatients of a tertiary care hospital in India

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Background: Antibiotics are extensively used drugs globally including Indian hospital settings and are associated with various Adverse Drug Reactions (ADRs) including dermatologic-hypersensitivity reactions. Antibiotics-induced hypersensitivity reactions constitute nearly 6-10% of all reported ADRs.

Objectives: The aim of this study was to identify and evaluate predisposing factors, incidence, and severity assessment of antibiotic-induced hypersensitivity in hospital admitted patients receiving antibiotics in departments of Medicine, Surgery and Pulmonology of an 1800-bed tertiary-care hospital.

Methods: A prospective observational study was conducted for a period of 9 months in selected inpatient departments of a tertiary care teaching hospital. Hypersensitivity reactions were assessed for its severity, preventability, and predictability causality by using various standard causality assessment scales.

Results: A total of 25 293 patients who had received aminoglycosides ($n = 650$), penicillin ($n = 2207$), tetracyclines ($n = 5389$), quinolones ($n = 6464$), and cephalosporins ($n = 10583$) antibiotics in 9 months of study period were observed for hypersensitivity by prescription event monitoring. Sixty-two patients developed antibiotic-induced hypersensitivity, 58% were male. The most common hypersensitivity reactions were rashes (43.5%) followed by itching (20.9%) and moderate severity (89%). Incidence rates found were aminoglycosides (0.46), penicillin (0.4), cephalosporins (0.3), quinolones (0.21), and tetracyclines (0.07). There were cases who had allergic history but no alert-card resulted in same drugs being used again unknowingly and hypersensitivity reactions. Numerous other possible factors for hypersensitivity including age, gender, multiple drugs, genetic, and disease state were observed.

Conclusions: Aminoglycosides, penicillin, and cephalosporins were found to be the most commonly implicated classes of antibiotics associated with hypersensitivity. Alert-cards and medication history databases are needed for better monitoring and care of cases of hypersensitivities.

623 | Risk of cardiovascular events among COPD patients using roflumilast

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Background: Roflumilast is a phosphodiesterase-4 (PDE4) inhibitor approved for patients with severe chronic obstructive pulmonary disease (COPD) to reduce the risk of exacerbations. Previous meta-analyses suggest conflicting results related to the cardiovascular safety of the drug.

Objectives: To assess the risk of cardiovascular events among roflumilast users compared with patients on triple combination therapy of long-acting beta agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS).

Methods: An active comparator, new user retrospective cohort study was conducted using the Truven Marketscan database from Mar 2010 to Sep 2015. Patients were included if they were (1) new-users of roflumilast or LABA+LAMA+ICS (initiation between Mar 2011 and Aug 2015 with no previous use of either regimen during the 1-year baseline period); (2) at least one inpatient or two outpatient COPD diagnoses during the baseline period; (3) continuous enrollment during baseline period; and (4) aged 40 and above at index date. The index date was defined as the first dispensing of roflumilast or combination of LABA+LAMA+ICS. The outcome of interest was an incident cardiovascular event during follow-up. Cardiovascular events were defined as hospitalization with primary diagnosis code of acute myocardial infarction (AMI), ischemic stroke, or arrhythmias at discharge. The roflumilast and LABA+LAMA+ICS cohorts were followed from index date until the earliest of outcome, disenrollment, or drug discontinuation. Baseline covariates were included in logistic regression to estimate propensity scores (PS). Roflumilast and LABA+LAMA+ICS cohorts were 1:1 matched on PS using greedy matching (8→1). Cox proportional hazards model was used to calculate the hazard ratio (HR).

Results: There were 4017 roflumilast users and 50 301 LABA+LAMA+ICS users included in the cohort. After 1:1 PS matching, 8034 subjects overall were included in the final analytic cohort. Distribution of PS and all covariates included in the PS models were balanced for the roflumilast and LABA+LAMA+ICS groups. 52 roflumilast users experienced events from 1495.3 person-year at-risk (IR = 0.0348) and 41 LABA+LAMA+ICS users from 1039.7 person-year at-risk (IR = 0.0394) had events during follow-up. HR of cardiovascular events among roflumilast users compared with LABA+LAMA+ICS users was 0.94 (95% CI 0.62-1.43).

Conclusions: This study suggests that roflumilast use is not associated with increased risk of cardiovascular events compared with LABA+LAMA+ICS.

624 | The effect of inhaled corticosteroids on hair cortisol

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Background: Inhaled corticosteroids (ICS) are advertised as relative safe, but high doses may lead to adrenal suppression. Measurement of hair cortisol in scalp hair (HC) is a non-invasive tool to assess cortisol levels, but its use for studying the association between cortisol and ICS use in children is yet unknown.

Objectives: To investigate if HC measurement can be used to evaluate adrenal suppression in asthmatic children using ICS

Methods: A case-control study, with children/young adults aged 4-21 years with asthma using ICS (n = 53) and without asthma (n = 258). From all children hair samples from the posterior vertex were obtained and data on patient characteristics and drug use were collected using questionnaires. ICS dose was categorized in low/medium/high according to the GINA guidelines. HC was compared between individuals with and without asthma using a linear regression model adjusted for age, sex, and BMI; and between different levels of ICS using ANOVA.

Results: Of all children, 27 used low dose of ICS, 22 medium dose, and 4 high dose. Median HC was lower in children with asthma (1.83 pg/mg) than in children without asthma (2.22 pg/mg) (p value 0.057). Within the asthmatic children, increasing dose of ICS was associated with lower HC; median HC of 1.46 pg/mg in high doses, 1.73 in medium, and 1.84 in low doses (p value 0.54).

Conclusions: We observed trends to a lower HC in asthmatic children using ICS compared with healthy controls, and a weak negative correlation between ICS dose and HC. These findings confirm the feasibility of measuring cortisol in scalp hair and suggest that this may reflect adrenal function in asthmatic children using ICS.

625 | Occurrence of infections associated with long-term add-on therapy of oral corticosteroids in elderly patients with severe asthma: A retrospective cohort study

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Background: Add-on oral corticosteroids (OCS) have been recommended for patients with severe asthma. However, evidence of infections related to the use of OCS in real world setting is sparse.

Objectives: To evaluate the occurrence of infections associated with long-term use of OCS in elderly patients with severe asthma.

Methods: This is a retrospective cohort study using nationally representative data, named Health Insurance Review and Assessment Service-Adult Patient Sample 2015, that included medical and pharmacy claims of approximately 1 million elderly patients aged 65 or older. We included patients with severe asthma (ICD-10: J45-J46) receiving step 5 treatment of the Global Initiative for Asthma (GINA) guideline which was add-on OCS or tiotropium to the combination of inhaled corticosteroids and long-acting β_2 -agonist (ICS/LABA). Patients were identified as long-term OCS users or tiotropium users if they had filled ≥ 90 days of prescriptions with no gap of ≥ 14 days between two consecutive claims. The index date was defined as the 91st date. Pre-index period was defined as 90-day period prior to the index date. Patients who used any immunosuppressants or experienced

OCS-related infections during pre-index period were excluded. The odds of OCS-related infections during 90 days of follow-up period, including fungal infection, pneumonia, sepsis, tuberculosis, urinary tract infection, varicella infection, and bursitis were compared with OCS users and tiotropium users. Multivariate logistic regression was used to obtain the odds ratio (OR) and 95% confidence interval (CI).

Results: A total of 51 users of OCS and 181 users of tiotropium were identified. The odds of developing associated any infections were slightly higher but not significant in OCS users compared with those in tiotropium users (OR: 1.50, 95% CI: 0.67-3.36). In sub-group analysis, the odds of developing pneumonia were slightly lower (OR: 0.78, 95% CI: 0.30-2.00) and developing fungal infection were higher (OR: 2.30, 95% CI: 0.89-6.00) in OCS users compared with tiotropium users but both were not significant.

Conclusions: Using a representative claims data, long-term add-on therapy of OCS was not associated with increased odds of infection compared with long-term add-on therapy of tiotropium in elderly patients with severe asthma.

626 | The effect of inhaler switching on asthma and COPD patients

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Background: Inhalers are very expensive and therefore often changed for financial reasons, the health impact of this is unclear.

Objectives: To estimate the association between non-clinical inhaler switching and exacerbations (acute worsening of respiratory symptoms) in asthma or COPD patients.

Methods: We used a self-controlled case-series design in a population of asthma or COPD regular inhaler users. Non-clinical switches were defined as same drug class, dose, and no clinical indication. The "risk period" was defined as 3-month post-switch; the "baseline period" was the rest of the observation time: 1-year pre-switch and 9-month post-risk period. Data sources were UK electronic health care records (Clinical Practice Research Datalink) linked to hospital data (Hospital Episodes Statistics), 2000 to 2016.

Results: There were 5242 patients, of whom 81% had asthma, 45% were males, and median age was 68 years. Most switches were between inhaled corticosteroids (ICS, 41%) or long-acting beta-agonist/ICS combination inhalers (LABA/ICS, 35%), and between generic to brand (46%) or brand to generic (33%). Over 95% were kept on the switched-inhaler. The age-adjusted incidence rate ratio (IRR) of an exacerbation during the risk period compared with the baseline period was 0.77 (95% CI 0.70-0.84); this was unaffected by gender, airways disease diagnosis (asthma/COPD), drug class, device type (dry powder/metered dose), or generic/brand (likelihood ratio test, $p > 0.05$).

Conclusions: Non-clinical inhaler switching was associated with a reduced exacerbation risk in COPD and asthma patients; this was not altered by drug class, airways disease diagnosis, inhaler device, or generic/branding. These findings may suggest switching to equivalent cheaper inhalers is a safe option, when cost savings are necessary

627 | Treatment patterns and survival among elderly patients with selected lymphomas—Findings from medicare claims data

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Background: With the advent of novel drug therapies for the treatment of lymphoma, there is a need for recent data on utilization and outcomes, especially among the elderly who tend to be underrepresented in many real-world databases.

Objectives: To assess rates of drug treatment and survival among elderly patients with newly diagnosed lymphomas using Medicare claims data.

Methods: Using data from the Medicare 5% claims files from 2010-2016, we identified patients 66+ years of age with selected lymphomas (NHL and others) and at least 1 year of Medicare eligibility in the prior 12 months with no lymphoma diagnoses in the same period. Patients were followed from diagnosis until death or end of the data. Treatment (injectable therapies only) was assessed in terms of chemotherapy alone (C), rituximab alone (R), and chemotherapy plus rituximab. The main outcome of interest was overall survival (OS). Kaplan-Meier curves were estimated for survival, stratified by treatment. In addition, a Cox proportional hazard model was estimated using patient characteristics and treatment variables for predicting survival. All analyses were undertaken using the Instant Health Data (IHD) platform (BHE, Boston, Massachusetts) and the R programming language.

Results: From 41 120 lymphoma patients identified between 2010 and 2016, we identified 5124 who met cohort inclusion criteria (mean age 76 years, 49% female, 93% White). Fifty-five percent (2832) of these patients were treated (median time to treatment was 40 days): C (579); R (455); R + C (1798). On an unadjusted basis, median OS was 28, 34, and 32 months for C, R, and R + C, respectively. In multivariate analyses, male gender, older age, and higher comorbidity were associated with higher mortality, while use of R + C (HR: 0.67; 95% CI: 0.58-0.76) and R (HR: 0.53; 95% CI: 0.44-0.64) were associated with better survival.

Conclusions: Among elderly lymphoma patients, the novel treatment rituximab (alone or with chemotherapy) was found to improve survival, with findings similar to other analyses using US claims and cancer registry data.

628 | Antiepileptic drug use and dementia risk—Analyses of Finnish health register and German health insurance data

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Background: Treatment with antiepileptic drugs (AED) is an effective way for controlling epileptic seizures. There are several publications that report acute cognitive adverse effects (CAE) of AEDs. However, the association of AED use and risk of dementia in the aged population has seldom been investigated. To our knowledge, there is only one study so far that analyzes the link between AED use and incident dementia risk. **Objectives:** To evaluate the association between AED use and incident dementia in Finnish health care register and German health insurance data.

Methods: We conducted case-control analyses in both datasets separately and evaluated the association between long-term and regular AED prescription (at least 12 months) and dementia. We further grouped the AEDs into those with and without CAE. Cases with Alzheimer's disease (AD; Finnish data, N = 70,718) and dementia of any type (German data, N = 20,325) were matched with up to four controls without dementia/AD. We introduced a lag time of 2 years between AED prescription and dementia diagnosis to address potential protopathic bias. Odds ratios were evaluated applying conditional logistic regression with adjustment for potential confounding factors such as comorbidities and polypharmacy.

Results: Regular use of AEDs was associated with a significantly increased risk of incident dementia (adjusted OR 1.28, 95% confidence interval [CI] 1.14-1.44) and AD (adjusted OR 1.15, 95% CI 1.09-1.22) compared with no AED prescription. There was also a trend for increased risk for dementia with higher doses. When we compared AEDs with and without known CAE, we detected a significantly increased risk for any dementia and for AD for substances with known CAE (OR: 1.59, 95% CI 1.36-1.86 for any dementia, and OR 1.19, 95% CI 1.11-1.27 for AD), but not for AEDs without known CAE.

Conclusions: The restricted use of AEDs, especially those with known CAE, may contribute to dementia/AD prevention among older persons.

629 | Preadmission antithrombotic therapy and risk of blood transfusion and 30-days mortality following hip fracture surgery: A Danish nationwide cohort study

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Background: Hip fracture is associated with high bleeding risk and mortality. The patients are often elderly and comorbid requiring various drugs; however, little is known about the effect of ongoing antithrombotic therapy on clinical outcomes among patients undergoing hip fracture surgery.

Objectives: To examine if preadmission therapy with non-vitamin K antagonist oral anticoagulant (NOAC), vitamin K antagonist (VKA), and antiplatelets is associated with the use of blood transfusion and 30-day mortality among hip fracture patients.

Methods: A nationwide cohort study was performed. We identified 74 791 patients aged ≥ 65 years who underwent hip fracture surgery during 2005-2016 in the Danish Hip Fracture Database. By comparing current and former users with non-users of antithrombotic therapy at the time of hospital admission, including NOAC, VKA, and antiplatelets, relative risks (RRs) with 95% confidence intervals (95% CIs) for red blood cell transfusion within 7 days of hip fracture surgery and hazard ratios (HRs) and 95% CIs for 30-days mortality were calculated. Results were presented as unadjusted and adjusted for age, gender, BMI, CCI, type of fracture, surgery delay, year of surgery, and other prescription medicine.

Results: In total, 29 792 hip fracture patients (39.8%) were on antithrombotic therapy upon admission; 1.4% were current users of NOAC, 5.6% were current users of VKA, and 32.9% were current users of antiplatelet drugs. Following hip fracture surgery, 45.3% received blood transfusion and 10.6% died within 30 days. NOAC treatment at time of hip fracture admission was associated with a slightly increased risk of transfusion, as the adjusted RR was 1.07 (95% CI 1.01-1.14) in current users compared with non-users. NOAC use was not associated with increased mortality; adjusted HR was 0.88 (95% CI 0.75-1.03) in current users compared with non-users. There was no association between use of VKA and transfusion or mortality. In contrast, antiplatelet treatment was associated with increased risk of both transfusion (RR 1.15, 95% CI 1.12-1.18) and 30-day mortality (HR 1.18, 95% CI 1.14-1.23) when comparing current users with non-users.

Conclusions: Ongoing NOAC and VKA therapy at the time of admission for hip fracture appears not to be associated with any clinically significant increased risk of transfusion or 30-day mortality. In contrast, use of antiplatelet drugs was associated with a higher risk of transfusion and 30-day mortality.

630 | Examining the risk of major gastrointestinal bleeding events in older people using antithrombotics: A nationwide study using a self-controlled case-series design

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Background: Antithrombotics can significantly reduce the risk of stroke associated with atrial fibrillation and acute coronary syndromes.

Real-world evidence for the safety of using antithrombotics in older people with multimorbidity is limited.

Objectives: The overarching objective of this study was to examine the risk of gastrointestinal (GI) bleeding events associated with aspirin, antiplatelets, anticoagulants, or combinations of these antithrombotics in older New Zealanders aged 65 and above at a population-level.

Methods: Using a self-controlled case-series design and national-level prescription and diagnosis databases, we identified 3378 individuals aged 65 and above, who had been diagnosed for the first time with GI-bleeding, between 01/01/2005 and 31/12/2014. For each individual, prescription intervals of drugs including aspirin, antiplatelets, and anticoagulants were mapped onto a timeline. The timeline was partitioned into intervals of different exposure combinations including non-exposure. The date of the first GI-bleeding event was mapped onto the partitioned timeline. Conditional Poisson regression (CPR) was used to estimate the changed risk of GI-bleeding due to the aforementioned antithrombotics as incident rate ratios (IRR). Multivariable CPR model was used to estimate the adjusted IRRs, to account for the use of other drugs that change the risk of GI-bleeding.

Results: Amongst the 3378 individuals, 78% ($n = 2624$) had a first-time GI-bleeding event following exposure to aspirin, antiplatelets, anticoagulants, or combinations of these antithrombotics. Concomitant exposure to anticoagulants and antiplatelets was associated with a higher GI-bleeding risk (adjusted IRR = 4.19, 95% CI = [1.78, 9.86]) compared with exposures to only one of the two antithrombotics. Concomitant exposure to all three antithrombotics was associated with highest increase of GI-bleeding risk (adjusted IRR = 10.02, 95% CI = [5.51, 18.21]).

Conclusions: Our analysis suggests that the risk of GI-bleeding was higher in older people who had concomitant exposures to combinations of aspirin, antiplatelets, and anticoagulants, compared with those exposed to only one of these antithrombotics. The findings inform the significant risk of GI-bleeding posed by the concomitant use of antithrombotics in older people where clinical trials do not provide adequate evidence of safety of using combinations of antithrombotics in this vulnerable population.

631 | Association of statins with functioning, rehospitalization, and mortality in frail older adults

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Background: Many studies have examined the effects of statins after acute myocardial infarction (AMI), but nearly all excluded frail older nursing home (NH) residents and few examined functional outcomes. The effect of statins on muscle pain, muscle fatigue, weakness, and functional decline is controversial and remains unclear. NH residents may benefit less from statins and be particularly susceptible to adverse drug events like muscle symptoms.

Objectives: To evaluate the effect of statins after AMI on 1-year functional decline, rehospitalization, and death among frail older adults in the NH setting.

Methods: We conducted a retrospective cohort study using a national US sample of 11 192 NH residents aged 65 and older who were statin nonusers for at least 12 months were hospitalized for AMI between May 2007 and March 2010 and subsequently returned to the NH. The dataset was linked Medicare claims, Minimum Data Set clinical assessments, and NH facility data. Outcomes included functional decline, rehospitalization, and death. Functional status was measured with the Morris scale of independence in activities of daily living. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and calculate 1-year restricted mean survival times (RMSTs) for outcomes comparing statin new users with nonusers after 1:1 propensity score matching. Fine and Gray competing risk regression models were used in stability analyses to assess the influence of death on functioning and rehospitalization estimates.

Results: Propensity-score matching yielded a cohort of 5440 NH residents. The mean age was 83 years, 69% were female, and 47% had at least moderate cognitive impairment. There were 1608 functional decline, 5180 rehospitalization, and 4693 death events. Statin use was associated with reduced mortality (HR 0.80, 95% CI 0.73-0.87; RMST 15.93 days, 95% CI 9.89-21.98), but no difference in rehospitalization (HR 1.06, 95% CI 0.98-1.14; RMST -4.25 days, 95% CI -11.64-3.14) or functional decline (HR 1.00, 95% CI 0.88-1.14; RMST -0.47 days, 95% CI -6.30-5.35). Fine and Gray estimates for rehospitalization (HR 1.06, 95% CI 0.99-1.15) and functional decline (HR 1.05, 95% CI 0.93-1.19) were similar to those from the main analyses.

Conclusions: NH residents who used statins had better 1-year survival, but no difference in functional decline or rehospitalization.

632 | Long-term thiazide use and risk of fractures among persons with alzheimer's disease-nested case-control study

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Background: Due to reduced renal calcium excretion and consequent increase in bone mineral density, thiazide diuretics may reduce risk of fractures.

Objectives: Objective of our study was to investigate the association between thiazide use and risk of any fracture, hip fracture and upper extremity fracture among community-dwelling persons with Alzheimer's disease.

Methods: Fracture cases were identified from the MEDALZ study, including all community-dwelling persons diagnosed with Alzheimer's disease in Finland 2005-2011 (mean age 80.1 years, 65.2% women). During the follow-up from AD diagnoses until the end of 2015, cases

with any fracture (N = 11 731), hip fracture (N = 7016), and upper extremity fracture (N = 8675) were identified. Fracture cases were matched with up to 2-3 controls without that specific fracture, at the date of fracture for the case which was assigned as the index date. Controls were matched according to time since AD diagnosis (proxy for duration of the disease), age, and gender. Thiazide use identified from the Prescription register data was modelled with PRE2DUP method. Current use was defined in 0- to 30-day time window before the index date and the duration of current use was assessed. The association between thiazide exposure and fractures was assessed with conditional logistic regression models, by adjusting for comorbid conditions.

Results: Current thiazide use was observed in 10.7% of any fracture cases and 12.8% of their controls. Current thiazide use was associated with a decreased risk of any fracture (adjusted OR [aOR] 0.81, 95% CI 0.75-0.88). When assessed according to the duration of thiazide use, long-term use (more than 3 years) was associated with reduced fracture risk while the shorter use was not. Over 5 years of use was associated with reduced risk of any fracture (aOR 0.74, 95% CI 0.67-0.83), hip fracture (aOR 0.74, 95% CI 0.64-0.86), and upper extremity fracture (aOR 0.74, 95% CI 0.66-0.84).

Conclusions: Thiazides are associated with a substantially reduced risk of fractures. The protective effect increases with the longer durations of thiazide use.

633 | The impact of CYP2D6 mediated drug-drug interaction in elderly: Co-prescription of metoprolol and paroxetine/fluoxetine

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Background: Co-prescription of paroxetine/fluoxetine (a strong CYP2D6 inhibitor) in metoprolol (a CYP2D6 substrate) users is common, but data on the clinical consequences of this drug-drug interaction are limited and inconclusive.

Objectives: To assess the effect of paroxetine/fluoxetine initiation on the existing treatment with metoprolol on the discontinuation and dose adjustment of metoprolol among elderly.

Methods: We performed a cohort study using the University of Groningen IADB.nl prescription database (www.IADB.nl). We selected all elderly (≥ 60 years) who had ever been prescribed metoprolol and had a first co-prescription of paroxetine/fluoxetine, citalopram (weak CYP2D6 inhibitor), or mirtazapine (negative control) from 1994 to 2015. The exposure group was metoprolol and paroxetine/fluoxetine co-prescription, and the other groups acted as controls. The outcomes were early discontinuation and dose adjustment of metoprolol. Logistic regression was applied to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI).

Results: Combinations of metoprolol-paroxetine/fluoxetine, metoprolol-citalopram, and metoprolol-mirtazapine were started in 528, 673,

and 625 patients, respectively. Compared with metoprolol-citalopram, metoprolol-paroxetine/fluoxetine was not significantly associated with the early discontinuation and dose adjustment of metoprolol (OR = 1.07, 95% CI: 0.77-1.48; OR = 0.87, 95% CI: 0.57-1.33, respectively). In comparison with metoprolol-mirtazapine, metoprolol-paroxetine/fluoxetine was associated with a significant 43% relative increase in early discontinuation of metoprolol (OR = 1.43, 95% CI: 1.01-2.02) but no difference in the risk of dose adjustment. Stratified analysis by gender showed that women have a significantly high risk of metoprolol early discontinuation (OR = 1.62, 95% CI: 1.03-2.53).

Conclusions: Paroxetine/fluoxetine initiation in metoprolol prescriptions, especially for female older patients, is associated with the risk of early discontinuation of metoprolol.

634 | Potential omissions of angiotensin inhibition treatment among older US adults after an acute myocardial infarction

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Background: Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) are recommended for secondary prevention in all patients after an acute myocardial infarction (AMI). Potential omission of angiotensin inhibition (POAI) among eligible older adults was included in the screening tool to alert to right treatment (START) criteria, version 2. Limited data on the burden of POAI after AMI in the United States is available using the START criteria.

Objectives: To describe the prevalence and determinants of POAI in older US adults after AMI.

Methods: We used a national 20% random sample of Medicare beneficiaries with fee-for-service coverage in Parts A, B, and D in at least 1 month from 2008-2014 to identify all patients with AMI. POAI was defined according to v2 of the START criteria for MI. We excluded beneficiaries with contraindications to ACEIs or ARBs (eg, codes for hyperkalemia, renal failure, and angioedema) during the 12 months prior to AMI. We calculated POAI prevalence within 4 months after AMI. We identified demographic characteristics, health care utilization, and comorbidities as predictors of POAI using multi-variable logistic regression.

Results: A total of 21 108 observations were included. The mean $\pm$ SD age was 77.2 ± 8.0 years, 54% were women, and 91% were white. The prevalence of POAI during the study period was 48% (95% CI: 47.7-49.0). The strongest predictors of POAI were age (PR 1.17; 95% CI 1.11-1.22; 85 years and older vs 66-69 years), number of medications (10 or more medications, prevalence: 54%; PR 0.48; 95% CI: 0.45-0.51 vs 1-2), number of outpatient visits within the previous 12 months (13 or more, prevalence: 64%; PR

1.27; 95% CI: 1.19-1.34 vs none), geriatrician prescriber (prevalence: 67%; PR 1.17; 95% CI 1.13-1.20), dementia (prevalence: 86%; PR 1.23; 95% CI: 1.17-1.29), and moderate liver disease (prevalence: 55%; PR 1.35; 95% CI: 1.13-1.60).

Conclusions: Approximately one in two older US people without contraindication did not fill a prescription for ACE/ARB within 4 months after an AMI between 2008 and 2014. POAI could represent high-quality care, based on individualized assessment of potential benefit and harm. Predictors of POAI could be used to target and assess potential interventions to improve care among older US people after AMI.

635 | Potential omissions of oral anticoagulant among older US adults with newly diagnosed atrial fibrillation

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Background: Atrial fibrillation (AF) is a major risk factor for ischemic stroke, and anticoagulation is recommended for the majority of older adults with AF.

Potential omission of oral anticoagulants (POOA) among eligible older adults increases risk of adverse outcomes, and thus was included in the screening tool to alert to right treatment (START) criteria, version 2. Limited data on the burden of POOA among older adults with AF in the United States is available using the START criteria.

Objectives: To describe the prevalence and determinants of POOA in older US adults with AF.

Methods: We used a national 20% random sample of Medicare beneficiaries covered by fee-for-service Parts A, B, and D in at least 1 month from 2008-2014 to identify patients with new onset AF. We excluded beneficiaries with contraindications to both warfarin and new oral anticoagulants (NOAC) (eg, codes for history of aneurysm, blood dyscrasias, and hemorrhage). We calculated prevalence of POOA within 4 months after newly diagnosed AF. We identified demographic characteristics, health care utilization, and comorbidities as predictors of POOA using multivariable logistic regression.

Results: A total of 110 832 older adults with new onset AF were included. The mean $\pm$ SD age was 79.0 ± 7.9 years, 60% were women, and 92% were white. The prevalence of POOA during the study period was 57% (95% CI: 56.6-57.2). The strongest predictors of POOA were age (PR 1.13; 95% CI: 1.11-1.15; older than 85 years vs 66-69 years), number of medications (10 or more medications; prevalence: 54%, PR 0.77; 95% CI: 0.75-0.79; vs 1-2), number of outpatient visits within the previous 12 months (13 or more; prevalence: 64%; PR 1.33; 95% CI: 1.31-1.35; vs none), and dementia (prevalence: 86%, PR 1.37; 95% CI: 1.35-1.39).

Conclusions: POOA is highly prevalent among older US people with new onset AF between 2008 and 2014. POOA prevalence and their predictors are a valuable tool to assess quality of care and to target and assess potential interventions to improve care. Future research will examine potential adverse outcomes of transient ischemic attack and stroke among this cohort.

636 | Concomitant sedative and opioid use: A dose response analysis

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Background: Older adults with chronic obstructive pulmonary disease (COPD) are at heightened risk for medication-induced respiratory depression. Despite concerns around opioid and other prescription drug abuse, prescription opioids and sedatives are frequently prescribed—alone and in combination—in the COPD population. Concomitant opioid and sedative use run the risk of exposing older adults with COPD to serious adverse events.

Objectives: To examine the association of opioid and concomitant opioid + sedative use with risk of respiratory events and death in older adults with COPD.

Methods: A retrospective study of a 5% nationally representative sample of Medicare beneficiaries. We included COPD patients aged 65 and older with continuous Parts A, B, and D enrollment during follow-up who had at least one opioid prescription filled between 1/1/2010-12/31/2013. We excluded beneficiaries resided in nursing homes or had cancer diagnoses. The main exposures were (1) opioid prescriptions and or (2) concomitant opioid and sedative prescriptions. The index date is the first date of opioid prescription, with 6 months follow-up or until death. We used a new-user design, requiring 6 months without opioid use. Concomitant users were categorized by total days overlap between opioids and sedatives. Outcomes included all-cause mortality and respiratory events (COPD exacerbations, respiratory depression) within 3 days of drug use. An adjusted Cox proportional hazards model was used to estimate hazard ratios of main outcomes.

Results: The study cohort ($n = 6747$) of COPD patients with opioid use were 63.6% female, 83.5% white, and had a median age of 80 years. More than 1 in 10 ($n = 737$) beneficiaries had concomitant opioid + sedative use. Beneficiaries received a median of 30 days opioid exposure, with a median morphine equivalent daily dose (MEDD) of 29 mg. We observed 111 (11.3%) and 988 (12.7%) respiratory events, and 417 (42.5%) and 2395 (30.9%) deaths in concomitant and opioid only users, respectively. Compared with non-concomitant users, respiratory events, and death increased (hazard ratio HR = 1.28, $p = 0.57$, 95% CI = 0.39-2.18; and HR = 1.17, $p = 0.48$, 95% CI = 0.76-1.69) with 20-30 days concomitant users. Higher MEDD (>90 mg) and total opioid days supplied (>30 days) were predictors of respiratory events (HR = 1.9, $p = 0.05$ and HR = 1.7, $p = 0.01$) and death (HR = 1.8, $p = 0.01$ and HR = 1.6, $p = 0.01$).

Conclusions: Risk of death and respiratory events among COPD patients with concomitant opioid and sedative use increase by concomitant use, MEDD, and total opioid days supplied

637 | Selective serotonin reuptake inhibitor use and adverse outcomes and quality of care in hip fracture patients

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Background: Many elderly hip fracture patients receive selective serotonin reuptake inhibitor (SSRI) treatment, which has been subject to concerns about adverse effects.

Objectives: To examine the association between SSRI use and mortality, postoperative complications, and quality of in-hospital care in elderly hip fracture patients.

Methods: Design: cohort study using Danish medical registries. Setting: the health care system in Denmark is tax funded, and all citizens have equal access to health care. In total, 68 487 hip fracture patients aged 65 years or older were identified between 2006 and 2016. Exposure: current SSRI users redeemed at least one prescription within 90 days, former users redeemed at least one prescription within 91-365 days, and non-users had no SSRI prescriptions within 365 days before hip fracture surgery. Main outcome measures: 30-day mortality, postoperative complications including any readmission, any reoperation, venous thromboembolism, myocardial infarction, stroke, and bleeding, and quality of in-hospital care represented by nine process-performance measures. Statistical analysis: Patients were followed from operation date until an adverse event or up to 30 days. Crude and adjusted hazard ratios (HRs) for mortality and postoperative complications and relative risks (RRs) for quality of in-hospital care with 95% confidence intervals (CIs) were estimated comparing current and former SSRI users with non-users.

Results: In total, 13 272 (19%) hip fracture patients were current SSRI users, 2777 (4%) were former users, and 52 438 (77%) were non-users. The 30-day mortality was 13% in current users (HR 1.16, CI 1.10 to 1.21) and 12% in former (HR 1.15, CI 1.04 to 1.27) compared with 10% in non-users. The HR for any readmission was 1.11 (CI 1.02 to 1.20) in current and 1.13 (CI 1.01 to 1.27) in former users and for any reoperation 1.21 (CI 1.11 to 1.31) in current and 1.04 (CI 0.84 to 1.28) in former users compared with non-users. The risk of other postoperative complications were similar irrespective of SSRI use. No association between SSRI use and quality of in-hospital care was found.

Conclusions: In patients undergoing hip fracture surgery, 30-day mortality and overall readmission risk were elevated in both current and former SSRI users compared with non-users. Those currently using SSRI had an increased reoperation risk compared with non-users. However, SSRI use was not associated with increased risk of postoperative complications and lower quality of in-hospital care.

638 | Antiepileptic drugs and accumulation of hospital days among persons with Alzheimer's disease

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Background: Antiepileptic drug (AED) use among older persons may lead to adverse drug events and therefore to higher number of hospital days.

Objectives: To compare the accumulation of hospital days between AED initiators and non-initiators among persons with Alzheimer's disease (AD) as well as between individual AEDs.

Methods: We conducted an exposure-matched cohort study on persons newly diagnosed with AD in 2005-2011 (n = 70 718) as identified from Finnish health care registers. AED initiation was measured from the Finnish Prescription register. For each AED initiator, one non-initiator matched on age, sex, and time since AD diagnosis was selected. Accumulation of hospital days was measured from the care register for health care during a 2-year follow-up. Association between AED initiation or use of individual AEDs and accumulation of hospital days was assessed using negative binomial model.

Results: AED initiators (n = 4878) were hospitalized on average for 42.3 (SD: 87.9) days and matched non-initiators for 28.0 (SD: 66.0) days during the 2-year follow-up. Zero hospital days were observed for 31.4% of the AED initiators and for 41.4% of the non-initiators. Expected number of accumulated hospital days during the follow-up was 52% higher (adjusted incidence rate ratio, IRR: 1.52; 95% confidence interval, CI: 1.38-1.67) among AED initiators than the non-initiators. Similar associations were observed for general and specialized health care, as well as for different specialties. Among pregabalin (adjusted IRR: 0.61, 95% CI: 0.52-0.72), gabapentin (adjusted IRR: 0.59, 95% CI: 0.44-0.80), and clonazepam (adjusted IRR: 0.72, 95% CI: 0.54-0.96) initiators the number of expected accumulated hospital days was 28%-41% lower than the days accumulated by initiators of valproic acid.

Conclusions: AED initiators are at increased risk of higher number of hospital days than non-initiators. Pregabalin and gabapentin were associated with lower number of hospital days than valproic acid.

639 | Impact of Drug Burden Index on adverse health outcomes in Irish community-dwelling older people: A cohort study

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Background: The Drug Burden Index (DBI) is a validated tool to quantify individual exposure to anticholinergic and sedative medications. The prevalence and impact of DBI exposure on health outcomes in the older Irish population has not been reported.

Objectives: To determine the prevalence of exposure to DBI medications and to examine the association between DBI exposure and adverse health outcomes in a national cohort of Irish community-dwelling older people.

Methods: This study was based on data from Wave 1 (2009/2010) of the Irish Longitudinal Study on Ageing (TILDA), a nationally representative cohort study of ageing, with linked pharmacy claims data. Individuals aged ≥ 65 years participating in TILDA who completed the computer-assisted personal interview (CAPI) and enrolled in the General Medical Services scheme were included. DBI exposure was determined by applying an Irish-adapted DBI medication list, and the DBI formula, to participants' medication dispensing data in the year prior to the time period specified for the outcome measure. Outcome measures referring to the 12 month period prior to the CAPI included any falls, any hospital admissions, and quality of life (QOL, CASP-19 measure). Outcome measures referring to the time of the CAPI included any impairment of instrumental activities of daily living (IADL, Barthel Index) and any frailty (Fried model). The associations of DBI exposure, tested as a categorical variable (none [0], low [>0 to <1], and high [≥ 1]), with outcome measures were analysed using multivariate logistic or linear regression after adjusting for confounders of age, sex, comorbidity, polypharmacy, education level, and depression.

Results: On average, 61.3% ($n = 1946$) of participants received at least one DBI prescription in the year prior to outcome measures. Any DBI exposure ($\text{DBI} > 0$) was significantly associated with falls (adjusted OR 1.41, 95% CI 1.09–1.82), frailty (adjusted OR 1.41, 95% CI 1.08–1.85), and reduced QOL ($P < 0.001$). IADL impairments were significantly associated with high DBI exposure ($\text{DBI} \geq 1$) vs none (adjusted OR 2.97, 95% CI 1.92–4.61). There was no significant association between DBI exposure and hospital admission ($P = 0.13$).

Conclusions: The majority of older Irish people are exposed to at least one DBI medication in any year. DBI exposure was associated with several negative health outcomes. Interventions to reduce inappropriate use of DBI medications in older patients may be an appropriate step forward to improve health outcomes in this population.

640 | Psychotropic drug use and psychotropic polypharmacy among persons with Alzheimer's disease

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Background: Psychotropic drugs are frequently used for the treatment of behavioural and psychological symptoms of dementia in persons with Alzheimer's disease (AD). Evidence for benefits are limited and

concerns have been raised about the safety, especially for the concomitant use of multiple psychotropic drugs.

Objectives: The objective of this study was to investigate prevalence of psychotropic drug and psychotropic polypharmacy (PPP) use and associations with PPP among persons with and without AD, from 5 years before until 4 years after AD diagnosis at time points every 6 months.

Methods: The study was a part of the nationwide MEDALZ study, including all community-dwelling persons who received a clinically verified diagnosis of AD between 2005 and 2011 in Finland ($n = 70\,719$). Drug exposure was modelled with PRE2DUP method based on purchases recorded in the prescription register (1995–2015). Point prevalence of antipsychotic, antidepressant and benzodiazepine, and related drug use was measured at 6 months time intervals, beginning 5 years before AD diagnoses and until 4 years after. Factors associated with PPP (use of 2 or more psychotropic drugs) were investigated with logistic regression.

Results: The prevalence of psychotropic drug use, especially use of antipsychotics and antidepressants, increased during the course of AD. The use of 2 or more psychotropic drugs increased from 5.9% 5 years before to 18.3% 4 years after AD diagnosis. The most frequently used combination was antipsychotics and antidepressants. Predictors for PPP were younger age (less than 75 years), female sex, and history of psychiatric disease. The use of acetylcholinesterase inhibitors was inversely associated with PPP. Four years after AD diagnosis, almost 50% of persons with AD used at least one psychotropic drug.

Conclusions: The high prevalence of psychotropic polypharmacy is concerning because of possible higher risks for adverse effects and events.

641 | Potentially inappropriate medication use and incident dementia in privately-insured older adults

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Background: The impact of potentially inappropriate medication (PIM) use on development of dementia in the elderly population is an area of critical concern among clinicians and researchers; however, the relationship between PIM-related drug and disease interactions (DDI and DZI, respectively) and cognitive function remains poorly characterized.

Objectives: To evaluate the association of PIM use and PIM-related DDI/DZI with incident dementia in older adults.

Methods: Using data from Truven Health Marketscan Research Database (2013–2015), we conducted a retrospective cohort study to investigate the association between PIM use and PIM-related DDI/DZI (defined using 2015 Beers' Criteria) and incident dementia. PIM exposure was measured in the year prior to dementia diagnosis or

the last year of the study period. Inclusion required subjects to be aged 65 years or older and continuously enrolled 2013-2015. We used logistic regression (generating odds ratios [OR] and 95% confidence intervals [CI]) to measure the association between PIM use and PIM-related DDI/DZI and incident dementia, adjusted for comorbidities and demographics.

Results: 487 866 subjects met inclusion criteria (54.5% female, mean age 77.3). When controlling for demographics and comorbid conditions, use of any PIM was associated with incident dementia (OR = 2.10; 95% CI 2.06-2.16). Considered individually, all PIMs in Beers' criteria were associated with increased odds of incident dementia, with the strongest predictor being antipsychotic use (OR = 5.14; 95% CI 4.93-5.36). Among subjects who used PIMs, having a PIM-related DDI was associated with increased odds of incident dementia, with the strongest predictor being antipsychotic use with two or more CNS-active drugs (OR = 4.45; 95% CI 4.18-4.73). Specific PIM use for certain comorbidities also increased odds of incident dementia, with the strongest predictor being use of Beers' specified PIMs in subjects with syncope (OR = 9.08; 95% CI 8.57-9.63).

Conclusions: Our study suggests an association between PIM use and PIM-related DDI/DZI and incident-dementia. Further research should investigate the underlying biological plausibility of this association, especially for medications that do not act on the central nervous system. Understanding the further complexities of PIM use may aid in the design of interventions to lessen cognitive burden and reduce PIM use in the aging population at risk for dementias.

642 | Potentially inappropriate medication use and emergency department visits in older women diagnosed with breast cancer initiating chemotherapy

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Background: Potentially inappropriate medications (PIMs) are drugs where the risk of treatment could outweigh potential benefits, when safer alternatives are available. Older women with breast cancer exposed to chemotherapy use a variety of concomitant medications, some of which are designated as PIMs. Yet the impact of PIM exposure on the risk of chemotherapy-related toxicity is unclear.

Objectives: Among breast cancer patients initiating chemotherapy, we evaluated the association between PIM use measured during the month of cancer diagnosis with 6-month all-cause emergency department (ED) visits following chemotherapy initiation.

Methods: We used the Surveillance, Epidemiology, and End Results (SEER) program-Medicare database, containing cancer registry and Medicare enrollment and claims data, to identify older women diagnosed with a first, primary breast cancer at age 66+ years from 2007-2011. All women underwent breast-directed surgery within 90 days from diagnosis and initiated adjuvant chemotherapy within 90 days from surgery. ED visits were ascertained during the 6-month

period following chemotherapy initiation. Linear-risk models were used to estimate crude and adjusted risk differences (aRD) and 95% confidence intervals (CIs).

Results: Among 2401 breast cancer patients, 21% visited an ED within 6 months of initiating adjuvant chemotherapy. In total, 725 women (30%) were exposed to at least one PIM during the month of cancer diagnosis at a mean age of 72 years. Correlates of PIM use (versus no PIM use) during the month of diagnosis included use of 5+ medications in the month prior to diagnosis (40% vs 20%), having a CCI score of 2 or higher (20% vs 10%), or having a predicted probability of frailty >10% (21% vs 13%). The crude RD for 6-month ED visits comparing PIM exposed with unexposed patients was 0.01 (95% CI: -0.02, 0.05). After adjusting for age, race, marital status, stage at diagnosis, claims-based predicted frailty, CCI, and medication burden, the aRD was -0.01 (95% CI: -0.05, 0.03). No differences were observed in crude and aRDs for 1-, 2-, and 3-month ED visits.

Conclusions: Overall, one in five women visited an ED in the 6-months following chemotherapy initiation. However, we found no association between exposure to PIM in the month of cancer diagnosis and 6-month risk of an ED visit following chemotherapy initiation. Future work should evaluate the time-varying association between PIM exposure and ED visits during chemotherapy.

643 | Comparative mortality risks of antipsychotic augmentation in treatment-resistant depression patients

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Background: Augmenting antipsychotics to antidepressant therapies was one of the strategies for elderly patients with treatment-resistant depression (TRD). However, concerns of increased mortality risks in the patients receiving antipsychotics are not negligible.

Objectives: To compare the risk of mortality in patients with TRD augmenting different antipsychotic agents to antidepressant therapies.

Methods: This is a retrospective cohort study using Taiwan's National Health Insurance Research Database from 2004 to 2013. We identified a cohort of patients with TRD aged 55 and older who newly augmenting antipsychotic to antidepressant treatments. We followed patients for a year and performed intention-to-treat analysis to compare the rates of all-cause mortality among different antipsychotic augmentations. Hazard ratios (HR) were derived from Cox proportional hazard models with adjustments of covariates such as age, sex, and baseline antidepressants. We selected quetiapine as reference group because it was the most prevalent used antipsychotics for elderly patients with TRD in Taiwan.

Results: We identified a cohort of 70 065 patients with mean age of 69.8 (± 9.8) years and 63% were female. Most patients received add-on antipsychotic therapy with quetiapine (38.04%), sulpiride (18.18%), and risperidone (11.78%). We found the mortality risks were higher in haloperidol (adjusted hazard ratio, 1.27; 95% CI, 1.21-1.34) and risperidone (1.19; 1.13-1.25) and were lower in trifluoperazine (0.58; 0.51-0.65), sulpiride (0.79; 95% CI, 0.74-0.83), and aripiprazole (0.73, 95% CI 0.61-0.88) compared with quetiapine group.

Conclusions: Considering the risk profiles of mortality, we found trifluoperazine, sulpiride, and aripiprazole could be better antipsychotic alternatives for quetiapine to add on antidepressant therapies for TDR patients.

644 | Polypharmacy and frailty in a longitudinal community-based cohort study

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Background: Frailty is associated with decreased quality of life and increased health care costs and is a syndrome of increased importance due to the aging US population. Proposed interventions to prevent frailty and its consequences have focused on non-pharmacologic (eg, exercise and diet) and pharmacologic modifications. While frailty prevalence is elevated among racial/ethnic minorities and persons living in the US South, little work has been done to inform pharmacologic interventions in these populations.

Objectives: To quantify the prevalence of frailty and polypharmacy in a biracial sample of middle and older adults and estimate the association between polypharmacy and incident frailty.

Methods: The Johnston County Osteoarthritis (OA) Project is a community-based 27+ year ongoing prospective cohort study of adults with and without OA residing in Johnston County, North Carolina. For each participant, all prescription and over-the-counter medications in containers were reviewed and recorded at each study visit. We estimated the prevalence of polypharmacy at the 2006-2010 visit ($n = 1697$). We then operationalized the Fried frailty phenotype to describe prevalent and incident frailty at two consecutive visits (2006-2010; 2013-2015). Using logistic regression, we estimated risk ratios (RRs) and 95% confidence intervals (CIs) for the association between polypharmacy and incident frailty, adjusted for age, sex, race, comorbidity, and body mass index.

Results: At the 2006-2010 visit, 680 (41%) and 269 (16%) participants were exposed to polypharmacy (5-9 medications) and excessive polypharmacy (10+ medications), respectively. In total, 335 participants

(20%) were frail at the 2006-2010 visit, while 176 participants (19%) were frail at the 2013-2015 visit. Frailty was more common among participants identifying as black, female, and not having completed high school, relative to those without these characteristics. Incident frailty at the 2013-2015 visit was 16% (mean follow-up: 5.5 years). Polypharmacy and excessive polypharmacy were associated with increased incident frailty (RR: 1.8 [95% CI: 1.2-2.8] and RR: 2.6 [95% CI: 1.6-4.1], respectively), but associations were attenuated after adjustment (RR: 1.2 [95% CI: 0.8-1.9] and RR: 1.3 [95% CI: 0.8-2.2], respectively).

Conclusions: In this cohort, polypharmacy was not associated with a statistically significant increase in incident frailty. De-prescribing interventions are needed to assess the causal effect of reducing polypharmacy on incident frailty.

645 | Beyond opioids: Pharmacologic intensification of pain management in nursing home residents with cancer

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Background: Opioids are frequently used to manage pain in nursing home residents with cancer. For residents unable to tolerate opioid side effects or who continue to have unsatisfactory analgesia, non-steroidal anti-inflammatory drugs (NSAIDs), or adjuvants (eg, gabapentin and other anticonvulsants, duloxetine and other antidepressants) may be added to the pain medication regimen. Information on such pain management practices in nursing home settings is scarce.

Objectives: To examine factors associated with the use of non-opioid analgesics and adjuvants to opioid therapy in nursing home residents with cancer.

Methods: We included Medicare beneficiaries with cancer and documented opioid use at nursing home admission in 2011-2013 ($N = 5,381$). The Minimum Data Set (MDS) 3.0 provided information on sociodemographic and clinical characteristics. Medicare Part D claims provided information on opioids, prescription non-opioid analgesics, and adjuvants used in the 7 days after admission. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were estimated from logistic models.

Results: Most residents with cancer who were prescribed opioids at admission were aged ≥ 75 years (60.3%), women (63.4%), and had frequent or almost constant pain (70.7%). The most commonly prescribed opioids were hydrocodone (40.5%), tramadol (25.8%), fentanyl (8.6%), and oxycodone (8.4%). Nearly 1 in 5 were also prescribed non-opioids and/or adjuvants, with gabapentin (26.2%), corticosteroids (25.3%), and NSAIDs (19.1%) most common, and 17.6% receiving multiple prescriptions. Being prescribed additional non-opioid analgesics or adjuvants was associated with arthritis (aOR: 0.83; 95% CI: 0.67 to 1.02),

surgical wounds (aOR: 0.67; 95% CI: 0.54 to 0.83), and depression (aOR: 1.41; 95% CI: 1.15 to 1.72).

Conclusions: Nursing home residents with cancer need effective pain management strategies to relieve suffering. The addition of non-opioid analgesics and adjuvants in this setting is common. Given aging-related changes in pharmacokinetics/dynamics and the presence of comorbid conditions, safety studies of these practices are warranted.

646 | Improving population-level PIM exposure metrics using Medicare claims data

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Background: Potentially inappropriate medications (PIMs) are drugs that when used in older adults have a high risk of harm relative to their potential benefit, especially when safer or more effective options are available. PIM use is often operationalized as a binary measure (yes/no) over a defined time period—eg, one calendar year—which could mask important heterogeneity in exposure.

Objectives: We sought to improve the claims-based characterization of PIM using the 2012 Beers criteria by adding more granular information about the intensity, duration, and type of PIM exposure.

Methods: We used a random 1% sample of Medicare beneficiaries with Parts A, B, and D coverage and at least one prescription dispensed (or days' supply coverage) in each month of 2012. Based on the 2012 Beers criteria, we estimated PIM prevalence over the calendar year and in each calendar-month using data on diagnoses or conditions present in the prior 12 months. PIM use was further operationalized, considering (1) intensity of PIM use, as the number of PIM fills during 2012; (2) duration of PIM use, as the number of months with any PIM fill in 2012; and (3) type of PIM use, as the category of PIM fill (eg, cardiovascular and endocrine).

Results: Among the sample of 14 948 adults, mean age was 77 years, 64% were female, and 87% were White. In 2012, the 12-month period prevalence of any PIM fill was 57%, while the average monthly point prevalence was 36%. Intensity of PIM use in 2012 varied from one PIM fill (8%), 2-4 fills (10%), 5-9 fills (9%), to 10+ fills (30%). Overall duration of PIM use was also heterogeneous, ranging from 1 month (9%), 2-11 months (31%), and exposure in all 12 months (17%). Among those with only 1 month of PIM exposure in 2012, the three most common medication categories were anticholinergics (19%), anti-infectives (12%), and endocrine drugs (5%) drugs; among those with 12 months of PIM exposure, the most common categories were cardiovascular (56%), endocrine (19%), and central nervous system (19%) drugs.

Conclusions: PIM use is multi-dimensional; binary claims-based measures likely mask important variation in PIM intensity, duration, and type. High- or low-level PIM exposure could differentially influence adverse outcomes in older adults. If these associations are observed

in future studies, there are implications for epidemiological studies as well as Medicare policies, which rely on these measures to assess the performance and adjust payments to health plans participating in the Medicare Advantage program.

647 | Anticholinergic and sedative drug burden in Irish community-dwelling older people: A cross-sectional national database study

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Background: The Drug Burden Index (DBI) quantifies individual exposure to anticholinergic and sedative medications. The DBI has been internationally validated against a range of adverse health outcomes in older people. DBI exposure has not been reported in the Irish older population.

Objectives: To develop a list of medications with clinically significant anticholinergic and/or sedative effects (DBI medications) relevant to Ireland, examine the prevalence of exposure to DBI medications in Irish community-dwelling older people in 2016, and explore patient factors associated with exposure to DBI medications.

Methods: A cross-sectional national pharmacy claims database study was conducted. A consensus list of DBI medications and their corresponding minimum effective daily doses was developed for Ireland. Prevalence rates were calculated for Irish community-dwelling older individuals (aged ≥65 years), enrolled in the General Medical Services (GMS) scheme and dispensed at least one prescription in 2016. Multivariate logistic regression was used to examine the association of patient age, sex, and number of chronic medications, with exposure to DBI medications. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were computed.

Results: 282 874 (66%) of the 428 516 GMS older population, dispensed at least one prescription in 2016, were exposed to at least one DBI medication. Prevalence of exposure to DBI medications was significantly higher in females than males (females 71.6% vs males 58.7%, adjusted OR 1.65, 95% CI 1.63-1.68). Prevalence of DBI exposure increased progressively with number of chronic drugs used, rising from 42.7% of those prescribed 0-4 chronic drugs to 95.4% of those on ≥12 chronic drugs (adjusted OR 27.8, 95% CI 26.7-29.0). The most frequently used DBI medications were codeine/paracetamol combination products (20.1% of patients), tramadol (11.5%), zopiclone (9.5%), zolpidem (8.5%), pregabalin (7.9%), and alprazolam (7.8%).

Conclusions: The majority of older people in Ireland are exposed to medications with anticholinergic and/or sedative effects, particularly females and those with multiple comorbidities. The high use of low-dose codeine/paracetamol combination products, Z-drugs, and benzodiazepines, suggests there are opportunities for deprescribing in this population.

648 | Validating the latent construct of problematic opioid use among medicare beneficiaries

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Background: Opioid misuse and abuse remain critical issues in the United States. Due to their restricted airways, older adults with chronic obstructive pulmonary disease (COPD) are at high risk of problematic opioid use and associated consequences, including respiratory events and mortality. Our goal is to use measures available in claims data to predict opioid misuse and outcomes using a latent construct in structural equation modeling (SEM). This approach has the potential to overcome over-fitting and multicollinearity issues in regression and has the ability to reflect distinct factors constituting opioid misuse.

Objectives: To conduct a factor analysis to determine the latent structure of problematic opioid use that can be used in a SEM to estimate adverse events.

Methods: Retrospective cohort using a 5% nationally representative Medicare population from claims data. We included a cohort of COPD beneficiaries aged 65 and older with continuous Parts A, B, and D enrollment from 1/1/2012-12/31/2013, who initiated opioids in 2013 (12-month washout period). Beneficiaries with cancer or residing in nursing homes were excluded. Ten characteristics of annual opioid use during 2013 were identified: (1) total days supplied; (2) average days supplied/prescriber; (3) number of opioid prescriptions (Rx); (4) morphine equivalent dose (MED); (5) number of active ingredients; (6) Rx overlap of >7 days; (7) number of prescribers; (8) number of pharmacies; (9) long-acting extended release (LAER) opioids; and (10) concomitant benzodiazepine use. Two random samples were created for exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). Competing models were selected using several fit indices.

Results: The population was mainly between 75 and 84 years of age (45%), females (62%), and white (85%). Both EFA and CFA indicated a two-factor model: (1) prescribing behaviors and (2) drug-shopping behaviors (with moderate correlation $r = 0.618$). Days supplied, number of Rxs, MED, LAER use, and concomitant benzodiazepine use loaded on factor one. The remaining items and number of Rxs loaded on the second factor. Model fit statistics were mixed, with strong Tucker-Lewis Index (TLI = 0.94) and standardized root mean square residual (SRMR = 0.05), but weak chi-square (p value < 0.01).

Conclusions: Multiple measures were used to predict problematic opioid use. We found two distinct but related constructs derived from these measures, corresponding to prescription behaviors and drug-shopping behaviors.

649 | The association between physical functioning and health care utilization in older adults: A retrospective longitudinal cohort study

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Background: Maintaining or improving physical functioning could be beneficial to improve health outcomes and decrease health utilization in increasingly older adults.

Objectives: To investigate the association between physical functioning and health utilization in a nationally representative sample of older adults.

Methods: A longitudinal cohort study was conducted using the 2013-2014 panel of the Medical Expenditure Panel Survey (MEPS). Health utilization was measured by ER visits, home health events, inpatient visits, office-based visits, outpatient visits, total medical visits, and total health care cost. Physical functioning was measured by physical component score (PCS) from the 12-item short form survey (SF-12) and four different survey questions related to physical activity from self-administered questionnaire (SAQ). Minimally significant changes in physical functioning were tracked across follow-up periods (Rounds 2 and 4) and classified based on categories of increased, decreased, or no change in physical functioning. Changes in health utilization were also measured across study years for each individual. Chi-square and t test was used to conduct descriptive analysis.

Results: 1576 individuals were included in the study cohort representing 43 463 583 older adults after weighted. Individuals in lower quartile of PCS were more likely to have significant improved PCS difference (percentage of the increased category in four quartiles of baseline PCS: Q1: 58.30%, Q2: 43.59%, Q3: 37.57%, Q4: 14.00%). Individuals in higher quartile were more likely to have significant declined PCS difference (percentage of the decreased category in four quartiles of baseline PCS: Q1: 22.27%, Q2: 37.24%, Q3: 42.52%, Q4: 44.94%). No change category was associated with higher health utilization (the mean [95% CI]: ER events 0.160 [0.0003, 0.32], home health events 0.37 [0.07, 0.66], inpatient visits 0.11 [0.004, 0.22], total health visits 1.96 [0.25, 3.66], total health care cost 2053 [614, 3493]). Declined category was also associated with higher health utilization (the mean [95% CI]: ER visits 0.11 [0.01, 0.22], office-based visits 2.43 [0.43, 4.43], total medical visits 3.17 [0.91, 5.43], total health care cost 1771 [317, 3226]).

Conclusions: Higher physical functioning was inversely related to health care utilization and improvements in physical functioning over time corresponded to decreases in health utilization as well.

650 | Potential inappropriate medications among inpatient older adults in a teaching hospital Chile

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Background: Potentially inappropriate medications (PIM) increase the risk for adverse effects of drugs in older adults. In 2015, a revised version of Beers Criteria and Screening Tool of Older Person's Prescriptions and Screening Tool to Alert doctors to Right (STOPP&START) Criteria to identify PIM have been published. Limited information is available of PIM among hospitalized older adults in Chile.

Objectives: To describe the frequency and characteristic of PIM in a sample of older adults hospitalized in a teaching hospital in Chile.

Methods: We used a sample of older adults 60 years and older hospitalized in a medicine unit of a teaching hospital in Chile. Each patient was interviewed, and their clinical information were collected by pharmacists using a standardized form, which were designed for the study. Sociodemographic characteristics, clinical, and pharmacotherapy profile were analyzed. PIM were defined according to 2015 Beers Criteria and STOPP version 2. Data were statistically analyzed by using STATA computer software.

Results: A total of 159 patients were included. The mean $\pm$ SD age was 73.2 ± 8.9 years, 50.3% were women, and 69.2% of patients were using 5 or more medications (mean 6.7 ± 3.8 drugs/patient). The most common comorbidity was hypertension (15.8%). The 56.6% and 59.8% of patients received at least 1 PIM according to 2015 Beers Criteria and 2015 STOPP Criteria version 2 at hospital admission, respectively. During the hospitalization, the frequency of PIM was 45.9% according to 2015 Beers Criteria (18.9% of reduction vs at hospital admission), instead of 59.8% according to STOPP Criteria version 2. The most common PIM were omeprazole for longer than 8 weeks (2015 Beers Criteria; 15.2%), clonazepam for longer than 4 weeks (STOPP Criteria version 2; 7.0%).

Conclusions: PIM is highly prevalent among older patients hospitalized in the sample studied. PIM prevalence and their characteristics will help to assess quality of care and to target and assess potential interventions to improve care.

651 | Potentially inappropriate medications use: Prevalence and predictors in Saudi Arabia

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Background: Older patients are commonly on multiple medications as the prevalence of disease increase with increased age. Therefore, medications misadventures are common among older patients

particularly the use of potentially inappropriate medications (PIMs). However, there are few studies that have assessed the prevalence of PIMs use among older adults in Saudi Arabia.

Objectives: This study aimed to determine the prevalence of PIMs among older patients and to explore predictors associated with increased PIMs in the ambulatory care setting.

Methods: A cross-sectional study was conducted among older patient's (age $>$: 65 years) who were treated in the ambulatory care setting in a large tertiary teaching hospital, Riyadh. PIMs use was defined using two categories of the American Geriatric Society (AGS) 2015 updated Beers criteria "medications to be avoided for older adults" and "medications to be used with caution." Data were retrieved retrospectively using electronic medical records from January 1 to December 31, 2016. Descriptive statistics were used to describe the study population and logistic regression was used to identify potential factors associated with PIMs use.

Results: This study included 4073 older adults; the mean age ($\pm$ SD) was 72.6 ± 6.2 years. The majority of the study population was females (56.8%). The prevalence of PIMs to be avoided for older adults was 57.6%. Among this, 39.9% of older adults used one PIM, 14.5% used two PIMs, and 3.3% used three or more PIMs. The most commonly prescribed PIMs were gastrointestinal agents (35.6%) followed by endocrine agents (34.3%). The prevalence of PIMs to be used with caution was 37.5%. The most commonly prescribed drugs where diuretics (33.2%) followed by SSRI anti-depressant (4.9%). Factors associated with PIMs use from regression analysis included polypharmacy (AOR = 7.79; 95% CI: 6.3-9.5) and having one of these diagnoses: diabetes (AOR = 2.03; 95% CI: 1.76, 2.34), heart failure (AOR = 8.19; 95% CI: 2.36, 28.38), ischemic heart disease (AOR = 2.74; 95% CI: 1.93, 3.88), chronic kidney disease (AOR = 2.34; 95% CI: 1.41, 3.87), osteoarthritis (AOR = 0.61; 95% CI: 0.481, 0.763), osteoporosis (AOR = 0.63; 95% CI: 0.49, 0.79), and anxiety (AOR = 1.50; 95% CI: 1.15, 1.96).

Conclusions: This study found a high prevalence of PIMs that should be avoided or to be used with caution among older adults. Elderly with co-existing chronic conditions have a higher risk of PIMs use; those may benefit from medication management interventions to avoid unnecessary medications.

652 | What is the impact of dementia diagnosis on patterns of medication use among older adults?

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Background: Considering common use of potentially inappropriate medications (PIM) among people with dementia, it is important to investigate whether a diagnosis of dementia may increase the likelihood of PIM use among older adults.

Objectives: We assessed the patterns of medication use from 1-year prior to dementia diagnosis, to 1-year after dementia diagnosis, compared with patterns of medication use in people without dementia.

Methods: We conducted a longitudinal study using the National Alzheimer's Coordinating Center data. Adults ≥ 65 years newly diagnosed with dementia ($n = 2418$) during 2005-2015 were matched 1:1 with controls. Incident dementia diagnosis was based on clinician diagnosis, comprehensive neuropsychiatric battery, and cognitive assessments. Medication use was assessed as total number of medications and PIM based on the 2015 Beers Criteria. Covariate adjusted, weighted generalized estimating equation models were performed.

Results: Among participants with dementia, total number of medications reported 1-year pre-diagnosis was 8% lower than the year of diagnosis ($P < 0.0001$), and 11% higher 1-year post-diagnosis compared with the year of diagnosis ($P < 0.0001$). The odds of PIMs exposure was 17% lower 1-year pre-diagnosis ($P < 0.0001$), and 17% higher 1-year post-diagnosis ($P = 0.006$) compared with year of diagnosis. Among controls, medications increased approximately 7% between consecutive years ($P < 0.0001$) and the odds of PIMs exposure increased 11% from pre-diagnosis to diagnosis year ($P = 0.006$), and 11% higher from the year of diagnosis to 1-year post diagnosis ($P = 0.047$). At each follow-up, participants with dementia had lower odds of PIMs exposure than their controls (pre-diagnosis $P < 0.0001$, at diagnosis $P = 0.0007$, and post-diagnosis $P = 0.03$, respectively).

Conclusions: Total medication and PIMs use increased annually for participants with and without dementia. Persistent challenge of increasing PIM use in this group of older adults is of major concern, and it warrants interventions to minimize such prescribing.

653 | Mean number of drugs and prevalence of polypharmacy among community-dwelling persons with and without Alzheimer's disease

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Background: High number of drugs and polypharmacy increase risk of adverse effects and possibility of drug-drug interactions.

Objectives: The objective of this study was to investigate mean number of drugs and prevalence of polypharmacy among persons with and without AD, from 5 years before until 4 years after AD diagnosis. Changes in ATC main groups were also described.

Methods: Persons with and without AD were a part of the nationwide MEDALZ study which includes all community-dwelling persons who received a clinically verified diagnosis of AD during 2005-2011 in Finland ($n = 70\,719$). One age, gender, and region of residence matched comparison person without AD was identified for each person with AD from register including all residents. PRE2DUP method was utilized in modelling of purchases recorded in the Prescription register (1995-2015). Point prevalence of drug use was assessed at 6 months

time intervals, from 5 years before AD diagnoses and until 4 years after (with corresponding index date for persons without AD). In each time point, mean number of drugs and according to ATC main groups was calculated for both groups.

Results: Mean number of drugs increased since 5 years before until AD diagnoses, and from AD diagnoses until 4 years after the diagnoses among both persons with AD and without AD. Among persons with AD, mean number of drugs was 3.2 per person 5 years before, 4.6 at the AD diagnoses, and 6.2 drugs 4 years after the diagnosis, increase of 0.3 drugs per year. For persons without AD, the corresponding means were 3.0, 4.3, and 4.8, respectively. The average increase was 0.2 drugs per year. Most prominent changes among persons with AD were increase in mean number of nervous system drugs (around time of AD diagnoses) and decrease in cardiovascular drugs from AD diagnoses until 4 years after. Prevalence of polypharmacy (5 or more drugs) increased from 27.4% to 68.2% and excessive polypharmacy (10 or more drugs) from 2.9% to 15.2% among persons with AD, from 5 years before until 4 years after the diagnoses.

Conclusions: With aging, the mean number of drugs increase steadily but AD diagnosis adds on about one new drug to the drug regimen. These were mostly nervous system drugs, including antidementia drugs and psychotropics.

654 | Potential drug-drug interactions among older emergency department patients in Chile

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Background: Polypharmacy and aging changes leading to greater challenges on pharmacotherapy in older adults in emergency department (ED). Older ED patients are a vulnerable patient group at risk of potential drug-drug interactions (PDDI). This problem is not well researched in low- and middle-income countries.

Objectives: To describe the frequency and predictors of PDDI in older ED patients.

Methods: We conducted a cross-sectional study in a random sample of older ED patients in a tertiary care private clinic in Chile. Each patient selected was interviewed by pharmacists during the ED visit. Sociodemographic, clinical, and pharmacotherapy profiles were collected and analyzed. PDDI were identified at admission using Micromedex 2.0 database. Each PDDI was classified by severity and therapeutic group implicated. We identified factors associated with PDDI using logistic regression.

Results: A total of 400 older patients were included. The mean $\pm$ SD age was 73.2 ± 6.9 years, 66.0% were women. The most common reason of ED visit was pain (41.1%). Polypharmacy (5 or more medications) was observed in 66.2% of patients. The mean $\pm$ SD number of medications per patient was 6.2 ± 3.3 . A total of 2499 prescriptions were assessed at admission of ED; 727 PDDI were detected in the 65% of patients. The 28.8% of PDDI were contraindicated/severe. The most common PDDI detected was the use of nonsteroidal anti-

inflammatory drugs (NSAIDs) with Angiotensin II receptor blockers (ARBs) (6.3%). The strongest predictors of PDDI at admission were polypharmacy (OR 3.7; 95% CI 2.1- 6.7), Charlson comorbidity index over 2 (OR 2.6; 95% CI 1.1-6.2; 3-4 vs 1-2; and OR 3.1; 95% CI 1.1-8.8; ≥ 5 vs 1-2).

Conclusions: PDDI were highly prevalent among older ED patients studied. Patients with polypharmacy and Charlson Comorbidity Index over 2 were more likely to have a PDDI. Approximately one in three PDDI were clinically relevant. Our results could help to design future interventions focused on detecting and monitoring drug combinations with potential negative effects.

655 | Health care professionals' attitudes towards deprescribing in patients nearing the end of their life: A systematic review

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Background: Deprescribing, defined as the planned, supervised dose reduction or stopping of a medication, may be particularly relevant in older people with a limited life expectancy where many medications no longer can be expected to provide clinical benefit. Although deprescribing has gained increased attention in recent years, little is known about health care professionals' (HCPs) attitudes towards deprescribing specifically in the context of "end of life" treatment.

Objectives: To explore HCPs' attitudes towards deprescribing in older people nearing the end of their life.

Methods: A systematic literature search for qualitative studies exploring HCPs' attitudes towards deprescribing in older people nearing the end of their life was conducted from inception to December 2017 using MEDLINE, EMBASE, and CINAHL. Only studies specifically concerning patients with a limited life expectancy were included, including patients residing in nursing homes, long-term care facilities, or residential care. Screening of abstracts, full text assessment, and data extraction was performed by two authors.

Results: A total of 2736 references were identified of which eight studies were ultimately included. Six studies explored HCPs' views on deprescribing in relation to multiple medications, while two studies focused specifically on hypnotics and antidepressants, respectively. While all eight studies explored the views of physicians, two also considered the views of pharmacists and two included caregivers.

Several barriers to deprescribing in older people with a limited life expectancy were identified among HCPs. These concerned uncertainty about the applicability of clinical guidelines to the patients, the high number of disease-specific guidelines, fear of disease relapse or drug withdrawal symptoms, pressure from patients or caregivers, and lack of communication between HCPs or health care systems. As potential enablers to deprescribing, evidence-based guidelines to

deprescribing in older people, more education, and more collaboration between health care systems were highlighted.

Conclusions: Several barriers and enablers towards deprescribing in older people nearing the end of their life exist among HCPs. Gaining insight into these is vital when designing tools and interventions aimed at reducing inappropriate prescribing among older patients with a limited life expectancy.

656 | Adherence, self-management, and beliefs about immunosuppressives in kidney transplant outpatients

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Background: Patients after kidney transplantation (Tx) are required to adhere to complex therapeutic regimens; however, medication adherence may be affected by patients' beliefs and attitudes.

Objectives: To analyse adherence to immunosuppressives (IS), attitudes to IS, and main self-management tasks in patients after Tx.

Methods: The prospective cross-sectional study was undertaken from March 2016 to March 2017 at the Haemodialysis Centre in the Teaching Hospital Hradec Kralove involving 412 patients in total. Patients ≥ 18 years old and ≥ 3 weeks after Tx were included in the study; however, those on initial/antirejective therapy with cognitive disorders or disapproved to participate were all excluded. Data from each patient was obtained through a pharmacist-led structured interview and a review of medical documentation. Medication adherence was measured by a combination of direct (IS serum levels) and indirect (Medication Adherence Report Scale, validated Czech version [MARS-CZ]) methods. Moreover, necessity and concerns about IS were measured by validated Czech version of Beliefs about Medicines Questionnaire (BMQ-CZ). In addition, patients were interviewed about self-management tasks directly (eg, sun protection) or indirectly (eg, dietary habits) related to the use of IS. Data analysis was performed by parametric and non-parametric tests using Wolfram, Mathematica 11.2 ($p < 0.05$) and by means of descriptive statistics.

Results: During the study period, 211 patients completed the interview (male 123; 58.3%). The mean age was 55.8 ± 12.41 years and the mean time after transplantation 7.4 ± 5.75 years. Full adherence to IS by MARS-CZ was found in 173 (82.0%) patients. Better adherence and feeling the necessity of treatment was significantly associated with older age, whereas concerns and non-adherence to IS increased with past time after Tx ($p < 0.05$). Self-reported adherence to IS correlated with the BMQ-CZ; however, none of them correlated with IS serum level. Inadequate sun protection (58; 27.4%), as well as incorrect administration of tacrolimus (44; 35.2%), and prednisone (160; 79.6%) were among the main problems related to self-management.

Conclusions: Limits in patients' medication behavior were detected with accent on decreased adherence to IS and increased concerns with past time after Tx. Targeted interventions implemented to daily routine may foster self-management capacity and improve transplantation outcomes. *This study was supported by Charles University (Project SVV 260 417).*

657 | Ledipasvir-sofosbuvir (Harvoni) response and treatment duration in a hepatitis C virus genotype 1 cohort: A claims data analysis from a health plan perspective

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Background: Oral direct-acting antiretrovirals (DAAs) have potential to cure chronic hepatitis C virus (HCV), but real-world effectiveness data are needed.

Objectives: Using claims data from individuals with HCV genotype 1 treated with ledipasvir-sofosbuvir (Harvoni) in a commercial benefit plan population, our objectives were (1) to quantify response rates and clinical covariates and (2) to quantify additional benefit of 12 versus 8 weeks' therapy in those eligible for 8 weeks.

Methods: Using 2016 claims data from Harvoni-eligible Cigna customers, we ascertained clinical characteristics, treatment duration, HCV ribonucleic acid (RNA) detection at treatment completion, and 12-week sustained viral response (SVR12). We used Pearson's chi-squared tests, analysis of variance (ANOVA), and Kruskal-Wallis tests, and logistic regression to model factors associated with response.

Results: SVR12 rates were 294/309 (95%) in those treated for 8 weeks, 413/433 (95%) in those treated for 12 weeks, and 20/22 (91%) in the 24-week group (ANOVA *p* value across groups = 0.64). Compared with non-responders, responders were younger (mean age = 51.7, ± 11.3 years, odds ratio [OR] = 0.83, 95% confidence interval [CI] = 0.72-0.95) and had lower fibrosis scores (OR = 0.43, 95% CI = 0.21-0.86). In 32/742 eligible for 8 weeks' treatment who received 12 weeks' treatment (medical necessity overrides), SVR12 rates remained above 95%, despite baseline differences in previous treatment, baseline viral load, or human immunodeficiency virus (HIV) prevalence (χ^2 *p* = 0.71).

Conclusions: Harvoni response exceeded 95%, providing evidence for clinical effectiveness concordant with clinical trial efficacy findings. In practice, continuity for follow-up 12 weeks of post-treatment should be an area of focus for disease management, to prevent relapse/reinfection. For non-cirrhotic patients with HCV RNA below six million IU/mL, we observed no additional benefit of overriding to 12 versus 8 weeks' treatment.

658 | Assessing the direct medical cost of treating patients with cancer in Kenya: A pilot study—Findings and implications for the future

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Background: The economic burden of cancer is a major issue across countries with the majority of cancer deaths in middle-income and low-income countries where there are appreciable concerns with funding of care. In Kenya, most patients pay out of pocket, and even those who are insured are not properly covered to cover the full costs of cancer treatment, placing a considerable burden on the family if members develop cancer. However, the actual cost of cancer treatment in Kenya has not been enumerated before. This is essential to inform future government as the health system evolves in Kenya

Objectives: To evaluate the economic burden of the treatment of cancer patients in a leading hospital in Kenya

Methods: Descriptive cross-sectional cost of illness study over a 1 year period (2016) in the leading teaching and referral hospital in Kenya, with data collected from hospital files of randomly sampled adult patients between January and March 2017. Outcomes included direct medical costs for managing cancer (chemotherapy, surgery, and radiotherapy)

Results: The cost of cancer therapy is highly dependent on the cancer modality. Of the 412 patients included, most cancer patients had surgery (25.4%), followed by chemotherapy (4.6%) and palliative care (21.7%). The most prevalent male cancer were prostate cancer (9.7%, *n* = 40) and colon cancer (2.9%, *n* = 12); while female cancers were mostly cervical cancer (23.78%, *n* = 98) and breast cancer (7.28%, *n* = 30). The cost of cancer therapy varied with the type of cancer and its stage. Patients on chemotherapy alone cost an average of KES 138,206 (1US\$ = KES 100) for the year, while those treated with surgery only cost an average of KES 128 207 and those on radiotherapy alone used KES 119 035. Some patients had a combination of all three costing on average KES 333 462 per patient

Conclusions: The cost of cancer treatment in Kenya depends on the type of cancer, the modality, cost of medicines, and the type of inpatient admission. The greatest contributors to the cost of cancer care are the cost of medicines and inpatient admissions. Pressure needs to be applied to the government and insurance companies to ease out-of-pocket payments especially for medicines

659 | Direct medical cost of metastatic colorectal cancer (mCRC) treatment in Indonesia

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Background: Studies of metastatic colorectal cancer (mCRC) should be performed to evaluate the use of bevacizumab in mCRC patients and provide scientific evidence for policymakers

Objectives: The aim of this study is to estimate the direct medical cost of mCRC treatment using bevacizumab added to the chemotherapy regimen for mCRC patients in Indonesia.

Methods: We conducted cost analysis from the perspective of health care provider (hospital) using prevalence-based approach to estimate the average direct medical cost of mCRC treatment per patient per year. **Setting:** Data were collected from hospital billing in 4 hospitals in Indonesia, retrospectively. **Exposures or interventions:** bevacizumab-chemotherapy and chemotherapy. **Main outcome measures:** direct medical cost. **Statistical analysis:** Descriptive analysis was used to present the study results

Results: The study found a different pattern of chemotherapy combination pattern among patients included in the analysis. The highest average cost of combination bevacizumab-chemotherapy was bevacizumab-irinotecan-leucovorin-5FU (IDR 280 million) and followed by bevacizumab-oxaliplatin-leucovorin-5FU (IDR 276 million) and bevacizumab-oxaliplatin-capecitabine (IDR 201 million). The highest average direct medical costs for the chemotherapy group alone was irinotecan-leucovorin-5FU (IDR 252 million) and followed by oxaliplatin-leucovorin-5FU group (IDR 176 million) and oxaliplatin-capecitabine group (IDR 104 million). The average direct medical cost of treatment using bevacizumab added to chemotherapy was IDR 242.679.325 (SD = 163 237 658), while the average direct medical cost of treatment using chemotherapy only was IDR 158 412 647 (SD=120 252 547).

Conclusions: The study shows that the direct medical cost of treatment using bevacizumab-based was greater than chemotherapy without bevacizumab

660 | Validation study of a novel method for predicting the budget impact of new innovative medicines

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Background: Many innovative hospital medicines are considered expensive and have raised affordability discussions. Data on the additional cost of the new drug (called budget impact [BI]) is limited at marketing authorization (MA), resulting in uncertainty around the financial impact for payers, health care, and society. Payers could then limit or delay patient access to new potentially effective therapies, to reduce the potential financial risk. We have constructed a mixed-effects model for BI prediction. This novel approach provides decision-makers and payers with a tool that predicts BI over time and that quantifies the associated uncertainty, to ultimately inform patient access decisions.

Objectives: To validate our mixed-effects model approach for BI prediction.

Methods: We used population-level sales data provided by FarmInform to estimate BI. This data source is crosschecked with Dutch patient-level PHARMO data and covers Dutch nationwide intramural and extramural expenditure per drug on a monthly basis from 2000 to 2017. For the validation, we included oncology drugs in the L01 ATC category which are considered New Active Substances by the EMA and received EMA MA between 2000-2017. A mixed-effects model was used for prediction of BI and included tumor site, orphan-, FDA First in Class- and exceptional or conditional approval designation as covariates. Data from 2000-2012 was used as a fixed training set. BI per drug was predicted per month from 0 to 42 months after MA. Leave-one-out cross-validation was performed for predicting new drugs with MA from 2012 onwards. We used $e^{| \ln(\text{actual BI}/\text{predicted BI}) |}$ as outcome as this ratio values overprediction and underprediction equally.

Results: We developed our model on a training set of 25 products and performed validation on a set of 44 products. The mean error, composed of the outcome for all timepoints for all validation set products, was 4.03 (SD 1.27, IQR 1.10, median 3.68). Error was highly dependent on the amount of data available for the left-out product as the mean errors for 0, 6, and 12 months of available data were 6.95, 4.27, and 3.83, respectively.

Conclusions: The relatively small error found in our validation leads us to conclude that this methodology predicts BI reasonably well. The current broad BI predictions performed by agencies regulating drug reimbursement could thus be enhanced by our new methodology. The resulting decrease in uncertainty could improve patient access to new oncology drugs.

661 | Abstract Withdrawn

662 | Cost analysis of anti-osteoporotic drugs in real-world clinical practice

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Background: Adherence of osteoporosis treatment has been shown to be problematic, if not worse, than that in other chronic diseases. Economic evaluations based on modelling are commonly used to compare alternative treatment strategies in osteoporosis, to support decision-makers and to inform treatment guidelines.

Objectives: The aim of this study is to analyse health care costs of osteoporosis and to build a economic model cost-effectiveness of pharmacological intervenes based on real world data.

Methods: The data of the analysed subjects were drawn from the administrative databases. Patients >60 years of age were included if at least one prescription for any antiosteoporosis drugs had been filled in 1 year observed. The patients were classified as exposed or not exposed to osteoporotic fracture. For each group, compliance with antiosteoporosis drugs was calculated. Patients were considered compliant if their Medication Possession Ratio (MPR) was $>80\%$. The cost analysis was conducted taking each health care service into account, ie, drug therapy, diagnostic tests, and hospitalization admissions, during the study period. A hypothetical scenario based on the real-life available evidence was constructed. The mean level of adherence to populate the hypothetical scenario of "full adherence" was set at MPR $>80\%$. The model built by adding a step value, constrained by a normal random variable, to the real-world adherence of each subject so that the subject shifted to the hypothetical scenario of full adherence, in order to quantify the clinical outcome (number of fractures) achievable in the hypothetical scenario. Cost-effectiveness of full adherence compared with real-world adherence was expressed in terms of Incremental Cost Effectiveness Ratio (ICER) and the number of fractures avoided was set as an effectiveness unit of measure.

Results: The mean annual health care cost per fracture avoided was € 247.44, of which medical treatments and diagnostic tests accounted for € 103.60 (41.9%) and € 143.84 (58.1%), respectively. The mean annual health care cost per fractured patient was € 1044.85, of which medical treatments, diagnostic tests, and hospitalizations for osteoporotic fracture accounted for € 88.73 (8.5%), € 169.48 (16.2%), and € 786.65 (75.3%), respectively.

Conclusions: Costs per fractured patients resulted to be about four times greater than those of not fractured patients. Therefore, only enhancing adherence to medication may lead to reductions in the number of patients requiring hospitalization.

663 | Clinical features, outcome, and hospital volume of pediatric brain tumor resection surgery in Japan

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Background: Pediatric brain tumor is rare disease and is second most common malignancy during childhood. Resection surgery is usually the first step in treating brain tumor in children; however, studies

regarding clinical features, outcome, and centralization of the surgery were lacking.

Objectives: The aim of this study was to describe current clinical features and outcomes according to hospital surgical volume in pediatric patients who underwent brain tumor resection surgery.

Methods: We retrospectively investigated pediatric patients who underwent brain tumor resection surgery in less than 16 years old, using the Japanese Diagnosis Procedure Combination inpatient database between April 2012 and March 2016. Patients who only had a brain tumor biopsy, who with outlier length of stay (>365 days), and who with outlier preoperative length of stay (>14 days) were excluded. We examined the patients' characteristics, chemotherapy, radiation therapy, and in-hospital mortality regarding hospital surgical volume by descriptive analysis. Subgroup analysis for patients aged 5 and younger was also performed.

Results: We identified 1354 pediatric patients who underwent brain tumor resection surgery after exclusions. The mean age was 8.2, and male/female ratio was 53/47. In terms of procedures, 56.8% underwent chemotherapy and 21.5% given radiation. Crude in-hospital mortality was 1.8% ($N = 24$). Seventy-five hospitals provided just one surgery during the study period. Higher crude in-hospital mortality was associated with lower hospital surgical volume. A more clear volume-outcome association was observed in patients aged 5 and younger.

Conclusions: The present study implies the volume-outcome relationship in pediatric brain tumor resection surgery although outcome analysis for this kind of surgery is complex due to its heterogeneity. Further centralization of the surgeries should be taken into consideration together with further efforts for risk-adjusted outcome analysis.

664 | Psychosocial factors in promoting patient safety culture: A structural equation modelling analysis

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Background: Evidence is needed in order to consolidate the theory that organizational conditions and psychosocial factors reflect on the safety of the care provided by health services.

Objectives: To assess whether patient safety culture is related to job satisfaction, depression, and burnout syndrome among hospital professionals.

Methods: A cross-sectional study, conducted between August and November of 2016 in a teaching hospital that is a reference in health care for 13 cities in the State of São Paulo, Brazil. The inclusion criteria involved all workers with an employment relationship greater than or equal to 3 months. Participants were recruited through random probabilistic sampling. Data collection was made by psychometric

instruments in order to analyse job satisfaction (Job Satisfaction Survey-JSS), the presence of depression (Patient Health Questionnaire-9), and burnout syndrome (Maslach Burnout Inventory-MBI), as well as the relationship between these factors and patient safety culture (Safety Attitudes Questionnaire-SAQ). Linear and Poisson regression were calculated to determine the association between the sociodemographic characteristics and the results obtained with the instruments. The partial least squares structural equation modeling (PLS-SEM) was used to estimate the type of relationship between the dependent variable and the independent variables. The confidence interval was set at 95% (95% CI) and the significance level at 5%.

Results: 271 professionals constituted the final sample of this study. The SAQ mean score was 68.2 (95% CI: 65.8-70.5), which indicates a level of safety culture below the ideal. The professionals with more time of work showed more negative perception of the safety culture ($p = 0.05$). The JSS defined neutrality regarding job satisfaction (mean score: 131.2, 95% CI: 128.1-134.3) and the hospital's administrative staff were more satisfied than health professionals ($p = 0.02$). The prevalence of depression was 22.1% (95% CI: 17.2-27.1%). Professionals with low monthly income had three times the risk of depression ($p = 0.01$). Burnout syndrome was present in 14.8% (95% CI: 10.5-19%) of the participants, and the risk was identified twice as high in men ($p=0.05$). The PLS-SEM confirmed that job satisfaction and absence of burnout are predictive factors to promote a patient safety culture ($p < 0.001$).

Conclusions: These findings suggest that the psychosocial work environment influences the quality of care provided.

665 | A systematic review of the methodological quality of economic studies evaluating ophthalmic drugs

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Background: Innovative drugs have been approved in ophthalmology. Pharmacoeconomics aims to support the decision-making process in the financing of therapeutic options.

Objectives: To assess the methodological quality of pharmacoeconomic studies of ophthalmic drugs.

Methods: Full economic evaluation studies were identified through a systematic search conducted in Medline and Embase from its inception until June 2017. The assessment of their methodological quality was based on the British Medical Journal (BMJ) checklist with 35 items, grouped in 10 sections under three headings, with four possible answers: "Yes," "No," "Not clear," or "Not appropriate." A score of 0 was assigned to each "Yes" answer, a score of 1 to "No," a score of 0.5 to "Not clear," and also a score of 0 to "Not appropriate" answers. The maximum score is 35 points. Higher scores represent poorer methodological quality.

Results: Eighty-six pharmacoeconomic studies were included. The median score was 9, and the minimum and maximum scores observed

were 3 and 22, respectively. The majority of the studies ($n = 46$; 53.5%) scored between 5 and 9.5 points. Only six (7.0%) studies scored between 0 and 5 points. All studies presented, at least, three methodological limitations. Only 21 (24.4%) studies justified the choice of type of analysis. The design and results of the effectiveness source were reported by 38 (44.2%) economic studies. Only 38 (44.2%) and 18 (20.9%) economic studies reported details of the study population and on the productivity changes, respectively. The justification for the discount rate applied and for the variables used in the sensitivity analysis were reported by 38 (44.2%) and 30 (34.9%) studies, respectively.

Conclusions: Pharmacoeconomic studies in ophthalmology demonstrated several methodological limitations, which can diminish its reliability.

666 | Measuring enhanced MTM services: Literature review and quality indicator development

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Background: Medication therapy management (MTM) programs are services targeting medication misuse, polypharmacy, preventable adverse drug events, and adherence to improve patient health and reduce health care costs. Measuring MTM activities, for example, the Part D Enhanced MTM Model, operated by the US Center for Medicare and Medicaid Innovation (CMMI), requires an approach that allows for program variability.

Objectives: To determine the availability of MTM monitoring measures and constructs and to apply them to monitor the enhanced MTM model.

Methods: We searched PubMed using keywords such as "medication therapy management"; "monitoring measures" and "implementation"; and synonyms of these terms. Articles with abstracts discussing MTM and monitoring were read in full. Additionally, we reviewed websites of pharmacy, MTM, and quality organization stakeholders. We compiled the monitoring measures and key constructs. We assessed the applicability of the findings for enhanced MTM model monitoring.

Results: Of 520 PubMed articles, 36 were reviewed in detail. The measures in published literature and stakeholder materials focused on clinical and economic outcomes and in some cases patient satisfaction. There was little discussion of MTM implementation or monitoring issues. Therefore, program-specific outreach and outcome measures were developed based on review of program objectives and discussions with CMMI. Data specifications and three quality indicator monitoring measures were published in 2016 that emphasize interoperability and monitor provision of MTM services. Data domains include record identifiers, MTM services (including referrals, procedures, medication therapy issues, and outcomes), and supplemental encounter details (such as provider type, service location, and cost-

sharing). Monitoring measures assess the proportions of targeted patients with at least one medication therapy issue, patients discharged from the hospital who received Enhanced MTM services, and implemented MTM recommendations.

Conclusions: We developed publically available data specifications and MTM monitoring measures that accommodate diverse interventions. These measures may be useful for pharmacoepidemiology research studies, for example, to measure MTM services as a potential confounder when assessing the association between medication use and chronic condition outcomes. Measures should be adapted to monitor the implementation of specific programs.

667 | Blood eosinophilia, use of inhaled corticosteroids, and risk of COPD exacerbations and mortality

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Background: Chronic obstructive pulmonary disease (COPD) is projected to be the leading cause of death by year 2030. Eosinophilic airway inflammation has been associated with an increased risk of exacerbations, and patients with elevated blood eosinophil counts have been reported to respond better to inhaled corticosteroid (ICS) therapy. It remains unclear whether blood eosinophil is useful in guiding ICS therapy in COPD patients.

Objectives: The goal of this study was to evaluate the risk of acute exacerbations, COPD-related hospitalizations/accident and emergency visits and all-cause mortality with various levels of absolute and relative eosinophil counts among COPD patients using ICS therapy.

Methods: Using the UK Clinical Practice Research Datalink, we conducted an observational cohort study among COPD patients aged ≥ 40 years from 2005 to 2014. Current users of ICS were stratified by relative blood eosinophil counts, low ($<2.0\%$), moderate (≥ 2.0 to 3.9%), high (4.0% to 5.9%) or very high ($\geq 6.0\%$), and absolute blood eosinophil counts ($<0.34 \times 10^9$ cells/L, $\geq 0.34 \times 10^9$ cells/L) to determine the risk of acute exacerbation, hospitalization/accident and emergency visits and all-cause mortality using Cox regression analysis. The analyses were adjusted for comorbidities and recent medication use.

Results: Among COPD patients, current use of ICS was not associated with a reduced risk of acute exacerbations of COPD (adjusted hazard ratio [adj.HR] 1.53; 95% confidence interval [CI] 1.45-1.59), COPD-related hospitalizations/accident and emergency visits (adj.HR 1.66; 95% CI: 1.49-1.86), and all-cause mortality (adj.HR 1.41; 95% CI

1.32-1.51). Stratification of ICS use by absolute or relative eosinophil counts did not result in significant differences in risk of COPD exacerbations or hospitalizations/accident and emergency visits. However, all-cause mortality was reduced by 16-30% among patients with elevated eosinophil counts.

Conclusions: COPD-related acute exacerbations or hospitalizations/accident and emergency visits were not reduced with elevated blood eosinophil counts among users of ICS with COPD. However, all-cause mortality was reduced by 16%-30%. These findings are potentially important and require further evaluation in prospective studies.

668 | Deep molecular response in chronic phase—Chronic myeloid leukemia patients treated with second-line nilotinib or dasatinib: A multi-country retrospective chart review study

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Background: Achievement of deep molecular response (ie, MR^{4.5}, BCR-ABL1 $\leq 0.0032\%$ on international scale) is an important goal of tyrosine kinase inhibitor (TKI) treatment for patients (pts) with chronic myeloid leukemia (CML). Pts achieving sustained MR^{4.5} are potential candidates for treatment-free remission.

Objectives: To describe patient and treatment characteristics by regions and assess time to achieving MR^{4.5} in pts with chronic phase (CP)-CML treated with second-line (2L) nilotinib or dasatinib in 10 countries, categorized into two regions, Europe (France, Germany, Italy, and Netherlands)/Australia - EU/AU and Latin America (Argentina, Brazil, Chile, Colombia, and Mexico) - LATAM.

Methods: A physician panel approach was used to conduct retrospective chart reviews on eligible pts diagnosed with CP-CML at age ≥ 18 years who initiated 2 L nilotinib or dasatinib between 1/1/11 and 7/1/15 and had ≥ 12 months of follow-up since TKI initiation. A multivariate Fine and Gray Cox proportional hazards model was used to assess time to MR^{4.5}. The model accounted for the competing-risk event of TKI resistance included random effects for country clustering of data and was adjusted for patient demographic, clinical, and treatment characteristics. Hazard ratios (HR) and 95% confidence intervals (CI) were reported.

Results: 280 pts treated with nilotinib (N = 135 [48%]) or dasatinib (N = 145 [52%]) as 2L TKI, including 108 nilotinib and 115 dasatinib pts from EU/AU (80%), and 27 nilotinib and 30 dasatinib pts from LATAM (20%) were included. Median follow-up time was 20 and 19 months for nilotinib and dasatinib, respectively. Median age was 58 years in EU/AU vs 49 years in LATAM. In EU/AU, 84% of pts had received imatinib as first-line TKI, and in LATAM, 96%. In EU/AU, 87% of pts discontinued first-line TKI due to ineffectiveness and

16% due to toxicity; corresponding percentages were 79% and 23% in LATAM. Nilotinib was associated with a significantly higher rate of achieving MR^{4,5} (HR = 1.37, 95% CI [1.11, 1.69], $p < 0.01$) than dasatinib. Both high-risk Sokal score (HR = 0.32, 95% CI [0.13, 0.79], $p = 0.01$) and discontinuation of first-line TKI due to resistance (HR = 0.62, 95% CI [0.42, 0.92], $p = 0.02$) were significantly inversely associated with achieving MR^{4,5}.

Conclusions: A significant proportion of 2L TKI pts can reach MR^{4,5} after failure with first-line TKI. Second-line nilotinib may be associated with a higher rate of MR^{4,5} than dasatinib.

669 | Real-world analysis of treatment patterns and long-term effectiveness among patients with advanced neuroendocrine tumors of lung origin: A multicenter study

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Background: Well-differentiated neuroendocrine tumors (known as NETs or carcinoid tumors) originate from neuroendocrine cells, grow slowly, and metastasize in the advanced stage. Lung is primary site for one-third of all NETs. US incidence rate of lung NETs has risen from 0.3 new cases in 1973 to 1.6 new cases per 100 000 persons in 2012.

Objectives: To report real-world treatment patterns and long-term effectiveness among patients (pts) with advanced lung NET based on data from four tertiary cancer centers (Dana-Farber, MD Anderson, Northwestern, and UCSF).

Methods: Retrospective chart review was conducted for pts diagnosed with advanced lung NET (typical/atypical) at age ≥ 18 years and treated with somatostatin analogs (SSAs), targeted therapy (TT), cytotoxic chemotherapy (CC), liver-directed therapy (LDT), or interferon between 7/2011-12/2014. Eligible pts were followed from advanced NET diagnosis date to end of follow-up/death. Treatment discontinuation and overall survival (OS) were estimated using Kaplan-Meier analysis.

Results: 83 (19 functional) lung NET pts were included with mean age of 59.7 years at advanced NET diagnosis. Median follow-up time after diagnosis was 49.1 (range: 4.0-155.4) months. As first line, 61.7% (50/81) of pts were treated with octreotide monotherapy or polytherapy, 18.5% (15/81) treated with CC alone, and 19.8% treated with EBRT, LDT, or TT. Of 60 pts with second-line, 55.0% (33/60) were treated with octreotide; 2 pts (3.3%) treated with lanreotide (90-120 mg/4 weeks); 16.7% (10/60) treated with CC, and 25.0% (15/60) underwent TT, LDT, or EBRT. 84.6% of octreotide doses given at initiation were ≤ 30 mg/4 weeks. In first-line, median time to treatment

discontinuation was 43.3 months for octreotide and 3.6 months for CC. Median OS was 49.0 (95% confidence interval [CI]: 34.2-65.9) months for all pts, 81.5 (95% CI: 43.4-126.6) months, and 50.2 (95% CI: 14.7-not reached) months for pts treated with first-line octreotide and CC, respectively. Variations in median durations across treatments may be due to underlying differences in disease severity.

Conclusions: Long-acting octreotide appears to be used widely in pts with advanced lung NET. Patients on average were treated with first-line octreotide for 3.6 years with median OS of 6.8 years. Treatment patterns for other therapies were less clear due to small sample size. Additional studies are needed to further understand clinical benefits of SSAs in real-world setting.

670 | Health care quality measures among diabetics using linked insurance claims-EMR data

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Background: Quality health care and management of blood glucose is associated with improved outcomes in diabetes.

Objectives: This study used the IBM MarketScan Explorers Claims-EMR Dataset to examine quality of care and clinical outcomes in diabetes.

Methods: Patients aged 18-75 continuously enrolled during 2015 with National Quality Forum (NQF) defined diabetes mellitus from 1/1/2014-12/31/2015 were identified in the Claims-EMR dataset. Four NQF measures (HbA1c testing, Eye Exams, Nephropathy Screening/Medical Care, and Blood Pressure [BP] Control [$<140/90$]) were evaluated. Patients with a HbA1c test results were stratified by the NQF HbA1c control measure into controlled (C) (<8.0) and not controlled (NC) (≥ 8.0) groups. Demographics, life style factors, clinical characteristics, and outcomes were evaluated in 2015 and compared between C and NC groups.

Results: A total of 134 317 diabetic patients met the inclusion criteria. Patients were 52% male and had a mean age of 58 years. The majority of patients had HbA1c testing (81.6%) performed, Nephropathy Care (88.1%) visits, and met the criteria for BP control (72.6%). Only 40.8% met the Eye Exam visit criteria. For patients with HbA1c values, 74.2% had an HbA1c $<8.0\%$. C patients were older than NC patients (60 vs 57 years), more likely to be female (48 vs 46%) and had a lower mean HbA1c (6.6 vs 9.7) ($p < 0.01$ for all). The prevalence of current tobacco exposure was similar between C and NC groups (16% both groups). C patients were slightly more likely to drink alcohol (29 vs 27%) and were less likely to have BMI ≥ 35 compared with NC patients (37 vs 41%) ($p < 0.01$ for all). Both groups showed high compliance with the NQF Nephropathy Care measure (C: 93%, NC: 94%). An increased proportion of C patients met the Eye Exam criteria (46 vs 22%) and BP control (76 vs 68%) measure compared with NC patients. C patients had lower prevalence of diabetic complications (neuropathy [16 vs 24%], nephropathy [18 vs 22%], retinopathy [15 vs 19%], and cardiovascular disease [18 vs 20%]) and lower all cause annual health

care costs (\$19,186 vs \$22,075) compared with NC patients ($p < 0.01$ for all).

Conclusions: Although the majority of patients were in compliance with most of the NQF measures, improvement in care is still needed, especially in ophthalmology. HbA1c control is a central focus of diabetes management and this study indicated a positive relationship between HbA1c control and improved health care quality, reduced costs as well as improved outcomes.

671 | Real-world study of comorbidities and complications in relapsed/refractory acute myeloid leukemia patients identified using a claims-based algorithm

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Background: Comorbidities and complications in Relapsed and/or Refractory Acute Myeloid Leukemia (R/R AML) patients have not been well described at the population level outside of clinical trials.

Objectives: We modified a previously validated claims-based algorithm to identify R/R AML patients to compare comorbidities and complications with an overall AML cohort.

Methods: Patients (≥ 18 years) with ≥ 1 inpatient or ≥ 2 outpatient claims indicating AML (ICD-9-CM code: 205.0x) between 1/1/2006 and 10/31/2015 were identified from the IQVIA Real-World Data Adjudicated Claims—US and followed from 12 months prior to first AML diagnosis (baseline) through 12/31/2015, disenrollment from health plan, or death (minimum 2 months follow-up). AML patients with > 2 cycles of chemotherapy (same cycle if < 14 days since previous chemotherapy; new cycle if between 14–60 days) were considered refractory. Relapsed AML had ≥ 1 one relapse claim (ICD-9 205.02), or who received chemotherapy after a > 60 -day period without any chemotherapy, or had diagnosis/procedure codes indicating repeated stem cell/bone marrow transplant. Comorbidities and incidence of infections, hematologic, cardio/cerebrovascular, hepatic, hemorrhagic, and renal events during follow-up were assessed.

Results: Most (60.4%) AML patients ($N = 3937$) were either relapsed (29%, $n = 1140$) or refractory (31.4%, $n = 1238$). Mean time to relapse/refractory disease was 5.4/3.7 months, respectively. R/R AML patients were similar in age (mean 53 vs 54 years), gender (45% female), and follow-up time (mean 25 months) to the overall AML cohort. R/R AML patients had fewer comorbidities at baseline (28.1% vs 32.6% with ≥ 1 comorbidity) but had consistently higher incidence of all events, and a higher frequency of in-patient deaths (16.1% vs 12.5%). The highest incidence rates (per 100 person-years [PYs]) in R/R AML and overall AML were neutropenia/febrile neutropenia (283 vs 69.4), pneumonia (40.8 vs 25.1), and other hemorrhages (32.4 vs 20.2). The most common chronic conditions were type 2

diabetes (13.4 vs 10.0 per 100 PYs), ischemic heart disease (7.5 vs 6.2), and congestive heart failure (7.3 vs 6.0).

Conclusions: Chronic conditions and complications were more common in R/R AML. Clinical management of this cohort is usually more challenging. A claims-based algorithm enabled identification and characterization R/R AML patients, improving understanding of disease burden and health outcomes.

672 | Health care resource burden among patients with severe aplastic anemia who have had insufficient response to immunosuppressive therapy: A retrospective chart review study

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Background: Aplastic anemia (AA) is a rare blood disorder with 1–2 new cases/million/year in Europe and North America. Primary therapy for patients with severe AA ineligible for allogeneic hematopoietic stem cell transplantation (HSCT) includes immunosuppressive therapy (IST) in combination of antithymocyte globulin (ATG) and calcineurin inhibitors. Therapeutic options beyond IST are limited. The health economic burden of this rare and debilitating condition is poorly understood, especially for refractory cases.

Objectives: To examine health care resource utilization (HRU) among patients with severe AA with insufficient response to IST in real-world practice.

Methods: A retrospective chart review was conducted at Dana-Farber Cancer Institute, US (DFCI) and Hôpital Saint-Louis, France (HSL). Eligible patients were ≥ 18 years old, diagnosed with acquired severe AA between 1/1/2006–7/31/2016, had insufficient response to ≥ 1 course of IST, and had ≥ 12 months follow-up post diagnosis. AA-related HRU was summarized with incidence rates.

Results: Among the 40 patients ($N_{DFCI} = 20$; $N_{HSL} = 20$), mean age at diagnosis was 44.1 years and 53% of patients were women. During follow-up, 25% of patients died; median follow-up time after severe AA diagnosis was 48.3 months. 95% of patients received ATG in combination with cyclosporine or tacrolimus as primary therapy prior to HSCT. The most common secondary severe AA therapies prior to HSCT were eltrombopag (28%) and androgens (15%). 75% of patients received ≥ 1 HSCT with a median time of 15.7 months after first IST. Prior to HSCT, the mean frequency of transfusions per patient per month (PPPM) was 2.7 red blood cell (RBC) and 3.3 platelet transfusions. The mean AA-related HRU rates per patient per year (PPPY) were 0.9 hospitalizations, 0.4 emergency room visits, and 12.8 office visits. Among patients treated with eltrombopag ($N = 11$), the mean number of RBC transfusions PPPM was reduced from 2.2 to 1.3 and platelet transfusions from 2.9 to 2.1 after eltrombopag treatment.

Similarly, AA-related HRU rates appeared lower after eltrombopag initiation (Δ hospitalizations: -0.5 ; Δ emergency room visits: -1.0 ; Δ office visits: -10.2 PPPY).

Conclusions: This study is among the first to quantify the transfusion and health care resource burden of severe AA. In a subgroup of patients receiving eltrombopag, there was a trend toward a reduction in transfusion frequency and HRU following eltrombopag initiation.

673 | Risk factors associated with 7-day versus 30-day readmission among patients with heart failure using nationwide readmission database

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Background: Thirty-day all-cause readmission for heart failure (HF) is a standard measure to evaluate hospital performance. However, a recent study found that a shorter period after discharge such as 7 days may be a better interval to assess hospital quality.

Objectives: To compare risk factors for 7-day versus 30-day all-cause readmission in patients with HF.

Methods: A retrospective cohort from Jan 2014 to Nov 2014 using 2014 Nationwide Readmission Database. 7-day or 30-day all-cause readmission were the main outcomes of interest. Covariates included patient characteristic, hospital characteristics, and admission related information. A patient's first HF admission during January to November 2014 was defined as index admission. Readmission following an index admission was based a guidance from Agency for Healthcare Research and Quality. HF-related readmission were secondary outcomes. Hierarchical regression analysis was used to evaluate the association between each co-variate and readmission status.

Results: The number of patient with all-cause readmission was 20 028 during 7 days after discharge and 62 283 during 30 days after discharge. Depression (odds ratio [OR] = 1.08, 95% confidence interval [CI] = 1.05-1.11), liver disease (OR = 1.15, CI = 1.09-1.21), low house hold income (OR = 1.07, CI = 1.04-1.10), high mortality risk score (OR = 1.09, CI = 1.05-1.13), and having surgery (OR = 1.10, CI = 1.06-1.15) were risks factors for 30-day all-cause readmission but not 7-day. In contrast, non-teaching compared with teaching hospitals were associated with an increased risk of 7-day all-cause readmission (OR = 1.04, CI = 1.01-1.08), but not 30-day.

Conclusions: Hospital-related factors were associated with readmission at shorter period, while other factors such as chronic disease or household status were associated with readmission at longer periods.

674 | Health care resource utilization of conjunctivitis in the general population and in patients with prior antibiotic-resistant infection: A retrospective US claims-based analysis

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Background: Conjunctivitis is a common eye condition characterized by inflammation of the conjunctiva. To date, there is limited information on the overall burden of illness of conjunctivitis in both the general population and among patients with a history of antibiotic-resistant infection (ARI).

Objectives: To compare health care resource utilization (HRU) in patients with conjunctivitis ("cases") versus those without conjunctivitis ("controls") in the general population (GP) and in those with prior ARI.

Methods: Data were from the Optum Healthcare Solutions database (1/1/1998-6/30/2016). GP cases had ≥ 1 diagnosis claim for any conjunctivitis type (index date defined as first claim), and ≥ 60 days of continuous enrolment prior to ("baseline period") and after the index date. A washout period of no conjunctivitis diagnoses/related medication claims was imposed in the 60 days prior to the index date. GP controls never had a conjunctivitis claim; index date was randomly assigned based on distribution of time between enrolment start and index date in GP cases. ARI cases were selected similarly as GP cases but had ≥ 1 ARI diagnosis within 180 days prior to first conjunctivitis diagnosis. Index date for ARI controls was based on time between ARI diagnosis and index date in ARI cases. All-cause HRU over 60 days post-index date was compared between cases and controls using incidence rate ratios (IRR) from Poisson regressions. Inverse probability of treatment weights were used to adjust for baseline differences.

Results: After weighting, baseline differences between cases and controls were well-balanced (GP cases $n = 1\ 002\ 188$, controls $n = 4\ 877\ 210$; ARI cases $n = 706$, controls $n = 15\ 368$). Mean age (years) in GP cases and controls was 39.3 and 38.0, respectively; 46.6% and 47.7% were male. Among ARI cases and controls, mean age was 53.4 and 51.1, respectively; 47.5% and 50.2% were male. HRU was higher in cases in both cohorts: all medical visits (GP: IRR = 2.12 [95% CI: 2.12-2.13]; ARI: 1.41 [1.23-1.63]), hospitalizations (GP: 1.66 [1.62-1.71]; ARI: 1.54 [1.16-2.03]), emergency room visits (GP: 3.10 [3.08-3.13]; ARI: 1.90 [1.37-2.63]), and outpatient visits (GP: 2.18 [2.17-2.18]; ARI: 1.35 [1.21-1.52]). GP cases also incurred more hospitalization days (1.46 [1.42-1.50]).

Conclusions: Conjunctivitis is associated with increased HRU in both GP and ARI patients. Research on cost implications is warranted.

675 | Predicting 30-day mortality or risk of re-hospitalization in Medicare patients discharged to skilled nursing facilities after hospitalization for heart failure

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Background: Nearly one-quarter of Medicare beneficiaries receive post-acute care in skilled nursing facilities (SNFs) after being hospitalized for heart failure (HF). The use of SNF care for patients with HF has steadily increased in recent decades. Despite this, there are no validated risk prediction models for hospitalized patients with HF after being discharged into SNFs.

Objectives: We developed separate predictive models for 30-day all-cause mortality and 30-day all-cause re-hospitalization among hospitalized patients with HF after being discharged into SNFs.

Methods: Using a nationwide dataset including Medicare claims data cross-linked with Minimum Data Set 3.0 (2011-2013), we conducted a retrospective cohort study of 79 329 hospitalized patients with HF discharged into 11 975 SNFs. With sociodemographics, clinical diagnoses, health service use, health conditions, and functional status, we developed separate logistic prediction models for 30-day mortality and re-hospitalization.

Results: The median age of the study population was 84 years and 60% were women. Of these, 6.9% died and 24.5% were re-hospitalized within 30-days after SNF admission. The leading causes for re-hospitalizations were HF (32%), septicemia (8%), and renal failure (7%). Of 48 potential predictors, 14 factors remained in the final parsimonious model for predicting 30-day mortality and 12 factors for re-hospitalization. The C-statistics were 0.70 for 30-day mortality and 0.63 for re-hospitalization. Dyspnea, depression severity, physical limitations, and cognitive impairment were important predictors of these outcomes.

Conclusions: Among hospitalized patients with HF discharged into SNFs, parsimonious models may be used to identify those at risk for dying and being re-hospitalized within 30 days. These models could aid clinicians and family members in improving care for hospitalized patients with HF during this vulnerable period.

676 | Access to patient-centered medical home care among adults with chronic conditions: Findings from the Medical Expenditures Panel Survey

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Background: The patient centered medical home (PCMH) has received considerable attention as a potential way to improve primary care

quality; and patient and health care provider experience, as well as limit the medical cost growth. However, PCMH care has not been explored among adult with chronic conditions in United States.

Objectives: To describe the changes in receiving PCMH among adults with chronic conditions that occurred from 2010 through 2015 and to identify factors associated with adults received a PCMH.

Methods: We conducted a cross-sectional analysis of the 2010-2015 Medical Expenditure Panel Surveys (MEPS) of adults with chronic conditions. Using AHRQ's definition as the basis, we determined whether respondents had a PCMH if they reported that the received comprehensive, patient-centered, and accessible care. Multivariate logistic regression analyses were conducted to explore the relationship between the different variables in the study with access to PCMH.

Results: A total of 20 403 patients with chronic conditions was identified, representing 213.7 million US lives. Approximately 19.7% of the patients were categorized as the PCMH group at baseline who met all the PCMH criteria defined in this study. Overall, the number of adults with chronic conditions received a PCMH decreased from 22.3% in 2010 to 17.8% in 2015. The multivariate analyses revealed that several subgroups including individuals aged 66 and older, with marital status separated, insured by public insurance or uninsured, with low family income, reside in the south or the west, and with poor health were less likely to receive a PCMH. While adults with education years more than 12 years, diagnosed hyperlipidemia or upper respiratory conditions, were positively associated with receiving a PCMH.

Conclusions: The analyses showed strong deficiencies in access to a PCMH between 2010 and 2015. That would raise concerns about the potential value of the PCMH for adults with chronic conditions and suggest that further actions are needed aimed at addressing accessibility to PCMH care to increase national access to PCMH care among US population.

677 | The impact of patient-centered medical home on hypertension-associated health care utilization and cost

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Background: The patient centered medical home (PCMH) has received considerable attention as a potential way to improve primary care quality and patient and health care provider experience, as well as limit the medical cost growth. However, little evidence exists with respect to the effect of PCMH on health care utilization and cost in patients with hypertension.

Objectives: We examined the effect of PCMH on health service expenditures and utilization in a national probability sample of US civilian noninstitutionalized adult population who were diagnosed with hypertension.

Methods: The 2010-2015 Medical Expenditure Panel Survey data were analyzed. Our study population was limited to noninstitutionalized US adults ≥ 18 years of age diagnosed with hypertension. We investigated the impact of PCMH on the direct hypertension-related total, inpatient,

prescription medications, outpatient, emergency room, office based, and other medical expenditures by employing Log transformed multiple linear regression models and the propensity score method.

Results: Of the 18 630 adults identified with hypertension, 19.2% ($n = 3583$) had received PCMH care during 2010 to 2015. After matching, No PCMH group showed greater mean in all hypertension-related health service expenditures and utilization. After adjusting for confounders, PCMH group showed significant lower total, office-based, outpatient, number of office-based visits, and outpatient visits compared with control group.

Conclusions: A significant relationship between experiencing PCMH care and a lower total health care expenditure were found among patient with hypertension. To reduce the overall cost of care for those patients, policy makers should implement new intervention strategies that are effective in facilitating the access to PCMH.

678 | Health care costs and utilization associated with high risk prescription opioid use

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Background: Rates of injuries and deaths from prescription opioids in the United States have never been greater, and the indirect and direct societal costs of the opioid epidemic have been studied. Little is yet known regarding the costs and resource utilization associated with high risk prescription opioid use.

Objectives: To estimate the costs and resource utilization associated with high-risk prescription opioid use through analysis of retrospective health plan claims data.

Methods: We conducted a retrospective cohort study of QuintilesIMS health plan claims for 191 405 non-elderly adults with at least 1 opioid prescription and continuous enrollment in 2012-2013. We used the Johns Hopkins Adjusted Clinical Group (ACG) Risk Adjustment System to create covariates, calculate costs and identify hospital and Emergency Department admissions. We used generalized linear models with propensity score weighting and covariates to quantify total, medical and pharmacy costs as well as any hospitalization and any emergency department visit associated with: (1) users of ≥ 100 morphine milligram equivalents per day for ≥ 90 consecutive days (chronic users); (2) ≥ 30 days of concomitant opioid and benzodiazepine use (concomitant users); and (3) individuals diagnosed with an opioid use disorder. We also examined how the associations varied based on the length of time individuals were characterized as a high-risk user.

Results: Of individuals with one or more opioid prescription, 1.45% were chronic users, 4.81% were concomitant users, and 0.94% were users with a diagnosed opioid use disorder. After adjustment and weighting, chronic users had higher prospective total (40%), medical (3%), and pharmacy (172%) costs. The corresponding increased costs

were 13% (total costs), 7% (medical costs), and 41% (pharmacy costs) for concomitant users, and 28% (total costs), 21% (medical costs), and 63% (pharmacy cost) for users with a diagnosed opioid use disorder. All estimates were statistically significant ($p < 0.01$), and both total and pharmacy costs increased with the length of time individuals were characterized as a high-risk user. Of the three risk groups, only concomitant users were associated with a higher odds of hospitalization or emergency department use.

Conclusions: Individuals with high-risk prescription opioid use have significantly higher health care costs and utilization than their counterparts, especially those with chronic high dose opioid use.

679 | Coverage and out-of-pocket spending on brand versus generic/biosimilar specialty drugs in Medicare part D

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Background: Generic price competition has historically been a successful strategy for lowering US prescription drug prices. However, under Medicare Part D manufacturer discounts reduces out-of-pocket spending for branded drugs but not generics.

Objectives: We compare price reductions and expected out-of-pocket spending for Medicare Part D enrollees for three brand-generic/biosimilar pairs to estimate potential savings for patients using generic/biosimilar products over branded counterparts: a small molecule product for treating high cholesterol (Crestor/rosuvastatin); a small molecule specialty drug for cancer (Gleevec/imatinib); a biosimilar drug approved in the United States for neutropenia (Neupogen/zarxio).

Methods: We used Medicare formulary files from CMS for Q3 2016. We analyzed 897 stand-alone and 1920 Medicare Advantage Prescription Drug formularies. We summarized drug prices at the point of sale and estimated out-of-pocket spending for beneficiaries filling 12 months of therapy. To ensure comparable estimates across products, we limited to a 30-day supply of therapy and a standard dose. We estimated spending based on actual formulary coverage and separately assuming that brand and generic drug users paid only 25% coinsurance in the coverage gap (to reflect expected changes to the Part D benefit in 2020).

Results: Median monthly prices and interquartile ranges (IQR) were \$250 (\$20) and \$61 (\$30), Crestor/rosuvastatin; \$10,152 (\$161) and \$8,661 (\$611), Gleevec/imatinib; and \$5,187 (\$78) and \$4,547 (\$64), Neupogen/zarxio. When considering coverage across all Part D formularies, 95.6% and 52.4% covered Crestor/rosuvastatin; 67.1% and 81.0% covered Gleevec/imatinib; 96.2% and 57.2% covered Neupogen/zarxio. For plans covering products, estimated annual out-of-pocket spending was \$492 lower for generic rosuvastatin versus Crestor (\$281 versus \$774 per year). Out-of-pocket spending was \$1,056 higher for generic imatinib versus Gleevec (\$9,573 versus \$8,517) and \$1,567 higher for the biosimilar zarxio versus Neupogen (\$7,105 versus \$5,538).

Conclusions: Generic competition and biosimilar entry in the specialty drug context may be less effective at reducing drug prices and patient out-of-pocket spending in the United States than anticipated. Fewer generic entrants and incentives for branded drug use within the doughnut hole are likely key contributors. Limitations include limited follow-up time and the inclusion of only three brand/generic/biosimilar comparators.

680 | Disinvestment of health technologies by the Brazilian National Health Technology Incorporation Committee, 2012-2016

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Background: Disinvestment policies for withdrawal of unsafe, ineffective, or low clinical value health technologies are essential for the efficient allocation of health care resources. This process is still little explored in Brazil. Since 2011, the National Health Technology Incorporation Committee (CONITEC) supports the Ministry of Health (MoH) in withdrawal decisions for the Brazilian Unified Health System (SUS).

Objectives: To analyze CONITEC's recommendations for exclusion of health technologies from SUS, between January/2012 and December/2016, examining the characteristics and rationale of withdrawal decisions.

Methods: This was an exploratory, descriptive study based on reports, ordinances, and public consultations available from CONITEC's website. Exclusions were categorized by decision year, type of applicant, type of technology (medicine, health product, or procedure), health care purpose, and disease indication, according to ICD-10. Medicines were classified using the ATC system. The presence of alternate technologies available in SUS and records of public consultations related to CONITEC were verified. The rationale presented for the exclusions was examined.

Results: Only 56 technology exclusions (13.6% of proposals received by CONITEC) were submitted in the period. All proposals originated in MoH secretariats and resulted in a recommendation to exclude the technology from SUS. The main type of excluded technology were medicines (93%). Infectious diseases and rheumatology were indications of 75% of excluded medicines. Immunosuppressants and immunostimulants represented 61% of medicines exclusions. Simplified procedures, without public consultation, accounted for 91% of withdrawal processes and 72% targeted a specific indication and not the medicine itself. Most withdrawn technologies presented available pharmacological alternatives within the system. The main rationale for exclusion included safety risk, alternatives with a better safety profile, and changes in the specific medical condition in MoH Clinical Guidelines.

Conclusions: The number of proposals for technology withdrawal from SUS was significantly lower than the number of approved requests for technology incorporation. This signals a growing pool of incorporated technologies and represents a significant challenge for the Brazilian Unified Health System. The justifications for disinvestment are consistent with criteria present in international guidelines and literature.

681 | Trends in coverage for disease modifying therapies for multiple sclerosis in Medicare part D

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Background: Multiple sclerosis (MS) disease modifying therapy (DMT) costs have risen rapidly over the last decade and currently exceed \$80,000 annually for most agents. One consequence of high DMT costs is greater use of utilization management tools (prior authorizations, step therapy, and cost-sharing) by payers, which may adversely impact medication access and patient care.

Objectives: To describe changes in pharmacy benefit coverage for MS DMTs in the US Medicare program over the last decade.

Methods: Using Prescription Drug Plan Formulary files from the Centers for Medicare and Medicaid Services, we quantified coverage, the use of utilization management policies, and formulary cost-share tiering by Medicare Part D Plans (PDPs) for 11 DMTs from 2007 to 2016. We also estimated monthly and cumulative out-of-pocket costs for Medicare beneficiaries using PDP benefit parameters and cost-sharing amounts for available DMTs in 2016.

Results: While the portion of PDPs covering three or more DMTs were relative stable, trends in coverage for individual DMTs generally declined between 2007 and 2016. The number of PDPs with at least one DMT available without a prior authorization also declined from 40% to 26%. Coinsurance was the predominate form of cost-sharing throughout the study period. The proportion of PDPs with DMTs placed in the highest formulary tiers (>tier 4) increased from a median 11% to 95%. The median coinsurance percentage increased from 25% 2007 to 30% in 2016. Using 2016 standard PDP parameters, the average cumulative annual out-of-pocket expense across DMTs was \$6,659. DMT prescriptions alone would drive beneficiaries into catastrophic coverage phase by March, after which an individual would pay out-of-pocket an average of \$290 per month for the remainder of the year. The DMT with the highest out-of-pocket cost was the generic version of glatiramer acetate (\$8,091) because of the smaller discounts paid by the PDP, which do not count towards an individual's total out-of-pocket maximum before the catastrophic coverage phase is reached.

Conclusions: As DMT prices have increased, Medicare PDPs have reduced coverage, increased access restrictions, and shifted DMTs to the highest cost-sharing tiers. Policy makers need to consider access restrictions and growing cost-sharing burdens as potential consequences of high and rising drug prices.

682 | The economic burden of preventable adverse drug reactions. A systematic review

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Background: Adverse drug reactions (ADRs) are an important cause of morbidity and mortality worldwide with a significant medical and economic burden. They are associated with health care costs due to hospital admissions or prolonged length of stay (LOS), and additional interventions or procedures. In 2012, a meta-analysis showed that 52% of adult outpatients experienced a preventable ADR versus 45% among inpatients

Objectives: The aim of this study was to conduct a systematic review of observational studies to evaluate the economic impact of preventable ADRs.

Methods: A systematic literature review was carried out in Medline, Scopus, and Web of Science from database inception to June 15, 2017. Only observational articles published in English, set in Europe and in the United States of America (USA) and were included. Two reviewers independently assessed the eligibility of each article for inclusion, with all disagreements being resolved by a third reviewer. All cost data were reported in euros.

Results: The systematic search yielded 746 articles, and 19 additional studies were found from reference lists of the articles originally identified. Only 17 articles were selected for inclusion. Among the 17 studies, 8 (47.0%) were published in the period 1996-2008, and 9 (53.0%) were published in 2010-2016. Twelve studies (70.6%) were conducted in Europe and only 5 (29.4%) in USA. More than half of the studies were based on a prospective study design. Three quarters of the studies (70.6%) concerned inpatient ADRs while the remaining studies (29.4%) evaluated outpatients who experienced ADRs leading to hospital admission or Emergency Department (ED) visits. On average, the frequency of preventable ADRs was approximately 40% of all ADRs detected in both inpatient and outpatient settings. Direct costs were the most frequently investigated cost categories. Overall, in the studies concerning inpatient ADRs, the cost of preventable ADRs due to excess LOS ranged from € 2800 to € 9000. In the studies concerning outpatient ADRs, the mean cost of preventable ADRs leading to hospital admission or ED visits was less than half of the inpatient cost, ranging from € 800 to € 3100.

Conclusions: Preventable adverse drug reactions have a significant clinical and economic impact on the health care system in both the outpatient and inpatient setting. Since most ADRs are often preventable, more awareness is needed on preventable ADR reduction and the impact of such reduction on health care costs.

683 | Comparison of outcome and cost between the open, laparoscopic, and robotic surgical treatments for colon cancer: A propensity score-matched analysis using nationwide hospital record database

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Background: There are limited studies that compare the cost and outcome of robotic-assisted surgery to open and laparoscopic surgery for colon cancer treatment.

Objectives: We aimed to compare the three surgical modalities for colon cancer treatment.

Methods: We performed a cohort study using the population-based Nationwide Inpatient Sample database. Patients with a primary diagnosis of colon cancer who underwent robotic, laparoscopic, or open surgeries between 2008 and 2012 were eligible for enrollment. We compared in-hospital mortality, complications, length of hospital stay, and cost for patients undergoing one of these three procedures using a multivariate adjusted logistic regression analysis and propensity score matching.

Results: Of the 386 505 patients undergoing surgical treatment for colon cancer during the study period, 268 605 (69.5%) patients underwent open surgeries, 114 988 (29.7%) underwent laparoscopic surgeries, and 2902 (0.75%) underwent robotic surgeries. Compared with those undergoing laparoscopic surgery, patients undergoing open surgery had a higher mortality rate (OR 2.39, 95% CI 2.04-2.80), more general medical complications (OR 1.60, 95% CI 1.50-1.72), a longer length of hospital stay (6.38 vs 4.47 days), and higher total cost (\$15,541 vs \$13,686) in the propensity score matched cohort. Mortality rate, general medical complications, and length of hospital stay were equivalent in the laparoscopic and robotic surgery groups, but median cost was lower in the laparoscopic group (\$14,102 vs \$16,600 USD).

Conclusions: Laparoscopic colon cancer surgery was associated with a favorable short-term outcome and lower cost compared with open surgery. Robot-assisted surgery had comparable outcomes but higher cost as compared with laparoscopic surgery.

684 | Comorbidity and treatment burden among HIV-infected patients in a US Medicaid population

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Background: Due to the advent of combination antiretroviral (ARV) regimens for human immunodeficiency virus (HIV) treatment, HIV has become a chronic rather than acute illness. As a result, patients are taking ARVs for longer durations, and adherence and tolerability have become key aspects of disease management. Therefore, it is important to understand characteristics of the current population of patients living with HIV.

Objectives: To describe the contemporary comorbidity profile and treatment burden among patients with HIV-1 infection.

Methods: A retrospective study utilizing Medicaid claims data from 4 states was conducted. Patients with at least 1 ARV claim in 2016-2017 (most recent claim defined the index date), at least 1 HIV diagnosis within 1 year prior to index, at least 18 years of age at first HIV diagnosis and less than 65 at index, at least 12 months of continuous eligibility prior to index, and no history of HIV-2 were included. Comorbidities, concomitant medication use, and pill burden were assessed in the years prior to index. Stratified analyses were conducted in patients less than 50 and at least 50 years of age.

Results: Among 3456 study patients, the mean (standard deviation [SD]) age was 47.1 (10.4) years; the majority were Black (55.1%) and male (62.8%). In the year prior to index, mean (SD) daily pill burden was 2.1 (1.4) for ARVs and 5.9 (5.9) for non-ARVs. Patients at least 50 years of age had higher daily pill burden (2.3 [1.5] ARVs, 6.9 [6.5] non-ARVs) than patients less than 50 years old (2.0 [1.3] ARVs, 5.0 [5.2] non-ARVs). Older patients had higher rates of comorbidities compared with younger patients (cardiovascular disease [CVD] 51.6% vs 30.7%, hypertension 46.6% vs 28.5%, asthma/chronic obstructive pulmonary disease [COPD] 22.8% vs 14.7%) in the year prior to index. Among all patients, the prevalence of comorbidities generally increased over time: 27.9% of patients had CVD in the fourth year prior to index, which increased to 40.3% in the first year prior to index. Similar increases were seen for hypertension (24.3% to 36.8%), hyperlipidemia (11.5% to 16.8%), and asthma/COPD (12.7% to 18.4%). Concomitant medication use corresponding to these comorbidities slightly increased over time.

Conclusions: As patients with HIV live longer, their comorbidities and corresponding concomitant medications increase. Treatment guidelines suggest that streamlined ARV regimens may be considered as patient complexity evolves over time.

685 | Estimated costs of pivotal trials for novel therapeutic agents approved by the FDA, 2015-2016

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Background: A critical question in health care is the level of scientific evidence that should be required to establish that a new therapeutic agent has benefits that outweigh its risks. Estimating costs of such evidence provides an important perspective.

Objectives: To assess the estimated costs and scientific characteristics of pivotal clinical trials that supported the approval of new therapeutic agents by the US Food and Drug Administration (FDA) in 2015-2016.

Methods: Novel therapeutic drugs were identified using the FDA's Center for Drug Evaluation and Research's annual summary reports on "Novel Drugs." We excluded diagnostic and imaging agents, adjuvants to surgical or medical procedures, and new formulations or delivery systems for previously approved molecular entities since these agents require markedly different forms of clinical testing to establish benefits. We used FDA reviews, ClinicalTrials.gov, and peer reviewed studies to identify 49 characteristics of each trial. Costs were calculated with a global clinical trial cost assessment tool available to contract research organizations and pharmaceutical sponsors. Main outcomes and measures of interest included estimated mean cost and 95% confidence intervals based on industry benchmark data from 60 countries. Measures of scientific rigor included design (uncontrolled, placebo, active drug), endpoint (surrogate, clinical scale, clinical benefit), enrollment, and treatment duration.

Results: In 2015-2016, based on preliminary analyses, 136 pivotal clinical trials supported the FDA approval of 59 new therapeutic agents with a median estimated cost of \$18 million (interquartile range [IQR], \$11.0M-\$33.6M). Estimated costs varied with scientific rigor and ranged from less than \$5 million for uncontrolled trials for 3 orphan drugs with fewer than 15 patients, to \$342 million (95% confidence interval [CI], \$247M-\$463M) for a non-inferiority trial with endpoints assessing clinical benefit. Twenty-five of 136 (18.4%) trials were uncontrolled, with a mean of \$11.6 million (95% CI, \$9.0M-\$14.2M). Trials with placebo or active comparators had an estimated mean cost of \$33.4 million (95% CI, \$24.3M-\$42.5M). Costs also varied by trial endpoint, treatment duration, patient enrollment, and therapeutic class.

Conclusions: The most expensive trials were ones where the new agent had to be proved non-inferior with clinical benefit endpoints to one already available, or required larger patient populations to document a treatment effect.

686 | Predictors of drug shortages and association with generic drug prices: A retrospective cohort study

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Background: Prescription drug shortages can disrupt essential patient care and drive up drug prices.

Objectives: To evaluate some predictors of shortages within a large cohort of generic drugs in the United States and to determine the

association between drug-shortages and changes in generic drug prices.

Methods: Design: Retrospective cohort study. Setting: Outpatient prescription claims from commercial health plans between 2008 and 2014. Measurements: 7 years of data were divided into fourteen 6-month periods; the first period was designated as the baseline period. The first model estimated the probability of experiencing a drug shortage using drug-specific competition levels, market sizes, formulations (eg, capsules), and drug prices as predictors. The second model estimated the percentage change in drug prices from baseline based on the drug shortage duration.

Results: From 1.3 billion prescription claims, a cohort of 1114 generic drugs was identified. Low-priced generic drugs were at a higher risk for drug shortages compared with medium- and high-priced generic drugs, with odds ratios of 0.60 (95% CI: 0.44-0.82) and 0.72 (95% CI, 0.52-1.00), respectively. Compared with periods of no shortage, drug shortages lasting less than 6 months, 6 to 12 months, 12 to 18 months, and at least 18 months had corresponding price increases of 6.0% (95% CI: 4.7-7.4), 10.9% (95% CI: 8.5-13.4), 14.2% (95% CI: 10.6-17.9), and 14.0% (95% CI: 9.1-19.2), respectively.

Conclusions: Study findings may not be generalizable to drugs that became generic after 2008 or those commonly used in an inpatient setting. The lowest priced drugs are at a substantially elevated risk of experiencing a drug shortage. Periods of drug shortages were associated with modest increases in drug prices.

687 | Patients' needs and wishes regarding pharmaceutical care provided by the pharmacist for women treated with adjuvant endocrine therapy for breast cancer

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Background: Adjuvant endocrine therapy (AET) for hormone receptor-positive (HRP) breast cancer reduces the risk of recurrence. However, non-adherence and early discontinuation rates of women who have been prescribed AET are high. Medication counselling and adherence support may improve adherence.

Objectives: To obtain insight into the needs and wishes of women using AET with respect to medication counselling and the role of the pharmacy team and to explore their views on the role of eHealth in AET.

Methods: A qualitative explorative study was conducted comprising semi-structured interviews (n = 16) and a focus group (n = 5) among women with HRP breast cancer who use or have used AET after initial treatment. A thematic analysis approach was used.

Results: Participants had a strong need for comprehensive information on (the risk of) side effects, what to do in case of side effects, drug-drug (including drug-self-care medicines) interactions, on a continuous

basis. In addition, the timing of the provision of information can be better tuned to the mental state of the patients. Participants reported to have been searching for missing information on the internet, leaflets, and books. However, they had difficulties with finding adequate information and doubted about the reliability of some resources. Participants indicated that pharmacies could play a larger role by providing information in a tailored manner, ie, asking patients after their questions, problems, and concerns on a continuous bases. Conversations should take place in a room with privacy. Finally, participants thought eHealth could contribute to information provision. Most participants had a slight preference towards the development of an application.

Conclusions: Participants expressed a wish for comprehensive information on AET, in particular about side effects, drug-drug interactions, and the use of concomitant self-care medicines. Information about AET was often not provided in a proactive manner nor was counselling on medicines well timed. Pharmacists could play a larger role in deprovision of information and eHealth could be a suitable tool for the provision of reliable information about medicines. An educational pharmacist-led intervention program including eHealth and tailored to patients' needs and wishes should be developed and implemented.

688 | Impact of the interaction between tizanidine and ciprofloxacin on health care utilisation in Swiss Claims Data

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Background: The CYP1A2-mediated interaction between tizanidine and ciprofloxacin has been well described in pharmacokinetic studies, carrying the risk of increased tizanidine exposure with severe adverse effects such as hypotension or alterations of mental status. Although the combination is contraindicated, co-prescribing still occurs in Switzerland.

Objectives: To assess the association of the combination regarding risk for outpatient physician visits and hospitalisations on a population level.

Methods: We conducted a retrospective cohort study using anonymised Swiss health insurance data from 524 797 adult patients in 2014-2015. Patients who were prescribed either ciprofloxacin (exposed, n = 199) or antibiotics other than ciprofloxacin (unexposed, n = 960) within 7 days after receiving a tizanidine prescription (between Feb 2014 and Nov 2015) were included in the study. Hospitalisations and outpatient physician visits within 7, 14, and 30 days after initiation of antibiotic therapy were evaluated as adverse

outcomes. Multiple binary logistic regression and multiple linear regression analysis were applied with adjusting for age, sex, and number of different drugs per year.

Results: A relevant discrepancy between exposed and unexposed group was found for the age variable (median 53.8 vs 54.4). No relevant differences were found for sex, number of drugs, or prescribed tizanidine package strength. Antibiotics received by unexposed patients were penicillins with/without clavulanic acid (36.9%), macrolides (16%), fosfomycin (15.1%), other fluoroquinolones (10.5%), oral cephalosporins (8.2%), sulfamethoxazole/trimethoprim (6.4%), nitrofurantoin (3.8%), and tetracyclines (3.1%). Significant associations between exposure to tizanidine and ciprofloxacin and outpatient physician visit (binary) were found for 30 and 14 days (OR 1.59 [95% CI 1.1-2.34], $p = 0.016$ and OR 1.61 [95% CI 1.17-2.24], $p = 0.004$). A non-significant trend for increase of risk for hospitalisation was found for all evaluated time periods (30 days, OR 1.68 [95% CI 0.84-3.17]; 14 days, OR 1.52 [95% CI 0.63-3.33], and 7 days, OR 2.19 [95% CI 0.88-5.02]). No relevant increase in the number of visits were found for all three observation periods.

Conclusions: The example of tizanidine and ciprofloxacin demonstrates that severe DDI are not only crucial for individual patients but may also have high relevance on a public health level by increasing the risk for health care utilisation.

689 | Improving the use of all-oral direct acting antivirals in hepatitis C virus infected patients with substance use disorder

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Background: Substance use disorders (SUD) account for a disproportionately large burden of hepatitis C virus (HCV) infection. Health disparity in access to HCV treatment remains even though the all-oral direct acting antivirals (DAAs) can be given to HCV-infected patients with SUD.

Objectives: To compare the treatment uptake with all-oral direct acting antivirals (DAA) between chronic hepatitis C virus (HCV)-infected patients with and without substance use disorder (SUD) and to identify patient-level factors associated with DAA uptake.

Methods: A retrospective cohort analysis of the Truven Health MarketScan database (2012-2015) was conducted. DAA initiation rate was calculated as the proportion initiating any kind of all-oral DAAs among newly diagnosed treatment naïve HCV patients (age ≥ 18). A multivariate Cox proportional hazards regression model was used to compare treatment initiation rate between HCV patients with SUD (SUD group) and without SUD (non-SUD group) and to identify patient characteristics associated with DAA uptake.

Results: We identified a total of 21 233 newly diagnosed HCV patients. Of this, 32% of HCV patients ($n = 6871$) had diagnosis of SUD. HCV patients with SUD were younger (24% of SUD group vs 6% of non-SUD group ≤ 35 years old). For SUD group, the DAA initiation rate was 21%, which was significantly lower compared with

non-SUD group (30%) ($P < 0.001$). The mean days to the DAA initiation was 831 days for SUD group, which was significantly longer than non-SUD group (777 days) ($P < 0.001$). SUD group was 25% less likely to initiate DAAs compared with non-SUD cohort (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.70-0.80). Other factors associated with a significantly lower probability of initiating DAAs included being younger (age ≤ 35) (HR, 0.72; 95% CI, 0.65-0.80), being female (HR, 0.89; 95% CI, 0.85-0.94), and comorbidities including hepatitis B virus (HR, 0.46; 95% CI, 0.35-0.61) and pregnancy (HR, 0.37; 95% CI, 0.24-0.56).

Conclusions: Despite effective the all-oral DAA therapies now available, HCV treatment uptake is significantly lower in HCV patients with SUD compared with those without SUD. More research is needed to identify barriers to treating HCV-infected SUDs to improve the linkage to curative HCV treatment in this population.

690 | Outcome and economic comparison for type B aortic dissection patients receiving open surgery, thoracic endovascular aortic repair, and medical treatment

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Background: The currently available clinical trials were underpowered to prove the superior outcome in patients with type B aortic dissection (TBAD) receiving thoracic endovascular aortic repair (TEVAR) as compared with those receiving open surgery (OS) or best medical treatment (BMT).

Objectives: We filled in the gap by analyzing the comparative effectiveness of these three treatment modalities in Nationwide Inpatient Sample, a large real-world database enrolling 1000 hospitals in 38 states.

Methods: Adult patients with a primary or secondary diagnosis of TBAD in NIS between 2005 and 2012 were eligible for inclusion. We excluded patients with aortic aneurysm or received cardioplegia, valve repair, or operations on vessels of the heart. We created a three-category propensity score (PS) by using multinomial logistic regression model and applied the novel three-way matching algorithm for 1:1:1 matching. In the matched cohort, we made a parallel comparison of mortality, complication, and medical cost between three treatment groups.

Results: A total of 73 628 patients were included in the primary cohort, of which 3612 were matched to form three equal sized treatment groups ($n = 1306$) for comparison. There was no significant difference in the 22 baseline covariates between three treatment groups after three-way PS matching. TEVAR was associated with significant lower mortality as compared with OS (OR 0.61, 95% CI: 0.47-0.81, $p = 0.0004$) or BMT (OR 0.70, 95% CI: 0.51-0.92, $p = 0.0091$). There was no significant mortality difference between OS and BMT

(OR 1.15, 95% CI: 0.89-1.48). TEVAR was also associated with lower complication rate, shorter hospital stay, and lower medical cost compared with OS though higher ones as compared with BMT (Table 1). **Conclusions:** TEVAR is associated with the lowest mortality as compared with BMT and OS in the management of TBAD and may be the most cost-effective treatment for TBAD.

691 | Association between use of phthalate-containing medication and semen quality among men in couples referred for assisted reproduction

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Background: Phthalates and their metabolites have been shown to disrupt the hormone signalling in animal studies. One study has shown associations between medicinal phthalate exposure and poor semen quality, suggesting similar effects in humans

Objectives: To investigate the association between medicinal phthalate exposure and semen quality within a cohort referred to assisted reproduction treatment

Methods: Exposure to phthalate-containing drugs was assessed from the Danish Register of Medicinal Product Statistics. Outcome measures were obtained at the first contact with the fertility clinic and categorized according to the International Statistical Classification of Diseases (ICD-10). The association between current use of phthalate-containing medications less than 90 days prior to semen sampling and reduced semen quality was analysed using unconditional logistic regression, adjusting for potential confounders

Results: In total, 57 cases and 72 controls redeemed at least one prescription for a drug containing ortho-phthalates in the 90 days before their first semen sample, yielding an adjusted odds ratio (OR) of 1.30 (95% CI: 0.91-1.85) for poor semen quality when compared with males exposed to phthalate-free generic drugs. Similarly, 81 cases and 78 controls exposed to a drug-containing polymers had increased odds of poor semen quality (OR = 1.71, 95% CI: 1.24-2.35). Current exposure to polymer-containing products from alimentary tract and metabolism drugs was associated with the highest OR of 2.80 (95% CI: 1.63-4.84). Comparing males exposed to drugs containing ortho-phthalates or polymers with males unexposed to prescription drugs, we found adjusted ORs of 1.32 (95% CI: 0.93-1.87) and 1.73 (95% CI: 1.26-2.36), respectively. We saw no clear relationship between degree of exposure and odds of poor semen quality

Conclusions: Our results support the likely negative effect of phthalate exposure from medicinal drugs on semen quality. As exposures from medicinal products are readily avoidable, our findings may be of relevance to regulatory authorities

692 | Abstract Withdrawn

693 | Prescribing patterns of benzodiazepine in Malaysia from 2014 to 2016

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Background: Although benzodiazepines (BZDs) are often prescribed to treat wide range of psychiatric and neurological conditions, they are also associated with various harms and risks, as well as tendency of inappropriate prescribing. To date, the prescribing patterns of BZDs at outpatient tertiary hospital in Malaysia are still scarce.

Objectives: To examine the patterns of BZDs prescribing at outpatient tertiary hospital in Malaysia.

Methods: A cross-sectional retrospective study was conducted from January 2014 to December 2016 using the prescriptions received by the outpatient pharmacy of tertiary hospital. Prescriptions with any seven types of BZDs (alprazolam, bromazepam, clobazam, diazepam, clonazepam, lorazepam, and midazolam) were identified and included in this study. Information on patients' age and gender, prescription date, drug name, dosage, frequency, duration, quantity supplied, and prescriber's name were extracted from the prescriptions. Only prescriptions for patients' age of 18 and above were included in this study. Total number of prescriptions with BZDs, total number of patients received BZDs, and total number of each type of BZDs were measured yearly and over 3 years. Data were analyzed descriptively using Stata v13.

Results: A total of 5711 BZDs prescriptions were issued ($n = 1959$, $n = 2051$, and $n = 1701$ for year 2014, 2015, and 2016, respectively) from January 2014 to December 2016. BZDs were prescribed for 1947 patients ($n = 895$ in year 2014, $n = 934$ in 2015, and $n = 782$ in 2016). Alprazolam (39.7%, $n = 3542$) was the most frequently prescribed followed by lorazepam (21.1%, $n = 1880$), diazepam (20.7%, $n = 1851$), clonazepam (17.1%, $n = 1530$), and less than 1% to other BZDs. Sixty percent ($n = 5422$) of patient were prescribed with short-acting BZDs, 21.6% ($n = 1928$) intermediate-acting BZDs and 17.1% ($n = 1530$) long acting BZDs. Majority (90.7%, $n = 5015$) of BZDs prescription were for psychiatric disorders, in which, higher percentage (82.3%) of BZDs were prescribed as anxiolytics followed by 17.1% as hypnotics. Among all BZDs, alprazolam, and lorazepam showed decreasing pattern over 3 years period.

Conclusions: Short-acting BZDs (alprazolam and lorazepam) were highly prescribed at the outpatient tertiary hospital in Malaysia. The main indication of the BZDs was as anti-anxiety. However, data available were from the prescriptions only. Thus, further research is required to examine the use of BZDs at patient-level.

694 | Comorbidities and treatment initiation in patients with Parkinson's disease: A retrospective cohort study using a US insurance claims database

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Background: Parkinson's disease (PD) is a neurodegenerative disorder affecting one in 100 people over the age of 60. PD patients often have pre-existing comorbid conditions, and despite the multiple symptomatic treatments available, a high unmet medical need remains due to loss of efficacy and accumulation of complications.

Objectives: Main objectives were to (1) describe demographics and comorbidity profiles of incident PD patients and (2) describe the most commonly used first-line treatments and the time from diagnosis until treatment initiation.

Methods: Retrospective cohort study using the Truven MarketScan Commercial and Medicare Supplemental databases between 2007 and 2016. We identified incident PD patients by selecting subjects with two PD-related claims (ICD9 332.0 and/or ICD10 G20) and no PD claim for ≥ 12 months beforehand. We summarised the patients' demographics and baseline Charlson Comorbidity Index (CCI). We estimated median time to initiation of treatment using the Kaplan Meier method and conducted Cox proportional hazards analyses to identify predictors. Treatments of interest were levodopa and levodopa combination therapies, dopamine agonists, adamantane, monoamine oxidase B inhibitors (MAO-Bi), and other dopaminergic agents.

Results: We identified 84 104 incident PD patients with mean (SD) follow-up time of 4.9 (2.6) years. Mean (SD) age at first diagnosis was 73.4 (12.0) years and 58.3% were male. The majority (64.7%) of patients had comorbid conditions, of which the most prevalent were diabetes mellitus (33.5%), cerebrovascular disease (21.8%), and congestive heart disease (17.6%). 68 532 (81.5%) patients had insurance drug coverage and were eligible for treatment pattern analyses. Levodopa and levodopa combination therapies were the most commonly prescribed treatments (52.6%), followed by dopamine agonists (12.4%) and MAO-Bi (6.7%). Overall, the median time between diagnosis and initiation of treatment was 37 days (95% CI 36-38). Gender (hazard ratio [HR] female vs male 0.93 [0.92-0.95]), age (HR 50-70 vs <50 1.37 [1.30-1.45]), and CCI (HR 3+ vs 0 0.79 [0.77-0.80]) were associated with time to treatment initiation.

Conclusions: Overall, the time from diagnosis to initiation of treatment was relatively short, suggesting that symptom management is a priority in PD patients. Patient age and specific comorbidities may play a role in the class of treatments prescribed and initiation of treatments relative to diagnosis.

695 | Treatment patterns among patients with multiple sclerosis initiating Glatopa therapy: A descriptive analysis using a large US claims database linked with electronic medical records

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Background: Glatopa 20 mg/mL was introduced in April 2015 as a follow-on glatiramer acetate (FOGA) therapy for patients with multiple sclerosis (MS). Persistence data on Glatopa 20 mg/mL (FOGA) is relevant to inform ongoing scientific discussions about the complexity of Copaxone (branded glatiramer acetate [GA]) and FOGAs.

Objectives: To characterize descriptively the demographics and switching patterns of FOGA use among MS patients from a large US claims database linked with electronic medical records.

Methods: Patients were from OM1 Data, a geographically representative US sample of health-insurance patients linked with electronic medical records. Adult MS patients with ≥ 1 pharmacy claim for FOGA between 01JUN2015 and 30SEPT2017 (identification period) were included (n = 3387, including 673 linked). The index date was the date of the first pharmacy claim for FOGA during the identification period. Patients had continuous enrollment in a single health plan ≥ 6 months prior to index date and at least 3 months following index date. Switches from FOGA to other DMTs were evaluated 1, 2, 3, and 6 months post-initiation.

Results: In all, 3387 patients were included (75% female, average age 50, median 1.23 years of follow-up). One thousand nine hundred patients (56%) had a prior fill at some time during baseline for once-daily branded GA 20 mg/mL. Of the 3387 patients, 38% (n = 1278) had switched to branded GA within 1 month after FOGA was dispensed, and 50% (n = 1703) patients had switched to branded GA within 6 months after starting FOGA. Patients switching to branded GA predominantly switched to 20 mg/mL, rather than to 40 mg/mL three-times-a-week. Of those switching to branded GA 20 mg/mL, 75% had been prior branded GA 20 mg/mL users before FOGA initiation.

Conclusions: While the exact reasons remain unknown, a proportion of FOGA patients are switching within a relatively short time period after initiation of FOGA to branded GA. This study highlights the importance of understanding switching behaviors associated with new MS therapies. Additional studies are needed to confirm these findings.

696 | Utilisation of antiepileptic drugs in girls and women of childbearing potential in three European countries

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Background: Following evidence in the literature relating to an increased risk of neurodevelopmental disorders in children exposed to valproate in utero, the European Medicines Agency has required a study to characterize the prescription patterns of antiepileptic drugs (AEDs) in women of childbearing age in Europe. The EUROMediSAFE Consortium proposed a study in 3 European countries, United Kingdom, Italy (Emilia Romagna and Tuscany), and France.

Objectives: To characterize the prescription patterns of antiepileptic drugs (AEDs) in women of childbearing age in Europe.

Methods: We performed a descriptive study using 4 electronic health care databases from January 1, 2007 to December 31, 2016. AED prescriptions (N03A and N05BA09) in females aged between 10 and 50 years and separately in pregnant women during the study period were examined. Prevalences, trends of AED prescriptions, and indications were described.

Results: Within the four databases, there were 5 439 534 eligible females. The prevalence of AED prescribing remained relatively stable in Emilia Romagna at approximately 13/1000 women over the 10-year study period, while in Tuscany there was a small and steady increase in prescribing until approximately 2015 when it leveled out at approximately 18/1000 women. In the United Kingdom, the prevalence of prescribing steadily increased and doubled during the study period from 14/1000 women to 29/1000. This increase was largely associated with an increase in both gabapentin and pregabalin prescribing. In France, a large decline in AED prescribing was observed during 2011 and 2012, associated with a reduction in the prescribing of clonazepam, before prescribing returned to more stable levels at approximately 18/1000 women. Overall, during the study period, we observed a slight decline in valproate prescribing and an increase of pregabalin/gabapentin prescribing. In all regions the prevalence increased with age. Prescribing in those aged 10-14 years was very similar in all regions. In all regions, AEDs were mainly prescribed for epilepsy and neuropathic pain.

Conclusions: This 10-year survey shows a steady decline in valproate prescriptions for women of childbearing age. Conversely, we observed

an increase in AED prescriptions for neuropathic pain, associated with an increase in the use of pregabalin and gabapentin, drugs which have shown adverse effects in rats on embryo-fetal development and viability, and for which human pregnancy data are sparse.

697 | Impact of new oral disease-modifying therapies on the prescription of injectable and off-label drugs in multiple sclerosis in France over 2011-2015 using national administrative databases

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Background: Multiple sclerosis (MS) is a chronic neurological disease starting in young adulthood and leading to disability on the long-term. Fifteen disease-modifying therapies (DMTs) specific for MS are available in France. Among these DMTs, six are injectable drugs (four beta-interferon, peginterferon and glatiramer acetate), three are in-hospital infused DMTs, and three are off-label drugs (azathioprine, methotrexate, and mycophenolate mofetil). From 2011 to 2015, three oral DMTs were introduced and widely prescribed: fingolimod (2011), teriflunomide (2014), and dimethyl fumarate (DMF) (2015).

Objectives: To describe the landscape of DMTs in France over the 2011-2015 period and evaluate the impact of oral drugs on the prescription of injectable and off-label DMTs.

Methods: An exhaustive study population was formed of the prevalent and incident persons with MS (PwMS) in the French national health insurance databases (97% of French population covered). They were identified over 2010-2015 thanks to a validated algorithm using diagnoses of hospital admissions, MS-specific DMTs and MS long disease duration status. Their care consumption, especially DMT prescription, was followed in the databases from January 1, 2011, until the earliest of death or December 31, 2015. For each category of DMT (injectable excluding peginterferon, off-label, and oral), the proportion of PwMS who used each DMT was computed annually and over all study period.

Results: In total, 111 334 PwMS, whom 56 122 (50.4%) had at least one delivery of a DMT, were identified in the databases, with a F:M sex-ratio of 2.5 and a median age of 47 years in 2011. Over 2011-2015, 40 721 (36.6%) and 8734 (7.8%) patients had at least one prescription of an injectable or off-label DMT, respectively. Since 2011, 23 062 patients (20.7%) had at least one delivery of an oral DMT, namely, 8912 had fingolimod, 8151 DMF, and 7206 teriflunomide. The proportion of PwMS using fingolimod rose from 0.1% to 6.7%, and teriflunomide from 1.5% to 6.4% over their respective availability period. DMF was used by 7.4% of PwMS its first year of availability. Conversely, use of injectable DMTs decreased from 24.8% to 19.3%

and use of off-label DMTs remained stable around 4.5% over the study period.

Conclusions: This first study on the whole population of PwMS in France permitted to highlight the increasing prescription of oral DMTs since their introduction at the expense of injectable drugs.

698 | Prescribing valproate to girls and women of childbearing age in Germany: Analysis of trends based on claims data

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Background: Exposure to valproate during pregnancy is associated with an increased risk of malformations and developmental disorders in the child. Due to the teratogenic risk valproate should not be used in girls or women who may become pregnant. In 2014, the European Medicines Agency (EMA) strengthened the warnings and advised not to prescribe valproate in women of childbearing age unless other treatments were ineffective or not tolerated.

Objectives: To examine time trends of valproate dispensations in girls and women of childbearing age and to assess treatment indications and medical specialties of prescribers.

Methods: Based on data from the German Pharmacoepidemiological Research Database (GePaRD) from 2004 to 2015 and claims data from the Techniker Krankenkasse (TK) for 2016, we selected yearly cohorts of girls and women between 12 and 50 years. For each year, the proportion of women with at least one valproate dispensation was calculated and indications and medical specialties of prescribers were analyzed.

Results: The age-standardized proportion of girls and women with at least one valproate dispensation declined by 28% between 2004 and 2016 (2.91/1000 vs 2.09/1000). The largest decline was observed for young women aged 16 to 20 years (−48% between 2004 and 2015). In 2015, epilepsy (66.9%) and bipolar disorder (13.6%) were the most frequent indications, but we also observed relevant off-label use for migraine/headache (5.6%), schizoaffective disorder (4.3%), and other mental disorders (8.9%). Among women with epilepsy, the proportion treated with valproate declined from 26.2% to 16.8% between 2004 and 2015, whereas there was little change in women with bipolar disorder (9.3% vs 8.0%). In 2015, 46.3% of valproate dispensations were issued by neurologists or psychiatrists

and 29.6% by general practitioners, internal medicine, or family doctors.

Conclusions: In Germany, exposure to valproate declined for girls and women of childbearing age, particularly in the age group 16 to 20 years and for the treatment of epilepsy. In women with bipolar disorder and in most off-label indications, no relevant decline was observed. Awareness of valproate's teratogenicity still needs to be improved among prescribing physicians.

699 | Disease modifying therapy dispensing during pregnancy: A multidatabase pregnancy cohort of women with multiple sclerosis

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Background: Despite recommendations of no use in pregnancy, women with multiple sclerosis (MS), particularly those with more active disease, may continue to use disease modifying therapies (DMTs) throughout pregnancy. Due to the relative low prevalence of MS in pregnant women, few studies have described patterns of DMT dispensing in this population.

Objectives: To describe dispensing patterns of DMTs during pregnancy in women with MS.

Methods: Pregnancy cohorts were identified within two large administrative health care databases in the United States: the Medicaid Analytic Extract (MAX) from 2000 to 2013 and the Truven Health Marketscan (Truven) from 2011 to 2015. Women were included if they were continuously enrolled from 90 days before the estimated last menstrual period date (LMP) until 90 days after delivery. MS was ascertained using ICD-9-CM diagnosis codes of 340.xx on at least two separate days from 90 days before LMP until delivery from medical claims. The proportion of women with DMT pharmacy dispensing or procedure claims around pregnancy were reported overall and by DMT type.

Results: Within a combined source population of 2.8 million pregnancies, we identified two cohorts of 746 (0.004%) and 1258 (0.2%) pregnant women with MS in MAX and Truven, respectively. Average cohort age was 24 years in MAX and 31 years in Truven. In both cohorts, approximately 35% of women with MS were exposed to a DMT in the 90 days before LMP. First trimester exposure to DMTs overall remained stable over calendar years at around 30% in MAX and around 25% in Truven. DMT use declined during the second (8% MAX, 5% Truven) and third trimesters (8% MAX, 7% Truven) but increased again after delivery (26% MAX, 30% Truven). The most commonly dispensed DMTs in the first trimester were glatiramer acetate (12% in both cohorts) and interferon beta (19% MAX, 7% Truven). Of the other DMTs, only natalizumab and fingolimod hydrochloride had a combined total of more than 11 exposed pregnancies.

Conclusions: DMT use in pregnant women with MS has remained stable in the last decade. While dispensing dropped as pregnancy progressed, approximately a quarter of pregnancies are exposed to DMTs in the first trimester, highlighting the need to define what, if any teratogenic risks are associated with these medications. Despite combining two large health care databases, the number of women with MS exposed to specific DMTs in the population is very low, challenging the assessment of their safety in pregnancy.

700 | Use of analgesics in France, following dextropropoxyphene withdrawal

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Background: In 2009, the European Medicines Agency recommended withdrawal of dextropropoxyphene (DXP); in March 2011, it was withdrawn from the market in France. Up until that time the combination dextropropoxyphene-paracetamol (DXP/PC) was widely used for analgesia. At withdrawal, French regulators recommended that DXP/PC be replaced by other step 2 analgesics, ie, tramadol, codeine, or opium-containing drugs, or by PC for a weak level of pain.

Objectives: To investigate prescribing behaviours after DXP/PC withdrawal, dispensations of analgesics before and after withdrawal were analysed.

Methods: Aggregated dispensation data of analgesics prescribed between January 2009 and December 2012 in the Rhône-Alpes region were obtained from the general health insurance claims data; changes in analgesic dispensation over time were analysed with the ATC/DDD methodology. Pre (Jan-June 2009) and post-withdrawal (Jan-June 2012) changes of DDDs were computed for each analgesic step.

Results: The dispensations of DXP/PC experienced a two-step decrease until 2011. Over the withdrawal period 2009-2012, there was a 14% decrease in the overall use of analgesic (from 109 to 94 DDDs), while the use of step 2 analgesics declined by 46% (-22 DDDs, from 47 to 25 DDDs). This latter decline included a cessation of use of DXP/PC (29 DDDs in 2009) that were only in part (+7 DDDs, from 18 to 25 DDDs) compensated by increased use of codeine, tramadol, and opium, in monotherapy or combined with PC. For step 1 analgesics, use increased with 9%, mostly PC (+8 DDDs, from 31 to 39 DDDs). Step 3 analgesics dispensations remained largely unchanged over this period (around 3 DDDs).

Conclusions: In the Rhône-Alpes region, DXP/PC withdrawal was accompanied in part by an increased use of same level analgesics, and in part by an increased use of PC in monotherapy. The extent of DXP/PC use before withdrawal, and the increased use of PC after DXP withdrawal, underline the complexity of pain management.

701 | Abstract Withdrawn

702 | Initiation of long-acting injectable antipsychotics in the Canadian province of Manitoba

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Background: First-generation antipsychotic (FGA) use declined after the introduction of second-generation antipsychotics (SGAs), including use of FGA long-acting injectable (LAI) antipsychotics. Risperidone was the first SGA LAI introduced in 2004, followed by paliperidone in 2010 and aripiprazole in 2014. While LAIs are typically reserved for patients who are nonadherent with oral formulation, recent evidence supports earlier treatment with LAIs in reducing relapse rates for all patients requiring maintenance antipsychotic therapy.

Objectives: This study aims to describe the use and users of LAI antipsychotics in Manitoba over a period of 20 years.

Methods: The Manitoba Population Research Data Repository at the Manitoba Centre for Health Policy (MCHP) was used to identify LAI antipsychotic users between 1996 and 2016. Diagnoses were identified by ICD codes in hospital abstracts and medical claims databases. All analyses were conducted with SAS statistical software.

Results: There were 3341 LAI antipsychotic users in the study period. LAI antipsychotics comprised an average 18.8% of incident antipsychotic prescriptions (oral and LAI) among individuals with schizophrenia; in 2015, incident LAI dispensations surpassed incident oral antipsychotic dispensations in those with schizophrenia (231 versus 206). LAI antipsychotics were initiated a mean of 3.1 (SD: 4.4) years after first record of schizophrenia diagnosis and 4.9 (SD: 6.1) years after bipolar disorder diagnosis. On average, 2.4 (SD: 1.6) different oral antipsychotics were dispensed prior to first LAI and only 42.2% of LAI users had a previous dispensation of the same drug in oral formulation.

Conclusions: LAI antipsychotic use in Manitoba is increasing, but LAIs are routinely prescribed with a delay after psychiatric diagnosis.

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703 | Trends in opioid and analgesic utilisation in Ireland from 2000 to 2015

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Background: Analgesic intensification has been a mainstay of pain management since the WHO analgesic ladder was published in 1986. During this time, opioid use has increased and become a major public health concern. To date, temporal trends in analgesic and opioid use have not been examined in Ireland.

Objectives: To characterise changes in analgesic prescribing in Ireland over a 15 years period from 2000 to 2015.

Methods: This is a repeated cross-sectional study of administrative pharmacy claims data from 2000 and 2015. It includes patients in the Eastern Health Board region of Ireland eligible for the General Medical Services (GMS) scheme. This public health scheme over-represents socioeconomically deprived and older people. The primary outcome is dispensing of opioid medications (both prevalence of any use and rate per 1000 items/1000 GMS eligible population (both standardised to the 2015 population). Secondary outcomes included dispensing of strong opioids and long-acting opioid formulations, and other analgesics (NSAIDs, paracetamol, lidocaine patches, gabapentinoids, and triptans). Logistic regression was used to determine the likelihood of an opioid dispensing in 2015 compared with 2000, controlling for age, sex, number of dispensed items, and other analgesics.

Results: The eligible study population increased from 364 436 in 2000 to 523 653 in 2015. In 2000, 19.6% had an opioid dispensed compared with 21% in 2015, while the rate increased from 1.77 to 2.03 items/1000 items/1000 individuals. Strong opioids composed 20.2% of opioids dispensed in 2000 compared with 43.7% in 2015, while long-acting opioids also increased (3.9% to 13.9%). Tramadol, codeine, oxycodone, fentanyl, and buprenorphine use increased over time while morphine, dihydrocodeine, and dextropropoxyphene decreased. Controlling for demographics and other prescribing, the likelihood of an opioid dispensing was significantly lower in 2015 compared with 2000 (adjusted odds ratio 0.7, 95% CI 0.69, 0.71); however, the odds of being dispensed a strong opioid (1.03, 95% CI 1.01, 1.06) or long-acting formulation (1.23, 95% CI 1.16, 1.29) were significantly higher.

Conclusions: Although opioid utilisation increased during this time in absolute terms, the likelihood of receiving an opioid has decreased when adjustment for demographic change and other analgesic prescribing is accounted for. However, patients are now more likely to receive a strong or long-acting opioid, and it is important to ensure appropriate use of these stronger preparations to minimise misuse, dependency and harm.

704 | Identifying pain medications for trigeminal neuralgia patients in a US claims database

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Background: Trigeminal neuralgia (TN) is a severely painful condition. Anti-epileptics, such as carbamazepine, are often prescribed for daily use to manage pain. However, the full picture of pain management in TN patients is not fully understood.

Objectives: Utilizing an insurance claims database, evaluate the use of pain medications in TN patients in the United States.

Methods: Analyses were performed in the Truven Health Analytics MarketScan insurance claims database, 2011-2017. A TN case was defined as 2 or more TN codes at least 27 days apart. At least 12 months of data after the first TN claim were required and cases were followed to their exit from the database. A list of pain medications of interest was created using NDC codes. In conducting this study, some methodologic issues were considered. Prescriptions for pain medications during the study period were not necessarily related to TN and instead could be for a surgery/procedure. To address this, prescription claims starting the day prior to and through the 60 days after a surgery/procedure were excluded. Approximately 60% of TN patients had an additional pain comorbidity. Therefore, TN cases were stratified by comorbid pain conditions.

Results: The most commonly prescribed pain medications in the overall TN population were codones (38%), tramadol (16%), and ketorolac injections (10%). As expected, these prescriptions were more prevalent among individuals with additional pain conditions. When comparing prescription claims in TN patients with and without an additional pain comorbidity, codones were prescribed for 53% vs 15%, tramadol was prescribed for 23% vs 4%, and ketorolac injections were prescribed for 15% vs 2%.

Conclusions: A substantial number of TN patients in the United States are prescribed pain medications, most commonly codones. Of note, this study is limited by the inability to examine the use of over-the-counter pain medications, such as acetaminophen, that may also be used in pain management. As always with insurance claims, only the prescription is captured and the pattern of actually ingesting the drug is unknown. Given the concerns around opioid use and its potential risks, the findings of this study are indicative of an unmet need for alternative pain management in TN patients.

705 | Recent pharmacoepidemiology of tic disorders in Korea: A nationwide population-based study

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Background: Tic disorders (TD) are known to be associated with a high prevalence and a high incidence of comorbidities among mental illnesses in a pediatric population; thus, it should be cautious about pharmacotherapy. However, there is a dearth of real-world evidence investigating pharmacoepidemiology of TD.

Objectives: The objective of this study is to examine the prevalence and prescription patterns among patients with TD according to comorbidities in Korea.

Methods: This study was designed as a population-based pharmacoepidemiology study using retrospective health insurance claims data. The study population was defined as patients (aged 2–19) diagnosed with TD (F95.x, ICD-10th-code) at least more than two times in 2014 Health Insurance Research and Assessment-Pediatric Patient Sample data. Patient-unit analysis and claims-unit analysis were performed to estimate demographic statistics and analyze prescription patterns by comorbidities.

Results: A prevalence of TD was 2.1 per 1000 pediatric population. Most patients were boys (82.7%) and the mean age (standard deviation) was 11 (3.7) years old. Three-quarters of patients with TD had more than one mental comorbidity, and half of them had attention-deficit hyperactivity disorders (ADHD; 50.9%). Of the TD patients without comorbidities, 44.2% had no drug prescription; however, only 4% of patients with both TD and ADHD had no drug prescription. Patients with both TD and ADHD were frequently prescribed with atomoxetine (15.6%), aripiprazole (15.1%), and methylphenidate (15.0%).

Conclusions: Findings demonstrate that it is common that patients with TD have associated mental comorbidities. This emphasizes the need for the long-term pharmacoepidemiology study to establish safe use based on evidence-based medicine in TD according to comorbidities.

706 | Benzodiazepines and Z-drug use in Canadian adults—Drug utilization study (2001–2016)

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Background: Benzodiazepines (BDZ) and Z-drugs (Z) remain widely used sedative-hypnotic medications which are not devoid of risks such as falls leading to fracture or motor vehicle accidents. Evaluation and monitoring of population-based use remains important for health policy considerations and feedback on prescribing practices.

Objectives: To determine trends over a 15-year period, in a general Canadian adult population, by drug class (BDZ, Z, BDZ + Z) for (a) estimated consumption, (b) mean daily doses, and (c) prevalence of any-use by age and sex category.

Methods: A drug-utilization study using administrative data from the period 01/04/2001–31/03/2016 covering all adult residents captured in the Manitoba Health Insurance Registry (>98% of adult population of ~850 000–1 000 000) was conducted. Eligible persons were those ≥18 years of age with receipt of ≥1 prescription for a BDZ or Z.

Prescriptions were categorized annually by fiscal year (April 1–March 31) prior to analysis. Consumption was determined using the WHO ATC-DDD methodology and calculated as DDD/1000 persons/day. Mean user daily doses by class were determined by conversion of individual drug doses to Diazepam Milligram Equivalents (DME). Prevalence was determined for males and females separately by age groups (18–64, 65+). Changes were assessed using simple linear regression at an a priori alpha of 0.05 with null-hypotheses of no change over time for all trends.

Results: 12 331 033 dispensations were analyzed for 394 126 patients from 2001–2016. (a) The DDD/1000 persons/day decreased by 3% for BDZ (30.86 to 29.97), increased by 350% for Z (8.13 to 28.60) and increased by 50% for BDZ/Z combined (38.99 to 58.57). Significant positive linear trends were observed for Z ($R^2 = 0.98$, 95% CL $\beta = 1.34$ –1.60) and BDZ/Z ($R^2 = 0.78$, 95% CL $\beta = 1.15$ –2.14) but not for BDZ alone ($R^2 = 0.06$, 95% CL $\beta = -0.21$ –0.56). (b) The average daily dose, in DME, increased by 20.6% for BDZ (12.60 to 15.20), 8.6% for Z (9.94 to 10.79) and 10.7% for BDZ/Z (12.15 to 13.46). Significant positive linear trends were observed on the mean DME/day for Z ($R^2 = 0.90$, 95% CL $\beta = 0.06$ –0.09), BDZ ($R^2 = 0.93$, 95% CL $\beta = 0.16$ –0.22), and BDZ/Z ($R^2 = 0.83$, 95% CL $\beta = 0.07$ –0.13). (c) There was no significant change in prevalence for any age-sex group. Prevalence was highest for older females (65+) at 26% and lowest for males (18–64) at 6.8%.

Conclusions: Overall consumption as well as dose intensity increased in the Manitoba population for BDZ/Z-Drugs, despite prevalence of “any” use remaining stable.

707 | Non-prescription use of opioids among university students

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Background: Opioids are prescription drugs subjected to commercialization control in Brazil and many countries. The increase in the non-prescription use and misuse of opioids in the recent years is associated with an escalated risk of substance abuse. It is a reason of significant concern for health authorities and professionals and a recognized public health problem worldwide.

Objectives: To estimate the frequency of the non-prescription use of opioids among undergraduate and graduate students.

Methods: We invited undergraduate and graduate students of the Universidade Federal de Minas Gerais, one of the largest Brazilian universities, to answer a web-based questionnaire comprising: (i) demographic characteristics; (ii) the use of medicines (ever and current use); and (iii) information on habits and lifestyle. Current use was defined as the use of opioids in the 4 weeks preceding the survey. Data were collected from September 2014 to January 2015. Absolute and relative frequencies were estimated.

Results: The study included 378 students. A total of 41 (10.9%) reported the non-prescription use of opioids; 17% reported current use of non-prescription opioids. Among the students who reported the non-prescription use of opioids, 70% were men, 68.3% were undergraduate students, and 46% reported the use of other non-prescription medicines.

Conclusions: We found a high frequency of non-prescription use of opioids among university students in Brazil, similar to frequencies observed in other countries (12%). The irrational use of medicines was not restricted to opioid drugs, and this scenario may impose a disturbing health risk to this population. The acquisition without an appropriate prescription demonstrates important failures in the control of the commercialization. It is essential to improve policies to control the commercialization of these drugs together with larger investments in health education to promote the safe use of these medicines.

708 | Trends in prescription opioid use among hemodialysis patients in the United States, 2007-2014

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Background: Hemodialysis (HD) patients frequently experience chronic pain and have an elevated risk of opioid-related adverse events. Few studies have examined opioid utilization among these patients.

Objectives: To quantify annual rates of opioid utilization among HD patients and identify sub-groups at high-risk of receiving opioids.

Methods: We used individual-level longitudinal Medicare data from the United States Renal Data System and Poisson regression to estimate the rates of opioid utilization among HD patients from 2007 through 2014. We limited our analysis to US HD patients 18 years and older with consistent Medicare part A, B, and D coverage; HD patients primarily obtain universal health coverage through Medicare. We examined four measures of opioid use: annual rates of opioid (1) prescriptions; (2) pills; (3) days supply; and (4) morphine milligram equivalents (MME) dispensed per 100 person-days.

Results: Of the 484 745 patients undergoing HD in our study, the mean age was 61 and 47% were female. The percentage of HD patients who received at least one opioid prescription remained stable (57-59%) between 2007 and 2013, then declined substantially in 2014 (50%). Overall rates of opioid prescriptions, pills, days supply, and total MME peaked between 2010 and 2012 then declined until 2014. The rate of opioid prescription among the entire population of HD patients declined from 1.24 (95% CI: 1.23, 1.24) in 2010 to 0.98 (0.98, 0.98) per 100 person-days 2014. The rate of opioid pills dispensed peaked in 2011 at 73.49 (73.47, 73.52) pills per 100 person-days. Rates of opioid use were highest among HD patients that were younger, female, black, non-hispanic, dually eligible for Medicaid, retired and

disabled, diabetic, and located in the rocky mountain region of the United States.

Conclusions: Trends in opioid use among HD patients mirrored trends observed in other studies of the general population. Although overall opioid utilization among HD patients has declined in recent years, HD patients continue to receive large amounts of opioids. Rates of opioid use varied widely by sociodemographic characteristics with females and dual-eligible patients receiving substantially more opioids than their counterparts.

709 | Opioid prescription patterns in UK primary care patients with knee osteoarthritis: A population-based study

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Background: Opioid prescribing has markedly increased in the United States, United Kingdom, and worldwide, predominantly for chronic non-cancer pain (CNC). CNC includes conditions such as fibromyalgia, low back pain, and osteoarthritis (OA). Evidence suggests that widespread use of opioids in CNC is associated with risks of diversion and abuse, overdose, and death. However, opioid prescription patterns in specific medical conditions are understudied and no study has examined the long-term use of opioids in patients with OA in the United Kingdom. OA affects around 7 million people in the United Kingdom with knee being the most commonly affected joint.

Objectives: To identify long-term prescription opioid users among primary care patients with knee osteoarthritis (KOA) in the United Kingdom, and to describe their daily doses

Methods: This retrospective cohort study used data from the Clinical Practice Research Datalink (CPRD), a large UK primary care research database. Opioid prescriptions for patients (≥ 18 years) with a clinician-recorded incident diagnosis of KOA over a period from 2000-2015 were retrieved. An episode of long-term opioid prescribing was defined as at least 3 prescriptions issued within a 90-day period from the date of opioid initiation (date of first opioid prescription after the incident KOA diagnosis, or the date of first prescription in a treatment episode inclusive of diagnosis date).

Outcome measures: Number of patients and prescriptions, number and percentage of patients prescribed opioids for long-term, and mean daily doses as defined daily doses (DDD) as well as oral morphine equivalents (OMEQ) during first treatment episode. Descriptive statistics were used to report prescribing in the first patient year.

Results: Overall, 125 211 patients with an incident KOA diagnosis were identified (58.3% female, mean age: 65.1 ± 12.9 years). In total 89 521 (71.5%) patients have initiated opioids and prescribed a total of 545 264 prescriptions over the first patient year. Of these, 30 974 (34.6%) patients were identified as long-term prescription opioid users. Mean (SD) DDD and OMEQ daily doses over the first long-term episode were 0.71(0.62) and 18.0 (30.9) mg/day, respectively.

The most frequently first prescribed opioids were codeine (61.9%), dihydrocodeine (20.8%), and tramadol (13.5%).

Conclusions: A third of patients with KOA were long-term opioid users. Further research into the duration of long-term episodes and risks associated with long-term opioid use in KOA is required.

710 | Chronic opioid use after surgery: A meta-analysis of observational studies

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Background: The opioid epidemic has become a major public health threat in the United States. Many people are initially exposed to opioids as part of routine pain management after surgery. Several observational studies have examined predictors of chronic opioid use after surgery, but there is no pooled consensus on these risk factors.

Objectives: To use systematic review and meta-analysis of observational studies to examine pattern and predictors of chronic opioid use after surgery.

Methods: We conducted a systematic literature review of articles published between 2012 and 2018 using PubMed. Eligible studies included either case-control or cohort designs that reported chronic opioid use events as a major outcome using baseline demographic and clinical characteristics and initial opioid use within 1-2 weeks after surgery as predictors. Studies involving patients with cancer pain or palliative care were excluded. A DerSimonian-Laird model was used to compute random-effects pooled risk ratios (RRs) for significant predictors. A generic inverse variance method was used to calculate random-effects pooled adjusted RRs (aRR) and 95% CI for important risk factors.

Results: Of 4163 potentially eligible studies identified, 23 were included in the analysis, of which 65% involved orthopedic surgery and 30% included only opioid-naïve patients. Overall there were 1 772 628 patients involved in the analysis. Pre-surgery opioid use was a strong predictor of chronic opioid use (pooled unadjusted RR: 9.5; 95% CI: 2.9-31.3; pooled aRR: 1.48, 95% CI: 1.20-1.81). Other significant baseline predictors included tobacco use (aRR: 1.11, 95% CI: 1.02-1.22) and substance abuse, including cocaine, marijuana, and drug dependence (aRR: 1.37, 95% CI: 1.25-1.49). Alcohol use (aRR: 1.08, 95% CI: 0.96-1.22), depression/antidepressants use (aRR: 0.99, 95% CI: 0.95-1.02), and pain conditions, including fibromyalgia, migraines, arthritis, and back/neck pain, (aRR: 1.07, 95% CI: 0.94-1.23) are not significant in the pooled results. Only two studies investigated the association between chronic opioid use after surgery and opioid perioperative use, with inconclusive results.

Conclusions: This review suggests that baseline opioid use, tobacco, and substance use are significantly associated with chronic opioid use after surgery. The role of initial perioperative prescription opioid use as a risk factor for subsequent chronic opioid use was not confirmed. Future studies should address this question for optimal pain management among opioid naïve patients.

711 | Chronic use of opioids before and after hysterectomy: Patterns and predictors

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Background: The opioid epidemic in the United States affects more women than men. Many women are initially exposed to opioids after surgery for pain management. As the most frequently performed non-obstetric surgery for women, hysterectomy poses a potential risk for chronic opioid use.

Objectives: The objective of this study was to determine whether initial opioid dispensing following hysterectomy is associated with chronic opioid use.

Methods: This study included adult women who were enrolled in the Optum Clinformatics Data Mart and had a hysterectomy between 2010 and 2013. The hysterectomy procedures were identified using ICD9 procedure/CPT/HCPCS codes from inpatient and outpatient claims. Chronic opioid use was defined using trajectory models which group patients with similar patterns of monthly opioid dispensing during a 6-months period following hysterectomy. Initial opioid dispensing was defined as the first opioid dispensed within 7 days following hysterectomy. The opioid daily dose was calculated and converted to *morphine milligram equivalent* (MME). A multivariate logistic regression model was used to examine the association between the characteristics of initial opioid dispensing and chronic opioid use after adjusting for potential confounders.

Results: A total of 2615 of 71 858 (3.65%) women became chronic opioid users within 6 months following hysterectomy. Initial opioid dispensing and baseline characteristics predicted the pattern of opioid use with very high discrimination in whole study cohort (c statistic = 0.90) and among opioid naïve patients (c statistic = 0.93). In subgroup analyses with opioid naïve patients dispensed opioids following surgery, significant predictors of chronic opioid use included type of opioid (hydrocodone vs oxycodone, aOR: 1.93, 95% CI: 1.66-2.25; other opioids vs oxycodone, aOR: 1.88, 95% CI: 1.50-2.36), daily dose (>45.7MME vs ≤30MME, aOR: 1.61, 95% CI: 1.37-1.89), and days' supply (>7 days vs 1-3 days, aOR: 15.23, 95% CI: 12.58-18.43; 4-6 days vs 1-3 days, aOR: 1.41, 95% CI: 1.13-1.76). Other significant baseline predictors included younger age, type of hysterectomy, tobacco use, back pain, fibromyalgia, and headache syndromes.

Conclusions: A small proportion of women become chronic opioid users after hysterectomy and initial type of opioid, daily dosage, and days' supply are significant predictors of this pattern of use. Our study suggests that oxycodone at the lowest effective dosage and shortest days' supply needed may be safer than hydrocodone following hysterectomy.

712 | Patterns of opioid utilization in the 90-days post-hospital discharge and risk of re-admissions and emergency department visits

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Background: As prescription opioid use and overdose has steadily increased in North America over the past two decades, a dramatic increase in hospitalizations has also been witnessed.

Objectives: This study prospectively followed a cohort of medical and surgical hospitalized patients in the three months after discharge to describe their opioid utilization patterns and to estimate the association between opioid use and risk of adverse health outcomes.

Methods: The source population included all patients discharged from surgical and medical hospital units at the McGill University Health Center (MUHC) between October 2014 and November 2016. The study population ($n = 3308$) included patients over the age of 18 upon admission, with continuous RAMQ coverage in the 1 year pre-admission and discharged alive to the community. Opioid utilization was measured using medication dispensing data from the Quebec provincial health care databases (RAMQ), while hospital re-admissions and ED visits were obtained from RAMQ medical services. Patient characteristics and discharge prescriptions were obtained from the hospital chart. Time-varying utilization of opioids after discharge was modeled as (1) current use, (2) cumulative duration of past use, and (3) cumulative duration of use within the last 10 days, using Cox models. All analyses were adjusted for age, sex, chronic conditions, concomitant medication use, and history of opioid use.

Results: Of the 3308 included patients, mean age was 70 (SD 14), 57% were male and 47% were discharged from surgical units. 856 (26%) patients had a history of opioid use in the 1-year prior to admission, 1528 (46%) were prescribed an opioid at discharge and 1481 (45%) filled an opioid in the 90-days post-discharge. Among patients prescribed an opioid at discharge, 79% filled their prescription, where opioid naïve patients were less likely to fill their prescriptions compared with those with a history of opioid use (40% vs 81%). Our multivariable Cox models suggested that cumulative duration of opioid exposure in the past 10 days post-discharge was associated with a 10% increased risk of ED visits and re-admissions.

Conclusions: Patients with a history of opioid use were more likely to both receive an opioid prescription at hospital discharge and fill their prescription. Our findings suggest that longer-term utilization patterns of these medications after hospitalization may increase the risk of re-admissions and ED visits.

713 | Prevalence and predictors of opioid use during pregnancy over 15 years in the Quebec pregnancy cohort

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Background: Opioids are used in the treatment of chronic and acute pain. A dramatic increase in the number of opioid prescriptions has been observed over the last 20 years, including among pregnant women.

Objectives: To determine the prevalence, indications and predictors of opioid use during pregnancy in a large population-based cohort of pregnant women.

Methods: This study was performed within the Quebec Pregnancy Cohort, which includes data on all pregnancies covered by the Quebec Provincial drug insurance plan between 1998 and 2015. Prescriptions filled for opioid agents were obtained using pharmacy claims. Opioids were first defined as a class and then by individual agent (ie, codeine, hydromorphone, meperidine, morphine, oxycodone, morphine, pentazocine, fentanyl, methadone, and buprenorphine). Pattern variations of filled opioid agent use are presented by calendar year and based on pregnancy outcome (live birth, planned abortion, or spontaneous abortion). Opioid user characteristics were compared with non-users to identify predictors.

Results: Among the 442 079 eligible pregnancies, 23 257 (52.6 per 1000) pregnancies were exposed to opioid agents during pregnancy; this prevalence increased from 42.7 in 1998 to 52.6 in 2015 per 1000 pregnancies ($p < 0.001$). Codeine and hydromorphone were the most commonly prescribed opioid agents. The prevalence of codeine use during pregnancy began to decrease in 2006 while the prevalence of hydromorphone and morphine increased. The median number of filled prescriptions for opioid agents was one (first quartile = 1; third quartile = 2). The prevalence of opioid use during pregnancy was higher among pregnancies ending in spontaneous abortion than in pregnancies ending in live birth (71.7 versus 54.9 per 1000 pregnancies). Users of opioids during pregnancy were more likely to live in rural area and be welfare recipient than non-users. Users had more comorbidities related to opioid (headaches and migraine, chronic pain, genitourinary pathologic evidence, and orthopedic pathologic evidence).

Conclusions: The prevalence of opioid use during pregnancy is increasing. Physicians need to carefully evaluate the risks and benefits when prescribing opioid agents during the sensitive period of pregnancy.

714 | Unpacking the association between mental health disorders and opioid prescribing

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Background: Marked increases in opioid prescribing have helped fuel the growing opioid epidemic in the United States. Patients with mental health disorders (MHDs) are prescribed opioids at higher rates, but it remains unclear what factors and specific diseases influence these prescribing patterns.

Objectives: To provide nationally representative estimates of the association between MHDs (including specific MHDs) and opioid prescribing.

Methods: We used data from the National (Hospital) Ambulatory Medical Care Surveys (NAMCS, 2002-2014; NHAMCS, 2002-2011) which provide demographic, clinical, and prescription information from a nationally representative sample of outpatient visits in the United States. We examined pain-related visits of individuals $\geq$ age 12. MHDs were identified by diagnosis codes. Primary outcome was a prescription for an opioid analgesic; secondary analyses examined new and repeat opioid prescriptions separately. We modeled the association between MHDs (general or specific) and opioid prescribing (overall, new, or continued) using logistic regression, adjusting for covariates and weighted to account for the complex sampling design.

Results: 176 639 pain-related visits were recorded in the sample, corresponding to 3.1 billion pain-related visits and 470 million (15.2%) visits with an opioid prescription in the United States between 2002 and 2014. 11.0% of visits were associated with a MHD diagnosis, most commonly mood disorders (87.5% of all MHDs). MHD diagnosis was associated with an increased risk of opioid prescriptions among adults (aOR 1.92 [95% CI 1.79, 2.07]) but not among children (aOR 0.90 [95% CI 0.55, 1.45]). In adults, the relationship between MHD and opioid prescriptions was strongest for mood disorders (aOR 1.81 [95% CI 1.67, 1.93]) and driven by continued opioid prescriptions (aOR 2.07 [95% CI 1.88, 2.26]). Mood disorders were not associated with new opioid prescriptions (aOR 1.13 [95% CI 0.98, 1.30]). Substance use disorder (aOR 1.31 [95% CI 1.02, 1.69]) was associated with a smaller increase in overall opioid prescribing, while diagnoses of psychotic disorders was associated with markedly reduced opioid prescribing (aOR 0.58 [95% CI 0.31, 1.07]).

Conclusions: In nationally representative US outpatient data, mood disorders are positively associated with continued but not new opioid prescribing in adults. Psychotic disorders are inversely associated with opioid prescribing. Given the risk of opioid dependency and misuse, more research is needed on the impact of MHDs on the use and outcomes of opioid treatment.

715 | Patterns and predictors of long-term opioid use in older adults

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Background: Although chronic pain is prevalent in older adults, it is challenging to treat pain in this population due to the high rate of polypharmacy, high potential of adverse events, and a lack of detailed guidance on prescribing opioids in older adults.

Objectives: (1) To investigate the trajectories of long-term opioid use in older adults; (2) to identify predictors associated with the trajectories indicating chronic opioid use.

Methods: Data were extracted from the National Alzheimer's Coordinating Center Uniform Data Set (2005-2017). We examined opioid use among participants age 65+ using group-based trajectory modeling. We used logistic regression with backward selection to evaluate demographics and comorbidities as potential predictors of each trajectory.

Results: Among 13 059 participants, four distinctive trajectories were identified for long-term use of any opioids: non-users (90.2%), incident chronic-users (5.1%), discontinuing-users (2.4%), and prevalent chronic-users (2.4%). At baseline, the prevalence of any opioid use was 3.92%. Female sex (adjusted odds ratio = 1.24; 95% CI 1.04-1.48), independent group living (1.88; 1.48-2.39), or assisted living (1.94; 1.24-3.03) vs private living, black vs white (1.46; 1.17-1.81), hypertension (1.45; 1.21-1.73), any cardiovascular disease (1.32; 1.10-1.57), urinary incontinence (1.46; 1.19-1.78), use of antidepressant agent (1.36; 1.12-1.64), higher education (0.96; 0.94-0.99), 5 or more (0.64; 0.49-0.85), or 1 to 4 medications (0.45; 0.34-0.60) vs none, and dementia (0.75; 0.59-0.94) were associated with incident chronic-users vs non-users. Predictors of prevalent chronic-users vs non-users included age (85+ [1.76; 1.23-2.53] vs 65 to 74), female sex (1.78; 1.36-2.34), black vs white (1.95; 1.44-2.64), type of residence (independent group living [1.73; 1.21-2.48] or assisted living [1.98; 1.04-3.74] vs private living), total number of medications (5 or more [1.92; 1.00-3.67] vs none), use of antidepressants (1.89; 1.46-2.45), use of anxiolytic, sedative, or hypnotic agent (2.20; 1.64-2.95), use of nonsteroidal anti-inflammatory (1.36; 1.06-1.75), higher education (0.95; 0.92-0.98), hypertension (1.35; 1.04-1.75), other drug abuse (2.68; 1.04-6.92), and dementia (0.48; 0.33-0.70).

Conclusions: Given that long-term opioid use was more frequent in participants who exhibited greater vulnerability due to age and chronic medical conditions, further studies should evaluate the safety of using opioids in this population.

716 | Comparing the patterns and predictors of opioid use in older adults with different cognitive status

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Background: The potential modification of patterns and predictors of opioid use by cognitive status has not been well studied.

Objectives: To compare the patterns and predictors of opioids use in older adults with baseline normal cognition, mildly impaired cognition, and dementia

Methods: Data were extracted from the National Alzheimer's Coordinating Center Uniform Data Set (2005-2017). We examined opioid use among participants age 65+ with baseline normal cognition (NC), mildly impaired cognition, and dementia at their enrollment using

group-based trajectory modeling. The number of visits was truncated when more than 95% of participants within the cognitive status group did not have data available. The potential predictors (demographics and comorbidities) of trajectory were identified using logistic regression with backward selection, and adjusted odds ratios (aOR) with 95% confidence intervals (CI) were estimated.

Results: Among 11 782 participants, 5993 had NC, 3560 had mildly impaired cognition, and 2229 had dementia at enrollment. Four distinctive trajectories were identified (non-users [89.9%], incident chronic-users [5.2%], discontinuing-users [2.1%], and prevalent chronic-users [2.8%]) for NC participants, three were identified (non-users [88.7%], episodic-users [7.9%], and chronic-users [3.5%]) for mildly impaired cognition participants, and three were identified (non-user [92.8%], incident-users [4.0%], and prevalent-users [3.2%]) for participants with dementia. For NC, predictors of incident chronic-users vs non-users included number of medications (1 to 4 (aOR = 0.50; 95% CI 0.34-0.73) vs none), black vs white (1.41; 1.04-1.92), independent group living vs private residence (2.19; 1.62-2.96), hypertension (1.55; 1.19-2.01), urinary incontinence (1.87; 1.40-2.51), higher education (0.93; 0.90-0.97), and use of anxiolytic, sedative, or hypnotic agent (1.47; 1.03-2.12). For dementia participants, predictors of incident-users vs non-users included assisted living vs private living (2.41; 1.34-4.34), have any cardiovascular disease (1.63; 1.04-2.54), and urinary incontinence (1.76; 1.12-2.78).

Conclusions: Given that the patterns and predictors of using opioids varied across the cognitive status, guidelines for prescribing, and interventions to prevent chronic opioid use may need to be tailored by cognitive status.

717 | Trends and patterns of analgesic utilization in Malaysia from 2010 to 2016: Preference for tramadol

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Background: Inappropriate or irrational use of analgesics not only leads to increased morbidity and mortality rates and deterioration in quality of life, but can also give rise to misuse of health care resources and increase health care costs.

Objectives: To evaluate the trends of analgesics prescribing at outpatient tertiary hospital settings and examine the patterns of their utilization in NSAIDs, tramadol, and opioid users.

Methods: This cross-sectional study was conducted from 2010-2016 using the prescription databases of two tertiary hospitals in Malaysia. Prescriptions for nine NSAIDs (ketoprofen, diclofenac, celecoxib, etoricoxib, ibuprofen, indomethacin, meloxicam, mefenamic acid, and naproxen), tramadol and five other opioids (morphine, fentanyl, oxycodone, dihydrocodeine, and buprenorphine) were included in this study.

Each prescription contains information on item name and strength, prescription date, frequency, quantity, and patients' age and gender. Annual number of patients, prescriptions, and prescriptions per patient were measured in repeat cross-sectional estimates. Descriptive statistics and linear trend analysis were performed using Stata v13

Results: A total of 192 747 analgesic prescriptions of the nine NSAIDs, tramadol, and five other opioids were prescribed for 97 227 patients (51.8% NSAIDs users, 46.6% tramadol users, and 1.7% opioid users) from 2010 to 2016. Tramadol (37.9%, n = 72 999) was the most frequently prescribed analgesic followed by ketoprofen (17.5%, n = 33 793), diclofenac (16.2%, n = 31 180), celecoxib (12.2%, n = 23 487), and other NSAIDs (<4.5%). All analgesics were increased over time except for meloxicam, indomethacin, and mefenamic acid. Opioids, primarily morphine (2.2%, n = 4021) and oxycodone (0.5%, n = 1049), were prescribed the least but the increase in utilization was greatest. The number of prescriptions/patient per year was higher in the opioid group (3.06 prescription/patient) than in the tramadol (1.30) and NSAID (1.65) groups.

Conclusions: Tramadol was the most frequently prescribed analgesic at outpatient hospital settings in Malaysia. NSAIDs, primarily for ketoprofen, diclofenac, and celecoxib. Opioids were prescribed the least but the increase in utilization was the largest. Further research is required to evaluate the indication of the analgesics used in this study and its relevant clinical outcomes particularly in patients using tramadol for long-term and concurrent usage with other CNS depressant drugs such as antidepressants.

718 | Opioid analgesic utilization, poisonings and deaths: The impact of hydrocodone rescheduling

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Background: In October 2014, the US Drug Enforcement Administration rescheduled hydrocodone combination products from a schedule III to a more restrictive schedule II controlled substance.

Objectives: To examine patterns of prescription drug utilization, abuse/misuse calls to poison control centers (PCCs), and deaths for select opioid analgesics (OAs) and heroin in relation to this action.

Methods: We examine a 10-quarter period, including pre- (Jul. 2013-Sep. 2014) and post- (Oct. 2014-Dec. 2015) hydrocodone rescheduling. We describe outpatient utilization trends for select oral solid OAs using IQVIA prescription data. We assess abuse and intentional misuse exposure calls to PCCs using the National Poison Data System and overdose deaths using National Vital Statistics System-Mortality and Drug-Involved Mortality files, which contains information extracted from death certificate literal text for people ages ≥ 12 years. We assess call and overdose death trends for hydrocodone, codeine, oxycodone, tramadol, morphine containing products, and heroin using Joinpoint.

Results: Prescriptions dispensed for hydrocodone fell 23% (149.3M to 115.4M) and rose 46% for codeine (12.9M to 18.8M) from the pre- to post-hydrocodone rescheduling period, but remained stable ($\pm 6\%$) for oxycodone, tramadol and morphine. The number of dosage units per hydrocodone prescription rose after rescheduling. PCC abuse/misuse calls fell for hydrocodone (-23% ; 4638 to 3579) and tramadol (-10% ; 2168 to 1945) but rose for codeine (25% ; 659 to 822) and heroin (15% ; 3892 to 4481) from the pre- to post-hydrocodone rescheduling period and remained constant ($\pm 5\%$) for oxycodone and morphine. Joinpoint analyses showed PCC calls decreased for hydrocodone and increased for heroin throughout the 10-quarter period. Overdose deaths mentioning heroin (32% ; 12277 to 16258), codeine (32% ; 635 to 839), and oxycodone (12% ; 6383 to 7129) rose from the pre- to post-hydrocodone rescheduling period, but remained stable ($\pm 8\%$) for morphine, tramadol, and hydrocodone. Joinpoint analyses showed heroin overdose deaths increased throughout the 10-quarter period.

Conclusions: Total prescription volume and misuse/abuse calls for hydrocodone appeared to decline after rescheduling. Trend analysis showed a continual decrease for abuse/misuse calls for hydrocodone throughout the study period. Multiple ongoing efforts to address the US opioid crisis and the changing nature of the epidemic make evaluating the impact of any single intervention difficult.

719 | Opioid use after hip fracture surgery

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Background: Persistent opioid use is a common risk after both minor and major surgery. However, little is known about opioid use before and after hip fracture surgery.

Objectives: To examine the use of opioids within the first year after hip fracture surgery in patients with and without opioid use before surgery.

Methods: This cohort study included all older patients (aged 65 or more) with a primary hip fracture surgery in Denmark in 2005-2015 registered in the Danish Multidisciplinary Hip Fracture Database. Information on redeemed opioid prescriptions from 6 month before to a year after surgery were collected from the Danish National Health Service Prescription Database. Prescriptions for opioids were converted into categorical yes/no variables and described for the 6-month period before surgery and for four 3-months periods (quarters) after surgery. Proportions difference and confidence intervals were calculated for opioid use in all quarters after surgery compared with the opioid use before surgery.

Results: The study included 69 456 hip fracture patients. In the period before surgery, 26.8% of the patients redeemed opioid prescription. After the surgery, 61.8% of the patients redeemed opioid prescriptions in the first quarter, which decreased to 33.8%, 29.8%, and 28.2%, in the subsequent quarters. This corresponded to an increase in proportion of opioid users of 34.0% (95% CI: 34.5-35.5), 7.0% (95% CI: 6.5-7.5), 2.9% (95% CI: 2.4-3.4), and 1.4% (95% CI: 0.7-1.7) in the four quarters after surgery compared with before. Of the patients with no opioid use before surgery 54.7%, 18.6%, 11.2%, and 8.3% redeemed opioid prescriptions continuously after the surgery in the four quarters. Among patients with opioid use before surgery, 81.2%, 65.0%, 57.1%, and 52.3% redeemed opioid prescriptions continuously in the four quarters after surgery, respectively.

Conclusions: More than one-fourth of hip fracture patients redeemed opioid prescriptions within 6 months before the fracture. The proportion of opioid users increased substantially shortly after surgery, and 28.2% of patients were still on opioids 1 year after surgery. Finally, almost 8.3% of patients who did not take opioids before fracture were still on opioids 1 year after the surgery.

720 | EHR-driven evidence for health and wellness research: Lessons from the NBA

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Background: The US NBA has implemented a system to monitor injury occurrence as part of a program to improve player health and wellness. Together with team medical staff, research partners, and key stakeholders, the NBA has built a comprehensive approach to injury monitoring and analytics. A clinical electronic health record (EHR) augmented by linkable external data sources enables the EHR to serve as the core of an agile evidence platform that can be used to address a broad spectrum of questions about player health, demonstrating how an EHR-based system can be utilized to inform policy and facilitate practical decision making.

Objectives: Describe adaptation, expansion, and curation of an existing EHR system to support analytic processes and evidence generation for monitoring and improving player health.

Methods: Since 2012, data on players' injuries and illnesses have been contemporaneously collected by team medical staff and entered into a league-wide customized EHR system as part of the player's clinical care, resulting in a comprehensive set of player health, injury, illness, and participation information. Injury reporting is mandated with clear reporting definitions, rigorous auditing and query processes, and proactive reporter education which achieves consistent, complete, and accurate reporting. To enable linkages with other league-wide statistics (eg, game schedule, travel, box scores, and optical player tracking data) and facilitate robust research, several link keys are integrated into each data source allowing seamless data incorporation.

Results: Integration of various data sources and prospective quality monitoring allow rapid analytics of injuries and in-depth investigations into potential health improvements. Individualized reports are provided to each team's medical staff on their team's data, mirroring a quality care benchmarking approach and providing useful clinical information to inform decisions as well as motivate complete reporting. Reporter training occurs regularly and data quality is reviewed daily by the NBA league office during the season.

Conclusions: Player information collected for the primary purpose of clinical management also can support research to improve player health. This type of integrated, curated data sourcing can be applied to other health care settings to facilitate evidence generation that can be used to enhance health. Using commercially available EHRs offer benefits and challenges compared with typical data collection strategies used in pharmacoepidemiology.

721 | Long-term use of high-dose opioid analgesics in Kentucky from 2012 to 2016

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Background: Long-term use of opioid analgesics, particularly at high dosage, increases the risk of serious adverse effects, addiction, and overdose, while its effectiveness in chronic non-cancer pain (CNCP) management has been unsatisfactory. Prescribing guidelines for opioid analgesics use in CNCP treatment have been promoted recently.

Objectives: This study investigated longitudinal trends in long-term high dose opioid analgesics prescribing (LTHDOAP) in Kentucky, 2012-2016, and the association with CNCP, and late-stage cancer.

Methods: This longitudinal study with analysis at the county-year level used a multitude of data sources, including the Kentucky All Schedule Prescription Electronic Reporting (KASPER) System, the American Community Survey, the Kentucky Inpatient and Outpatient Claims, and Death Certificates. Marginal models employing generalized estimating equations were used to model repeated counts of residents with LTHDOAP, with offset for resident population, regressing on rates of inpatient hospitalizations and emergency department (ED) visits involving CNCP per 1000 residents, rates of cancer deaths as a proxy for late-stage cancer prevalence, and their interactions with time. Residents with LTHDOAP were identified as those with dispensed opioid analgesics for more than 90 consecutive days with an average daily cumulative morphine milligram equivalent dose of 100 or greater, according to KASPER records.

Results: The statewide LTHDOAP rate declined from 6 per 1000 residents in 2012 to 4/1000 in 2016 ($p < 0.0001$). About 33% of the residents with LTHDOAP received their opioid prescriptions by a single prescriber. Every one-per-thousand increase in the cancer death rate was associated with a 26/1000 increase in the adjusted LTHDOAP rate ($p = 0.002$). At baseline, counties with 1/1000-higher in CNCP rates had 10/1000-higher in the adjusted LTHDOAP rates ($p < 0.0001$). However, the strength of the positive association

between CNCP and LTHDOAP significantly decreased by 2/1000 every year ($p < 0.0001$).

Conclusions: Rates of LTHDOAP were significantly positively associated with cancer mortality rates with no substantial change in the association magnitude over time. Further research is needed to identify the factors contributing to the declining strength of the positive association between LTHDOAP and CNCP over time (eg, improved prescriber education and clinical practice guidelines for opioid use in CNCP treatment, or increased availability of heroin and illicit fentanyl).

722 | A retrospective analysis on pattern of poisoning and its treatment outcome

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Background: Poisoning is a major public health problem worldwide and is considered as one of the major causes of patient admissions to emergency departments and intensive care units, especially in developing countries.

Objectives: The objective of the study is to assess the pattern and determinants of poisoning in the Emergency Care Unit. The present study provides the data on exposure of the different types of poison, which help in future to establish the poison information center.

Methods: A retrospective study has been carried out for a period of 3 years. The data on demographic details, time of admission, time lapsed from exposure to hospital arrival before intake, type of poison, route of administration, and duration of hospitalization was collected from the patient case file, nursing notes and medication charts in a suitably designed proforma. The pattern of poisoning was analyzed.

Results: Out of the 320 poisoning cases recorded, most of them are males 176 (55%) and female 144 (45%). 147 (45.9%) were single and 173 (54.1%) were married. Majority of the patients are in the age group of 26-45 years 134 (41.8%) with an average duration of 6 days of hospital stay. Snakebites 71 (22.2%) and organophosphates 58 (18.1%) are the most commonly occurred poisonings followed by benzodiazepines 35 (10.9%), unknown rat poison 16 (5%), aluminium phosphide 15 (4.7%), paracetamol 13 (4.1%), pyrethrins 11 (3.4%), and barbiturates 9 (2.8%). Most of the cases were suicidal 208 (65%) with the number of female patients 112 (53.8%) slightly more than male 96 (46.1%). The accidental poisonings are 112 (35%) with 80 (71.4%) in males and 32 (28.6%) in females. The common route of exposure was oral (75.6%). The case fatality rate is 3.75%. The seasonal variation in incidences of poisoning indicates that most of the patients were admitted in spring 97 (30.3%), ie, March to May followed by summer 91 (28.4%). 239 (74.7%) patients were recovered, 69 (21.6%) patients were discharged against medical advice, and 12 (3.75%) were dead, which necessitates the establishment of Poison Information Centre and patient counseling in the emergency care unit.

Conclusions: Educating the community on the effects of suicidal poisonings would enable people to tackle their problems and may help to prevent poisoning in future. More research needs to be done on a

global scale or national level in order to understand the pattern of poisoning in a cultural context that would aid in developing more valuable intervention and management programs.

723 | Treatment characteristics of patients with binge-eating disorder

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Background: Current treatment guidelines for binge-eating disorder (BED) focus on behavioral interventions (eg, cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], behavioral weight loss). Although lisdexamfetamine is approved for the treatment of BED, pharmacotherapy, when applied, chiefly consists of antidepressants and anticonvulsants. Understanding current treatment patterns may identify potential gaps in BED treatment.

Objectives: To characterize real-world treatment patterns of patients with BED identified in a large electronic health record (EHR) database.

Methods: We used natural language processing (NLP) of clinical notes to identify patients with potential BED. Full text notes were extracted into unique NLP fields such as concept (eg, binge-eating), note section (eg, history of present illness), and modifiers (eg, chronic). Algorithms applied to the EHR used combinations of NLP fields to identify BED and probable BED patients. NLP concepts such as “cognitive therapy” and “behavioral therapy” were used to identify subcategories of psychotherapy. Structured data within the EHR database were used to characterize pharmacotherapy.

Results: We identified 384 BED patients (with NLP affirmation of BED) between January 2009 and September 2015 and an additional 658 probable BED patients who met less stringent criteria. These patients were 81% female and 87% White. BED and probable BED patients had similar pharmacotherapy treatment in follow-up. Among BED patients, 44% were taking antidepressants, 23% stimulants, 16% anticonvulsants, and 14% antiobesity agents. Probable BED patients had an average of 2.6 (SD 7.7) psychotherapy visits in follow-up and BED patients 2.2 (SD 7.7) visits. Nonspecific therapy was the most common type of behavioral therapy among all BED patients (32% of BED and 25% of probable BED patients) and less than 21% of patients had or discussed the following types of therapy: CBT, behavior therapy, group therapy, or family therapy. No NLP terms were specific to IPT or behavioral weight loss.

Conclusions: While CBT is the gold-standard treatment, these data suggest that the majority of patients with BED are either not receiving this type of treatment or receiving inadequate trials of evidence-informed behavioral treatment.

724 | The incidence of glaucoma in the United Kingdom, 2000-2015

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Background: Glaucoma refers to a group of diseases, with optic nerve damage as the common pathology leading to vision loss. The most common types of glaucoma are primary open angle glaucoma (POAG) (almost three-quarters of cases), and primary angle closure glaucoma (PACG). POAG and PACG are aging-related diseases with the highest incidence around 70 years old (yo). To our knowledge, incidence rates (IR) of glaucoma have not been quantified before in a large sample in the United Kingdom (UK).

Objectives: To quantify IR of glaucoma overall as well as for the subtypes POAG, PACG, and secondary glaucoma (SG) in the United Kingdom.

Methods: Using the Clinical Practice Research Datalink (CPRD), we calculated crude and age-standardised (AS) IR for glaucoma from 2000 to 2015 using the European standard population. We assessed person-time of all patients at risk and the number of incident cases of glaucoma, stratified by age, sex, and year of diagnosis. Glaucoma cases had to have a READ code for glaucoma plus antiglaucoma treatment and/or glaucoma surgery. In a sensitivity analysis, we included all individuals with a glaucoma diagnosis (treated and untreated).

Results: We identified 40 292 glaucoma cases in 41.4 million person-years (py) from 2000 to 2015. The AS-IR (per 100 000 py [95% CI]) for glaucoma overall decreased from 104.9 [100.6-109.2] in 2000, to 60.7 [56.8-64.7] in 2015. The IR always peaked in the 80-89 yo group with 422.9 [384.5-461.3] and 220.4 [188.1-252.7], respectively. The IR of POAG, PACG, and SG followed the same trend as for glaucoma overall (which included the unspecified glaucoma diagnoses). Glaucoma was evenly distributed among the sexes except for PCAG (36.7% women). Our sensitivity analysis (glaucoma diagnosis irrespective of treatment) yielded about 20% more cases and showed the same trend of decreased IR.

Conclusions: In the United Kingdom, the AS-IR of glaucoma seems to have decreased considerably from 2000 to 2015 by more than a third (-42.1%). This reduction started in 2005, maintaining the same magnitude within sexes and being more pronounced in the elderly group (-47.9%). Contrary to publications from other countries, our results show PACG to be more incident in men. One explanation for the observed AS-IR reduction could be the implementation of the glaucoma guidance by the Royal College of Ophthalmologists in 2004 and the NICE guidance in 2009. Both have defined more strict criteria for the diagnosis/management of glaucoma. Our results suggest that around 20% of patients with incident glaucoma diagnosis are not treated pharmacologically and/or with glaucoma surgery.

725 | Organ damage in systemic lupus erythematosus (SLE) is consistently associated with increased mortality: A meta-analysis

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Background: More than half of patients with SLE develop organ damage over time, including damage to the kidney, skin, and cardiovascular, musculoskeletal, and central nervous systems. Long-term steroid use is associated with organ damage. SLE organ damage, like comorbid disease, may contribute to increased mortality.

Objectives: We conducted a systematic literature review and meta-analysis of the association between organ damage in SLE and mortality.

Methods: A literature search (Jan 2000-Feb 2017) of PubMed, EMBASE, Cochrane Library, and Latin American and Caribbean Health Sciences Literature evaluating organ damage by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) and mortality was conducted. Exclusion criteria included non-English language articles and study designs without original, population-level measures of association. We used a random-effects meta-analysis to evaluate studies that modeled SDI as a continuous predictor of mortality and reported hazard ratios (HR) associated with a 1-unit SDI increase.

Results: The search yielded 10 420 articles, of which 21 prospective cohort studies were selected. Ten studies evaluating SDI as a continuous variable and reporting HR as a measure of association were pooled and meta-analyzed. Pooled HR of mortality for a 1-unit increase in SDI was 1.34 (95% CI: 1.21-1.44; $p < 0.001$; Cochrane Q $p = 0.027$, I^2 statistic = 52.1%). A study of 213 patients followed for 13 years in China yielded the greatest risk of mortality for a 1-unit SDI increase (HR 3.65, [95% CI: 1.52-8.76]). When excluded from the meta-analysis, pooled HR of mortality for a 1-unit increase in SDI was 1.32 (95% CI: 1.25-1.42; $p < 0.001$; Cochrane Q $p = 0.087$, I^2 statistic = 42.0%). Four studies that evaluated SDI as a binary variable reported HR for various SDI reference groups: SDI = 0: HR 5.10 (95% CI: 1.99-13.03); SDI <1: HR 3.8 (95% CI: 1.30-16.40); SDI <3: HR 4.74 (95% CI: 1.55-14.51); and SDI <5: HR 55.12 (95% CI: 19.15-158.63). Two studies reported odds ratios (OR) as the measure of association. For a 1-unit SDI increase, OR was 19.7 (95% CI: 5.30-72.50); for SDI = 0 as reference, OR was 12 (95% CI: 1.60-92.00).

Conclusions: Organ damage in SLE is consistently associated with increased mortality across studies from various countries, regardless of how it is modeled. Novel therapies that are both disease modifying and steroid sparing could reduce organ damage, improve overall outcomes, and decrease mortality in patients with SLE.

726 | Organ damage and health-related quality of life (HRQOL) in systemic lupus erythematosus (SLE): A systematic review

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Background: The comorbid burden of SLE involves various organ systems and may be associated with pain, fatigue, and physical and emotional difficulties.

Objectives: We analyzed studies of association between SLE-related organ damage and HRQOL.

Methods: A systematic literature search (Jan 2000-Feb 2017) was done to find studies of association between organ damage (measured by SLICC/ACR Damage Index [SDI]) and HRQOL for adults with SLE. Instruments used were the Short Form 36 Health Survey (SF-36: Physical and Mental Component Summaries [PCS and MCS], 15 studies); Fatigue Severity Scale (FSS) and EuroQOL 5D (2 studies each); and the LupusQOL, Multidimensional Fatigue Inventory, Quality of Life Questionnaire of the European Foundation for Osteoporosis, and WHO Quality of Life Scale (WHOQOL-BREF) (1 study each).

Results: Of 10 420 articles screened, 20 were included (3 prospective cohort studies, 17 cross-sectional studies). Prospective studies assessed HRQOL by the SF-36, 2 of which modeled SDI as a binary variable. For patients with no baseline damage, any damage accrual over 2 years was associated with a 5.5-fold increased risk of reduced HRQOL (SF-36 overall relative risk [RR] 5.5 [95% CI: 1.1-26.6; $p = 0.03$]). Increased risk of reduced HRQOL was also seen with PCS: RR 2.5 (95% CI: 0.6-10.0; $p = 0.19$) and MCS: RR 4.6 (95% CI: 0.9-22.8; $p = 0.06$). Baseline damage was associated with 67% reduced odds of clinically important improvement in SF-36 PCS: odds ratio 0.33 (95% CI: 0.13-0.85; $p = 0.02$); no association was seen for MCS. When SDI was modeled as a continuous variable, increased damage was associated dose-dependently with reduced SF-36 PCS compared with SDI = 0; SDI 1: -2.64, $p < 0.001$; SDI 2: -2.86, $p = 0.003$; SDI 3: -5.94, $p < 0.001$; SDI 4: -6.35, $p < 0.001$; and SDI 5+: -8.11, $p < 0.001$. In cross-sectional evaluations, increasing SDI was modestly correlated with reduced HRQOL: SF-36 correlation coefficient scores: -0.12 to -0.30; SF-36 regression coefficient scores: -0.011 to -4.65; LupusQOL correlation coefficient -0.31, $p < 0.01$; and WHOQOL-BREF regression coefficient -0.06, $p = 0.57$. Increasing fatigue displayed weak correlation with damage: FSS correlation coefficients: 0.04 to 0.15.

Conclusions: Organ damage was associated with reduced HRQOL in most studies. Heterogeneity in HRQOL instruments and methodology was seen across studies. Improving construct validity of instruments and consistent evaluation will improve burden of SLE estimates and enhance efforts to improve HRQOL in patients with SLE.

727 | Epidemiology and burden of illness in systemic lupus erythematosus: Analysis using the Japanese health insurance claims database and disease blogs on the internet

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Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that substantially impairs patients' quality of life. To our knowledge, however, few studies have existed to understand epidemiology and burden of illness in Japanese patients with SLE. In particular, no studies have explicitly identified the patient-level information sources to evaluate the burden of SLE.

Objectives: To understand epidemiology and burden of illness in Japanese patients with SLE.

Methods: We used two independent databases in this study. First, to understand epidemiology of SLE, we analyzed Japanese health insurance claims database maintained by Japan Medical Data Center for more than three million individuals who have been enrolled in the database in 2015. Patients with SLE were identified by ICD-10 code of M32. We calculated the prevalence of SLE stratified by demographic status such as age and gender. Concomitant therapies were also analyzed descriptively. Second, to understand burden of SLE, we analyzed textual data collected from the Japanese disease blogs on the Internet: *tōbyōki* blogs, which translate literally as a diary-like account of a struggle with disease (Matsuda S, et al. JPH 2017). Using such unstructured texts written by patients, we applied natural language processing techniques to identify frequently appearing medical terms such as symptoms and evaluated patient-level burden of SLE.

Results: We identified 3063 patients with SLE in the claims database. Prevalence of SLE was 102.0 per 100 000 person-years (4.4 times higher among women) that was similar trends as reported from other countries. Immunosuppressive drugs such as steroids, tacrolimus, mizoribine, and azathioprine were frequently prescribed. As of February 7, 2018, we identified 635 patients with SLE who have written *tōbyōki* blogs. Overall, more entries were written by female bloggers (95%, 603/635) than by male bloggers (5%, 31/635). The peak age at onset was 20–34 years (35%, 222/635). Some medical terms including disease symptoms and therapeutic drugs could be identified from the patient narratives.

Conclusions: This study showed information to understand the epidemiology, status on therapies, disease symptoms, and burden of SLE that are important to consider the needs on public health interventions. We also proposed a combined use of the independent databases to facilitate deeper understanding of the relation between disease and patients' honest feelings.

728 | Economic burden in patients with primary dysmenorrhea: A cross-sectional survey

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Background: Although primary dysmenorrhea is highly prevalent in women and it is suspected to have enormous socioeconomic impact, a population-based information on the treatment pattern and economic burden in patients with primary dysmenorrhea is limited.

Objectives: To assess health care resource use and the economic burden associated with primary dysmenorrhea in Korea.

Methods: An online survey was administered to women of reproductive age in Korea from January 2017 to February 2017. The 50-item survey was developed to assess costs of complementary medicine including Korean medicine, over-the-counter (OTC) medications, dietary supplements, and folk remedies and productivity-loss cost in patients with primary dysmenorrhea. The questionnaires were developed from a literature review and were revised after discussion with Korean Medicine Doctors at a tertiary hospital in Korea. Questionnaires about all resources consumed for primary dysmenorrhea as well as Work Productivity and Activity Impairment plus Classroom Impairment Questions (WPAI+CIQ) questionnaire were asked to complete. Costs were in 2017 Korean won. Among complementary medicine, patients' perceptions of Korean medicine including advantages, disadvantages, and reasons for using Korean medicine were also investigated.

Results: A total of 104 participants completed the survey. The mean annual out-of-pocket cost for using Korean medicine, over-the-counter products, dietary supplements, and folk remedies per patient with primary dysmenorrhea was \$1,142 and the productivity-loss cost was \$2,807. The productivity-loss cost due to presenteeism (65%) was identified as the major cost component of the whole costs. There were no patients with primary dysmenorrhea who experienced adverse events due to Korean medicine and 55% of respondents reported that the advantage of Korean medicine is in having almost no adverse events. On the other hand, 49% of respondents reported that long-term treatment period as a disadvantage of Korean medicine. The most common reasons for using Korean medicine was insufficient analgesic effects from conventional treatment (44%), followed by concerns about pain medication dependence (36%).

Conclusions: There is a high need for effective and inexpensive therapies, which emphasizes the need for well conducted clinical trials and strategies for guiding patients with primary dysmenorrhea to receive cost-effective therapies.

729 | Prevalence and disease characteristics of lupus patients across markets

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Background: Lupus is an autoimmune disease with no available cure and a high disease burden.

Objectives: To assess the prevalence and treatment of systemic lupus erythematosus (SLE) along with variations which may exist across markets and patient demographics.

Methods: A cross-sectional study of SLE patients ages 18+ years was conducted using *patient-reported survey* data from the National Health and Wellness Survey (NHWS) and *literature-based* estimates from Epi Database; countries included the United States, Japan, and five European Union (5EU) countries (France, Germany, Italy, Spain, and the United Kingdom). The results of the NHWS survey were weighted, and Epi Database was projected to reflect the gender and age proportions, as determined by the US Census Bureau and the United Nations. In NHWS, respondents reported lupus diagnosed by a physician while Epi Database used studies based on registries and administrative databases. Demographics, clinical characteristics, prevalence, and prescription drug use were examined.

Results: The prevalence of lupus was highest in the United States and lowest in Japan with comparable estimates reported between Epi Database and NHWS (US: 275K, 245K; Japan: 68K, 48K; Epi Database, NHWS respectively). Patient characteristics were similar across data sources and geographies with prevalence highest in females, minorities, and adults. While SLE was more common in females and adults, the presence of lupus nephritis (LN) was more prevalent in male patients and children (85% of men with lupus and 81% of children). Drug treatment rates were higher in the United States compared with Europe (61% versus 53%), but disease severity was nearly identical between markets (42%-46% mild, 54%-58% moderate/severe).

Conclusions: Collecting and analyzing data from diverse patient populations across geographies, health care systems, and data sources is essential for providing informative real-world evidence of prevalence, burden of illness, and disease management. While some people with SLE have only mild symptoms, the disease is lifelong and impacts patients differently, especially minority populations who more commonly develop lupus nephritis.

730 | Greater severity of atopic dermatitis (AD) is associated with poorer patient-reported outcomes among adults with moderate-to-severe AD

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Background: AD can impose considerable burden on patients' quality of life at higher severity levels, but limited data are available on the relationship between severity of AD and outcomes from the patient perspective.

Objectives: To assess the relationship between AD severity and patient-reported outcomes among adults with moderate-to-severe AD.

Methods: Respondents previously reporting dermatitis, AD, or eczema in panel-based general health surveys in 4 countries were invited to an internet survey to confirm their dermatitis was AD and collect additional information. They completed the patient-oriented score of atopic dermatitis (PO-SCORAD) to assess severity of AD, measures of general (EuroQol 5 dimensions questionnaire [EQ-5D]) and dermatology-specific (Dermatology Life Quality Index [DLQI]) health-related quality of life, disease activity (Patient-Oriented Eczema Measure [POEM]), and impairment to work and daily activities (Work Productivity and Activity Impairment questionnaire, Specific Health Problem [WPAI-SHP]). Moderate or severe AD were classified using established PO-SCORAD cutoffs (25-50, and >50 points). Severity groups were compared using Student's *t* tests. Correlations between PO-SCORAD and outcome measures were estimated.

Results: The 1098 respondents with moderate-to-severe AD (US 550; France 221; Germany 209; UK 118) were mostly women (69%), mean age 48, 61% employed, with AD diagnosis since 19 years on average. Relative to moderate AD (N = 825), those with severe AD (N = 273) had lower mean EQ-5D scores (0.65 vs 0.79), and higher mean DLQI (13.5 vs 6.0) and POEM scores (15.8 vs 9.2), all $p < 0.001$. Minimal important difference thresholds were exceeded for EQ-5D (>0.07 points), DLQI (>4 points), and POEM (>3.4 points) scores between severity groups. Severe AD respondents had higher impairment to work (48% vs 24%), and daily activities (52% vs 26%), all $p < 0.001$. Subgroup analyses showed worse outcomes as PO-SCORAD scores increased. The impact of AD severity was also clearly seen in correlations between PO-SCORAD and EQ-5D scores ($r_s = -0.37$), DLQI scores ($r_s = 0.61$), POEM scores ($r_s = 0.51$), impairment to work ($r_s = 0.46$), and daily activity ($r_s = 0.53$), all $p < 0.001$. The pattern of results was similar within individual countries.

Conclusions: Greater AD severity is associated with poorer patient-reported outcomes across multiple health-related quality of life domains. Improving disease management for severe AD patients may reduce burden of disease.

731 | Assessing the use of complex case definitions on measures of incidence in a US claims database

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Background: Often pharmacoepidemiology studies define a "case" based on a requirement for multiple events separated in time. An implicit assumption is that all patients are observed for long enough to be at risk of meeting the full case definition.

Objectives: We studied the time taken to meet case definitions requiring multiple events using the example of rheumatoid arthritis (RA) and compared incidence rates in analyses where all follow-up was used versus those where the last 6 months of enrollment are set aside from potential time at risk. In this second design, defining a "post-risk" period ensured that all enrollees with a first event of RA during time

at risk had at least 6 further months of follow-up to search for additional evidence to refine their case status.

Methods: Analyses were conducted in the US MarketScan commercial claims database including 35 372 664 patients aged 18-64 in 2012-14. Cases were identified based on published algorithms for RA requiring 2 events on separate days (RA1), 2 records at least 60 days apart (RA2), 3 records on separate days (RA3), and 3 records each separated by 7 days (RA4). The first event was taken as the date of onset when calculating time at risk for cases. Incident cases had 6 months of enrollment prior to a first record of RA.

Results: Of 115 813 enrollees with a record of RA, 55.9%, 63.3%, 70.0%, and 71.2% did not meet the case definition within 365 days for RA1 to RA4, respectively. Median time (IQR) from first event to fulfilling the definition was 57 (20, 182), 125 (84, 262), 123 (56, 282), and 135 (66, 297) days. Incidence rates per 100 000 patient years (95% CI) were 116.5 (115.5, 117.4), 99.5 (98.6, 100.3), 82.6 (81.8, 83.3), and 79.5 (78.7, 80.2) with a 6-month post risk period, and 108.1 (107.3, 108.9), 87.9 (87.2, 88.6), 74.2 (73.5, 74.8), and 70.8 (70.2, 71.5) including all follow-up as potential time at risk.

Conclusions: Many patients with at least one event subsequently did not meet the full case definition. In part, this may reflect a lack of specificity using only single events and support the use of case algorithms. However, cases usually required several months to accumulate the evidence needed to meet definitions. Rates increased by 7.8%, 13.2%, 11.3%, and 12.3% for RA1 to RA4, comparing rates calculated with a post-risk time period versus any available time at risk. While the impact will differ between diseases and algorithms, results suggest that analyses failing to account for the time needed to accumulate multiple records markedly underestimate the incidence of disease. A GSK-funded study.

732 | Changing causes of mortality for people with chronic respiratory diseases in England, 2005-2015

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Background: Chronic respiratory diseases (CRD) are common, increasing in prevalence, and cause significant morbidity and mortality worldwide. Lung diseases are responsible for 20% of all deaths in the United Kingdom and has remained constant in recent years. Whether these trends observed in the general population are reflected among patients with CRD has not been established.

Objectives: The aim of this study was to calculate the all-cause and disease-specific mortality rates by age and sex in a CRD patient cohort (those with asthma, bronchiectasis, COPD, and/or ILD) compared with the general population. Additionally, we investigated changes in causes of death for people with CRD and with each disease separately between 2005 and 2015 in England.

Methods: We used primary care data (Clinical Practice Research Datalink) linked with mortality data (Office for National Statistics) and Index of Multiple Deprivation (IMD 2015) to determine the most common causes of mortality in people with asthma, bronchiectasis, chronic obstructive pulmonary disease (COPD), and interstitial lung diseases (ILD), during 2005-2014 in England. We calculated all-cause and disease-specific mortality rates.

Results: We identified 483 099 CRD patients, 48.6% were female (n = 36 862), 25% current smokers (n = 18 720) and mean age at death was 78 years (SD = 11). The age standardised mortality rate of patients with CRD was 1607 per 100 000 person-years (asthma = 856, COPD = 1503, ILD = 2,609, and bronchiectasis = 1463). The CRD mortality rate was 54% higher than the general population. Leading causes of death in CRD patients were respiratory (32%), circulatory (26%), and neoplasms (24%). In asthma patients, it was circulatory (28%), neoplasms (27%), and respiratory (24%).

Conclusions: This is the most comprehensive study, to date, of causes of death in the CRD population in England. Deaths due to circulatory diseases have decreased in the past 10 years; however, there has not been the same impact on respiratory-related deaths suggesting efficiencies in disease management may need to be addressed. CRD patient mortality rates are much higher than the general population.

733 | Clinical and economic burden of community-acquired pneumonia among adults low-risk inpatient: A retrospective analysis of nationwide registry data in Japan

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Background: Community-acquired pneumonia (CAP) is one of the major causes of mortality and morbidity worldwide, having a significant impact on health care system. Incidence of CAP was about 20 case per 10,000 population, and it became higher rate with increased ages. A multicenter prospective surveillance for CAP have found approximately 70% of CAP inpatients were elderly. Despite no need of intensive care, a large number of mild CAP patients were admitted to a hospital. Hospitalization costs of CAP is approximately 15 times higher than outpatient care. Thus, admitted mild CAP patients are considered to affect total CAP treatment costs largely. Many studies about the burden of CAP hospitalization were conducted, but it still has not been clear in Japan.

Objectives: The aim of our study was to evaluate the prevalence and the burden of CAP in-patients divided by its severity, using health care database in Japan.

Methods: We performed a retrospective observation study for nationally representative samples of hospitalized patients with CAP using the administrative database from the Diagnosis Procedure Combination Per-Diem Payment System (DPC/PDPS) in 2014. The severity

of CAP was classified into 4 categories, ie, mild, moderate, severe, and extremely severe, based on A-DROP scoring system. According to the practice guideline, outpatient care is recommended for mild CAP patients, while either outpatient or hospitalization care for moderate CAP patients.

Results: Hospitalized CAP patients evaluated in this study included 14 406 mild cases (19.3%) and 42 435 moderate cases (56.9%). The median age was younger in mild cases (58 years old) compared with moderate cases (79 years old). In addition, mild cases had lower rates of emergency transfer and in-hospital death. The average length of stay was 10.1 and 13.4 days in mild and moderate cases, respectively, which tended to be shorter compared with that in severe or extremely severe patients. There was no trend to lower daily cost and antibiotic use in mild CAP patients compared with patients with other severities.

Conclusions: Mild cases accounted for 19.3% of total CAP adult patients hospitalized in acute care hospitals, although the guideline recommends outpatient care for this category. Based on our results, the gap between guidance recommendation and actual therapeutic status may need to be carefully evaluated.

734 | Persistent severe asthma: Health care resource utilization and costs for patients receiving multiple controller medications

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Background: An estimated 26 million people in the United States have asthma, with 5%-10% having severe disease.

Objectives: To describe health care resource utilization (HRU) and costs for asthma patients who require multiple classes of controller medication to control their disease.

Methods: This retrospective study used claims data from a commercial and Medicare Advantage health plan. Patients, ≥ 12 years of age, met Healthcare Effectiveness Data and Information Set (HEDIS) criteria for persistent asthma for 2 consecutive years during 2007-2012 and received Global Initiative for Asthma $\geq$ Step 4 therapy. Index date was January 1 of the third year. Patients were followed for 1 year. HRU and costs were described for patients at 2 levels of controller medication use: those receiving medium-dose inhaled corticosteroid (ICS) + concomitant long-acting β_2 agonist (LABA) +/- other controllers (Group A) and patients receiving either high-dose ICS + LABA or chronic oral corticosteroid (OCS) for $\geq 50\%$ of baseline year in addition to medium- or high-dose ICS + LABA +/- other controllers (Group B).

Results: A total of 34 080 patients were identified, with 80% in Group A. Compared with patients in Group A, patients in Group B were older (46.0 vs 44.5 years), had greater comorbidity index (1.10 vs 0.96), and were more likely to have had ≥ 1 baseline exacerbation (35.5% vs 24.5%) (all $P < 0.001$). In the follow-up period, the exacerbation rate was 0.28 (95% confidence interval: 0.27-0.28) and 0.47 (0.45-0.49) for patients in Group A and Group B, respectively. Follow-up all-cause

mean HRU (SD) for patients in Group A was 12.5 (14.1) office visits, 3.2 (5.6) outpatient visits, 0.08 (0.34) inpatient stays, and incurred all-cause costs of \$10,183 (\$19,912). For patients in Group B, all-cause mean HRU (SD) was 14.2 (15.2) office visits, 4.0 (6.9) outpatient visits, 0.11 (0.44) inpatient stays, and incurred all-cause costs of \$13,953 (\$28,128), (\$32,936 [\$55,693] for 286 chronic OCS users). Two-thirds of the total cost was for medical, \$6,345 (\$17,883) and \$8,814 (\$25,506) for patients in Group A and Group B, respectively.

Conclusions: Patients who received multiple controller medications for their persistent severe asthma had considerable numbers of exacerbations and incurred substantial costs over 1 year. These patients may benefit from optimizing asthma management, including novel treatments and enhanced education. Sponsor: AstraZeneca

735 | Characterization of elderly patients with idiopathic pulmonary fibrosis within a US administrative claims database

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Background: Idiopathic pulmonary fibrosis (IPF) is a rare progressive and life-threatening interstitial lung disease (ILD). This study focuses on time prior to the marketing of pharmaceutical IPF treatments to provide background information about disease outcomes and comorbidities.

Objectives: Idiopathic pulmonary fibrosis (IPF) is a rare progressive and life-threatening interstitial lung disease (ILD). This study focuses on time prior to the marketing of pharmaceutical IPF treatments to provide background information about disease outcomes and comorbidities.

Methods: Cohort study using a large US health insurance database (Optum's Medicare Advantage plan). Inclusion criteria: ≥ 1 medical claim with a diagnosis code of IPF (January 1, 2008-September 30, 2014), age ≥ 65 , medical and pharmacy benefits, no claims for IPF or other ILD during the 12 month baseline period. The IPF cohort and a subgroup with IPF diagnostic testing were described with respect to demographics, HCRU, and comorbidities prior to cohort entry date. IRs for primary outcomes (acute respiratory worsening, pulmonary hypertension, pulmonary arterial hypertension, lung transplantation [LT], lung cancer, and acute myocardial infarction) and a series of secondary outcomes were assessed. Follow-up continued until the earliest of health plan disenrollment, death, a claim for another known cause of ILD, or end of the study period. Only the first occurrence of each outcome was counted.

Results: Eligibility criteria were met by 4716 patients; 53.4% had diagnostic testing. Median age was 77.5 years (interquartile range [IQR]: 72.0, 82.0), 50.3% were male and median follow-up was 0.8 years (IQR: 0.2-1.8). IRs for primary outcomes ranged from 1.0/1000 person-years (pys, LT) to 180.4/1000 pys (all-cause mortality). IRs for secondary outcomes ranged from 3.7/1000 pys (hepatic failure) to 374.3/

1000 pys (arterial hypertension). Baseline characteristics and IRs were similar among the subgroup with diagnostic testing.

Conclusions: Elderly patients experience a variety of comorbidities. Therapies for IPF and for the associated comorbidities may reduce morbidity and associated HCRU of these patients.

736 | Comparison of CT scan and chest X-ray recording in chronic obstructive pulmonary disease patients in a large UK primary and secondary care setting (Clinical Practice Research Datalink and Hospital Episode Statistics)

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Background: Secondary care data is commonly used to identify diagnostic imaging tests such as CT scans and chest X-rays in UK data and little is known about how well these are recorded in primary care.

Objectives: We compared the recording of chest CT scans and chest X-rays in primary and secondary care in a population of people with chronic obstructive pulmonary disease (COPD).

Methods: Clinical Practice Research Datalink (primary care data; CPRD) and Hospital Episode Statistics Diagnostic Imaging Dataset (secondary care imaging data; HES-DID) were used to identify current/ex-smokers aged ≥ 35 years with COPD. COPD patients were followed up from 2012 until death, leaving the database or 2015. Chest CT scans and chest X-rays were identified during follow-up in CPRD and HES-DID. CPRD recorded CT scans and X-rays that were recorded within 1 month of HES-DID recorded scans, and vice versa, were identified. We assumed that scans or X-rays recorded within 1 month of each other in HES-DID and CPRD are the same image.

Results: 73 697 COPD patients were included in the study. 3225 individual chest CT scans were recorded in HES-DID during follow-up. 1222 chest CT-scans were recorded in CPRD during follow-up. In total, 185 chest CT-scans were recorded in both CPRD and HES-DID. 130 140 chest X-rays were identified in HES-DID and 39 971 in CPRD. In total, 35 229 chest X-rays were included in both CPRD and HES-DID. The sensitivity of identifying chest CT-scans in CPRD was 5.7% and of identifying chest X-rays in CPRD was 26.9%.

Conclusions: HES-DID is the gold standard for identifying diagnostic imaging tests such as CT scans and X-rays. Very few chest CTs or chest X-rays were recorded in CPRD, notably CT scans. GPs may be unaware of diagnostic imaging tests being performed at hospitals and hence do not report it in their GP records or it is possible this information is recorded in hospital letters or free text rather than appearing as Read coded events. Communication between the linkage of CPRD to HES DID improves our ability to determine if patients with conditions such as COPD have received diagnostic imaging tests, information which was clearly not always previously available for primary care cohorts.

737 | Asthma treatment in real life

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Background: The controller to total asthma medication ratio (CTR) is a good measure of controller adherence and has been related to asthma outcomes. Better knowledge on drug use of asthmatics in the general population might provide directions to improve asthma control in real life.

Objectives: To describe the use of respiratory drugs in asthmatics and investigate factors associated with a high CTR.

Methods: A retrospective cohort study (2007-2016) in patients with asthma, 5 years or older from 2 primary care databases, namely, IPCI (NL) and THIN (UK). Asthma was defined as at least 1 asthma disease code in combination with at least 2 prescriptions of respiratory drugs in 1 year. Respiratory drug use was retrieved by ATC code from patient records and expressed as number of users/1000 patient-years (PY). Baseline patient characteristics were compared between patients with a low (<0.5) and high (≥ 0.5) CTR.

Results: In the IPCI database, 144 245 asthma patients contributed to 503 606 PY; in THIN, 728 233 patients to 3 939 817 PY. Short-acting β -agonists were most frequently used (IPCI: 340/1000 PY, THIN: 579/1000 PY), followed by long-acting β -agonists in IPCI and inhaled corticosteroids in THIN. The mean CTR in was higher in adults than in children (IPCI: 0.6 vs 0.5, THIN: 0.5 vs 0.4). In both databases, patients with a high CTR were significantly older, more often female, had more often chronic rhinosinusitis, diabetes, heart failure and gastroesophageal reflux disease but less often eczema than patients with a low CTR.

Conclusions: Use of rescue therapy is high in the general population, resulting in a suboptimal CTR. CTR increases with age, sex, and underlying comorbidity. Additionally, in the future, we will investigate the association between CTR and asthma outcomes.

738 | Abstract Withdrawn

739 | Association between systemic fluoroquinolone exposure and peripheral neuropathy: Population-based nested case-control study

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Background: Fluoroquinolone antibiotics are listed as causing peripheral neuropathy but this association has been poorly quantified, with limited information on the impact of cumulative exposure and risk factors associated with peripheral neuropathy.

Objectives: To better quantify the association between fluoroquinolone exposure and risk of peripheral neuropathy.

Methods: Data from the UK The Health Improvement Network was used to perform a nested case-control study among a cohort of adults without diabetes prescribed either systemic fluoroquinolone, or co-amoxiclav exposure that was evaluated as a negative control. Participants were matched on age, sex, general practice, and calendar time. Adjusted incidence rate ratios (IRR) were calculated for the association between current and cumulative fluoroquinolone and co-amoxiclav exposure and incident peripheral neuropathy using conditional logistic regression, with risk evaluated using different risk windows up to 180 days in the past.

Results: A total of 5357 incident peripheral neuropathy cases were matched to 17 285 controls. Current fluoroquinolone exposure was associated with a significantly increased risk of incident peripheral neuropathy (IRR 1.47, 95% CI 1.13-1.92, $p = 0.005$) but not with current co-amoxiclav exposure (IRR 1.10, 95% CI 0.86-1.40, $p = 0.454$). The association remained statistically significant with fluoroquinolone exposure occurring up to 90-180 days in the past (IRR 1.22, 95% CI 1.01-1.47, $p = 0.038$). There was no significant interaction with other drugs associated with peripheral neuropathy including phenytoin and nitrofurantoin. The association with current fluoroquinolone exposure was greater when excluding patients with other conditions strongly associated with peripheral neuropathy (IRR 1.62, 95% CI 1.22-2.18, $p = 0.001$).

Conclusions: Current systemic fluoroquinolone exposure was associated with an increased relative incidence of peripheral neuropathy and remains significant with both current and recent past exposure.

740 | Profiling the safety of anti-tuberculosis medicines in Ugandan patients

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Background: Prevalence of Adverse Drug Events (ADRs) due to anti-tuberculosis (TB) medicines in Uganda is unpublished, including their effect on TB therapy outcomes.

Objectives: To describe the common ADRs associated to TB therapy among both patients on first and second line anti-TB medicines.

Methods: Retrospective review of 858 TB patients' records captured between 2012 and 2015 was done. Data was collected from the Mulago national referral Hospital TB clinic and the Mildmay Uganda TB clinics. Descriptive data analysis was performed.

Results: The first cohort had 202 cases of MDR TB patients with 126 males (62%) and 76 females (38%) and median age 32 years (IQR 25.1-41.6). More than a half (53%; $n = 107$) had HIV. Other co-morbidities were hypertension and diabetes. Pyrazinamide ($n = 168$, 42%), kanamycin ($n = 68$, 17%), and ethionamide ($n = 56$, 14%) were commonly

associated with ADRs. Joint pains, ototoxicity, and gastrointestinal disorders were commonly reported. More than two-thirds (76.2%; $n = 154$) of the patients recovered from the ADRs, 13.3% ($n = 27$) were lost to follow, 7% ($n = 14$) had their ADRs continuing, and 3.5% ($n = 7$) were fatal. Another cohort had 656 patients receiving treatment for drug sensitive TB, 10.7% ($n = 70$) experienced ADRs, with more females ($n = 42$, 60%) than males ($n = 28$, 40%). The Median age was 37.7 years (IQR 31.5-45.2). Seventy-seven percent (77%; $n = 54$) were on ART, while 22% ($n = 15$) were ART naïve at the time of initiating anti TB medicines. A third (28.6%; $n = 20$) had hepatotoxicity and 61.4% ($n = 43$) had peripheral neuropathy. Other ADRs were uveitis and allergic conjunctivitis, vestibulotoxicity, arthralgia, and skin hypersensitivity. Almost a quarter (24.3%; $n = 17$) of them had severe ADRs, of which 47.1% ($n = 8$) died from hepatotoxicity.

Conclusions: Anti-TB medication related ADRs were common and compromise treatment outcomes due to interruptions and death. Further analysis is required to fully establish incidence patterns, risk factors, and attributable risk on poor TB treatment outcomes.

741 | Prevalence and determinants of antibiotic-related adverse drug reactions in Kenya: Spontaneously reported cases at the pharmacy and poisons board database

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Background: Antibiotics are useful in the treatment and prevention of many infections. Despite this, they may cause adverse drug reactions (ADRs) which could further increase the morbidity, mortality, and treatment costs. The national pharmacovigilance system of the Pharmacy and Poisons board in Kenya has a database in which all actual and suspected adverse drug reactions nationally from hospitals are reported and analysed

Objectives: To describe the prevalence, characteristics, severity, and outcome of antibiotic-related adverse reactions between January 2010 and December 2015

Methods: This was a retrospective cross-sectional study in which all case reports of the reported antibiotic-related ADRs were reviewed. Information on the patient demographics, types of antibiotics and concomitant drugs used, adverse reaction reported, the severity, and outcome was abstracted and analysed using STATA version 13. Bivariate analysis and logistic regression were conducted to determine the risk factors associated with severity and outcomes of antibiotic-related ADRs. Ethical approval was obtained from the Kenyatta National Hospital/University of Nairobi Research and Ethics Committee and the Pharmacy and Poisons board

Results: A total of 550 case reports were analysed. The majority of patients were female (62.3%, $n = 330$), median age of 34 (IQR 22.0-45.0) years. The most commonly affected system was the integumentary system (60.9%, $n = 388$), with skin rash as the most commonly

reported ADR (39.7%, $n = 253$). Cotrimoxazole contributed the majority of the adverse reactions (55.3%, $n = 304$). Most of the reactions were mild to moderate (82.6%, $n = 440$), leading to drug withdrawal for 79.1% ($n = 435$). Sulphonamides and anti-TB drugs produced the most severe reactions ($n = 15.8\%$, $n = 84$), while fatal reactions were only 1.5% ($n = 8$). Older age was significantly associated with severity of the reported ADRs ($p = 0.003$), while HIV status ($p = 0.011$) and severity of the ADR ($p = <0.001$) were associated with poor outcomes. Causality assessment attributed 15.6% ($n = 86$) of the ADRs to the suspected antibiotic while 56.5% ($n = 311$) were probable

Conclusions: There is a high burden of antibiotic-related ADRs, most of which are skin related. HIV status and severity of the ADRs are associated with poor outcomes, and the elderly experience more severe ADRs

742 | Association between systemic fluoroquinolone exposure and tendon rupture: Population-based nested case-control study

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Background: Fluoroquinolone antibiotics are listed as causing tendon rupture, but this risk has been poorly quantified, with limited information on the impact of cumulative exposure and interaction with co-prescribed medicines.

Objectives: To better quantify the association between fluoroquinolone exposure and tendon rupture.

Methods: Data from the UK The Health Improvement Network was used to perform a nested case-control study among a cohort of adults prescribed either systemic fluoroquinolone, or co-amoxiclav exposure that was evaluated as a negative control. Participants were matched on age, sex, general practice, and calendar time. Adjusted incidence rate ratios (IRR) were calculated for the association between current and cumulative fluoroquinolone and co-amoxiclav exposure and tendon ruptures using different risk windows and conditional logistic regression. Analyses were stratified by type of tendon rupture.

Results: The cohort consisted of 1 351 780 adults, of which 34.3% and 65.7% were prescribed fluoroquinolones and co-amoxiclav, respectively. Current fluoroquinolone exposure was associated with a significantly increased risk of any tendon rupture (IRR 1.60, 95% CI 1.23-2.07, $p \leq 0.001$) and Achilles tendon rupture (IRR 3.15, 95% CI 2.12-4.67, $p < 0.001$), but not biceps or other tendon rupture. The association increased with increasing cumulative days of current exposure within each risk window evaluated. The association was greatest when systemic fluoroquinolone exposure was co-prescribed with systemic corticosteroids (IRR 6.88, 95% CI 3.94-12.03, and IRR 19.73, 95% CI 7.93-49.11 for any tendon rupture and Achilles tendon rupture, respectively). Current statin exposure was not associated with an increased risk of tendon rupture.

Conclusions: Current systemic fluoroquinolone exposure is associated with and increased relative incidence of Achilles tendon rupture but not biceps or other tendon ruptures. The size of the association increases with cumulative current fluoroquinolone exposure and when co-prescribed with systemic corticosteroid, but not statin therapy.

743 | Passive enhanced safety surveillance in children receiving Fluenz Tetra vaccination in England during the early 2017-2018 influenza season

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Background: Fluenz Tetra is a quadrivalent, live attenuated, intranasal, influenza vaccine recommended for use in children aged 2 to 17 years vaccinated as part of the seasonal influenza immunisation campaign in the United Kingdom. This is the third post-approval season of passive enhanced safety surveillance (ESS) for the vaccine in 2017/2018.

Objectives: To measure and assess the frequencies of suspected adverse drug reactions (sADRs) in children receiving Fluenz Tetra during the early 2017/2018 influenza season in England.

Methods: Vaccinees or parents/guardians received a Safety Report Card (SRC) to return if children experienced sADRs after vaccination with Fluenz Tetra. At participating sites, 38 general practices and 36 primary schools in England, immunisation teams recorded numbers of SRCs distributed. The project was approved by an NHS Research Ethics Committee (Hampshire B South Central NRES Committee).

Results: Between September 29 and December 2, 2017, 12 193 children were vaccinated at participating sites, with 16 different vaccine lots used. In total, 10 793 SRCs were issued for children aged 2 to 17 years including 5189 children (48.1%) aged 2 to 4 years, 5036 (46.7%) aged 5 to 10 years and 568 (5.3%) aged 11 to 17 years. Of 114 SRCs returned (by January 9, 2018 datalock), 101 reported at least one sADR (0.9% of all SRCs issued). The most frequently reported sADRs were rhinorrhoea ($n = 36$), pyrexia (31), and cough (14). Three reported sADRs were classified as serious due to hospitalisation (0.03% of all SRCs issued) including nasal symptoms, general cold/flu symptoms and croup, from which all three children recovered. The frequency of sADRs reported in the current ESS season was consistent with that reported in previous seasons.

Conclusions: Overall, the number of sADRs reported for Fluenz Tetra in the 2017/2018 ESS remains low. Reported sADRs were typically minor expected events with serious sADRs rarely reported. The pattern and frequency of reported sADRs in the current season were consistent with previous seasons with no safety signals detected. Despite the limited number of reports received, the ESS method continues to be a useful extension to routine pharmacovigilance activities in the monitoring of possible sADRs. Project co-sponsored by DSRU and AstraZeneca.

744 | Adverse drug reactions reported to the Western Cape programmatic pharmacovigilance programme in South Africa: 2005 to 2017

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Background: In 2005, the Western Cape Province Department of Health in collaboration with the Division of Clinical Pharmacology, University of Cape Town, established a targeted spontaneous reporting system for suspected serious adverse drug reactions (ADRs) in patients receiving antiretroviral therapy (ART). Goals were to identify signals of new ADRs and/or ADR patterns, identify risk factors, inform treatment policy, and promote drug safety awareness. The programme expanded to include ADRs in patients receiving tuberculosis treatment in 2012.

Objectives: To describe reported ADRs. To explore changes in ADRs reported over time.

Methods: The programme solicits reports of suspected ADRs that are fatal, life-threatening, result in/prolong hospitalisation, cause disability, and/or result in cessation of the implicated drug. HCWs submitted reports using a standardised reporting form, which includes case definitions of priority ADRs. All reports were reviewed by a pharmacist; review of deaths and complex cases included a clinical pharmacologist and/or physician. We compared characteristics of patients with confirmed ADRs and most commonly reported ADRs between period 1 (2005–2011) and period 2 (2012–2017).

Results: We received 3734 reports: doctors submitted 67.0%, nurses 14.8%, and pharmacists 7.7%. There were 3213 confirmed ADRs involving 3050 patients. A higher proportion of patients were female in period 1 (1222/1751, 69.8%) than period 2 (741/1296 (57.2%), $p < 0.001$. Median weight of adults with ADRs was higher in period 1 (65 kg, IQR 56–74) than period 2 (57 kg, IQR 49–69), $p < 0.0001$. In period 1, the most commonly reported ADRs were lipodystrophy, hyperlactataemia, and peripheral neuropathy, with stavudine most frequently implicated. In period 2, the most commonly reported ADR was kidney injury, with tenofovir most frequently implicated. In 92 of the confirmed ADR reports, the patient died. Most common ADRs in the deaths were hyperlactataemia ($n = 18$) and kidney injury ($n = 12$).

Conclusions: The pattern of reports reflects key safety concerns with ART regimens in use at the time. Reports of ADRs caused by stavudine dominate period 1. The most commonly reported ADR in period 2 was kidney injury, with tenofovir (which replaced stavudine in standard regimens in 2010) most frequently implicated. With increasing focus on nurse-based care in ART programmes, encouraging reporting of ADRs by nurses and supporting nurses in diagnosing and managing ADRs are priorities.

745 | Adverse reactions to bedaquiline in South African patients

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Background: Bedaquiline was introduced into the TB treatment programme in South Africa in March 2015, for use in selected patients with multidrug resistant TB and all patients with extensively drug resistant TB. There is limited long-term safety data on bedaquiline and concerns about safety due to excess mortality in bedaquiline-exposed participants in a randomised controlled trial. Bedaquiline is known to cause QT prolongation. The Western Cape pharmacovigilance programme is a targeted spontaneous reporting system for suspected adverse drug reactions (ADRs) in patients with HIV-1 and/or tuberculosis (TB) infection in the Western Cape, South Africa. Health care workers were encouraged to report all suspected ADRs and all deaths in patients receiving bedaquiline to the pharmacovigilance programme.

Objectives: To describe ADRs to bedaquiline reported to the pharmacovigilance programme.

Methods: We assessed causality using the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) system. A team including a pharmacist, a clinical pharmacologist, and a physician assessed causality. "Confirmed ADRs" include all suspected ADRs that we categorised as definite, possible, or probable according to the WHO-UMC criteria. In the event of death, we further categorised the ADR as a major contributor, contributor, or non-contributor to the patient's death.

Results: From March 2015 to June 2016, 35 suspected ADRs in patients taking bedaquiline were reported, involving 32 patients, including 13 deaths. During this time, 549 patients were initiated on bedaquiline in the Western Cape. We confirmed 30 ADRs, 23 classified as "possible" and seven as "probable." Bedaquiline was implicated in 22 of the confirmed ADRs (73%). In all cases, this was together with one or more concomitant drugs that were also implicated in the ADR. The most common bedaquiline-associated ADR was QTcF prolongation (8 cases of which 7 were severe). There were 4 sudden deaths in which fatal arrhythmia was suspected; all were patients on bedaquiline together with other QT-prolonging drugs. Seven of the 8 non-bedaquiline-associated ADRs contributed to deaths.

Conclusions: Confirmed ADRs were consistent with the known safety profile of bedaquiline. Data on incidence and consequences of severe QT-prolongation with bedaquiline-containing regimens is a research priority to guide programmatic recommendations for optimal monitoring of patients receiving bedaquiline. Ongoing monitoring for serious ADRs should be supported and encouraged within tuberculosis treatment programmes.

746 | A safety profile and characterization of antiretroviral drugs—An analysis of the Uganda national pharmacovigilance centre spontaneous reporting system

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Background: Since 2014, the Uganda Health Sector has been implementing HIV “test and treat” policy for all HIV positive people. The “test and treat” policy involves providing lifelong ART to people living with HIV irrespective of CD4 or WHO HIV clinical staging. By the end of June 2016, out of an estimated 1.5 million individuals living with HIV, 898 197 individuals were already initiated on ART.

Objectives: To explore data from Ugandan spontaneous reporting system to assess the safety profiles of antiretroviral drugs in the treatment of HIV.

Methods: All the adverse drug reactions (ADR) attributed to antiretroviral drugs in the Uganda's national pharmacovigilance centre (NPC) of national drug authority from 2008 to 2016 were extracted from Vigibase. Descriptive analyses of patient demographic characteristics, type and seriousness of the ADRs, ADR outcome, and the time taken between treatment start and onset of ADR. A comparison was made between pediatric and adults patients.

Results: The national pharmacovigilance centre has collected over 2400 individual case reports have since 2008. By end of 2016, a total of 1500 (62%) suspected individual case reports related to ARV drugs were received. There were fewer pediatric patients on ARVs compared with adults (7.1% [95% CI: 5.8–8.6] vs 86.6 [85–88.3]). The top ARVs that were suspected to cause an ADR were nevirapine (34%), tenofovir 15%), zidovudine (13%), and efavirenze (12%) not as a combination with others. Patients taking nevirapine were more likely to develop skin reactions and Stevens Johnson's disease, those taking Tenofovir mostly reported renal impairment and increased blood creatinine, those on zidovudine were more likely to reports anemia, while those taking efavirenz reported rash macular-popular as the common ADR. Most reactions were life threatening (47%), prolonged hospitalization (42.5%), disabling/incapacitated (6%), death (2.9%), and congenital anomaly/birth defect (0.3%). The NPC has received reports (40 cases) indicating fanconi syndrome related to use of Tenofovir

Conclusions: There is need for enhanced monitoring the safety of ARVs because of their widespread use in Uganda. ARVs are taken in combination which makes it hard to precisely related the ADR and a particular drug within the combination. Interest should be put in identifying signals like the Fanconi Syndrome.

747 | Oral fluoroquinolone and the risk of aortic dissection: A population-based case-crossover study

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Background: Previous studies raised safety concerns on the association between fluoroquinolone treatment and serious collagen disorders, aortic aneurysm, and dissection (AA/AD).

Objectives: To evaluate this association via a case-crossover analysis in a large national administrative database.

Methods: A case-crossover design was used to compare the distributions of fluoroquinolone exposure for the same patient across 60-day period before AA/AD event (hazard period) and 5 randomly selected 60-day periods(reference periods) between 60 to 660 days before the AA/AD events. Adjustments were made for co-medications and infectious disease episode. A disease-risk score (DRS) matched time control analysis was performed to investigate the potential time-trend bias. The risks were calculated by a conditional logistic regression model.

Results: A total of 1213 hospitalized AA/AD patients were identified between 2001–2011. In the case-crossover analysis, exposure to fluoroquinolone was more frequent during the hazard periods than during the referent periods (1.7% vs 0.8%; odds ratio 2.52, 95% CI, 1.44–4.44). After adjustment for infections and co-medications, the risk remains significant (OR 2.05; 95% CI, 1.13–3.71). An increased risk of AA/AD was observed for prolonged exposure to fluoroquinolones (OR, 2.41 for 3–14 days of exposure, OR 2.83 for >14 days of exposure). In the case-time control analysis, there is no evidence that the observed association is due to temporal-changes in fluoroquinolone exposure.

Conclusions: Exposure to fluoroquinolone was substantially associated with AA/AD. This risk was modified by the duration of fluoroquinolone use and the length of the hazard period.

748 | Fluoroquinolone use and risk of arterial aneurysm or dissection

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Background: Fluoroquinolones (FQ) have been associated with collagen-related adverse events including a risk of aortic aneurysm or dissection. This could be hypothesized for other large or smaller arteries.

Objectives: To assess FQ-associated risk of arterial aneurysm or dissection (Art-A/D).

Methods: We performed case-time control (CTC) and nested case-control (NCC) studies from the cohort of patients ≥ 18 years affiliated to the General Scheme of the nationwide French Health Insurance database. In CTC studies, cases were patients with ≥ 1 Art-A/D between 2010/07/01 and 2015/12/31 (aortic, iliac, visceral, intracranial, or cervical arteries; date of first event = index date), and ≥ 1 reimbursement of FQ in the 180 days before index date. In NCC studies, cases were patients with ≥ 1 event in 2013-2015. Each case was matched to up to 10 controls randomly selected by incidence density sampling (on age ± 5 years and sex in CTC; on a disease risk score in NCC). In CTC studies, acute exposure was assessed in the 30-day period preceding the event; 30-day periods from 91 to 180 days before index date constituted the controls. In NCC studies, exposure to FQ was assessed within 60 days (recent) and 61 to 365 days before event (past). Exposure assessment considered dispensings of oral or i. v. FQ. Art-A/D were identified from hospitalisation data (diagnosis, imaging, and surgical procedure). Similar designs were used to estimate the associations with amoxicillin (amx; exposure negative control). Associations were estimated using conditional logistic regressions adjusted for corticosteroids and anti-biotic (others), anti-coagulant, anti-platelet, and anti-hypertensive uses. For CTCs, ratios of ORs (FQ/amx; OR-Rs) were estimated to strengthen indication bias controlling.

Results: FQ use was associated with an increased risk of aortic or iliac Art-A/D in CTC (acute: OR-R 1.5, 1.1-2.2) and NCC (recent: OR 1.8, 1.4-2.3) but not with intracranial Art-A/D. This was conversely associated with recent amx use in NCC (OR 1.2, 1.0-1.4). Risk of visceral Art-A/D was increased for FQ recent (OR 2.6, 1.1-6.3) and past use (OR 2.0, 1.1-3.6) in NCC but not in CTC analyses. Results were confirmed by sensitivity analyses (for risk period duration, outcome measurement, etc.). Cervical Art-A/Ds were too rare to allow concluding for these events.

Conclusions: Whereas the increased risk of aortic and iliac Art-A/D was confirmed for FQ use, there was no evidence for an increased risk of such events for intracranial arteries. Further research is needed to explore the impact of FQ use on visceral and cervical arteries.

749 | Quantification of the association between ciprofloxacin use and observed ciprofloxacin resistance

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Background: One of the largest challenges in modern infectious disease epidemiology is a better understanding of how antibiotic resistance develops, which is crucial for prolonging the lifespan of available antibiotics. We hypothesized that the risk of resistance in the general population is associated with the patterns (duration, dose) of previous antibiotic use. To test this hypothesis, we focussed on ciprofloxacin as resistance to this second line antibiotic severely limits treatment options.

Objectives: To assess and quantify the association between previous time-varying ciprofloxacin use and observed ciprofloxacin resistance.

Methods: Dutch observational hospitalization records and in- and out-patient dispensing data gathered by the PHARMO Database Network were linked probabilistically on a person level to antimicrobial resistance (AMR) test results from one regional laboratory (PAMM). The cohort was defined as a random selection of persons who received ciprofloxacin from a pharmacist from 2003 to 2014, excluding persons who used antibiotics from 2001 to 2002. Follow-up began when ciprofloxacin was first dispensed and ended when resistance was first observed, enhancing comparability of person-time and reducing unmeasured confounding. Observed resistance was defined as any AMR test where ciprofloxacin susceptibility was assessed, regardless of the microorganism, with "resistant" (EUCAST threshold) as outcome. The association between ciprofloxacin use and observed resistance was quantified using Cox regression adjusted for age, sex, hospitalization, and other antibiotic use. Ciprofloxacin defined daily dose (DDD) and other time-varying confounders were modelled as weighted cumulative effect variables.

Results: The cohort consisted of 1054 ciprofloxacin users contributing 4969 follow-up years. Ciprofloxacin was dispensed, proportional to person-time, twice as often to men (11 vs 6/1 000 person-years) and 55.9% of the time to persons ≥ 80 years. Ciprofloxacin resistance was observed in 51 persons. The hazard of observed resistance depended on when ciprofloxacin was used. The hazard ratio for 1 vs 0 DDD in the past 2 weeks, for example, was 4.3 (95% CI: 1.2, 29.8), while use >3 weeks ago was not significantly associated with resistance.

Conclusions: Previous recent ciprofloxacin use was strongly associated at the person-level with a risk of observing ciprofloxacin resistance, suggesting that restricting ciprofloxacin use is crucial to delay the development of resistance.

750 | Statins and all-cause mortality among patients with heart failure: Minimizing immeasurable time bias in the setting of a nested case-control study

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Background: Immeasurable time bias, which is induced by the lack of inpatient medication data in most administrative databases, may exaggerate the benefits of drug in pharmacoepidemiologic studies.

Objectives: To examine different methodological approaches to reduce immeasurable time bias in the setting of a nested case-control study using the example of statins and mortality in the patients with heart failure.

Methods: We conducted a nested case-control study within a cohort of 102 460 patients with heart failure using a 2% sample of the Korean nationwide health insurance database. Cohort entry was defined by an incident diagnosis of heart failure from 2003 to 2013. Cases were defined as patients with a record of death, and 10 controls were matched on age, sex, date of diagnosis of heart failure, and duration of follow-up using risk-set sampling. Current use was defined by any dispensing in the 90 days prior to the index date. We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). To estimate the magnitude of immeasurable time bias, we first defined exposure using both in-hospital and outpatient medication data (gold standard) and then repeated analyses by limiting exposure assessment to outpatient data. We compared different methodological approaches with reducing immeasurable time bias: restricting to non-hospitalized patients, adjusting for hospitalization, weighting by either exposable time (non-hospitalized time during 90-day period) or outpatient time, and computing the ORs using 90-day cumulative probability of exposure produced by the Kaplan-Meier product-limit estimator for cases and controls.

Results: Our study included 3093 cases and 29 930 controls. Our gold standard analysis revealed an adjusted OR of 1.20 (95% CI: 1.05-1.37). In contrast, restricting to outpatient produced a protective association (OR = 0.80, 95% CI: 0.68-0.94). The results by restriction to non-hospitalized or adjustment for hospitalization were not in proximity to those of gold standard. Weighting by exposable time (OR = 1.09, 95% CI: 0.92-1.28), outpatient time (OR = 1.14, 95% CI: 0.96-1.34), or the cumulative incidence of exposure (OR = 1.31, 95% CI: 1.11-1.51) all produced estimates consistent with those of gold standard.

Conclusions: Weighting by either exposable time or outpatient time or estimating the 90-day exposure probability may reduce immeasurable time bias in nested case-control studies.

751 | A word of caution: All-cause mortality and residual confounding in Medicare claims data

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Background: Claims databases might not capture or surrogate all the prognostic factors that influence health care delivery; thus, residual confounding might obscure causal effects. Screening sigmoidoscopy provides a relative reduction of 2% in the hazard of death. A reduction >10% should not be expected for screening colonoscopy.

Objectives: To estimate the amount of residual confounding in a scenario where causation of small magnitude, if any, is expected: screening colonoscopy and all-cause mortality.

Methods: We emulated a target trial of one-time screening colonoscopy in Medicare (2004-2012) beneficiaries aged 70-74. To adjust for potential baseline confounding, we used both a structural and a non-structural approach. For the structural approach, we used subject-matter knowledge to identify the potential confounders: age, race, sex, calendar year, reason for entitlement, use of preventive services, US Census Bureau division, comorbidity score, and history of 25 chronic conditions. We then used multivariate outcome regression, inverse probability of treatment weighting (IPW) and propensity score using deciles for adjustment. The non-structural approach consisted on the use of a "high-dimensional propensity score" (HDPS) to create indicators for adjustment using data dimensions (ICD-9 diagnosis codes and CPT procedure codes from carrier claims, ICD-9 diagnosis codes, ICD-9 procedures codes and CPT procedure codes from outpatient and inpatient claims), which we added to the rest of confounders. The outcome model for all analyses was a pooled logistic regression model for monthly risk of death that included an indicator for screening strategy, a flexible function of follow-up, and adjustment indicators, covariates or weights, as applicable.

Results: In the screening colonoscopy group, there were 46 872 individuals and 2592 deaths during a total of 174 230 follow-up years. In the no screening group, there were 1 762 816 individuals and 162 298 deaths during a total of 6 362 550 follow-up years. The unadjusted hazard ratio (HR) for all-cause mortality was 0.58 (95% CI 0.55-0.60). The adjusted HR was 0.69 (0.66-0.72) using multivariate outcome regression, 0.70 (0.67-0.73) using IPW, 0.69 (0.67-0.72) using propensity score, and 0.72 (0.69-0.74) using HDPS. The HDPS estimate did not change substantially under various choices of parameters for indicator selection.

Conclusions: Residual confounding can be intractable for the effect of preventive services on all-cause mortality in Medicare.

752 | Use of real-world evidence in personalized benefit-risk assessment: Detecting treatment patterns using Gaussian mixture models

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Background: Randomized trials typically explore potential benefits and harms for the overall trial population and, as feasible, in larger subgroups defined by factors thought to increase baseline risk. However, limiting the analyses to predefined risk factors can obscure important characterization of treatment patterns.

Objectives: To characterize the benefit-risk (B-R) profile of patients who are expected to benefit most from use of a new oral antiplatelet agent.

Methods: The expected distribution of net clinical benefit (NCB) among patients indicated for use of a new oral antiplatelet, vorapaxar,

was examined. The study sample included patients with a prior myocardial infarction (MI) and no prior stroke, TIA, or severe bleeding, as identified in the Clinical Practice Research Datalink, linked to the Hospital Episode Statistics and Office of National Statistics databases. NCB components were defined as cardiovascular (CV) death excluding fatal bleed, non-fatal MI, non-fatal stroke, and severe bleeds to avoid double counting of events. Risk prediction models were developed to estimate baseline risk of each outcome for each patient over 3-years of follow-up. The drug's hazard ratios (HRs) relative to placebo, as observed in the pivotal RCT, were applied to baseline risk estimates to compute expected attributable risks, summed to estimate per-patient NCB. Gaussian mixture models were fit to characterize NCB distribution.

Results: The sample included 31 941 adults, median (IQR) age of 71 (60-81) years, 93% white, and 64% male. Estimated baseline risks of ischemic and bleeding events were highly correlated (Spearman's $\rho = 0.82$). 3-class mixture model had better Bayesian Information Criterion fit than 1- or 2-class models and resulted in low NCB class ($n = 11\ 308$; mean NCB = 2.3; SD = 0.4) including younger (mean age 58/75/83) males (76/62/51%) compared with those in the intermediate ($n = 12\ 554$; mean NCB = 3.6; SD = 0.9) or high NCB class ($n = 8079$; mean NCB = 5.4; SD = 1.7). Compared with the low NCB class, patients with the highest NCB more often had CV comorbidities, with the most notable differences in the prevalence of heart failure (5 vs 61%), atrial fibrillation (3 vs 44%), chronic kidney disease (2 vs 39%) and peripheral vascular disease (2 vs 29%), respectively.

Conclusions: Latent class modeling can be used to identify important B-R treatment patterns that might otherwise be obscured, and profile characteristics of patients who may benefit most from therapy.

753 | The use of propensity score distributions to gain understanding on drug utilization in routine clinical practice: A case study on newer vs older oral anticoagulants

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Background: Propensity scores (PS) are mainly used to control for confounding in observational drugs' effectiveness studies. However, PS distribution curves are also useful to gain understanding on routine clinical practice.

Objectives: (1) To explore whether patients with atrial fibrillation (AF) using direct oral anticoagulants (DOAC) differ globally from patients using Vitamin K Antagonists (VKA) and (2) to identify which patients' characteristics differ across therapeutic groups

Methods: A national, cohort study was conducted in France. Between 2013 and 2016, 118 cardiologists and 32 general practitioners included 4810 adults with AF. Upon inclusion, physicians collected clinical data and patients informed the 12-month history of oral anti-coagulant therapy. First, to explore the "overall similarity" of covariates distributions between therapeutic groups (dabigatran,

rivaroxaban, or apixaban, vs VKA), the PS was computed using three multivariable logistic regression models in which potential confounders (age, gender, BMI, HAS-BLED and CHA₂DS₂VASc scores, cardiovascular disease, hyperlipidaemia, use of antiplatelet drugs, type and duration of AF) were independent variables. The PS distribution curves were compared as a qualitative indicator for the "overall similarity" of covariates distributions across treatment groups. Second, to identify which patients' characteristics differ across therapeutic groups (all DOAC vs VKA), parametric tests were performed, as adequate

Results: 3693 (76.8%) patients were included in the analyses: 1429 used VKA, 334 used dabigatran, 781 used rivaroxaban and 386 used apixaban for stroke prevention. PS distribution curves were almost equal for patients on dabigatran vs VKA, and patients on rivaroxaban vs VKA, meaning that the two groups were very similar with respect to the observed covariates. However, several covariates differed across groups: compared with VKA users, patients taking DOAC were younger ($p < 0.0001$), more recently diagnosed with NVAf ($p < 0.0001$), less likely to have a permanent AF ($p < 0.0001$) and less likely also to have a cardiac comorbidity ($p < 0.0001$). Moreover, their bleeding risk was lower ($p < 0.0001$). No difference was evidenced in terms of gender ($p = 0.084$)

Conclusions: Both PS scores and comparative tests are useful to describe routine clinical practice and in turn, the extent and nature of an indication bias in effectiveness studies

754 | Observational studies on non-specific effects (NSE) of diphtheria-tetanus-pertussis vaccination (DTP) in low-income countries: Assessing the impact of bias and confounding by using meta-regression

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Background: It has been suggested that vaccines have NSE on morbidity and mortality due to infections others than those targeted by the vaccine or for unknown reasons. Some observational studies showed increased relative risks (RR) of all-cause mortality with DTP containing a whole-cell pertussis component. Based on a recent review and meta-analysis of selected studies (Higgins, BMJ 2016), the WHO concluded that the results are inconsistent. However, the WHO meta-analysis and its conclusions were challenged.

Objectives: To assess the potential impact of bias and confounding on the estimated RR of all-cause mortality after DTP.

Methods: Based on methodological considerations on study design and analysis, we systematically assessed all 17 DTP studies from the WHO review for risk of selection bias, exposure and outcome misclassification, confounding, and differential co-interventions with other vaccines including co-administration. We performed meta-analyses on all studies and complemented with meta-regression, including the assessed sources of bias and confounding as covariates.

Permutation tests were used to control the risk of false positives. Results are expressed as relative risk ratios (RRRs), with $RRR > 1$ indicating that the RR estimate is larger when the covariate is present, compared with absent. Uni- and multi-variable meta-regressions were performed.

Results: The overall RR of all-cause mortality after DTP vaccination based on all studies was 1.32 (95% CI: 0.83-2.08). Based on uni-variable meta-regression, the highest RR estimate was for studies conducted in Africa ($RRR = 3.16$, $p = 0.002$), studies using the landmark approach ($RRR = 2.97$, $p = 0.015$) and studies at high risk of selection bias ($RRR = 2.28$, $p = 0.039$), exposure misclassification ($RRR = 2.28$, $p = 0.05$) and confounding ($RRR = 2.65$, $p = 0.052$). These covariates cluster in studies from Africa ($n = 11$) and their individual impact could not be disentangled using multi-variable regression.

Conclusions: Our results suggest that several potential sources of bias and confounding are significantly associated with increased RR of all-cause mortality after DTP. Bias and confounding can therefore not be ruled out as an explanation of the increased RR. Higher quality data are needed for a robust evaluation of NSE of DTP studies.

755 | Quantification of unmeasured confounding in a post-marketing drug monitoring program

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Background: A limitation often cited of analyses using only administrative claims data is residual confounding due to unmeasured factors.

Objectives: Using linked claims-electronic health records (EHR) data on select clinical parameters, we quantified the impact of potential residual confounding in analyses of claims data only. We illustrate this in an ongoing monitoring program on the effectiveness and safety of linagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i).

Methods: Within two US claims datasets (05/2011-12/2015), we identified 1:1 propensity score (PS)-matched cohorts of type 2 diabetes patients ≥ 18 years initiating linagliptin or a comparator (other DPP-4is [$n = 31\,492$ pairs], pioglitazone [$n = 23\,316$ pairs], or sulfonylureas [SUs] [$n = 19\,731$ pairs]), and compared the risk of the primary cardiovascular (CV) outcome (hospitalization for myocardial infarction, stroke, unstable angina, or coronary revascularization). We estimated pooled hazard ratios (HR) and 95% confidence intervals (CI) controlling for >180 baseline claims-based patient characteristics. We recorded residual imbalances in EHR-observed clinical parameters in 7219 patients linked to claims in a prior validation study, and observed effect estimates from the ongoing cohort study. We quantified the residual bias assuming a range of associations between EHR-observed clinical parameters and the CV outcome (RR_{CD}) and estimated fully adjusted relative risks (aRR).

Results: After PS-matching, claims-based patient characteristics were balanced. Linagliptin had a similar CV risk vs other DPP-4is (HR [95% CI] = 0.91 [0.79-1.05]) and pioglitazone (HR [95% CI] = 0.98 [0.84-1.15]), but showed a decreased risk vs SUs (HR [95% CI] = 0.76 [0.64-0.92]). For the latter comparison, if the clinical parameter "longer vs shorter duration of diabetes" would truly increase the outcome risk by 50% ($RR_{CD} = 1.5$), the aRR in claims would change to 0.77 from 0.76. Similarly, if a 1% point increase in hemoglobin A1c would truly result in a 25% increase in outcome risk, the aRR would change to 0.81 from 0.76.

Conclusions: After PS matching, any residual confounding even under extreme assumptions is unlikely to explain the findings of an interim analysis in a current post-marketing drug monitoring program.

756 | Deep learning to detect features of a population of anti-osteoporosis drug users

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Background: We have previously demonstrated that data-driven cluster analysis can be used to identify subgroups within a population of users of specific drugs, based on key baseline characteristics. Here, we demonstrate how deep learning methods can be applied to identify such key features, and to detect sub-groups of interest.

Objectives: To test a data-driven method to learn the features of a population of anti-osteoporosis drug users, and whether these features can be used to derive patient sub-groups.

Methods: Using the SIDIAP Database (anonymized primary care records for $>80\%$ of the population of Catalonia), 37 996 incident users of anti-osteoporosis drugs (2007-2014) with complete data on risk factors were analysed. All available risk factors were included. A machine learning method called "autoencoder" (see Hinton et al, 2006) was used to learn the key features of the population, distributed in n hidden nodes. Our previous work using traditional unsupervised learning methods (hierarchical and k -means clustering) showed the presence of at least $n = 5$ clusters in this dataset, which we used as reference. The "importance" of a given feature would be determined by its weight P , where the most important feature would have $P = 1$, and unimportant features would have $P = 0$. Our proposed approach thus provides (a) the important features in the detected clusters, and (b) additionally, the probability of membership of any given patient in each cluster.

Results: At $n = 5$ (the number of plausible sub-groups detected by hierarchical and k -means clustering), the autoencoder model detected 9 features to be important ($P = 1$): age, gender, body mass index, smoking, alcohol drinking, fracture history, co-morbidity, sedative use, and steroid use. Anticoagulants, aromatase inhibitors, and HRT/contraceptives were not considered important features ($P = 0$).

Conclusions: Our study proposed a novel approach for determining the characteristics of a population of AOD users, which is increasingly useful in drug utilisation research where there can be a large number

of overlapping risk factors. The features selected by the model were the same as those independently deemed by clinical expert opinion to be important factors considered by GPs when prescribing AODs, which adds face validity to our findings. Further research is needed on the use of this method for drug utilisation research, especially for high-volume, high dimensional data.

757 | Does hyperparameter tuning improve the performance of super learning for predicting when antidepressants are prescribed for indications other than depression?

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Background: Super learning is an ensemble machine-learning approach that is being increasingly used in pharmacoepidemiological analyses to predict outcomes and create propensity scores for the estimation of causal effects. However, the hyperparameter values of the machine-learning algorithms in the super learner may not always be considered by investigators when using super learning.

Objectives: To determine whether the performance of super learning improves when machine-learning algorithms employ hyperparameter values that are tuned versus set to the default in their respective statistical packages within the R programming language.

Methods: This prediction study used super learning to identify when antidepressants were prescribed for indications other than depression. The analytical dataset contained 73 576 antidepressant prescriptions that were written between Jan 2003 and Dec 2012 by 141 primary care physicians in Quebec using an electronic prescribing system that required them to document treatment indications. Super learning was used to combine the prediction functions of five machine-learning algorithms: LASSO penalized regression, decision tree, random forest, artificial neural network, and support vector machine. Each algorithm considered over 370 predictor variables derived using linked health services data. To identify the optimal hyperparameter values for each algorithm, a cross-validated grid search procedure was used. The performance of the “tuned” super learner (derived using the best hyperparameter values from the grid search) was compared with that of the “untuned” super learner (derived using the default hyperparameter values in R).

Results: Overall, 44% of all antidepressant prescriptions were written for indications other than depression. The R^2 statistic for the tuned super learner was 0.322 (95% CI 0.267-0.362), which was 4% (1%-8%) higher than the R^2 statistic of 0.309 (0.256-0.353) for the untuned super learner. The discrimination of the tuned super learner (c statistic of 0.822, 0.795-0.847) was also slightly better than that of the untuned super learner (c statistic of 0.817, 0.791-0.846).

Conclusions: Super learning is a powerful method for combining the predictions from multiple machine-learning algorithms. However, if

the hyperparameter values of the algorithms in the super learner are not carefully tuned, super learning may not achieve its best performance.

758 | Signal detection using tree-temporal scan statistics in the sentinel system

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Background: Routine signal detection in health care databases remains a challenge. Self-controlled designs are easy to implement but their performance in a data-mining context with minimal exclusion criteria is unknown.

Objectives: To empirically test tree-temporal scan statistics with a self-controlled design on three types of medical products whose indications vary in the extent of underlying comorbidities and health status: statins, long acting reversible contraceptives, and antibiotics.

Methods: We identified all new users of the study products with at least 183 days of prior enrollment from three health plan insurers in the Sentinel Distributed Database from 2000-2016. We scanned for all incident outcomes (defined as the first in 183 days) using a tree containing hierarchical groupings of more than 8000 outcome codes in the 56 days following exposure initiation. Using a self-controlled risk interval design to account for time-invariant confounders, we implemented the tree-temporal scan statistic to detect elevated frequencies of events while controlling for multiple testing. We identified alerts for triage and evaluation based on a pre-specified threshold of $p \leq 0.01$. Only some alerts are deemed true signals.

Results: We identified 1 695 892 incident simvastatin episodes that produced 405 468 incident outcomes for evaluation. There were eleven alerts, all of which were consistent with confounding by indication. Other statins had similar results. In the second test case, we identified 217 339 intrauterine device insertions resulting in 19 396 outcomes. Three alerts were identified and consistent with known adverse complications. Evaluations of other long acting reversible contraceptives did not yield alerts. In the third test case, we identified 7.5 million azithromycin episodes resulting in 1.4 million outcomes for evaluation and 174 alerts. Other antibiotics performed similarly with many of the alerts attributed to the underlying infection and not the antibiotics themselves. No alerts in any of the test cases were deemed true signals.

Conclusions: Tree-temporal scan statistics used with self-controlled designs can be a useful signal detection method but are subject to time-varying confounding and protopathic bias. Drugs used for primary prevention (eg, contraception, statins) are better candidates for

this method. Drugs used for acutely ill populations (eg, antibiotics) require different approaches. All signals generated by TreeScan require further investigation.

759 | Data mining for adverse drug events with a propensity score matched tree-based scan statistic

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Background: The tree-based scan statistic (TreeScan) is a data mining tool that adjusts for multiple testing in evaluation of thousands of potential adverse events. It has been used for signal detection with a self-controlled design in vaccine safety studies. However, many drug safety questions are not well-suited for self-controlled analysis. A propensity score (PS) matched cohort design is robust for many drug safety investigations.

Objectives: To propose a method that combines TreeScan with a new initiator, PS-matched cohort design and conduct simulations evaluating power and type 1 error with this method, which involves scanning across an outcome tree with >8000 hierarchical groupings of diagnosis codes.

Methods: Simulation data was based on permutation of a real dataset, and retained the observed correlation among covariates and exposure as well as clustering of co-occurring outcomes within patients. We generated scenarios that varied the magnitude of true effect for 3 adverse events, strength and direction of confounding, and degree of PS model misspecification.

Results: TreeScan in cohorts that were PS matched to adjust for confounding outperformed TreeScan in unmatched cohorts. In scenarios with positive confounding (which moved estimates away from the null), adjusted analyses recovered the pre-specified type 1 error ($p = 0.01$) while unadjusted analyses inflated type 1 error (up to $p = 0.40$). In scenarios with negative confounding (which moved estimates toward the null), adjusted analyses preserved power whereas unadjusted analyses greatly reduced power. Although complete adjustment of true confounders had the best performance, matching on a moderately misspecified PS substantially improved type 1 error and power compared with no adjustment. When we simulated a true effect of exposure on a specific outcome (eg, cerebrovascular disease), we detected co-occurring signals for clinically related concepts (eg, hemiplegia).

Conclusions: TreeScan with PS matching shows promise as a method for screening and prioritization of potential adverse events. In realistic scenarios, the method detected signals in areas of the tree where true effects of exposure were simulated. However, this evaluation was

restricted to binary outcomes with fixed follow up. Screening should be followed by clinical review and studies specifically designed to quantify the magnitude of effect, with confounding control targeted to the outcome of interest.

760 | Probabilistic record linkage to detect duplicated content in twitter prior to pharmacovigilance analyses

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Background: One obstacle for use of social media for pharmacovigilance is duplication of content. Some duplicates can be hard to detect: users can repeatedly refer to the same event or multiple users can describe the same event, often in different words. Conversely, textually similar posts may not necessarily be duplicates but could represent distinct events of similar nature.

Objectives: Estimate the extent of duplicated content related to drugs in Twitter and evaluate the performance of vigiMatch duplicate detection trained through active learning in this information source.

Methods: In total 13 820 posts (tweets) were collected from Twitter in Sep and Oct of 2016, using a set of search terms derived from trade names in WHODrug, for a convenience sample of 23 drugs. Posts explicitly marked as retweets were removed prior to analysis. Our duplicate detection was based on probabilistic record linkage as implemented in vigiMatch, a published duplicate detection method used for the same purpose in large collections of individual case safety reports. vigiMatch was applied to the set of words in each tweet. Since we did not have access to a representative set of known duplicates to use for training, we applied active learning, a semi-supervised procedure in which the algorithm to be trained is used to select data points that are submitted to manual annotation, and iteratively learn from the annotated samples. The trained algorithm was applied to one of the WEB-RADR partners' proprietary collection of historical tweets, which had already been subjected to duplicate detection with a rule-based method.

Results: In total, our active learning approach selected 974 pairs of tweets for review. Out of these, 411 were classified as duplicates. At the selected threshold, 17% of the posts in our own data were classified as suspected duplicates, at an estimated precision of 99%. In our partner's data set, the corresponding proportion was 9%. At the same time, only 0.008% of all the possible pairs of tweets in our data were suspected duplicates, which supports the need for active learning.

Conclusions: There is substantial duplication of tweets related to drugs, beyond explicitly marked retweets. Probabilistic record linkage with vigiMatch trained through active learning proved feasible and detected a significant number of duplicates that had been missed with a rule-based method.

761 | Time-to-onset in statistical signal detection of ADRs: A follow-up study

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Background: In a previous study, the use of the time-to-onset (TTO) of Adverse Drug Reactions (ADRs) did not have additional value compared with disproportionality analysis (DPA) in statistical signal detection using spontaneous reports. This was possibly due to the abundance of reports with a short TTO of 1-2 days and as a result decreased discriminative power.

Objectives: To investigate whether the TTO can be a useful addition to DPA in statistical signal detection for ADRs with a higher latency.

Methods: All drug - ADR associations from reports in the Netherlands national pharmacovigilance database with a median TTO of 7 days or more and a minimum of 5 reports were included. For each association, the TTO of the reports were tested against the TTO of the same ADR for all other drugs using two-sample Anderson-Darling (AD) testing. Several combinations of the number of reports per association (N), ranging from 5-15 and TTO, ranging from 7-60 days were tested. Performance was based on sensitivity and positive predictive value (PPV) using the presence of the ADR in the summary of product characteristics (SPC) as the gold standard for the outcome. Results were compared with the performance of DPA, which was based on the lower limit of the 95% CI of the reporting odds ratio (ROR).

Results: A total of 31 958 reports containing 50 504 associations were included, resulting in 3379 unique drug - ADR combinations. The sensitivity for the TTO was low (range 0.08-0.38) compared with DPA (range 0.63-0.88). PPV was similar for both methods (range 0.90-1.00). For the TTO method, sensitivity increased with an increasing number of reports, whereas for DPA the sensitivity increased with both increasing number of reports and increasing TTO. Nearly all associations detected by TTO were also detected by DPA.

Conclusions: Although sensitivity was low, the TTO method performed well in terms of PPV. However, since DPA detected almost all associations identified by TTO, the latter seems to have little additional value in statistical signal detection. However, selection bias (presence in the SPC based on DPA in the past) could not be ruled out.

762 | Risk and prognosis of acute kidney injury in bisphosphonate users undergoing hip fracture surgery

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Background: Bisphosphonates may be nephrotoxic, but no study has examined risk or prognosis of laboratory confirmed acute kidney injury (AKI) in bisphosphonate users undergoing hip fracture surgery.

Objectives: To examine the risk and prognosis of AKI in bisphosphonate users undergoing hip fracture surgery.

Methods: This cohort study included older patients (≥ 65 years) with hip fracture surgery during 2005-2016 ($n = 22\,380$) in the Central Denmark Region. By individual-level linkage of registries, we obtained information on hip fracture surgery, filled prescriptions, laboratory data, and comorbidities. We excluded patients with a history of chronic dialysis/transplant or preadmission AKI. Dispensing for bisphosphonates were used to assess current use (prescription filled 0-90 days before surgery), former use (91-365 days), and non-use (no prescription within 365 days). The 5-day risk of AKI was assessed as $\geq 50\%$ increase in creatinine from baseline level. Adjusted relative risks (aRRs) were computed using log-binomial regression, accounting for potential confounders based on propensity-score weighting. Mortality within 6-30 days (short-term) and 31-365 days (long-term) following surgery was computed and compared by adjusted hazard ratios (aHR) using Cox regression with propensity-score weighting.

Results: Among the 21 515 included patients, 1641 (7.6%) were current users and 542 (2.5%) were former users of bisphosphonates. Current users and non-users had similar distribution of age (median 83 vs 84 years), comorbidity, sex, and body-mass index. Fewer current users than non-users had an estimate glomerular filtration rate (eGFR) < 30 (2.0% vs 3.6%), but more had used preadmission medications other than bisphosphonates. The 5-day risk of AKI was 12% in current and former bisphosphonate users and 15% in non-users. Compared with non-users, the aRR was 1.0 (95% confidence interval [CI]: 0.9-1.1) in current users and 1.0 (95% CI: 0.8-1.3) in former users. Among patients with AKI, short-term mortality was 13% in current users, 15% in former users, and 16% in non-users. The aHR was 0.9 (95% CI: 0.6-1.4) in current users compared with non-users. The long-term mortality was 22% in current users, 24% in former users, and 26% in non-users. The aHR was 0.7 (95% CI: 0.5-1.1) in current users compared with non-users.

Conclusions: Bisphosphonate use was not associated with an increased risk of post-fracture AKI or post-AKI mortality up to 1 year of hip fracture surgery compared with non-users.

763 | Optimal plasma potassium ranges for mortality prediction across chronic kidney disease stages: The Stockholm Creatinine Measurements (Scream) project

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Background: Small-scale studies in high-risk populations suggest that hyperkalaemia is a less threatening condition in chronic kidney disease (CKD), arguing adaptation and tolerance to potassium (K^+) retention by the failing kidneys.

Objectives: To estimate the distributions of plasma potassium levels across CKD stages and evaluate optimal potassium ranges across CKD stage by linking to mortality.

Methods: Observational study including all patients undergoing plasma K^+ testing in Stockholm during 2006-2011. We randomly selected one K^+ measurement per patient and constructed a cross-sectional cohort with mortality follow-up. Covariates included demographic characteristics, comorbidities, medications and eGFR values. We estimated K^+ distribution (median, 95% confidence interval) by eGFR using quantile regression. We also assessed the optimal K^+ ranges associated with 90-day, 180-day, and 365-day mortality by eGFR category using cox regression models with restrictive cubic splines. We repeated the random K^+ selection 99 additional times to assess consistency of results.

Results: Included were 831 760 participants with median age 55 years, 55% women and median K^+ 4.00 mmol/L. 70 403 (8.5%) individuals had CKD G3 (eGFR <60-30 mL/min), and 8594 (1.1%) had CKD G4-G5 (eGFR <30 mL/min). 66 317 deaths were registered within one year. Adjusted plasma K^+ increased across worse CKD stages with median K^+ rising from 3.98 (95% CI 3.49-4.59) mmol/L for eGFR >90 mL/min/1.73m² to 4.43 (3.22-5.65) for eGFR ≤15 mL/min/1.73m². The association between K^+ and mortality was U-shaped, but flattened at lower CKD strata; Optimal K^+ ranges gradually shifted upwards with worse CKD stages. For instance, optimal ranges within a 50% mortality risk increase within 90-days mortality were 3.61-4.61 mmol/L in eGFR category G1-G2, 3.57-4.87 mmol/L in G3, and 3.50-5.09 mmol/L in G4-G5. Results were consistent in our 99 additional cohort iterations.

Conclusions: CKD stage modifies both K^+ distribution and optimal K^+ ranges in the community. While our study supports the view that K^+ is better tolerated with worse kidney function, it challenges the current use of a single K^+ range for all patients.

764 | Influence of statin potency on the risk of renal failure—A nationwide cohort study using laboratory data

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Background: The effect of statin therapy on renal function is controversial. Recent evidence suggests that the adverse effects may be related to statin potency.

Objectives: To assess the risk of renal failure in patients treated with high-potency statins compared with those treated with low-potency by combining information on renal function tests from routine laboratory data with data from health care databases.

Methods: A nationwide cohort study was performed using data from the Swedish health care registers (dispensed drugs, hospitalization, and death) and linked with information on glomerular filtration rate (eGFR) and low-density lipoprotein cholesterol (LDL-C), which was obtained from routine laboratory data. Incident statin users 40 years of age or older with a baseline eGFR >60 mL/min/1.73m² and no recorded diagnosis of renal failure before treatment initiation were

identified. At the baseline (years 2006-2007) the cohort was classified according to low- or high-potency statins and to the level of LDL-C (low, medium, high, very high). The cohort was followed until December 2010. The outcome was renal failure identified by the presence of diagnostic code in the health care registers or ≥30% decrease in eGFR from baseline. A Cox regression model was used to estimate the hazard ratio (HR) with 95% confidence interval (CI) for the association between statin potency and renal failure adjusted for demographic and clinical factors.

Results: A total of 34 560 patients were identified, of which 23.8% were treated with high-potency statins. In the registers 115 (0.33%) patients were recorded with a diagnosis of renal failure and when adding those with a decrease in eGFR (1731, 5.01%) the proportion with the outcome increased to 5.34%. Compared with subjects treated with low-potency statins, those receiving high-potency statins had a higher risk of renal failure (HR 1.25; 1.12-1.39 95% CI). Stratifying by the LDL-C value at baseline, the results were confirmed in the medium, high, and very high groups. No statistically significant association was found between statin potency and renal impairment when the outcome was detected through register data only.

Conclusions: A significantly greater decrease in renal function was found for patients treated with high-potency statins compared with those treated with low-potency statins. The addition of laboratory data improved the ability to detect renal failure.

765 | Tacrolimus pharmacogenetics and acute kidney injury after lung transplantation

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Background: Tacrolimus (TAC), a cornerstone of immunosuppression after lung transplant (LTx), has an unpredictable dose response in the early post-operative period. Excessive TAC exposure is potentially nephrotoxic, but its impact on post-LTx acute kidney injury (AKI) is not well-quantified. Genetic variation of TAC metabolism could explain substantial variability of TAC dose response but is understudied in the early post-LTx period.

Objectives: Examine the effect of TAC concentration on AKI risk during the first 14 days after LTx, and identify clinical and genetic factors that explain variability in early TAC exposure.

Methods: We performed a retrospective cohort study of patients from one center of the multicenter Lung Transplant Outcomes Group study. We defined AKI using consensus criteria and TAC dose response by the concentration/dose (C/D) ratio. Cox regression was used to estimate the adjusted association between TAC concentration, modeled as a time varying exposure, with subsequent AKI through post-LTx day 14. We used linear mixed effects regression to estimate the adjusted association of clinical and genetic variables with log-

transformed TAC C/D ratio. Specifically, we included genetic variants known to regulate TAC metabolism: CYP3A4 (rs35599367), POR (rs1057868), PPAR (rs4823613), and CYP3A5 (rs776746, rs10264272, rs41303343).

Results: From 2003-2015, 484 patients were enrolled. AKI occurred in 290 (60%) patients and was associated with 1-year mortality: RR 3.5 (95% CI 1.8, 6.7). AKI was independently associated with increasing TAC concentration: adjusted HR 1.5, (95% CI 1.2, 1.9) for each 5-mg/dL increase. In the 376 patients who were genotyped, those with a single loss-of-function (LoF) allele for CYP3A5 had a non-significant reduction of the C/D ratio: -21% (95% CI -72.6%, 14.9%), whereas those with two LoF alleles had a significant reduction of the C/D ratio: -140% (95% CI -243.5%, -70.7%). Other genetic variants were not significantly associated with C/D ratio. Clinical factors associated with TAC C/D ratio in multivariable analysis included concomitant exposure to voriconazole, amiodarone, and vasopressors; body weight; hematocrit; and acute infection.

Conclusions: TAC concentration is an independent risk factor for AKI during the early post-operative period after LTx. CYP3A5 LoF alleles are associated with TAC dose response. Future studies should examine whether dosing algorithms based on genetic and clinical predictors can reduce excessive TAC exposure and post-LTx AKI.

766 | Comparative safety of calcium-free phosphate binders vs calcium-based phosphate binders in patients with end-stage renal disease requiring maintenance hemodialysis

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Background: Phosphate binders are standard care in patients with end-stage renal disease (ESRD), but calcium-based binders (mainly calcium acetate) are hypothesized to increase the risk of cardiovascular events and death compared with calcium-free binders (mainly sevelamer). However, comparative safety data are sparse.

Objectives: To assess the comparative risk of death in sevelamer vs calcium acetate treated ESRD patients requiring maintenance hemodialysis (HD) in the US.

Methods: We performed a retrospective cohort study using data from the Medicare-linked United States Renal Data System (USRDS, 2008-2013). We identified all patients aged ≥ 65 years who initiated sevelamer or calcium acetate within 180 days of starting HD, following ≥ 6 months of Medicare enrollment. We selected sevelamer and calcium acetate initiators 1:1 matched on a propensity score (PS), which accounted for demographics, cardiovascular comorbidities and comedication, vitamin D use, and health care utilization factors. The primary endpoint was all-cause mortality. In the primary as-treated analysis, patients were followed from the date of the first prescription to the earliest occurrence of the following events: death,

treatment switch or discontinuation, HD discontinuation, or loss to follow up. We also conducted an intention to treat (ITT) analysis in which we followed patients up to 180 days without censoring on treatment discontinuation or switch. Cox proportional hazards models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI).

Results: We identified 12 578 PS-matched pairs of sevelamer and calcium acetate initiators, with a mean age of 75.8 years (SD 6.9). In total, 46.3% of patients were men, and 71.7% were white. The mean follow up was 260 days (SD 279) among calcium acetate initiators and 252 days (SD 270) among sevelamer initiators, resulting in an incidence rate for death of 22.7 per 100 person-years (py) in sevelamer initiators and 22.0 per 100 py in calcium acetate initiators. When compared with calcium acetate initiators, sevelamer initiators had a HR for all-cause death of 1.03 (95% CI 0.96-1.09). The ITT analyses revealed a HR of 0.99 (95% CI 0.96-1.04).

Conclusions: ESRD patients treated with phosphate binders had high mortality rates, amounting to 22% in the first year of starting the treatment; however, no substantial differences in the risk of all-cause mortality were observed between calcium-free and calcium-based binders.

767 | Lithium treatment and risk of chronic kidney disease—A Danish population-based case-control study

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Background: Long-term use of lithium may result in reduced renal function. Recently, a large observational study using laboratory-confirmed estimates of glomerular filtration rate (eGFR) has questioned whether lithium use is also associated with an increased risk of chronic kidney disease (CKD).

Objectives: To assess the potential association between lithium use and risk of CKD.

Methods: We conducted a population-based case-control study based on Danish health register data combined with data from a large laboratory database (Funen Laboratory Cohort [FLaC]). We identified all adults (≥ 18 years) with CKD from 2000-2016 ($n = 18\ 631$), defining their index date as the date of their first eGFR < 60 mL/min and further requiring a mean eGFR < 60 mL/min within the two periods 0-3 months, and 3-6 months after the index date. For each case, we age- and sex-matched up to 10 population controls ($n = 104\ 360$) with a eGFR ≥ 60 mL/min measured in the same quarter as the case eGFR, and with a subsequent mean eGFR ≥ 60 mL/min in the two periods 0-3 months and 3-6 months after. Using conditional logistic regression, we estimated odds ratios (ORs) for CKD associated with cumulative use of lithium.

Results: In total, 214 cases (1.1%) and 1407 controls (1.3%) had ever used lithium within the study period, and of those 78 (0.4%) cases

and 505 (0.5%) were long-term users (≥ 5 years). Half of cases (10 364; 55%) and controls (54 476; 52%) were current users of antihypertensive drugs. In total, 2689 (14%) cases, and 18 616 (18%) had type I or II diabetes. Ever use of lithium was not associated with the risk of CKD (adjusted OR: 0.89, 95% confidence interval [95% CI] 0.77-1.04), nor was cumulative use (≥ 2000 Defined Daily Doses [DDD] adjusted OR: 0.96, 95% CI 0.64-1.45) or long-term use (≥ 10 years adjusted OR: 1.01, 95% CI 0.61-1.68). We did not observe dose-response patterns related to cumulative amount used or the duration of treatment. **Conclusions:** In this case-control study, we found no association between lithium treatment and CKD.

768 | Metformin versus insulin for initial treatment of gestational diabetes: Maternal and neonatal outcomes

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Background: Gestational diabetes mellitus (GDM) is a common pregnancy complication, requiring pharmacologic treatment in up to one-third of women. The comparative safety/effectiveness of metformin (oral) versus insulin (injected, standard of care) remains controversial.

Objectives: To estimate the comparative effectiveness of metformin versus insulin for initial pharmacological management of GDM.

Methods: We conducted a retrospective cohort study using routinely-collected health care data from New Zealand. We followed pregnant women aged 15-45 from the time of GDM diagnosis through the postpartum period and assessed maternal and neonatal outcomes. We used pharmaceutical claims data to identify new users of metformin or insulin monotherapy at 24-28 weeks' gestation. Outcomes were defined using a maternity care dataset and hospitalization data. We adjusted for measured covariates using inverse probability of treatment weights (IPTW), and imputed missing covariate data. We calculated unadjusted and adjusted risk differences (RD) and 95% confidence intervals (CI) for dichotomous outcomes. We estimated the treatment effect on birthweight (primary effectiveness outcome) using linear regression.

Results: We compared 3818 metformin-treated pregnancies with 3450 insulin-treated pregnancies. The average maternal age was 32 years, and average BMI was 29 kg/m². Both groups were similar with respect to age, BMI, and timing of diagnosis and treatment initiation. We observed differences in treatment by parity, smoking status, ethnicity and socioeconomic status. These differences were balanced after applying IPTW. Approximately 12% of women who initiated metformin required supplemental insulin, while just 1% of insulin initiators required supplemental treatment with metformin. Mean birthweights were similar for metformin-treated (3367.6 g) and insulin-treated pregnancies (3390.8 g) and not significantly different in adjusted models ($\beta = 0.58$, 95% CI -27.06, 28.23). After adjusting, metformin was associated with a reduced absolute risk of elective c-section (aRD = -2.3 95% CI -4.3, -0.3), large-for-gestational-age

(aRD = -3.7, 95% CI -5.5, -1.8), and neonatal hypoglycemia (aRD = -5.0, 95% CI -6.9, -3.2).

Conclusions: Metformin was as effective as insulin for women with GDM, and associated with a reduced risk of some serious adverse neonatal outcomes like neonatal hypoglycemia when compared with insulin.

769 | Child growth and developmental outcomes following in-utero exposure to metformin versus insulin for treatment of gestational diabetes

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Background: Metformin is an emerging option for treating gestational diabetes (GDM). Unlike insulin, metformin crosses the placenta, causing concerns that it may impact fetal development in ways that insulin would not and result in adverse childhood outcomes.

Objectives: To estimate the association of in-utero exposure to metformin versus insulin with child growth and development.

Methods: We conducted a cohort study using 2005-2012 New Zealand (NZ) health care data. We linked pregnant women with GDM to their children with results from a pre-school readiness screening program administered to all children in NZ at age 4. We analyzed age- and sex-standardized z-scores and percentiles for weight, height, weight-for-height, and body mass index (BMI). We categorized parent- and teacher-reported Strengths and Difficulties Questionnaire Difficulties Scores (SDQ-P and SDQ-T) based on NZ-specific cut points. We estimated risk ratios (RR) and 95% confidence intervals (CI) for the association of metformin versus insulin with these outcomes and used inverse probability of treatment weights (IPTW) to control confounding. We stratified analyses by sex to investigate a possible sex difference observed in other clinical settings.

Results: We identified 3928 GDM-affected pregnancies initially managed with metformin (n = 1996) or insulin (n = 1932). These women were similar with respect to average age, BMI, and timing of treatment. We observed baseline differences in treatment by maternal smoking status, ethnicity and socioeconomic status. These were balanced after applying IPTW. After adjustment, children of metformin-treated mothers were not more likely to be ≥ 85 th percentile for weight (aRR = 1.04, 95% CI 0.93 1.16) or weight-for-height (aRR = 0.92, 95% CI 0.83, 1.02) than children of insulin-treated mothers. Children of metformin-treated mothers were also not more likely to have concerning Difficulties Scores on the SDQ-T (aRR = 0.99, 95% CI 0.60, 1.62) or SDQ-P (aRR = 1.15, 95% CI 0.89, 1.48), although the upper confidence limit for the SDQ-P does not exclude a modest increase in risk. In analyses stratified by sex, we observed overlapping 95% confidence intervals for all outcomes of interest.

Conclusions: In the first study to examine child growth and developmental outcomes at age 4, we found no evidence of clinically

meaningful differences between children exposed in utero to metformin versus insulin treatment for GDM.

770 | First trimester exposure to varenicline was not associated with increased risk of major birth defects: Findings from the smoking MUMS (Maternal Use of Medications and Safety) study

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Background: Varenicline is an effective smoking cessation pharmacotherapy in the general population but guidelines recommend against its use during pregnancy, because data about maternal and fetal safety are insufficient.

Objectives: To assess the effects of exposure to varenicline in the first trimester on major birth defects in liveborn children.

Methods: Routinely-collected records of births (conceived between Jan 2008 and Apr 2012) in New South Wales, Australia were linked to administrative pharmaceutical dispensing data for mothers and hospital records for both mothers and children. First trimester exposure was defined as days covered by dispensing of varenicline (anatomical therapeutic chemical code N07BA03) overlapping with the first 12 weeks of gestation. The outcome was any major birth defects, identified from children's hospital admissions in the first 18 months of life, excluding chromosome disorders and anomalies due to viral infections and exogenous agents. Children exposed to teratogenic medications in the first trimester were excluded. Logistic regression models were used to compare the outcome in varenicline-exposed children with that in children born to (a) mothers who smoked and did not use any smoking cessation pharmacotherapy during pregnancy and (b) mothers who did not smoke during pregnancy, adjusting for maternal socio-demographic characteristics, obstetric factors and medical conditions.

Results: Among 884 varenicline-exposed children, 25 (2.83%) had a major birth defect. Among 44 368 unexposed children of smoking mothers and 336 090 unexposed children of non-smoking mothers, 3.00% and 3.03% respectively had a major birth defect. After adjusting for potential confounders, varenicline exposure was associated with 2% and 6% reduction in the likelihood of birth defects, compared with untreated smoking (odds ratio [OR]: 0.98, 95% confidence interval [CI]: 0.66-1.47) and non-smoking (OR: 0.94, 95% CI: 0.63-1.40), respectively.

Conclusions: First trimester use of varenicline was not associated with increased risk of major birth defects compared with no therapy. Although this is the largest study investigating the possible teratogenic effects of varenicline to date, the number of exposed cases was still limited. Precaution in interpreting these findings is recommended, as

is further research with larger sample sizes, to increase precision and examine specific birth defects.

771 | Algorithms to estimate the timing of pregnancy for stillbirths in pregnancy safety studies

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Background: Administrative databases are increasingly used to study drug safety during pregnancy. The gestational age is typically not available in these data sources and needs to be estimated. In contrast to live births, no validated algorithms are currently available to estimate the gestational age for non-live births hampering their inclusion as outcomes in drug safety studies.

Objectives: To evaluate whether the gestational age at which stillbirths occur can reliably be predicted based on maternal risk factors and proximal causes of stillbirth.

Methods: We conducted a population-based cohort study including all deliveries between 2005-2010 using the administrative databases of the Lombardy region in Italy, which include information on the exact gestational age of all live and non-live births. Stillbirths were defined using ICD-9 diagnostic codes (V27.1, V27.3, V27.4, V27.6, V27.7, 656.4). We evaluated the gestational age at which the stillbirths occurred in relation to (i) medical/obstetrical risk factors (maternal age, use of assisted reproductive technology, pre-existing and gestational hypertension and diabetes, systemic lupus erythematosus, multiple births), and (ii) proximal causes, defined as conditions which act to directly cause intrauterine fetal demise (preeclampsia, infections, placental abruption, fetal growth restriction). We then used regression analyses to predict the timing of stillbirth as a function of these factors, using both a categorical (stillbirth at <28, <32, <34, <37 weeks) and a continuous outcome.

Results: In this cohort of 541 970 pregnancies, there were 1712 stillbirths (0.32%). The factors considered did not reliably predict the timing of stillbirth: the *c*-statistic of the logistic models ranged from 0.59 to 0.62, and the *R*² for the linear model was 0.05. Factors associated with a 1 to 2 week decrease in gestational age at stillbirth diagnosis were use of assisted reproductive technology, fetal growth restriction, pre-existing hypertension, preeclampsia, placental abruption, multiple births, and ≥2 chronic maternal risk factors.

Conclusions: Algorithms based on known chronic risk factors and proximal causes for stillbirth had limited ability to predict gestational age in stillbirths. Other approaches need to be evaluated (eg, timing of prenatal screening test, number of prenatal visits) to improve the accuracy of classification of drug exposure at specific pregnancy periods.

772 | The impact of naive identification of pregnancies on cohort inclusion and misclassification of person-time in insurance claims data

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Background: Validated algorithms that identify timing of pregnancy in claims data may be used to study pregnant women or pregnancy as an outcome. Correct identification of, control for, or exclusion of pregnancy is critical to the study of drugs contraindicated during pregnancy and studies where pregnancy is a modifier. However, in a targeted literature review, we found that few studies in claims data reported any exclusion based on pregnancy; of those that did, most excluded pregnant patients based solely on occurrence of pregnancy-related claims during the study baseline or entire study period. This approach may result in failure to exclude women during early gestation or the misclassification of person-time before or during pregnancy.

Objectives: To estimate the delay in pregnancy identification when relying on occurrence of diagnosis and procedure codes in claims data.

Methods: We used diagnosis and procedure code-based algorithms to capture pregnancy episodes and estimate the date of conception based on algorithms developed by Margulis, Andrade, and the Mini-Sentinel project. Two cohorts of pregnant women were included from the Optum Clinformatics Data Mart de-identified database: an ICD-9-based cohort spanning Jan 2013-Jun 2014 and an ICD-10-based cohort spanning Jan 2016-Jun 2017. Women with any claim for pregnancy screening, miscarriage, or delivery were followed for 294 days from the estimated date of conception. The proportion of women with medical claims for screening and the time to the first pregnancy-related claim were estimated.

Results: A total of 172 896 women were included (85 784 through ICD-9 and HCPCS codes, median age 30 years; 87 112 through ICD-10 and HCPCS codes, median age 31). In both cohorts, a large proportion of women had a claim for first trimester screening (78.8% for ICD-9 and 88.6% for ICD-10 cohort) with a median time from conception of 79 days (IQR: [79, 109] and [79,110], respectively). More women in the ICD-9 cohort had second trimester screening as the first indication of pregnancy (11.5% vs 5.8%) after a median of 158 days (IQR 158,158) from conception for both. The remaining women had their first indication of pregnancy only on the delivery (10.2% for ICD-9 and 5.6% for ICD-10 cohort).

Conclusions: Failing to use algorithms to estimate the beginning of pregnancy can lead to misclassification of person-time or under-identification of women in early stages of pregnancy.

773 | Periconceptional oral contraceptive use and adverse perinatal outcomes: The pride study

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Background: Oral contraceptives are widely used by women of reproductive age, but conclusive evidence on associations between perinatal outcome and use just before or even during pregnancy is lacking.

Objectives: To determine whether periconceptional use of oral contraceptives is associated with adverse perinatal outcomes.

Methods: We analyzed data from the Pregnancy and Infant Development (PRIDE) Study, a prospective cohort study among pregnant women in The Netherlands. Participants enrolled in 2012-2016 provided information on the use of oral contraceptives in the year before and during pregnancy through Web-based questionnaires completed before gestational week 17. Outcomes of interest included preterm birth, low birth weight, macrosomia, small or large for gestational age, and low Apgar score. A Directed Acyclic Graph (DAG) approach was used to obtain a minimally sufficient set of adjustment factors. We estimated odds ratios (ORs) with 95% confidence intervals (CIs) using multivariable logistic regression. In sensitivity analyses, we used exposure data from prescription records.

Results: A total of 2699 pregnancies in 2601 women were included, of which 1396 (51.7%) were exposed to oral contraceptives in the periconceptional period. The use of any oral contraceptive 4-12 months or 0-3 months before pregnancy was not associated with adverse perinatal outcome. However, use of combination oral contraceptives containing gestodene 0-3 months before pregnancy was associated with low birth weight (OR 4.9, 95% CI 1.6-15.2). Using prescription records, additional associations were observed between combination oral contraceptives and macrosomia (exposure 0-3 months before pregnancy: OR 4.0, 95% CI 1.8-9.1) or low birth weight (exposure during pregnancy: OR 2.2, 95% CI 1.0-5.0).

Conclusions: Most oral contraceptives used in the periconceptional period were not associated with adverse perinatal outcomes, but some may affect birth weight. Due to potential over-reporting resulting in exposure misclassification, analyses based on prescription data may lead to spurious associations. Therefore, exposure assessment of hormonal contraceptive use with detailed self-reported data is preferable.

774 | The association between treatment with systemic prednisolone and insomnia—A symmetry analysis

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Background: It is well-established that treatment with systemic corticosteroids can cause disturbances in initiating and maintaining sleep. However, this association has not been quantified among patients treated for obstructive airway diseases.

Objectives: To assess whether treatment with systemic prednisolone is associated with the initiation of non-benzodiazepine hypnotics and melatonin (non-BZDH).

Methods: A prescription sequence symmetry analysis was employed on all Danish residents aged ≥ 18 years with at least one filled prescription of treatment for obstructive airway diseases (ATC R03) from 2000-2016, who also filled their first ever prescription for prednisolone (ATC H02AB06) and non-BZDH (ATC N05CF N05CH) within an interval of 7 days before or after the prednisolone treatment. Patients with a previous cancer diagnosis were excluded from the study. We calculated the crude sequence ratio (SR) and corresponding 95% confidence intervals. The SR is the ratio between subjects with prednisolone prescribed before non-BZDH and subjects with prednisolone prescribed after non-BZDH, which is a valid estimate of the incidence rate ratio. The attributable number of post-prednisolone non-BZDH treatment was also calculated.

Results: During the study period, 678 persons were identified initiating non-BZDH within 7 days before and after their initial prednisolone prescription. Of those, 366 (54%) were females, and 321 (47%) had a Charlson Comorbidity Index (CCI) of 0 corresponding to a low comorbidity burden. Of the incident users of prednisolone and non-BZDH, 459 initiated prednisolone before and 219 initiated prednisolone after non-BZDH, yielding a SR of 2.10 (1.79-2.47). The attributable number was 240 (52.3%). The SR of females and males was 2.16 (1.74-2.71), and 2.03 (1.62-2.59), respectively. An increased. The most pronounced association was a large number of prednisolone DDDs redeemed (250 DDD: SR 3.29 [2.27-5.09]). Post-hoc analyses with a time-window of 1, 3, 6, and 12 months showed decreasing SRs (1.71 [1.57-1.87], 1.57 [1.48-1.67], 1.44 [1.38-1.51], and 1.29 [1.25-1.34]), respectively.

Conclusions: We found a substantial association between the initiation of systemic prednisolone and subsequent treatment with non-BZDH among patients treated for obstructive airway disease. Compared with the baseline rate of non-BZDH treatment, a 52% increase was induced secondary to prednisolone initiation, but the association decreased when expanding the time-interval.

775 | Safety of baclofen for alcohol use disorders: Comparison with nalmefene, acamprosate and naltrexone in a cohort study of 165 334 patients between 2009 and 2015 in France

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Background: Baclofen has been widely used off-label for alcohol use disorders (AUD) in France since 2008, despite uncertainties concerning its efficacy and safety, particularly at high doses.

Objectives: We aimed to evaluate the safety of this use relative to the main approved treatments for AUD (acamprosate, naltrexone, nalmefene).

Methods: This cohort study based on data from the French national health insurance claims database included patients beginning baclofen or approved treatments for AUD, aged 18 to 70 years, with no serious comorbidity (eg, cancer, cardiovascular disease), and no serious alcohol-related disease (eg, alcoholic liver disease, chronic pancreatitis). Safety was evaluated by assessing the risks of specific and all-cause hospitalisation or death for patients exposed to baclofen with doses varying over time, relative to those for patients exposed to approved treatments, through a Cox model adjusted for socio-demographic and medical characteristics. This analysis was repeated for patients with a history of hospitalisation for alcohol-related problems (eg, acute intoxication, dependence syndrome).

Results: The cohort included 165 334 patients, 47 614 of whom were exposed to baclofen. Median follow-up times of patients exposed to baclofen or approved treatments were 87 and 81 days. The patients exposed to baclofen differed from those given approved treatments in terms of their socio-demographic and medical characteristics: they were more likely to be female (43.8% vs 30.8%), with a higher socioeconomic status (17.9% vs 13.9% in the least deprived area of residence) and a lower frequency of history of hospitalisation for alcohol-related problems (12.7% vs 23.5%). Baclofen exposure was found to be significantly associated with all-cause hospitalisation (HR = 1.13 [95% CI: 1.09-1.17]) and death (HR = 1.31 [95% CI: 1.08-1.60]). The risks increased with dose, reaching 1.48 [1.31-1.67] for hospitalisation and 2.27 [1.27-4.07] for death at high doses (≥ 180 mg/day). These associations related particularly to drug intoxication (hospitalisation and death) and death from unspecified causes. Similar results were obtained for the analysis restricted to patients with a history of hospitalisation for alcohol-related problems.

Conclusions: This study raises concerns about the safety of baclofen for AUD, particularly at high doses, with higher risks of hospitalisation and mortality than approved treatments.

776 | Evaluating the assumptions of the self-controlled case series design in studies investigating the risks of antipsychotic use in the older population

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Background: The self-controlled case series (SCCS) design is a within-person design which controls for time-constant patient specific confounding. One of the assumptions of this method is that the occurrence of the outcome event does not alter the probability of a subsequent exposure. This assumption may not be valid when

investigating the risk of adverse events associated with antipsychotics in an elderly population. In particular, hospitalisation events such as myocardial infarction (MI) and hip fracture in the elderly can lead to hospital-induced delirium of which the treatment is antipsychotics. Not accounting for this will potentially lead to biased results. Pre-exposure initiation risk periods can be used to determine if exposures are event-dependent and help to eliminate bias.

Objectives: To investigate if the assumption of the SCCS was violated when exploring the association between atypical antipsychotics and hospital outcomes including MI, deep vein thrombosis, stroke, pneumonia and hip fracture.

Methods: Department of Veterans' Affairs administrative claims database was used to identify subjects who had a hospitalisation event, between July 1, 2010 to June 30, 2016. A SCCS analysis was undertaken with and without pre-exposure initiation periods. Rate ratios (RR) and 95% confidence intervals (CI) were calculated using conditional Poisson regression.

Results: When pre-exposure initiation risk periods were included, the risk for MI was elevated in the first week post initiation (RR 1.78 [95% CI 1.18-2.67]), however risk was attenuated when pre-exposure initiation risk periods were excluded (RR 1.49 [95% CI 0.99-2.25]). An increased risk of MI prior to antipsychotic exposure was seen in all pre-initiation risk periods up to 29-56 days (RR 1.74 [95% CI 1.32-2.30]). Similar, results of including or excluding pre-exposure initiation risk periods were observed for the other outcomes.

Conclusions: Evaluating the assumptions of the SCCS design is particularly important when undertaking analysis of antipsychotics in an elderly population, where the event of interest, hospitalisation occurrence, have a high risk of hospital-induced delirium and consequently are treated by antipsychotics. In our example, the significant pre-exposure initiation risk periods indicated that exposure is event-dependent and ignoring this led to rate ratios that were biased.

777 | Comparative effectiveness of adjunctive psychotropic medications in schizophrenia

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Background: Antipsychotic medications are the first-line treatment for schizophrenia, but often inadequate to address all of the disease's symptoms and functional limitations. Little is known about the comparative effectiveness of secondary treatment options that are commonly used in this situation.

Objectives: To compare the effectiveness and safety of initiating adjunctive treatment with different classes of psychotropic medications in the community treatment of adults with antipsychotic-treated schizophrenia.

Methods: US national Medicaid data from 2001 to 2010 were used to examine treatment outcomes among patients with schizophrenia who were stably treated with a single antipsychotic medication and then initiated either another antipsychotic, a mood stabilizer, an antidepressant, or a benzodiazepine (N = 103 858). Cox proportional hazards models adjusted by multinomial propensity score weighting were used to compare outcomes between the four adjunctive treatment groups. The primary outcome was hospitalization for a mental disorder. Secondary outcomes included emergency department (ED) visits for a mental disorder, self-injury, and death. Propensity scores to control confounding were based on more than 100 demographic, clinical, and prior service use variables and achieved very good balance between the four adjunctive treatment groups. Follow-up was for 365 days on an intent-to-treat basis.

Results: Compared with initiating another antipsychotic, starting an antidepressant was associated with a lower risk of psychiatric hospitalization (0.85; 95% CI 0.81-0.88) and ED visits (0.92; 95% CI 0.89-0.95). By contrast, starting a benzodiazepine was associated with higher risk of psychiatric hospitalization (1.08; 95% CI 1.02-1.13) and ED visits (1.12; 95% CI 1.07-1.17) compared with initiating another antipsychotic, while starting a mood stabilizer was associated with an increased risk of death (1.33; 95% CI 1.09-1.63).

Conclusions: In the community treatment of individuals with schizophrenia, initiating adjunctive treatment with an antidepressant was associated with reduced risk of psychiatric hospitalization and ED visits compared with initiating alternative psychotropic medication strategies. The associations of benzodiazepines and mood stabilizers with poorer outcomes warrant clinical caution and further investigation.

778 | Latent class analysis of anticholinergic and sedative medication use: A national population study

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Background: Anticholinergic/sedative medications are prescribed frequently to older patients, despite their negative effects on physical and cognitive function. A wide range of medications have anticholinergic/sedative effects including analgesics, psycholeptics, and psychoanaleptics.

Objectives: To identify subgroups of anticholinergic/sedative medications used in patients with a high cumulative anticholinergic/sedative drug exposure as measured by the Drug Burden Index (DBI).

Methods: A national population study of patients with high anticholinergic/sedative drug exposure in the Netherlands. We used a

nationwide dataset including all anticholinergic/sedative medications dispensed from community pharmacies throughout November 2016 in the Netherlands. Data were provided by the Dutch Foundation for Pharmaceutical Statistics. We selected patients with high exposure to anticholinergic/sedative medications defined by having a DBI ≥ 1 . A latent class analysis was performed on medications grouped by ATC level 2 to identify classes of patients with specific medication use.

Results: Data were available from 1773 pharmacies (89.5% of total community pharmacies). Overall, 218 722 patients had a DBI ≥ 1 . Patients had a mean age of 76.0 years (SD, 7.5), 66.8% were female, used on average 2.6 (SD, 0.9) anticholinergic/sedative medications and had a mean DBI of 1.6 (SD, 0.6). Latent class analysis identified four classes of patients. Class 1: "combined psycholeptic/psychoanaleptic medication use" (55.1%), class 2: "high analgesics use" (18.8%), class 3: "high anti-epileptic medication use" (17.4%), and class 4: "high anti-parkinson medication use." The most used medication groups in class 1-4 were, respectively, antidepressants (55.7%), opioids (96.5%), antiepileptics (100.0%), and dopaminergic antiparkinson medication (98.3%).

Conclusions: A large proportion of older patients in the Netherlands had a high anticholinergic/sedative load. Distinct subpopulations of users were identified. Interventions aiming at reducing the overall anticholinergic and sedative drug burden should be targeted to these subpopulations.

779 | The risk of Alzheimer's disease associated with benzodiazepines and related drugs: A nationwide nested case-control study

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Background: Benzodiazepines and related drugs (BZDRs) are frequently used among older people and, despite recommendations, they are commonly used long term. Previous studies have yielded controversial results of BZDR use as a risk factor for Alzheimer's disease (AD) and even opposite dose-response relationships.

Objectives: To assess the association between BZDR use and risk of AD with cumulative consumption duration of use and average dose based models with 5-year lag time between exposure and outcome. In addition, different BZDR subcategories, ie, benzodiazepines, Z drugs, short/medium and long acting BZDRs, were investigated separately.

Methods: A nationwide nested case-control study of all Finnish community dwelling persons who had clinically verified AD diagnosis in 2005-2011 (N = 70 719) and their age, sex and region of residence matched controls (N = 282 862). AD diagnosis was based on DSM-IV and NINCDS-ADRDA criteria. BZDR purchase data in Defined Daily Doses, were extracted from the Prescription register since 1995. BZDR use periods, ie, when continuous use started and ended, were calculated using validated PRE2DUP-method. The association between BZDR use and AD was assessed using conditional logistic regression.

Results: Use of BZDRs were associated with somewhat increased risk of AD (adjusted OR 1.05, 95% CI 1.03-1.07). A dose-response relationship was observed with both cumulative consumption and duration when accounting for occupational social class and comorbidities. The association between BZDR use in general and AD was evident also after additional adjustment for other psychotropic use. However, adjustment for antidepressants and antipsychotics removed the cumulative dose-response relationship by attenuating the ORs in the highest dose category.

Conclusions: BZDR use in general was associated with somewhat increased risk of Alzheimer's disease with no major differences were observed between different subcategories of BZDRs (ie, benzodiazepines, Z drugs, short/medium acting or long acting BZDRs). Cumulative dose-response relationship was abolished after adjustment for other psychotropics suggesting that the association was at least partially explained by more frequent use of antidepressants and/or antipsychotics, or reasons for concomitant use of these medications.

780 | Treatment for older diffuse large B-cell lymphoma patients with cognitive impairment and dementia

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Background: Diffuse large B-cell lymphoma (DLBCL), the most common lymphoid malignancy in adults, is often diagnosed between ages 60 and 70 years old. The population of older adults in the United States is projected to undergo rapid growth and increased life expectancy over the coming decades; thus, cancer cases among older adults will jointly be expected to increase. Comorbid conditions, such as cognitive impairment or dementia (CID), will also be more likely to be present at diagnosis of cancer in older adults and affect both treatment decision-making and prognosis. Few studies have evaluated treatment utilization patterns among older DLBCL patients with CID.

Objectives: Our objective was to describe treatment utilization patterns in older DLBCL patients with CID.

Methods: We performed a retrospective cohort study of 10 626 DLBCL patients ages 66 and older in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, of whom 410 (3.9%) had CID prior to cancer diagnosis. Medicare beneficiaries with a first primary DLBCL diagnosis between 2001 and 2011 were identified. Validated algorithms utilizing administrative claims, diagnoses and procedures codes were used to identify CID and primary treatment with chemo-immunotherapy and radiation. The association between CID and receipt of treatment was determined using multivariable logistic regression models to estimate odd ratios (OR) and 95% confidence intervals (CI).

Results: Fewer patients with CID diagnoses received any DLBCL treatment (chemo-immunotherapy or radiation) compared with

patients without CID (41% versus 65%). In multivariable models, patients with CID had significantly lower odds of any treatment (OR = 0.47; 95% CI: 0.38-0.59). These findings were consistent for treatment with chemo-immunotherapy (OR = 0.44; 95% CI: 0.35-0.55) but not radiation (OR = 0.79; 95% CI: 0.59-1.06). In stratified analyses, patients aged 66-74 years (OR = 0.42; 95% CI: 0.23-0.76) and Ann Arbor stage I-II (OR = 0.39; 95% CI: 0.29-0.53) had the lowest odds of treatment.

Conclusions: In summary, patients with CID were less likely to receive chemo-immunotherapy or radiation to treat DLBCL, and multiple factors could explain this less aggressive approach taken among these older patients. It remains unclear how CID and these differences in care influence survival. Further research on patient and caregiver preferences, treatment decision-making, and alternative treatment options for older patients with comorbid lymphoma and CID is warranted.

781 | Understanding treatment pathways for HER2-positive metastatic breast cancer (HER2 + MBC) patients: Analysis using group-based trajectory models (GBTM)

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Background: In Australia, access to publicly funded HER2-targeted agents for HER2 + MBC is governed by evidence-based prescribing restrictions specifying when and how these agents are to be used in combination with specific chemotherapies. Previous research has suggested significant departures from a number of these restrictions; further analysis is required to better understand the real-world treatment pathways of HER + MBC patients.

Objectives: Exploratory analysis to assess how well treatment for HER + MBC adheres to prescribing restrictions using GBTM.

Methods: We used national dispensing records to identify patients initiating trastuzumab (H) between 2001-2013, followed through 2016. We created binary indicators of monthly use for H (first line therapy), lapatinib (L: second line therapy), and 5 chemotherapy (CT) partners up to 3 years after first H initiation. We used GBTM, accounting for non-random dropout due to death, to cluster patients based trajectories of H use. Within each H trajectory group we further clustered patients into subgroups based on multiple trajectories of L and CT use. Finally, for each patient we used dispensing records to determine the combinations and sequence of treatments, and classified treatment episodes as adhering or not adhering to prescribing restrictions.

Results: 5052 patients initiated H. GBTM identified 7 distinct H trajectory groups, each with 3 subgroups based on L and CT trajectories. Initially most patients adhered to restrictions, though in several subgroups 20-37% of initial therapy was non-adherent. Following treatment initiation, we found that up to 68% of patients received H, L, and CT combinations outside restrictions in groups where initial H was discontinued after 6-18 months.

Conclusions: We observed considerable heterogeneity in therapy dispensed to HER2 + MBC patients. GBTM were an effective means of

consolidating this complexity and their use facilitated the interpretation of treatment pathways by clustering patients based on the patterns of their cancer medicine use.

782 | Potential for using external control arms derived from electronic health records to replace control arms from randomized controlled trials

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Background: The gold standard clinical trial includes a randomized control; however, oncology drug development is increasingly forced to rely on single arm clinical trials. Interpretation of single arm trials can be challenging. Comparison with external controls (EC) may provide context for study findings.

Objectives: Replicate overall survival (OS) results from multiple RCTs in advanced non-small cell lung cancer (aNSCLC) using EC groups derived from an electronic health record (EHR).

Methods: Design: All Roche aNSCLC RCTs enrolling from 2011 onward were reviewed. Trial selection criteria included sufficient follow-up, ≥ 1 US trial site, and relevant biomarkers captured in both the trial and EC group databases. Trial specific eligibility criteria were applied to the EHR data to form the EC cohorts for each trial. Setting: EC patients were identified in the Flatiron Health (FIH) an EHR-derived longitudinal database which reflects cancer care received and patient outcomes. The FIH lung cohort contains aNSCLC patients diagnosed from 1/1/11. Exposures: Various Outcome: The primary outcome was OS, defined as time from randomization (trial pts) or treatment initiation (EC pts) to death. Patients were censored at the end of trial follow-up, FIH analysis cutoff date (10/31/17), or last contact date. Statistical Analysis: Propensity score (PS) methods were used to adjust for differences between the trial population and EC pts. The Kaplan-Meier (KM) method was used to estimate survival. Adjusted Cox models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) comparing the trial experimental arms with the EC arms. For each study, HRs and KM plots derived using the EHR EC were compared with the RCT results.

Results: Nine aNSCLC trials met the trial selection criteria. Findings from the first 2 trials showed concordance between the adjusted HR comparing the trial experimental arm with the EC arm with the corresponding RCT HR. For example, trial NCT02008227 reported a HR = 0.79. The estimated HR for the corresponding EC analysis was 0.80 (95% CI: 0.65, 0.98). Similarly, the result within trial NCT01903993 produced a HR = 0.72 compared with the EC derived HR = 0.74 (95% CI: 0.54, 1.00). Results for all 9 trials will be presented.

Conclusions: For the trials investigated, HR estimates based on the EC group closely matched those from the RCT. Hence, control arms

derived from contemporaneous EHR data may be useful for interpreting findings on OS from single arm trials in aNSCLC.

783 | Using group-based trajectory models and propensity score weighting to detect heterogeneous treatment effects: The case study of generic hormonal therapy for women with breast cancer

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Background: Researchers often use interrupted time series (ITS) to identify the effect of a new policy or program on individuals' outcomes. We extend this design to identify heterogeneous treatment effects (HTE) using group based trajectory models (GBTM) to identify groups before a new policy and then examine if the effects of the policy has consistent impacts across groups.

Objectives: To describe a new approach that parsimoniously identifies HTEs in ITS models using GBTM combined with propensity score weighting. We explore this by looking at how adherence to hormonal therapy (HT) for women with breast cancer was impacted by reducing copays for medications by the introduction of generic HTs.

Methods: We examined monthly adherence to HT using the proportion of days covered (PDC) for women diagnosed with breast cancer between 2008-2009 using SEER-Medicare data. First, we examined adherence for 1 year before generic HT was available. Second, we characterized pre-generic adherence using GBTM. Third, within each group we generate inverse probability treatment weights (IPTWs) using propensity scoring between those who receive a subsidy for their medication (and are not exposed to changing copay once generics are available) and those that do not receive a subsidy. Fourth, we examined adherence after generic HT was introduced and compared the impact of declining copays from generic HT by comparing individuals that do and do not receive subsidies using a modified Poisson model using the IPTWs created in step 3.

Results: GBTM for adherence in the 1-year pre-generic identified six groups: (1) consistently high, (2) slow decline, then increase, (3) rapid decline, then increase, (4) slow decline, (5) rapid decline, and (6) consistently low. Adherence after generic HTs, was not impacted by the introduction of generic HT overall. When looking within adherence trajectory groups, we found evidence of HTEs. When comparing patients that did and did not receive a subsidy, we found reduced copays increased adherence for 2 of the 6 groups ("consistent low" [aRR = 1.74, {1.21, 2.34}; $p \leq 0.01$] and "rapid decline" [aRR = 3.01, {1.20, 7.54}; $p = 0.02$]) and found 1 group with the opposite relationship, reduced copays decreased adherence ("consistently high" [aRR = 0.98, {0.96, 1.00}; $p = 0.04$]).

Conclusions: This study describes a new approach to identify HTEs when using ITS. When applying this approach to the effect of generic introduction to HT, we find evidence of HTEs.

784 | Characterization of chronic lymphocytic leukemia (CLL) patients in real-life clinical practice in Helsinki, Finland 2005-2015

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Background: The Finnish Hematology Registry (FHR) allows for the collection of real-world practice data on haematological malignancies including chronic lymphocytic leukemia (CLL). Finland's centralized nationwide health care system makes reliable patient identification and comprehensive follow-up possible. In the absence of direct head-to-head trials for all treatment combinations, robust historical comparator data have become important in the evaluation of novel therapies, especially in Finland where more robust real world data is now requisite for patient access.

Objectives: To describe CLL patient characteristics, treatment patterns and disease outcomes in routine practice settings.

Methods: Data from the FHR were analyzed for patients aged ≥ 18 years, diagnosed with CLL, and receiving ≥ 1 treatment lines during 2005-2015 from the Helsinki University Hospital, Finland, a hospital region accounting for 30% of the total national CLL incidence (approximately 350). Patient characteristics and received therapies were analysed descriptively. Crude overall survival (OS) and time-to-next-treatment (TTNT) were investigated using the Kaplan-Meier method.

Results: In total 124 and 64 CLL patients were identified having at least first and second line treatment during the study period, respectively. Patients' mean age was 64 years, 69% being male. At baseline, clinical CLL data were available with varying density, eg, fluorescence in situ hybridisation test results were available for 48% of patients, and Binet stage for 98%. Subtle changes in overall treatment practice were observed over time, with fludarabine-cyclophosphamide-rituximab and bendamustine-rituximab becoming the mainstay over fludarabine-cyclophosphamide after 2008. The median OS from the start of any given first and second line treatment was 82 and 37 months, respectively. The corresponding respective median TTNTs were 45 and 19 months.

Conclusions: In the Nordics, real-world evidence has become essential when introducing novel targeted therapies into clinical practice settings, with comprehensive disease registries expanding to allow for more detailed follow-up. We are able to describe a decade of real-world treatment trends and disease outcomes of CLL patients in the Helsinki hospital region, using the FHR.

785 | Developing a model of theory-based behavioural influences on endocrine therapy medication taking behaviour in women with breast cancer

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Background: Taking endocrine therapy for 5-10 years is recommended to prevent breast cancer recurrence. Despite the proven clinical efficacy of this treatment many women do not take their therapy as prescribed.

Objectives: The aim was to develop a model examining the theory-based behavioural determinants of endocrine therapy medication taking behaviour (MTB).

Methods: Women with a diagnosis of stage I-III breast cancer prescribed endocrine therapy were identified from the National Cancer Registry Ireland (N = 2423) and invited to complete a postal survey based on the Theoretical Domains Framework (TDF) and the Functional Assessment of Cancer Therapy and endocrine subscale (FACT-ES). The TDF is an integrative framework consisting of 14 domains of behaviour change, developed to inform intervention design. The FACT-ES assesses four primary domains of quality of life; physical, social and family, emotional and functional well-being and adverse effects of endocrine therapy. MTB was measured by participant self-report with early treatment discontinuation classified as non-persistence and failure to take the correct dosage at the prescribed frequency classified as non-adherence. The theory-based model of MTB was tested using structural equation modelling.

Results: 1606 women completed the questionnaire (response rate = 66%); 1211 (75%) women were adherent; 180 (11%) women were non-adherent and; 215 (14%) women were non-persistent. The final model included seven domains and produced a reasonable fit ($\chi^2[321] = 964$, $p < 0.001$; RMSEA = 0.03; CFI = 0.96 and WRMR = 1.35). Significant direct pathways were determined on MTB for the domains, *Beliefs about Capabilities*, *Beliefs about Consequences*, *Goals*, *Behaviour Regulation* and *Memory*, *Attention*, *Decision Processes* and *Environment* ($p < 0.01$). The domains *Beliefs about Consequences*, *Goals* and *Behaviour Regulation* also had an indirect effect on MTB ($p < 0.01$). These behavioural determinants accounted for 62% of the variance in MTB. Contrary to expectation, endocrine therapy adverse effects had neither a direct nor a mediating effect on MTB.

Conclusions: The results suggest that an intervention to improve endocrine therapy MTB should target these domains using effective behaviour change techniques in order to prevent breast cancer recurrence and mortality in women with breast cancer.

786 | Adventures in replication: Initial experiences related to the Joint ISPE/ISPOR guidance

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Background: Replication in observational pharmacoepidemiology is so critically important that ISPE/ISPOR recently commissioned a consensus document on best practices.

Objectives: This symposium will examine early lessons learned in replication studies.

Description: The symposium panel agenda follows: 1. Overview of ISPE/ISPOR guidance papers on real world evidence (Wang, 10 min): In 2017, ISPE and ISPOR endorsed papers from a joint task force providing recommendations on good procedural practices as well as specific reporting to facilitate reproducibility and assessment of validity. 2. REPEAT Initiative (Wang, 15 min): The REPEAT Initiative is a non-profit program with numerous projects focused on improving transparency, reproducibility and validity of longitudinal health care database research. These projects include large scale replication of a random sample of published database studies as well as evaluation of the robustness of results to alternative design and implementation parameters. 3. CNODES (Platt, 15 min): The Canadian Network for Observational Drug Effect Studies (CNODES) conducts studies in parallel in several sites. Internal replication is ensured by the use of structured protocols with statistical analysis plans, and pre-specified plans for outlier detection and evaluation. Examples highlighted will include studies of anti-diabetic medications, and of SNRI antidepressants. 4. Sentinel (Huang, 15 min): In the US Food and Drug Administration's Sentinel System, replication studies have required data and analysis feasibility assessment, as well as programming code review, in order to accurately implement prior study protocols. Examples highlighted will include acute myocardial infarction following anticoagulant exposure; acute pancreatitis and acute myocardial infarction following new oral anti-diabetic exposure. 5. PROTECT (Kurz, 15 min): In the European Union, PROTECT examined the extent to which differences in the study design, methodology and choice for data sources can contribute to discrepant results from observational studies on drug safety. To evaluate the effect of these differences, the project applied different designs and analytic methodology for six drug-adverse event pairs across several electronic health care databases and registries. The findings of these multi-database studies will be discussed. 6. Moderator questions (Maro), discussion and questions from the audience. (All) (20 min)

787 | Quantitative benefit-risk assessment: Hands-on workshop

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Background: Quantitative methods for drug benefit-risk assessment (qBRA) are gaining interest from experts in regulatory agencies, academia, and industry due to their capability to integrate stakeholder preferences and treatment performance data. However, routine utilization of such methods by pharmacoepidemiologists in the field is still limited due to their lack of familiarity with the practical aspects of conducting a qBRA.

Objectives: To familiarize attendees with the analytic steps and resource requirements for qBRA through a real time, interactive modeling exercise, using publicly available, open source tools.

Description: Preference based qBRA methods allow transparent and reproducible analysis of the benefit-risk assessment of medicines by elicitation of explicit preferences or weights from stakeholders and by statistically incorporating the weights with benefit and risk performance data. The models account for multiple benefit and risk criteria simultaneously, generate composite scores, and provide visual outputs that are easy to interpret and communicate. A range of sensitivity analyses can be performed to assess the robustness of the conclusions in situations with varying degrees of uncertainties around data on both performance and preference. The workshop will start with a brief overview of the underlying theoretical principles of preference based qBRA. The fundamental steps of such analyses will be presented. Then a case study will be introduced and the relevant treatment data (ie, efficacy, safety, tolerability parameters) for the treatment options will be presented in the form of an effects table. The audience will be divided in groups playing the roles of different stakeholders (patients, physicians and regulators). Each group will first generate their numeric preferences on the relative importance of the B-R variables through an interactive swing weight method. Next, the preferences of each stakeholder group will be fed into separate MCDA/SMAA models and the ranking of the treatment options based on these preferences will be calculated in real time using a web-based analytical tool (ADDIS). Finally, the audience will discuss plenary the different value judgments and resulting treatment rankings using various graphical outputs and sensitivity analyses. The exercise will demonstrate potential discordance of BRA conclusions based on different value judgements from different stakeholder groups and how these differences can be made explicit and transparent using qBRA methods.

788 | It takes a village part II: Workshop to reconsider core competencies for new generations in the global and rapidly changing community of pharmacoepidemiology

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Background: Through the practice of education, we foster the next generation of pharmacoepidemiologists and exchange with peers the high standards of knowledge, skills, and scientific inquiry in the field. Last year in the symposium "It Takes a Village" Part I, after hearing from educators in the US, Europe, and Asia about their philosophy and experiences, participants identified unmet competencies needed to work in academia, government or the private sector. This gap is likely due to globalization, new technologies, and changing characteristics of both students and job environments, which affect what and how we shall best foster next generations. The goal of this workshop is to bring together interested ISPE members with various backgrounds to continue the discussion.

Objectives: (1) To reconsider and form a consensus on core competencies and modalities for teaching the new generations. (2) To present the results of this discussion to the ISPE Education Committee and the pharmacoepidemiology community overall

Description: This workshop will be led by 6 pharmacoepidemiologists with experience educating and mentoring junior colleagues in different sectors and geographic regions as well as 6 recent graduates and current students in pharmacoepidemiology (group leads). After a brief introduction (5 min), these leads will coordinate small group discussions (40 min). Participants will break into 6 groups (academia, pharma, government, service providers, students, and recent graduates) to define the most important core competencies from their perspectives. Each group will then discuss the most effective teaching modalities (eg, lectures, case-based format, practicum, mobile technology) for a few competencies rated high by their group. One lead from each group will summarize the conclusions. We will then open the discussion to all participants to develop a list of top competencies and the optimal methods for teaching them (40 min). A moderator will briefly

summarize the key points (5 min). Each lead and moderator will record the discussion and hand in a summary after the workshop. The summaries will be compiled and submitted to the Education Committee. Moderators: Setoguchi and Hernandez-Diaz, Leads/Panelists: Academia: Klungel and Strom, Government: Shahin and Caduff, Pharma: Zhou and Stang, Service providers: Perez-Gutthann and May, Students: Young, Su and Cesta, Recent graduates: Hester, Zhu, Zabiuddin Ahad and Horton

789 | Increasing access to drug utilization data globally: Developing an action plan

Monique Elseviers¹; Ria Benko²; Johanita Burger³; Claudia Osorio-de-Castro⁴; Frank May⁵; Robert Vander Stichele¹; Veronika Wirtz⁶; Katja Taxis⁷; Björn Wettermark⁸

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Background: Drug utilization (DU) research intends to support health authorities in the development of evidence-informed pharmaceutical policy and practice guidelines, with the interest of the patients and communities in mind. DU data is often proprietary and challenging to access for researchers, in particular in resource-restricted settings. Therefore, governments in low- and middle-income countries should facilitate access to these data, from public and private sources, to researchers in the field of health economics, pharmacoepidemiology, drug utilization, and pharmacovigilance.

Objectives: The workshop intends (1) to provide an overview of challenges that researchers encounter when studying drug utilization in different parts of the world, (2) to identify barriers and enablers of access to DU data, and (3) to propose an action plan to increase DU data access. The workshop is of general interest for all those involved in global DU research and of particular interest for policymakers and researchers confronted with limited access to DU data in their own constituencies.

Description: After an introduction (Monique Elseviers) highlighting the importance to have access to high quality DU data at a regional and national level, an overview of specific challenges of access to DU data will be given for Central and Eastern Europe (Ria Benko), Africa (Johanita Burger), Latin America (Claudia Osorio-de-Castro), and Asia (Frank May). Thereafter, participants will assemble per region to identify barriers and enablers to DU data access and propose strategies to address them. Results of the discussion will be noted on poster boards and panellists will register the most important conclusions. During the final panel debate and discussion with the audience (moderated by Robert Vander Stichele), participants will jointly develop an action plan to increase DU data access (panel of all presenters together with Veronika Wirtz, Katja Taxis, Björn Wettermark).

790 | Challenges and potential of vaccine post-licensure benefit-risk assessments in resource limited countries

Daniel Weibel^{1,2}; Patrick Zuber³; Alena Khromava⁴; Abraham Oduro⁵; Andy Stergachis⁶; James Stark⁷; Harry Seifert⁸; Miriam Sturkenboom²; Steve Black²; Andrea Sutherland⁸

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Background: Vaccines are cost-effective health interventions and are especially valuable in resource limited countries (RLCs), where infectious disease morbidity and mortality is high. Some vaccines are exclusively introduced in RLCs (eg, dengue, malaria), while safety profiles are still evolving. For example, recent safety concerns regarding the first vaccine against dengue virus has limited its introduction and use globally. The introduction of novel, new vaccines into RLCs is likely to continue over the next decade. Effective benefit-risk assessments of vaccines, particularly post-licensure, are pivotal to maintaining confidence and uptake of vaccines. In RLCs monitoring and assessment of vaccine benefit-risk issues are still challenging, even though they are pivotal to ensure the safe and effective use and maintain confidence of vaccines.

Objectives: (1) Present findings from assessments of available capacity and infrastructure for vaccine benefit-risk monitoring and evaluation in RLCs. (2) Learn from vaccine benefit-risk monitoring conducted in RLCs. (3) Define opportunities and propose a roadmap to support building sustainable capacity and infrastructure to generate real world evidence on safety and effectiveness of vaccines within an integrated health system

Description: The symposium will be devoted to sharing experiences, gaps and successes using real-world examples. Manufacturers, regulators, public health specialists, and academics discuss the various scenarios, adaptations, and opportunities they have assessed, experienced or envision to meet the desired objectives related to strengthening monitoring and assessing the benefit-risk vaccine profiles in RLCs. International institutions will share their perspectives. Lessons learned will inform monitoring of available vaccines and the introduction of new vaccines or drugs in RLCs.

Symposium format (90 min, moderators VAXSIG representatives)

- 1 Introduction (5 min., VAXSIG representatives)
- 2 WHO perspective on needs, gaps, and capacity in RLCs (15 min P. Zuber, WHO, Geneva, Switzerland)
- 3 Manufacturer perspective on needs, gaps, and capacity in RLCs (15 min, Alena Khromava, Sanofi Pasteur, Toronto, Canada)
- 4 Examples of distributed network studies in RLCs (10 min, Daniel Weibel, Erasmus University Medical Center) Ongoing activities to build capacity in RLCs (15 min. Abraham Oduro, INDEPTH Navrongo, Ghana)

- 5 The Way forward (15 min Andy Stergachis, University of Washington, USA)
- 6 Panel discussion and Q & As (15 min.)

791 | Drug-drug interaction of non-potassium-sparing diuretics and laxatives is associated with cardiovascular mortality in hypertension-treated subjects

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Background: The risk of serious drug-drug interactions may be underestimated by analyses of medication claims databases as they do not record over-the-counter (OTC) drugs, which are, however, often additionally used by older adults. An example is the interaction of prescribed diuretics with OTC-drugs against constipation (laxatives) both decreasing serum potassium levels. Potassium depletion can result in hypokalemia, which might cause arrhythmia, and even cardiac death.

Objectives: First, to assess the prevalence of hypertension-treated subjects taking both non-potassium-sparing diuretics and laxatives, only non-potassium-sparing diuretics, only laxatives, or neither diuretics nor laxatives. Second, to investigate the association of these different treatments with cardiovascular mortality (CVM) among hypertension-treated individuals.

Methods: This analysis is based on the ESTHER study, an ongoing German cohort study comprising 9949 men and women, aged 50–74 years at baseline (2000 to 2002), with 14 years of mortality follow-up. Cox proportional hazard regression models were applied to assess the association with CVM and were adjusted for age, sex, body mass index, smoking status, physical activity, alcohol consumption, diabetes mellitus, chronic kidney disease, heart failure, coronary heart disease, history of stroke, history of myocardial infarction, use of opioids, and use of anticholinergic drugs.

Results: Approximately half of the ESTHER cohort received antihypertensive treatment ($n = 4320$). Thereof, 57 participants (1.3%) used both non-potassium-sparing diuretics and laxatives, 437 (10.1%) used only non-potassium-sparing diuretics, 247 (5.7%) used only laxatives and 3160 (73.1%) used neither diuretics nor laxatives. In comparison with the latter group, subjects receiving only non-potassium-sparing diuretics had a 1.5-fold increased CVM (risk ratio [95% confidence interval]: 1.50 [1.16; 1.93]), and a 2-fold increased CVM was observed if laxatives were used in addition (2.05 [1.20; 3.51]). Only laxative use was not associated with CVM (0.84 [0.55; 1.28]).

Conclusions: Regular laxative use may increase the already high risk for cardiovascular death of users of non-potassium-sparing diuretics but this result needs to be confirmed in larger studies. Nevertheless, patients, physicians and pharmacists should be aware of this potentially serious interaction of prescribed and OTC drugs.

792 | The use of propensity score distributions to gain understanding on drug utilization in routine clinical practice: A case study on newer vs older antiplatelet agents

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Background: Propensity scores (PS) are mainly used to control for confounding in observational drugs' effectiveness studies. However, PS distribution curves are also useful to gain understanding on routine clinical practice.

Objectives: (1) To explore whether patients with acute coronary syndrome (ACS) using new antiplatelet agents (newer APA - ticagrelor or prasugrel) differ globally from patients using clopidogrel and (2) to identify which patients' characteristics differ across therapeutic groups.

Methods: A national, prospective cohort study was conducted in France. Between 2013 and 2016, 275 cardiology centers included 3122 adults with ACS. Clinical data were collected at baseline and 1 year, by physicians and patients (telephone interviews). To explore the "overall similarity" of covariates distributions between therapeutic groups (newer APA vs clopidogrel), the PS was computed using three multivariable logistic regression models in which potential confounders (age, gender, BMI, type of index ACS, history of ACS, cardiovascular comorbidities, and coronary surgery) were independent variables. PS distribution curves were compared as an indicator for the "overall similarity" of covariates distributions across treatment groups. Then, to identify which patients' characteristics differ across therapeutic groups, parametric tests were performed, as adequate.

Results: 839 (27%) patients used clopidogrel, 1148 (37%) used ticagrelor and 549 (18%) used prasugrel. The overlaps in PS distribution curves were small for patients on ticagrelor vs. clopidogrel, and for patients on prasugrel vs clopidogrel, indicating that the two groups were not comparable, with respect to the observed covariates. In particular, compared with clopidogrel users, ticagrelor users were younger (mean age = 62 years old, SD = 12 vs mean = 71, SD = 13), more frequently male (77% vs 67%), had fewer cardiovascular comorbidities and benefited more frequently from an angioplasty (92% vs 76%). The index ACS was more frequently a first one (10% vs 22%), of STEMI type (52% vs 32%). The same patterns of difference were observed for prasugrel users, compared with clopidogrel users, possibly reflecting the market authorization restrictions in France.

Conclusions: Both PS scores and comparative tests are useful to describe routine clinical practice and in turn, the extent and nature of an indication bias in effectiveness studies.

793 | Preadmission use of aspirin or clopidogrel on sepsis outcome: A population-based cohort study

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Background: Sepsis is the leading causes of death in hospitalized patients. Activated platelets in sepsis have been associated with thrombotic microangiopathy and acute organ dysfunction. The effect of antiplatelet treatment on sepsis outcome, however, remains controversial.

Objectives: To examine the effect of the preadmission antiplatelet treatment on sepsis outcome in a population-based cohort

Methods: We performed a population-based cohort study using the National Health Insurance Research Database (NHIRD) of Taiwan. We used the data from 2001 to 2011. Adult patients with a hospitalization record for sepsis were eligible for inclusion. Sepsis was defined as the presence of an ICD-9-CM code for a infection and at least one organ/system dysfunctions. The approach has been validated extensively in literature. The association between aspirin or clopidogrel treatment and mortality of sepsis patients was determined by Cox models, adjusting for either individual covariate or a propensity score. Restricted mean survival time (RMST) analysis was performed as a way of sensitivity analysis. RMST refers to the mean survival time of all patients within the follow-up period, which can be used to calculate absolute RMST difference and relative RMST ratio between the comparison cohorts. To assess the interaction between drugs, we compared the outcome in patients receiving a combination therapy to aspirin monotherapy.

Results: Of 52 982 patients with sepsis, 12 776 were assigned to pre-hospital uses of aspirin, 1125 to clopidogrel, and 39 081 did not receive any antiplatelet drugs. Prehospital use of aspirin within 90 days of sepsis was associated with a decreased risk of mortality (PS-adjusted HR: 0.89, 95% CI: 0.84-0.93). Prehospital use of clopidogrel, however, was not found beneficial (PS-adjusted HR: 1.06, 95% CI: 0.94-1.20). RMST analysis confirmed the beneficial effect of aspirin which increased mean survival time by 1.31 days (95% CI: 0.42-2.19), when compared with nonuse. On drug-drug interaction analysis, we found the combined use of aspirin and calcium channel blockers (CCBs) was associated with an incremental improvement in 90-day survival in comparison with aspirin monotherapy (HR 0.85, 95% CI: 0.78-0.92).

Conclusions: Our study confirms that prehospital use of aspirin reduces mortality in patients with sepsis, while the use of clopidogrel does not. The combined use of aspirin and CCBs has incremental value in lowering sepsis mortality. More studies in different populations are needed to confirm our findings.

794 | Utilization and clinical outcomes of ticagrelor in patients following percutaneous coronary intervention

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Background: While clinical trials compared either ticagrelor (T) or prasugrel (P) to clopidogrel (C) in patients that underwent percutaneous intervention (PCI), there are limited reports of ticagrelor's utilization and clinical outcomes in large populations.

Objectives: To examine the utilization pattern and clinical outcomes of ticagrelor relative to prasugrel and clopidogrel post-PCI.

Methods: This study included 74 430 US commercial insurance beneficiaries who underwent a PCI from Sept 2011 to Dec 2015 captured in the Optum Clinformatics™ database. Secular trends and clinical outcomes were evaluated for the P2Y12 medications. The primary outcome was defined by the composite endpoints: incident myocardial infarction, ischemic stroke, or all-cause death. The secondary outcome included incident intracranial hemorrhage, gastrointestinal bleed, or other major hemorrhage. Cox proportional hazard models with propensity score inverse weighting were used to assess the hazard ratios between ticagrelor and clopidogrel after adjusting for demographic and clinical characteristics. The presence of acute coronary syndrome (ACS) at baseline was assessed through stratification.

Results: There were 5604 patients prescribed ticagrelor, 11 046 prescribed prasugrel, and 57 764 prescribed clopidogrel. Patients prescribed ticagrelor were over 65 (mean age: T 64.3 vs C 66.7 vs P 60.0, $p < 0.01$), mostly male (T 72% vs C 67% vs P 77%, $p < 0.01$), had hypertension (T 76% vs C 83% vs P 75%, $p < 0.01$), and hyperlipidemia (T 76% vs C 77% vs P 75%, $p < 0.01$). Yearly ticagrelor initiation increased from 2.6% in 2012 to 13.8% in 2015 (slope 3.6 ± 0.3 , $p < 0.01$). During the same time, prasugrel decreased from 17% in 2012 to 13% in 2015 (slope -1.3 ± 0.2 , $p = 0.02$) and clopidogrel decreased from 80% in 2012 to 73% in 2015 (slope -2.3 ± 0.2 , $p < 0.01$). Compared with clopidogrel, ticagrelor was associated with a lower risk of ischemic events or death (HR: 0.81, 95% CI 0.76-0.87) and bleeding (HR: 0.73, 95% CI 0.69-0.78). When stratified and compared with clopidogrel, patients without ACS taking ticagrelor achieved a lower risk ($p < 0.01$) in primary endpoints (HR: 0.37, 95% CI: 0.26-0.52) than those with ACS (HR: 0.85, 95% CI 0.79-0.91).

Conclusions: Ticagrelor was associated with a lower risk in primary and secondary outcomes when compared with clopidogrel. Patients without ACS at baseline taking ticagrelor achieved a lower hazard ratio of cardiovascular outcomes when compared with clopidogrel than patients with ACS.

795 | Comparative effectiveness of prasugrel versus ticagrelor for the prevention of cardiovascular diseases in patients with acute coronary syndrome

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Background: The effectiveness of prasugrel compared with ticagrelor in reducing recurrent cardiovascular diseases (CVD) was demonstrated in randomized clinical trials but evidence from real-world setting is limited.

Objectives: To assess the effectiveness of prasugrel in preventing cardiovascular diseases (CVD) compared with ticagrelor in patients with acute coronary syndrome (ACS).

Methods: A retrospective cohort analysis of Truven Commercial and Medicare supplemental database (2013-2015) was conducted for ACS patients (unstable angina: ICD-9 CM: 411.x, NSTEMI: ICD-9: 410.7, 410.8, 410.9, STEMI: ICD-9: all other 410.x). Patients who newly initiated prasugrel or ticagrelor who had no prior use for at least 12 months (baseline period) were included. The study outcomes including CVD (non-fatal myocardial-infarction [ICD-9: 410.x], and non-fatal stroke [ICD-9: 433.x1, 434 {excluding 434.x0}, 436]) were compared between prasugrel and ticagrelor. Follow-up continued until the occurrence of the first CVD event, switch to the comparator, end of study period, or end of enrollment. Propensity score matching (PSM) was used to balance the two groups (eg, gender, use of medications, or CVD risk factors). Cox-proportional hazard model after PSM was used to obtain the hazard ratio (HR) and 95% confidence-interval (CI). Heterogeneity of treatment effect was examined in a subgroup of ACS patients with prior diagnosis of type II diabetes.

Results: Before PSM adjustment, 15 268 new-users of prasugrel (71% male, 77% hypertension, 12% chronic kidney disease [CKD]), and 39 030 new-users of ticagrelor (76% male, 73% hypertension, 8% CKD) were identified. The incidence rates of CVD were 94, and 142.5 per 1000 person-years in the prasugrel and the ticagrelor groups, respectively. After PSM, the use of prasugrel was associated with 18% reduction in the risk of CVD compared with ticagrelor (HR: 0.82, 95% CI [0.76, 0.88]). Subgroup analysis found no significant difference in the risk of CVD between prasugrel and ticagrelor in patients with type 2 diabetes (HR: 0.95, 95% CI [0.71, 1.29]).

Conclusions: Using a population US-based claim database, the use of prasugrel was associated with a reduction in the risk of CVD compared with ticagrelor. However, the cardioprotective effect was not observed in patients with type 2 diabetes.

796 | Preventive effects of single and dual anti-platelets use on long-term survival among out-hospital cardiac arrest survivors

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Background: Aspirin use for 1 year among cardiogenic out-hospital cardiac arrest (OHCA) survivors has been recommended to improve short-term survival. The preventive effects of dual antiplatelet use on long-term overall survival in these patients are not clear.

Objectives: The objective of this study is to compare the preventive effects of single and dual antiplatelet use on long-term survival among OHCA survivors.

Methods: We conducted a cohort study of a random subset of one million population on the national health insurance claims database (NHIRD) between 2000 and 2013. Patients aged above 18 years who survived from cardiogenic OHCA were ascertained and enrolled based on inpatient and outpatient ICD-9 codes and pharmacy transcripts. Patients with short-term mortality (within 30 days) after discharge were excluded. The exposure was defined as the continuous use of drugs more than 7 days after discharge hospital and classified into three groups: single (aspirin), dual (aspirin plus clopidogrel), and none users. The primary analysis used an as-treated, new-user design to compare the 1-year and 5-year overall survival. A propensity score (PS) analysis was used to adjust for confounding, including prior medications, co-morbidities, demographics, and health-care utilization. The effects were measured in odds ratio (OR) in crude logistic regression models, risk ratio (RR) in matched PS analyses, and hazard ratio (HR) in cox proportional hazard models with restricted mean survival time (RMST) analyses.

Results: We identified a cohort of 3,788 individuals (1438 for single, 441 for dual, and 1909 for non-users). The 1:1 PS-matched cohorts included 244 (single versus none) and 1050 (dual versus none) subjects. In terms of the 1-year survival, aspirin users versus controls had a 3.7% increased HR (HR 1.037, 95% CI 1.007, 1.067) and 11.5-days higher survival time (risk difference 11.485, 95% CI 2.233, 20.736) in PS-matched RMST survival analyses; dual users versus controls had no better survival in HR (HR 0.999, 95% CI 0.934, 1.068) and RD (RD -0.406, 95% CI -21.046, 20.234). Regarding to the 5-year survival, the single users (single versus controls, HR 1.036, 95% CI 0.995, 1.079) and dual users (single versus controls, HR 0.948, 95% CI 0.864, 1.040) all didn't show better effects on survival.

Conclusions: Among cardiogenic OHCA survivors, aspirin users versus non-users had a significantly better 1-year, but not 5-year, survival rate. Dual users showed no superior effects on long-term survival.

797 | Prescribing antimicrobial drugs for urinary tract infections in primary care in the Netherlands

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Background: Urinary tract infections (UTIs) are among the most prevalent infections and are an important reason to contact a General Practitioner (GP) in the Netherlands. Since antimicrobial resistance is rising worldwide, it is important to study trends of prescribing of antimicrobial drugs.

Objectives: This study aims to describe antimicrobial drug prescriptions patterns for UTIs and to investigate adherence to Dutch guidelines on the treatment of UTIs in primary care.

Methods: We conducted a population-based cohort study in IPCI, a Dutch GP database with complete electronic medical records. We included all antimicrobial drug prescriptions to patients ≥ 12 years in the period 1996-2014 and identified the corresponding International Classification of Primary Care (ICPC) code for indication of use. Next, the number of users and the number of prescriptions of several antimicrobial drugs classes were expressed per personyear (PY). Analysis were stratified for calendar year, age category and gender. The rates were compared with the Dutch primary care guidelines for treatment of UTIs. Furthermore, the duration of nitrofurantoin prescriptions for women was determined and stratified for calendar year. These results were compared with the Dutch guidelines, which advised 3 days in the guidelines of 1989 and 1999 and 5 days in the guidelines of 2005 and 2013.

Results: The source population comprised 1 755 085 patients who received in total 2 019 335 prescriptions, 401 655 (35.1%) prescriptions were for UTIs. In women, 45.2% of the prescriptions were for a UTI, whereas this was 12.6% in men. In men, UTIs were mainly treated with fluoroquinolones, especially in the higher age groups, which however was only advised as a first choice in the latest guideline of 2013. In women, UTIs were mainly treated with nitrofurantoin derivatives in all age groups, especially since 2005. The adherence of Dutch GPs regarding the duration of nitrofurantoin prescriptions for women increased since the guideline of 2005.

Conclusions: The adherence of GPs to the Dutch guidelines for the treatment of UTIs seems to have improved in recent years. However, in the same time period the number of prescriptions of antimicrobial drugs for UTIs seems to have increased, which is worrisome considering the fight against antimicrobial resistance.

798 | National estimates for gabapentin- and pregabalin-involved deaths from 2010 to 2015 using a novel data resource

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Background: As gabapentinoids are used increasingly to treat certain types of pain, recent data suggest these drugs may be abused and misused alone, and concurrently with opioids and other CNS depressants.

Objectives: To describe counts, rates, and trends of gabapentinoid-involved deaths, including those where opioids or benzodiazepines are involved, from 2010 to 2015 in the United States.

Methods: Drug-Involved Mortality (DIM) data, a novel data resource, combines ICD-10 cause-of-death, demographic, and geographic data from National Vital Statistics System-Mortality with information extracted from death certificate literal text allowing for capture of specific drug(s) potentially involved in the death. We performed a descriptive analysis using DIM to identify gabapentinoid-involved deaths, and those also involving opioids or benzodiazepines, from 2010 to 2015. Mortality rates per million prescriptions were calculated using utilization data from IQVIA™ (2012 to 2015). We also calculated the proportion of gabapentinoid-involved deaths containing an ICD-10 poisoning code as the underlying cause-of-death.

Results: We identified 3340 gabapentin-involved deaths, including: 40 (1.2%) involving only gabapentin, 1322 (40%) also involving opioids without benzodiazepines, 1286 (39%) also involving opioids and benzodiazepines, and 264 (8%) also involving benzodiazepines without opioids. We identified 448 pregabalin-involved deaths, including: 4 (0.9%) involving only pregabalin, 163 (36%) also involving opioids without benzodiazepines, 203 (45%) also involving opioids and benzodiazepines, and 32 (7%) also involving benzodiazepines without opioids. Gabapentin- and pregabalin-involved deaths increased from 180 and 34 in 2010 to 1294 and 169 in 2015, respectively. Similarly, from 2012 to 2015, deaths per million prescriptions increased from 11 to 26 for gabapentin, and from 5 to 19 for pregabalin. Nearly all (94%) gabapentin-involved deaths, and all (100%) pregabalin-involved deaths had an ICD-10 poisoning code, and most gabapentin- (75%) and pregabalin-involved (76%) deaths were classified as "accidental."

Conclusions: We found increasing counts and rates of gabapentinoid-involved deaths during the study period, with the majority of gabapentinoid-involved deaths also involving an opioid and/or a benzodiazepine. DIM data provide increased granularity compared with ICD-10 codes, allowing for identification of specific drugs potentially involved with death.

799 | Multi-level modelling to investigate factors impacting prescribing variability

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Background: Prescribing guidelines influence treatment choice based on patient (pt) and health care system factors. Multi-level modelling (MLM) can provide insight into sources of variability in health care, especially where nested hierarchical structures exist. A Specialist Cohort Event Monitoring study investigated the safety and use of rivaroxaban in clinical use, with a warfarin cohort for context.

Objectives: Study to investigate prescribing variability using MLM.

Methods: Data on NHS acute trusts in England/Wales (eg, population size, trust type) were linked to study pt demographic and drug utilization data, and prescriber details (eg, degree, specialty). Using MLM we explored the influence of pt, prescriber and trust characteristics on prescribing variability in 2106 rivaroxaban (59%) vs 1468 warfarin (41%) adult pt nested in 780 prescribers, nested in 73 trusts. The majority of pt had an indication of DVT/PE (56.4%) or non-valvular AF (AF) (41.2%). The binary outcome was rivaroxaban or warfarin treatment. Variance components estimate the variability accounted for by each level in the model and are expressed as: Median Odd Ratios (MOR - median relative increase in odds of rivaroxaban treatment if pt changed prescriber [PR] or trust [T]); Proportional Change in Variance (PCV) between models when successively adding fixed effects.

Results: DVT/PE group: Adjusting for pt factors, $MOR_T = 6.9$ (PCV = -0.6%); $MOR_{PR} = 2.8$ (PCV = 3.8%). Adjusting for pt and prescriber factors, $MOR_T = 6.8$ (PCV = -2.9%); $MOR_{PR} = 2.6$ (PCV = -15.4%). Adjusting for pt, prescriber and trust factors, $MOR_T = 4.9$ (PCV = -30.2%); $MOR_{PR} = 2.6$ (PCV = 3.4%). Differences between trusts and prescribers (in trusts) are important in treatment choice; trust being more influential. Some pt factors had a relatively large effect on odds of treatment choice, although the absolute number of pt impacted was often small. Trust type was shown to be associated with the odds of treatment choice (Final model: foundation vs acute trusts OR 4.0 [95% CI 1.5, 9.9]). Data on AF and all indications (combined) will be included in the final presentation.

Conclusions: This study highlights the utility of MLM in exploring pt and non-pt factors in nested hierarchical health care settings. Prescribing variability appears dominated by differences between trusts and prescribers (in trusts). Some pt factors were important in treatment choice, but PCV between models suggest that accounting for pt differences does not fully explain the variance between prescribers (in trusts) and between trusts.

800 | The introduction of new anticoagulation therapy in the European Union: The case of rivaroxaban

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Background: New oral anticoagulants have been introduced in recent years. The availability of these new drugs for individual patients differs by country, depending on local policies and medical need.

Objectives: To assess the characteristics of rivaroxaban users compared with those using the vitamin K antagonists (warfarin/

phenprocoumon/acenocoumarol) as standard of care (SOC) following the introduction of rivaroxaban in four EU countries.

Methods: Data were obtained from electronic health care records from four European countries as part of an ongoing post-authorization pharmacoepidemiological study programme investigating the safety profile and patterns of rivaroxaban use compared with current SOC. The programme commenced in December 2011; this analysis was performed at the time of latest data collection at each study site (December 2014 to December 2016). All patients 2 years or older enrolled in The Health Improvement Network database (THIN) in the United Kingdom, the German Pharmacoepidemiological Research Database (GePaRD), the PHARMO Database Network in the Netherlands and the Swedish National Public Health Registers were included.

Results: Over the study period, 191 665 and 338 415 new users of rivaroxaban and SOC, respectively, were identified. Of those, 136 927 (71%) rivaroxaban patients and 248 694 (73%) SOC patients were naïve to any prior oral anticoagulant use (no identifiable record in the database), constituting the two mutually exclusive study cohorts. In 2012, the SOC cohort was larger than the rivaroxaban cohort in all countries with relative sizes (SOC: rivaroxaban) ranging from 2:1 in Germany to 47:1 in the United Kingdom. From 2013, the rivaroxaban cohort outnumbered the SOC cohort in Germany; in Sweden, the cohorts only achieved size parity in 2015, while in the United Kingdom and Netherlands, the SOC cohort still outnumbered the rivaroxaban cohort by 2:1 and 5:1, respectively, in 2015. In the United Kingdom, Germany, and Sweden, the most common indications for rivaroxaban initiation were stroke prevention in atrial fibrillation patients followed by treatment of venous thromboembolism. However, in the Netherlands, the prevention of venous thromboembolism after elective hip or knee replacement surgery was the most common indication for rivaroxaban initiation.

Conclusions: In all countries, the usage of rivaroxaban increased continuously during the study period. However, the rate of rivaroxaban adoption into clinical practice and the most common indications for rivaroxaban use varied broadly between countries

801 | The Right-Rx medication reconciliation trial: Impact on potential adverse drug events

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Background: Adverse drug events account for approximately 8.1% of hospital admissions and more than half of admissions are preventable. Implementation of medication reconciliation at discharge aims to address this problem but low levels of adoption have limited its utility. An electronic medrec application has automated the process and achieved adoption rates of over 80%.

Objectives: To determine if automated medrec can reduce the rate of potential adverse drug events (PADEs) in hospitalized medical and surgical patients post discharge compared with usual care.

Methods: Design: Pragmatic randomized trial with medical and surgical unit pairs randomized to intervention and control between 2014-2016. PADEs were measured at discharge. Setting: Academic health center in Quebec, Canada. Intervention: The automated medrec application retrieves community-based medications from the provincial insurance agency and aligns it with in-hospital medications from the hospital drug information system. The discharge prescription is generated using a one-click action bar where the community and hospital drugs to be continued, stopped, modified or started are determined. Control units used a fillable PDF form to complete medication reconciliation. Outcomes: PADEs included errors in omission of community medications not continued and therapy duplications of 2 or more medications from the same therapeutic class. Analysis: Multivariate logistic regression adjusting for age, sex, number of medications, and prior hospital admission.

Results: 4674 patients were eligible and 1885 (75.6%) control and 1692 (77.5%) intervention unit patients consented to participate. Mean age was 69.7 years, 57.8% were men, and mean number of medications at admission was 5.7 (SD 4.3). At discharge, the rate of PADEs in the intervention units was 21.0% compared with 44.1% in the control (OR 0.31, 95% CI 0.27-0.37), errors of omission were 21.0% in intervention and 42.3% in control units (OR 0.35, 95% CI 0.29-0.40), and therapy duplications were 2.3% in intervention and 9.9% in control units (OR 0.22, 95% CI 0.15-0.30).

Conclusions: An automated medrec application with high rates of adoption significantly reduces potential adverse drug events among hospitalized patients at discharge.

802 | Evaluation of switching patterns in FDA's Sentinel system—A new tool to assess the substitutability of generic drugs

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Background: Given that nearly 90% of dispensed drugs in the United States are for generic products, ensuring the effectiveness, safety, and substitutability of generic drugs is of great public health importance. Sentinel is the Food and Drug Administration's (FDA) active surveillance system for medical products, using electronic health care data in a distributed data network of 18 data partners formatted in a common data model.

Objectives: To develop and evaluate a modular tool for analyzing manufacturer-level drug utilization and switching patterns within the US FDA's Sentinel system.

Methods: A descriptive tool was designed to provide information on drug utilization and switching for user-specified groups based on national drug codes. Utilization metrics include trends over time in new users, prevalent users, and dispensings, as well as summary statistics on days supply, product uptake, and duration of use. Switching was flexibly defined to identify consecutive dispensings between any two user-specified product groups, and the tool can evaluate up to two switches per pattern. Switching metrics include summary statistics on time to switch and switch pattern duration of use, frequency distributions of switchers by number of months to the switch, and Kaplan-Meier curves depicting the time to switch. We tested the tool with two case studies—metoprolol ER and lamotrigine ER—using claims data on commercially insured individuals from four Sentinel data partners. For these use cases, groups were defined for each product manufacturer.

Results: We identified 1 651 285 new users of metoprolol ER products between July 2008 and September 2015. We observed a large decrease in the number of monthly metoprolol ER initiators (from 25 465 new users in December 2008 to 13 128 in February 2009), corresponding to recalls by several generic manufacturers. We observed simultaneous increases in utilization of the authorized generic and brand products. We identified 4266 new users of lamotrigine ER with an epilepsy diagnosis between January 2012 and September 2015. Among those who switched from brand to generic, the cumulative incidence of switching back was close to 20% at 2 years. Switchback rates were higher for the first available generic products.

Conclusions: This newly developed tool elucidated expected utilization and switching patterns in two case studies. Such information can be used to identify potential signals of inequivalence and support post-marketing surveillance of generic drugs and biosimilars.

803 | Early lessons on ICD-10-CM/PCS transition in claims-based drug safety assessments

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Background: Electronic health care data in the United States transitioned from the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to its 10th Revision (ICD-10-CM/PCS) in October 2015. Most existing algorithms used to identify medical conditions from claims were validated using ICD-9-CM data, and their performance in the ICD-10 data is unknown.

Objectives: To explore methods for crude evaluation of algorithm performance in identifying medical conditions across ICD data eras.

Methods: A trend analysis was conducted using a sample of the 2010-2016 Truven Health MarketScan® Research Database. We examined population occurrence of several medical conditions commonly assessed in anticoagulant-related safety studies. Specifically, we evaluated the outcomes of gastrointestinal bleeding (GIB) and intracranial hemorrhage (ICH); the inclusion/exclusion criteria of atrial fibrillation, dialysis, deep vein thrombosis, and joint replacement. For each condition, the ICD-9-CM algorithm used in prior Sentinel studies was identified and mapped to ICD-10-CM/PCS codes via the Centers for Medicare and Medicaid Services General Equivalence Mappings with the Forward Backward Mapping method. We calculated and visually compared per 1000 eligible members per month, the number of members with: (1) a new diagnosis with 183-day washout, first-ever in database (first incidence); (2) a new diagnosis with 183-day washout, anytime during observation period (new incidence); and (3) any diagnosis, anytime during observation period (prevalence).

Results: For all conditions, the *prevalence* trend pre- and post-transition was consistent. An exception was dialysis, for which both mapped ICD-10 diagnosis and non-ICD procedure codes were needed to align trends. The two new diagnosis approaches captured vastly different results. Specifically, for the outcomes, the *first incidence* trend showed sharp increases immediately after the ICD transition (the 12-month incidence average respectively increased by 21.3% and 18.2% for GIB and ICH from pre- to post-transition periods), whereas the *new incidence* trends appeared to neutralize such increases and attenuated the changes to within 5% difference.

Conclusions: For epidemiological studies to use data across the ICD eras, consistency in algorithm performance should be examined carefully in advance. We recommend a trend analysis on prevalence in general. Additionally, for study outcomes, a trend analysis on new incidence may be useful.

804 | Intussusception risk after pentavalent rotavirus vaccination in Finnish infants: Validity study comparing results from patient file verified and register-based data in Finland

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Background: Register-based health studies have been questioned because of claimed poor validity.

Objectives: To evaluate the validity of register-based research with previous research based on validated data from patient files on association between rotavirus vaccination and intussusception risk.

Methods: Cases of children less than 1 year of age with intussusception (ICD-10 K56.1) diagnosed in all Finnish hospitals during 1999-2013 were identified from the national hospital discharge register including all ambulatory hospital visits and in-patient hospitalizations. Information on rotavirus vaccination was obtained from the national vaccination register. The association of the first dose of vaccination

on the risk of intussusception was analysed with the self-controlled case series (SCCS) method (risk period 1-21 days and control period 22-42 days following vaccination). The case definitions were based on following data sources: (1) validated data and (2) register-based data. We conducted sensitivity analysis whether in-patient hospitalization affected the results.

Results: The number of intussusception cases was low and varied according to the case definition and the time window ($n = 2-9$). The relative risk (RR) of intussusception was 3.6 (95% confidence intervals [95% CI] 1.0-13.5) based on the register-based data during the risk period in relation to the control period and 2.0 (95% CI 0.5-8.5) based on the validated data. When the case definition was restricted to hospitalized patients only, RR remained the same in the validated data (RR 1.8, 95% CI 0.3-10.9), but was higher in the register-based data (RR 4.9, 95% CI 1.0-22.9) during the risk period in relation to the control period.

Conclusions: The association between the rotavirus vaccination and intussusception was seen using register data only and the point estimates were actually higher although with wide overlapping confidence intervals. One explanation for the higher point estimates might be the known risk after vaccination resulting in hospital visits of other gastrointestinal symptoms.

805 | Validation of transfusion administrations among potential transfusion-related acute lung injury (TRALI) patients included in the sentinel distributed database

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Background: The Blood Safety Continuous Active Surveillance Network (BloodSCAN) is sponsored by the US FDA's Center for Biologics Evaluation and Research to monitor recipient safety of regulated blood components and blood-derived products. Inpatient transfusion data were provided by a Sentinel data partner for BloodSCAN use.

Objectives: To evaluate the positive predictive value (PPV) of transfusion data among potential TRALI inpatient stays included in the Sentinel database, 2013-2015.

Methods: We selected inpatient transfusion stays with TRALI diagnosis codes, and examined the PPV of electronic transfusion data

compared with medical record review. ISBT-128 and Codabar codes defined blood components, processing, and collection methods (eg, leukocyte-reduction [LR], irradiation [IR], apheresis [AP], whole blood derived [WBD]). Transfusions immediately prior to the potential TRALI event were confirmed by a physician with critical care expertise.

Results: Among almost four million inpatient stays, we identified 208 potential TRALI cases and retrieved 195 medical records; electronic transfusion data were available for 182 cases with medical records. High concordance was observed between transfusion data and medical charts for any transfusion event (PPV = 98.4%; 95% confidence intervals [CI] 95.3%-99.7%; $n = 179/182$), as well as administered blood components (Red Blood Cells any, PPV = 100% [CI 97.5%-100%]; platelets any, PPV = 100% [CI 91.8%-100%]; plasma any, PPV = 97.3% [CI 85.8%-99.9%]; cryoprecipitate any, PPV = 90.9% [CI 58.7%-99.8%]). When available processing and collection methods in transfusion data and medical charts were compared, PPVs were <61% for LR, IR, AP, or WBD components. When analyses were restricted to events in which adjudicators located a processing or collection method in charts, there was perfect concordance between electronic and medical chart information.

Conclusions: Sentinel inpatient transfusion data, including blood component, corresponded well with medical charts (PPV >90% in all analyses conducted). Sentinel transfusion data may contain more information on processing methods than typically available in medical charts. This validation demonstrates the potential utility of Sentinel transfusion data.

806 | Validation of the combined comorbidity score in the ICD-10 Era: Application to high-risk populations

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Background: The US transitioned to the 10th revision of the International Classification of Diseases, Clinical Modification (ICD-10-CM) in October 2015. Investigators must now choose how to define previously validated comorbidity scores, such as the Charlson-Elixhauser combined comorbidity score (CCS), in the ICD-10-CM era.

Objectives: To assess the performance of several ICD-10-CM versions of the CCS developed using several ICD-10-CM mapping strategies, and to determine how such scores perform in high-risk patient populations of particular interest in pharmacoepidemiology.

Methods: We identified health plan members hospitalized between January and September of 2015 and 2016 in the Truven Health MarketScan® Commercial Claims and Encounters and Medicare Supplemental databases. High risk populations consisted of those with a history of atrial fibrillation (AF), type 2 diabetes (T2DM), or inflammatory bowel disease (IBD). Along with the ICD-9-CM version of the CCS, 4 CCSs using ICD-10-CM codes were examined: two using

the Centers for Medicare & Medicaid Services General Equivalence Mappings (simple-backward mapping [SBM] and forward-backward mapping [FBM]), one using ICD-10-CA (Canadian modification), and one combining all three ICD-10-CM algorithms. Patients were followed for re-hospitalization within 30 days. In sensitivity analyses, we varied covariate lookback (90 vs 183 days) and follow-up periods (30 vs 90 days).

Results: We identified 792 298 and 697 115 newly hospitalized patients in the ICD-9-CM and ICD-10-CM eras, respectively. A CCS developed with all three ICD-10-CM algorithms combined had better discrimination (c-statistic 0.652, 95% CI 0.649 to 0.655) compared with those based on other mapping strategies, and to the CCS in the ICD-9-CM population (c-statistic 0.646, 95% CI 0.643 to 0.649). Across eras and mapping strategies, the CCS discriminated best among the general hospitalized population, and tended to discriminate better among the T2DM population than among the IBD or AF populations. Results did not vary materially when the covariate lookback period was extended to 183 days or when the follow-up period was extended to 90 days.

Conclusions: In the largest-yet study of comorbidity score performance in the ICD-10-CM era, we found that a CCS defined using the most inclusive list of mapped codes best discriminated between those who were re-hospitalized within 30 days and those who were not, compared with the ICD-9-CM version and single mappings of the ICD-10-CM score.

807 | Validating prescription registry data on statins use by blood measurements

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Background: Registry data on prescriptions are independent of patient's recall, but do not reflect adherence.

Objectives: We developed LCMS assays for selected statins in blood and used serial blood samples collected from two cohorts of Danish colorectal cancer patients to confirm the presence of statins in prescribed patients and its absence in patients who were not prescribed.

Methods: We linked information on statin prescriptions from the Aarhus University Prescription Database with the cancer cohorts from Aalborg University Hospital. Among ever statin prescribed, we calculated the prescription window as the period starting on the date of prescription plus seven days and ending on the date that was the prescription date plus the number of days equal to the number of pills in the prescription. For each statin prescribed patient with at least one blood sample in a prescription window, we selected without

replacement a never statin prescribed patient matched on sex, age, and calendar year of surgery. Each of the selected blood samples were analyzed using assays to detect statins. We calculated the positive predictive value (PPV) and negative predictive value (NPV) of the prescription registry reporting ever statin prescribed or never statin prescribed using the assay result as the gold-standard.

Results: We identified 73 ever statin prescribed patients with a total of 253 blood samples and 74 blood samples among never statin prescribed patients. The PPV for all the blood samples was 89% (95% CI: 85%-93%) and the PPV for patients with presence of statins in at least one blood sample was 93% (95% CI: 86%-97%). The NPV was 93% (95% CI: 86%-97%). Stratified results did not reveal substantial differences in predictive values. 53 of 73 (73%) of the statin prescribed had confirmation of statins in each of their blood samples, suggesting continuous adherence.

Conclusions: This study showed a high adherence with treatment with statins among colorectal cancer patients.

808 | Documenting diagnosis: Comparing mild cognitive impairment diagnosis rates from ICD codes vs clinical notes

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Background: Alzheimer's disease (AD) is predicted to affect 1 in 85 people globally by 2050. Understanding of the disease is still evolving. Evidence now suggests that the pathophysiological process of AD begins years before the diagnosis of dementia. There is interest in early identification of AD patients, especially those with mild cognitive impairment (MCI). However, there is a lack of clarity around the diagnosis rate of MCI for many reasons, including suspected underuse of the specific diagnostic codes for MCI.

Objectives: To estimate and compare diagnosis rates of MCI in structured diagnosis codes vs documentation of MCI in clinical notes in two integrated US health care systems.

Methods: Using electronic health records (EHR), patients diagnosed with MCI were determined based on ICD diagnosis codes or on physician documentation in a clinical note, extracted using natural language processing (NLP). ICD-based MCI diagnosis was defined as at least one diagnosis code for MCI (331.83 [ICD-9-CM], G31.84 [ICD-10-CM]) recorded between 01 January 2006-31 December 2015. NLP-based MCI diagnosis was determined by at least one explicit physician reference in a clinical note. The NLP algorithm was designed to account for the use of acronyms, misspellings and negation, and was validated for precision and recall by random-sample manual chart review.

Results: Combined results found 128 620 patients with ICD-based MCI diagnosis and 249 842 patients with NLP-based MCI diagnosis. Validation of the NLP algorithm demonstrated 97% precision and 83% recall at the patient level. Only 74 602 patients were found to have both an ICD-based and NLP-based MCI diagnosis. 54 018 (42%) of patients found with ICD-based MCI diagnosis did not have a corresponding NLP-based MCI diagnosis. 175 240 (70%) of patients found with NLP-based MCI diagnosis did not have a corresponding diagnosis with MCI ICD codes; however, 114 905 (66%) of these patients did have an ICD code for other dementia diagnoses.

Conclusions: Very high precision indicates that NLP-identified cases accurately represent physician-documented MCI diagnosis; however, moderate recall suggests some cases may be missed. Despite the precision of the NLP algorithm and confidence in ICD-based diagnosis, relatively little overlap between ICD-based and NLP-based MCI diagnosis was found. Use of either method alone significantly underestimates the true diagnosis rate of MCI.

809 | Identification of binge-eating disorder patients in electronic health record data

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Background: Although binge-eating disorder (BED) is common, with a lifetime prevalence of 3% in the United States, it was not recognized as a unique eating disorder until the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders, published in 2013. Hence, there is no International Classification of Diseases, 9th revision (ICD-9) code specific to BED and the ICD-10 code for BED became effective in October 2016. Lack of a specific code makes studying patients with BED in order to characterize them and their treatment patterns challenging.

Objectives: To develop and validate a BED identification algorithm using data on BED symptoms within an electronic health record (EHR) database.

Methods: Patients with BED were identified using natural language processing (NLP) of clinical notes within Optum's EHR database. Full text notes were extracted into unique NLP fields such as concept (eg, binge-eating), note section (eg, assessment), fact type (eg, symptom), modifiers (eg, chronic), and sentiment (eg, deny). The algorithm applied to the EHR used combinations of NLP fields (eg, affirmation of binge-eating + negation of bulimia) to identify BED patients between January 2009 and September 2015. Clinical experts reviewed patient profiles (the sequence of NLP concepts and modifiers extracted from the clinical notes) for a sample of patients, in order to refine the algorithms in an iterative process. After the algorithm was refined, de-identified clinical notes were sought for a sample of 250 patients (1321 notes) to manually assess the performance of the algorithm. Clinicians (psychiatrists or psychologists) reviewed the notes to confirm the presence of BED. Adjudication

results were used to modify and finalize the algorithm. The positive predictive value (PPV) was calculated as the number of confirmed BED patients divided by the total number of algorithm-identified BED patients.

Results: A total of 1221 notes were received for 212 patients, of which 173 patients had all notes requested. We used this subset of patients with complete notes, with the same set of notes used for algorithm classification and clinician adjudication, to calculate the PPV. The final algorithm identified 822 probable BED and 618 BED patients. The PPV was 83% (95% CI 61 to 95%) for BED patients and 64% (95% CI 44 to 81%) for probable BED patients.

Conclusions: Using combinations of BED-related NLP terms, we were able to identify patients with clinical presentations consistent with BED with varying degrees of certainty in a large EHR database.

810 | Methods to detect dementia in electronic health data: Comparing cognitive tests scores with algorithms for dementia

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Background: There is interest in leveraging electronic health record (EHR) data to study dementia risk factors and treatments. A concern is whether dementia outcomes can be accurately measured from EHR data.

Objectives: To extract results from a widely used cognitive screening test, the Mini Mental State Examination (MMSE), from the EHR and compare with algorithms identifying dementia-related care.

Methods: This cohort study used data on 362 665 individuals age 50 or older during 1/1/2013-12/31/2017 who were enrolled in the Kaiser Permanente Washington health care system for 2+ years prior to baseline. MMSE test results were extracted and classified as showing dementia (<24/30 points) or normal (24+/30). We created 3 dementia algorithms: (1) ≥ 2 dementia diagnosis codes (International Classification of Diseases Ninth Revision (ICD-9) or (ICD-10) within 1 year; (2) ≥ 2 dementia or mild cognitive impairment (MCI) codes within 1 year; and (3) ≥ 2 dementia codes within 1 year or ≥ 1 code plus either a dementia medication fill or a visit to neurology, psychiatry, or speech, language and learning within 1 year. We evaluated how many people met algorithm criteria given they had a test score and the converse. We assessed the sensitivity of algorithms against the gold standard MMSE test results for identifying individuals with dementia.

Results: In our cohort of 362 665 people, we identified 5610 complete tests performed in 4285 unique individuals (1.2%). 2023 (36%) of these tests had a score indicating dementia. Overall, 15 310 (4.2% of population) people met any of the 3 algorithms. Of those meeting algorithms, 11 569 (75.5%) met algorithm 1; 13 223 (86.4%)

met algorithm 2; 13 656 (89.2%) met algorithm 3; and 1950 (13%) had an MMSE score available. Algorithm 1 had a sensitivity of 64.8%. When we relaxed algorithm criteria, the sensitivity was 68.3% for algorithm 2, which included MCI diagnoses and 70.7% for algorithm 3, which added medications and specialty referrals. We could confirm dementia using MMSE test scores for 8.8% of that met algorithm 1, 8.2% that meet algorithm 2, and 8.2% that met algorithm 3.

Conclusions: In this setting, MMSE results were readily accessible in EHR data but available on few people. The sensitivity of algorithms was moderate. We could not confirm dementia using MMSE scores for many individuals because so few were available. Further research into how MMSE scores and dementia algorithms relate as well as how MMSE scores can help identify individuals with dementia is warranted.

811 | How valid are the codes used to identify acute liver injury (ALI)? A study in 3 European data sources

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Background: Identifying valid cases of ALI in automated data sources is challenging. Most previous case-identifying algorithms had positive predictive values (PPVs) around 50%. A case validation process was implemented in the framework of a PASS assessing the risk of ALI in users of agomelatine and other antidepressants

Objectives: To identify valid cases of ALI and evaluate the PPVs of algorithms used to detect potential ALI cases

Methods: Three data sources were used: EpiChron and SIDIAP in Spain (primary care and hospital cases) and the Danish National Health Registers (inpatient and outpatient hospital cases) in Denmark. Algorithms for three ALI endpoints defined by literature review using ICD and ICPC codes were validated: primary (specific hospital discharge diagnosis codes), secondary (specific and non-specific hospital discharge diagnosis codes), and tertiary (specific and non-specific hospital and outpatient diagnosis codes). The validation strategy included review of patient profiles (SIDIAP and EpiChron) and of data abstracted from medical records (EpiChron and Denmark). ALI cases were confirmed when liver enzyme values met the consensus definition of an international DILI Expert Working Group

Results: In SIDIAP, EpiChron, and Denmark, respectively, 10, 19, and 50 potential cases of the primary algorithm; 34, 59, and 489 of the secondary algorithm; and 2826, 268, and 1008 of the tertiary algorithm were identified. PPV (95% CI) of the primary algorithm was 60% (26%-88%) in SIDIAP, 84% (60%-97%) in EpiChron, and 74% (60%-85%) in Denmark; of the secondary algorithm, 40% (19%-64%) in SIDIAP, 65% (45%-81%) in EpiChron, and 70% (64%-77%) in Denmark; and of the tertiary algorithm, 8% (7%-9%) in SIDIAP, 25% (18%-34%) in EpiChron, and 47% (42%-52%) in Denmark. The overall PPVs were higher for specific than for non-specific codes and for hospital discharge than for outpatient codes. The non-specific code "Unspecified jaundice" had a high PPV in all data sources and was the largest contributor of confirmed cases in Denmark (75 of 79 and 82 of 90 confirmed cases for the secondary and tertiary algorithms, respectively).

Conclusions: To maximise internal validity, studies on ALI in these and similar data sources should prioritize use of hospital discharge and specific codes. Conducting validation activities is required, especially when ALI outpatient potential cases are included. Case-identifying algorithms should include ICD codes for unspecified jaundice

812 | Algorithm to classify patient immunocompromise level in database studies

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Background: Immune compromise (IC) status is an important factor to take into account in vaccine studies. For vaccine effectiveness (VE) studies, IC may be a potential confounder (ie, related to both vaccination and outcome) and/or effect modifier (eg, VE may be lower in persons vaccinated when IC). We developed an algorithm to classify IC and change in IC in a large observational study of zoster live VE against herpes zoster (HZ) among Kaiser Permanente Northern California (KPNC) members ≥ 50 years of age.

Objectives: To describe an IC algorithm that can be used in database observational studies.

Methods: We based IC status assessment on 8 variables indicative of IC conditions and treatments: blood cancer, metastatic cancer, bone marrow or hematopoietic stem cell transplant (BMT/HSCT), human immunodeficiency virus (HIV) infection, rare immune deficiency condition (RIDC), cancer radiotherapy, corticosteroids, and other immunosuppressing medications. Using data from KPNC health care databases, these variables were updated quarterly based on diagnoses, prescriptions, and laboratory data during the past 12 months. Using these 8 variables, we also created a 3-level summary measure of IC status at the time of vaccination (not IC, mild IC, high IC).

Results: Of the 5.8 million person-years (PY) of follow-up of study individuals in 2007-2014, 402 874 PY (6.9%) were spent IC, including 273 622 PY with mild IC and 129 252 PY with high IC. Main reasons

for IC were corticosteroids (3.6%), other medications (2.3%), and metastatic cancer (1.4%), while blood cancer, radiotherapy, HIV, RIDC and BMT/HSCT each contributed $<1\%$ of total PY. The prevalence of IC increased with age from $\sim 6\%$ in ages 50-59 to $\sim 10\%$ in ages 80+. Of the 392 677 subjects who received zoster vaccine in 2007-2014, 21 665 (5.5%) were IC at the time of vaccination (4.4% mild IC; 1.1% high IC). Individuals with IC were less likely to get vaccinated and more likely to get HZ.

Conclusions: We developed an IC algorithm to adjust for differences in IC status between vaccinees and the unvaccinated when estimating VE and to examine the effect of IC status at the time of vaccination on VE. This algorithm was utilized in a recent publication reporting VE estimates against HZ¹.¹Baxter R et al. Long-term effectiveness of the live zoster vaccine in preventing shingles: a cohort study. *Am J Epidemiol* 2018;187(1):161-169

813 | Incorporating time-varying clinical data into a machine learning algorithm to detect atrial fibrillation and flutter

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Background: Atrial fibrillation/flutter (AF/F) is associated with significant morbidity, mortality, and reduced quality of life; consequently, detecting those at high risk of AF/F is important. Established risk models typically utilise baseline profiles only, ignoring risk factor evolution.

Objectives: To evaluate the accuracy of machine learning (ML) methods utilising baseline plus time-varying covariates, compared with conventional statistical approaches, to detect incident AF/F.

Methods: This was a retrospective study of UK primary care patients (≥ 30 years old and without a history of AF/F) recorded on the Clinical Practice Research Datalink (CPRD) between 01-01-2006 and 31-12-2016. Index date was defined as a complete set of key clinical measurements within a rolling 12-month period over the study period. Annual AF/F risk was estimated over each of five years of follow-up using a neural network (NN) incorporating baseline and annually-updated covariates (time-varying covariates) and benchmarked against conventional Cox regression (CR). Accuracy was assessed by area under the 'receiver operating characteristic' curve (AUC).

Results: Of 3 054 875 analysed patients (mean follow-up time 4.09 years over the 5-year period), 73 835 (2.4%) developed AF/F during follow-up. Using baseline information only, the CR model prediction of AF/F resulted in an AUC of 0.810 (sensitivity 66.0%, specificity 83.4%), compared with 0.821 (68.3%, 82.9%) for the NN. After incorporating annually-updated time-varying covariates the AUC achieved by the CR was 0.813 (sensitivity 68.2%, specificity 80.4%), compared with an AUC of 0.907 (82.4%, 86.5%) for the NN (+11.6%

AUC vs baseline CR). The most important predictors of AF/F identified by the NN were cardiovascular co-morbidities or diagnosis of diabetes in the past 12 months, and systolic blood pressure.

Conclusions: A ML algorithm using time-varying data was associated with improved performance in the detection of incident AF/F compared with CR and baseline risk models. The enhanced discriminatory performance of time-varying ML models could lead to increased identification of at-risk patients as part of a screening strategy, enabling preventative treatment, improved patient outcomes and more efficient use of health care resources.

814 | Algorithms to predict left ventricular ejection fraction class in patients with heart failure using Medicare claims data

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Background: Left ventricular ejection fraction (EF) is an important prognostic factor in heart failure (HF); however, administrative claims lack information on EF limiting their usefulness in clinical and epidemiologic research of HF.

Objectives: To develop and validate a claims-based algorithm to identify EF categories using specific ICD-9 codes in combination with additional patient characteristics.

Methods: We linked Medicare claims data (2007-2014) to electronic medical records (EMR) containing EF measurements for HF patients ≥ 65 years from two academic medical centers separated into training and testing datasets. Eight claims-based algorithms were implemented using linear or logistic regression models with regularization using the least absolute square shrinkage operator (LASSO) and Bayes Information Criteria (BIC) to select the most relevant predictors out of 57 investigator-specified variables in the training dataset. The linear models predicted numeric values of EF, while logistic models predicted EF classes into two [reduced EF (<0.45) versus preserved EF (≥ 0.45)] or three categories [reduced (<0.40), moderately reduced ($0.40-0.49$) or preserved (≥ 0.50)]. In the testing dataset, positive predictive values (PPV) and overall accuracy along with 95% confidence intervals (CIs) for claims-based algorithms were reported using the EMR-recorded EF class as the reference.

Results: A total of 7105 HF patients were included in the training dataset (average age 78 years) and 3968 patients were included in the testing dataset (average age 77 years). All algorithms had better discrimination when classifying patients into two EF classes as compared with three EF classes. The most efficient algorithm was based on a logistic model predicting reduced versus preserved EF from 35 predictors and resulted in 83% accuracy in the testing dataset (95% CI: 82% to 84%). The PPV (95% CI) for this algorithm was 0.73 (0.68-0.78) for reduced EF and 0.84 (0.83-0.86) for preserved EF. In addition to HF-specific diagnosis codes, other factors including age,

gender, medication use, and cardiovascular co-morbidities, including myocardial infarction were important discriminators between EF classes.

Conclusions: The claims-based algorithm developed in this study can be used to identify patient subgroups with specific EF class in claims database studies evaluating health outcomes, treatment utilization patterns and cost of HF patients in routine care, when EF measurements are not available.

815 | A novel claims-based algorithm to predict opioid overdose in the United States

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Background: With the increasing rate of overdose deaths involving opioids in the United States, use of a surveillance tool to predict high-risk patients would offer a potentially valuable tool for facilitating early intervention.

Objectives: To develop a claims-based algorithm to detect patients at high risk of opioid overdose.

Methods: All patients with 1+ opioid prescription from the Optum Clinformatics insurance claims database (2011-2015) were identified and randomly allocated to the training (50% of cohort), validation (25%), or test set (25%). Patients were followed until first opioid overdose or a censorship event. In the training set, pooled logistic regression was used to predict the odds of opioid overdose at each month during follow-up based on patient history from the preceding 3 to 6 months. Over 80 clinically relevant candidate predictors including demographics, medical diagnoses, and prescriptions were identified. Elastic net regularization was used for variable selection and minimization of overfitting. The optimal regularization parameter was determined in the validation set.

Results: We identified 5 293 880 opioid users; 2682 patients (0.05%) had a claim indicating opioid overdose during follow-up (mean duration = 14.7 months). On average, patients who overdosed were younger and had more medical diagnoses and prescriptions for opioid and non-opioid medications. The final model comprised of 40 predictors. The strongest predictors were age 18-25 years (OR = 2.21, compared with 26+ years), 1+ diagnosis of suicide attempt (OR = 3.68), opioid dependence (OR = 3.14), or opioid abuse without dependence (OR = 2.63) during the previous 6 months. In the test set, the model achieved a c-statistic of 0.89 and was well calibrated. Several cutoff points could be used to dichotomize patients into high and low risk groups, such as an optimal cut point (cutoff point = 0.004%, sensitivity = 80.2%, specificity = 80.1%, PPV = 0.2%, NPV = 99.9%).

Conclusions: We propose an algorithm to prospectively identify patients at high-risk for opioid overdose using routinely collected

health care utilization claims. Active monitoring programs using claims data would create an opportunity for intervention before an overdose occurs.

816 | Long-acting opioid selection and the risk of serious infections

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Background: Certain opioids inhibit the immune response and increase susceptibility to serious infection. Whether the use of individual opioids differentially impacts the risk of infection among humans remains unclear.

Objectives: To compare the risk of serious infection among patients initiating use of different long-acting opioid analgesics, specifically those with and without previously reported immunosuppressive properties.

Methods: We conducted a retrospective cohort study among Tennessee Medicaid enrollees ≥ 18 years initiating use of long-acting opioids (1995-2015). Hospitalizations for serious infection were identified using specific coding algorithms for pneumonia, bacteremia/sepsis, pyelonephritis, meningitis/encephalitis, osteomyelitis/septic arthritis, endocarditis, and cellulitis. We used multivariable Poisson regression to calculate incidence rate ratios (IRR) and 95% confidence intervals (CI) (robust standard errors) to compare the risk of serious infection between non-immunosuppressive opioid use (oxycodone, oxymorphone, and tramadol) and immunosuppressive opioid use (fentanyl, methadone, and morphine). In addition, separate multivariable Poisson models were used to compare the risk of serious infection associated with individual opioids compared with morphine use. Each model accounted for demographics, opioid dose, prior medication use, comorbidities and health care encounter history using model-specific exposure propensity scores as a spline-transformed covariate.

Results: We identified 1825 hospitalizations for serious infection among 83 321 new users of long-acting opioids. The distribution of the propensity scores between immunosuppressive and non-immunosuppressive opioid users was similar and had good overlap. In the adjusted analysis, non-immunosuppressive opioid users had a significantly lower rate of serious infections compared with immunosuppressive opioid users (IRR: 0.76 [95% CI: 0.64-0.89]). In individual comparisons, there were no significant differences between morphine and other immunosuppressive opioids (methadone, fentanyl). However, oxycodone users had a significantly lower rate of infection compared with morphine users (IRR: 0.74 [95% CI: 0.61-0.90]). There were no significant differences in risk between other non-immunosuppressive opioids relative to morphine.

Conclusions: The risk of serious infections is increased among users of long-acting opioids and varies by opioid type. This information should help inform pain management decisions.

817 | Geographic variation of high-risk opioid use and risk of overdose among disabled medicare beneficiaries in the United States from 2011 to 2015

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Background: To address the opioid epidemic in the United States, the Pharmacy Quality Alliance (PQA) has developed quality measures of high-risk opioid prescribing/use that address (1) high-dose use, (2) receipt of opioid prescriptions from multiple providers, and (3) concurrent benzodiazepine use.

Objectives: To examine the patterns of high-risk opioid use across regions and the association with subsequent overdose risk in Medicare from 2011 to 2015.

Methods: Among 249 594 non-cancer, disabled Medicare beneficiaries who had ≥ 2 opioid prescriptions, we identified individuals with high-dose use (>120 daily morphine milligram equivalents for ≥ 90 consecutive days) and multiple providers (≥ 4 prescribers and ≥ 4 pharmacies) each year; and concurrent benzodiazepine use (≥ 30 cumulative days) from 2013-2015 when Part D began coverage for benzodiazepines. We obtained adjusted annual rates of high-risk measures across 306 hospital referral regions (HRRs) using multivariable logistic regression. We examined the association between these measures and risk of overdose from inpatient and emergency department visits in the subsequent year using Cox proportional regression, adjusting for sociodemographic, health status, and access-to-care factors.

Results: Adjusted annual rates of high-dose use (~9%), having multiple providers (~5%), and concurrent benzodiazepine use (~34%) remained stable over five years. In 2015, the ratio of 75th-to-25th percentile rates of high-risk measures across HRRs were 1.80 for high-dose use, 1.87 for having multiple providers, and 1.33 for concurrent benzodiazepine use. The top 3 HRRs with the highest rate of: high-dose use were Sarasota, FL (17.2%), Sun City, AZ (17.2%) and Clearwater, FL (16.9%); multiple providers were Slidell, LA (14.0%), Muskegon, MI (12.5%), and Bryan, TX (12.0%); and concurrent benzodiazepine use were Dearborn, MI (58.0%), Miami, FL (55.4%), and Spartanburg, SC (55.1%). These measures were associated with subsequent overdose risk for high-dose (hazard ratio [HR] = 2.19, 95% CI = 1.86-2.57); multiple providers (HR = 1.58, 95% CI = 1.30-1.92); and concurrent benzodiazepine use (HR = 1.82, 95% CI = 1.58-2.10).

Conclusions: High-risk opioid use measures were associated with overdose risk among disabled Medicare beneficiaries. Substantial HRR-level variation in high-risk opioid use exists, and area/individuals with prevalent high-risk opioid use may benefit from targeted interventions (eg, lock-in programs) to prevent overdose.

818 | Incident opioid use and risk of hip fracture among persons with Alzheimer's disease: A nationwide matched cohort study

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Background: No previous studies have assessed risk of hip fracture associated with opioid use in persons with Alzheimer's disease (AD).

Objectives: The objective of this study was to investigate whether incident opioid use is associated with an increased risk of hip fractures among community-dwelling persons with AD and to assess the association in term of duration of use and opioid strength.

Methods: Among community-dwelling persons with AD diagnosed in 2010-2011 (N = 23 100), a matched cohort study comparing incident opioid users (N = 4750) with opioid nonusers (N = 4750) was constructed. We utilized the MEDALZ cohort for this study. Matching was conducted at the time of opioid initiation and was based on age, gender and time since AD diagnosis. Data on drug use (dispensed drugs, modelled with PRE2DUP method), hospitalizations (with diagnoses of hip fractures) and causes of deaths were retrieved from nationwide registers (until end of 2015). Incident opioid users were identified with a one-year washout period before AD diagnoses. Cox proportional hazard models compared risk of hip fracture between opioid use and nonuse and were weighted with inverse probability of treatment (IPT), based on a propensity score.

Results: Age-adjusted incidence rate of hip fractures was 3.22 (95% CI 2.35-4.10) during opioid use and 1.80 (95% CI 1.50-2.09) during non-use. Opioid use was associated with an increased risk of hip fracture (IPT-weighted HR 1.96, 95% CI 1.27-3.02). The risk was observed during the first 2 months of use (IPT weighted HR 2.36, 95% CI 1.03-5.41) and attenuated after that. The results suggest an increase in the risk of hip fracture by increasing opioid strength; weak opioids IPT-weighted HR 1.64 (0.86-3.15), buprenorphine IPT-weighted HR 2.06 (1.38-3.08), and strong opioids IPT-weighted HR 2.81 (1.29-6.15).

Conclusions: As older persons with AD are at increased risk of falling and fractures, safety of opioid use should be carefully considered and monitored especially when initiating new treatment.

819 | Comparative safety of commonly used opioids and fracture hospitalizations in United States nursing homes

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Background: Opioids are commonly used in US nursing homes to manage pain, but evidence of their comparative safety to guide clinical decision-making is limited.

Objectives: To examine the risk of fracture hospitalization (hip, femur, humerus, pelvis, radius/ulna) following the initiation of commonly used short-acting opioids.

Methods: We used 2011-2013 Minimum Data Set 3.0 linked to Medicare Part A and D claims to implement a new-user, retrospective cohort study among residents ≥ 65 years old without cancer or receiving hospice care. New use was defined as initiating short-acting oxycodone, hydrocodone, or tramadol using a 120 day washout period. Residents were followed through time using an as-treated approach until the earliest of the following: first fracture, death, treatment changes (eg, discontinuation), 180 days of treatment, or administrative censoring. Fracture hospitalizations were identified using Part A claims and ICD-9 codes. Inverse probability of treatment weights balanced baseline confounders across treatments; time-varying inverse probability of censoring weights were used to mitigate potential selection bias from loss to follow-up. We used competing risk survival models to estimate crude and weighted hazard ratios and robust 95% confidence intervals (CI) while accounting for death.

Results: 110 862 residents contributed 134 432 initiation episodes (10.7% oxycodone; 51.4% hydrocodone; 37.9% tramadol). Fractures occurred in 77 oxycodone initiators (crude incidence rate per 100 person-years: 9.4, 95% CI: 7.5-11.7), 345 hydrocodone initiators (incidence rate: 8.2, 95% CI: 7.3-9.1), and 229 tramadol initiators (incidence rate: 5.5, 95% CI: 4.8-6.2). In weighted competing risk analyses, oxycodone was associated with increased hazard of fractures (vs hydrocodone; HR = 1.09, 95% CI: 0.85-1.40) whereas tramadol was associated with decreased hazard of fractures (vs hydrocodone; HR = 0.69, 95% CI: 0.57-0.82).

Conclusions: The safety profiles of commonly used opioids may differ in nursing home residents. That tramadol was associated with lower risk of fractures over 180 days of follow-up is consistent with a prior study in community-dwelling adults, though further research is needed to confirm these findings.

820 | Prevalence and incidence trends of opioid use disorder and prior prescription opioid utilization, 2005-2015

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Background: Opioid use disorder (OUD) has contributed to a significant number of drug overdoses and deaths. There is limited data on the epidemiology of OUD and prescription opioid utilization prior to the diagnosis.

Objectives: To evaluate prevalence and incidence trends in OUD diagnosis and use of prescription opioids within 1 year before the diagnosis.

Methods: We conducted a multi-year, cross-sectional study using 2005-2015 MarketScan Commercial and Medicare databases.

Patients with OUD were defined as those with ≥ 1 inpatient or outpatient billing record with ICD-9-CM codes (304.0x and 304.7x) or ICD-10-CM codes (F11.xx) in any diagnostic position. Annual prevalence was calculated as the number of OUD cases divided by the total number of individuals continuously enrolled in the corresponding year. Annual incidence was measured as the proportion of individuals with a 2-year (current and prior year) continuous enrollment who were newly diagnosed with OUD in a current year. We also estimated the proportion of patients with incident OUD diagnosis who filled opioid prescriptions in the preceding year using pharmacy billing records. Linear regression was used to test secular trends and to examine differences across age groups and sex.

Results: Prevalence and incidence of OUD increased fivefold (0.58 to 2.56 per 1000 people) and over threefold (0.47 to 2.09 per 1000 people), respectively, from 2005 to 2015 (p -trend < 0.001 for both estimates). When stratified by age and sex, OUD prevalence and incidence were significantly higher in males and young adults (18–30 years). We also observed a significant increase in OUD diagnosis among older adults aged ≥ 65 years (from 0.3 to 2.2 per 1000 people). Over the study period, between 27% and 35% of newly diagnosed OUD cases had no prescription opioids during the 1-year pre-diagnosis period, with the highest proportion (>70%) observed among patients <18 years, followed by patients aged 18–30 years (40%–60%). Higher proportions of male OUD patients than female patients had no prescription opioids (33%–42% vs 21%–26%, respectively, p < 0.001).

Conclusions: In a US commercially insured population, the prevalence and incidence of OUD have increased over the last decade. About one-third of patients, in particular, male adolescents and younger adults, developed OUD after ≥ 1 -year period with no reimbursed opioid prescription fills pointing to sole non-medical sources.

821 | Prevalence of thrombocytopenia upon acute hospital admission: A study in Denmark

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Background: Thrombocytopenia may predict poor outcomes for many medical conditions. However, the prevalence of thrombocytopenia upon acute hospital admission is unknown in adults unselected as concerns the reason for hospitalization.

Objectives: To assess this prevalence, both overall and by age, sex, malignancy, other comorbidities, and reason for hospitalization.

Methods: All adults (>15 years old) in the North and Central Denmark Regions were included in the study at the time of their first acute admission to an internal medicine ward during 2006–2012. Platelet count measurements within ± 24 hours of admission were categorized as severe ($< 50 \times 10^9/L$), moderate ($50-99 \times 10^9/L$), or mild ($100-149 \times 10^9/L$) thrombocytopenia. We retrieved information on diagnoses recorded during the current and previous hospital admissions from the Danish National Patient Registry. The diagnoses were encoded

using the ICD-10. The reason for hospitalization was defined as the primary diagnosis for each acute hospital stay. Comorbidities were identified using all prior inpatient and outpatient hospital diagnoses.

Results: Out of 342 765 acutely hospitalized patients, 274 393 (80.0%) had a platelet count measurement at admission. Median age was 62.6 years and 49.7% were men. At hospital admission, 6.8% had any thrombocytopenia ($< 150 \times 10^9/L$), 0.5% had severe thrombocytopenia, 1.3% had moderate thrombocytopenia, and 5.0% had mild thrombocytopenia. The prevalence of thrombocytopenia varied by age (4.8% of patients <45 years; up to 8.0% of patients ≥ 75 years); by sex (9.0% in men vs 4.6% in women); by the presence/absence of cancer (11.0% vs 6.3%), by presence of comorbidities (5.6%, 7.4%, and 11.2% for Charlson Comorbidity Index scores of 0, 1–2, and >2, respectively). It was the highest in patients admitted for liver disease (26.1%), sepsis (21.3%), cancer (15.7%), gastrointestinal bleeds (11.6%), hemorrhagic stroke (10.7%), congestive heart failure (9.6%), and kidney disease (9.2%). The comorbidities associated with the highest prevalence of thrombocytopenia were liver disease (up to 47.6% of patients with severe liver disease), leukemia (39.4%), lymphoma (25.2%), HIV infection (15.9%), metastatic cancer (11.8%), chronic heart failure (10.2%), and moderate to severe kidney disease (9.7%).

Conclusions: Thrombocytopenia is around 7% upon acute hospital admission in adults, while severe thrombocytopenia is rare. Variations were observed by age, sex, comorbidities, and reasons for hospitalization.

822 | Association between fluoroquinolone use and anterior cruciate ligament injury in the United States

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Background: Fluoroquinolone (FQ) use has been shown to have a negative effect on tendon tissue leading to increased risk of rupture, particularly of the Achilles tendon. The anterior cruciate ligament (ACL) is similarly comprised of types I and III collagen, yet no studies have evaluated the association between FQ use and ACL injury.

Objectives: Quantify the association between FQ use and ACL injury in a large population of commercially-insured individuals.

Methods: An active comparator design was used to compare the rate of ACL injury between initiators of FQ and amoxicillin (a similar medication with no hypothesized effect on ACL injury). Individuals aged 13–64 years initiating an oral FQ or oral amoxicillin from 2000 and 2014 were identified in the Truven Health MarketScan Commercial Claims and Encounters database. Initiators were defined using a 180-day washout period with multiple periods of new use included. Incident ACL injury was identified by CPT or ICD-9 codes with a 180-day washout period. Individuals were followed for ACL injury starting 3 days after initiation with a 60-day grace period. Individuals were censored at end of continuous enrollment or initiation of the

other medication. Selected baseline comorbidities and indications were identified in the 180 and 7 days prior to initiation, respectively. Weighted Cox proportional hazard models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) after standardizing the overall cohort by age, sex, baseline comorbidities, and indications using inverse probability of treatment weighting (IPTW).

Results: There were 13 694 500 FQ initiators and 15 326 421 amoxicillin initiators. FQ initiators were more commonly female (8 688 575; 63.5% vs 9 010 934; 58.8%), older (45.5 ± 12.7 vs 39.2 ± 15.4 years), and had more baseline comorbidities. FQ initiators were also more likely to have a diagnosis code indicating urinary tract infection (21.7% vs 0.9%), bronchitis (2.6% vs 0.7%), or pneumonia (3.4% vs 0.2%). There were 4987 (0.04%) ACL injuries among FQ initiators during an average 70.5 days follow-up and 5707 (0.04%) ACL injuries among amoxicillin initiators during an average 69.2 days follow-up (HR = 0.96, 95% CI 0.93, 1.00). After IPTW, FQ initiators were 17% more likely to have an ACL injury compared with amoxicillin initiators (adjHR = 1.17, 95% CI 1.12, 1.21).

Conclusions: Fluoroquinolone initiators may have a modestly increased risk of ACL injury during or shortly following treatment, although the absolute risk of rupture is low.

823 | The impact of an in-hospital multifaceted clinical pharmacist intervention on the risk of readmission: A randomized clinical trial

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Background: The value of clinical pharmaceutical interventions at hospital discharge is controversial. There are few high-quality trials.

Objectives: To determine if a multifaceted pharmacist intervention based on medication review, medication interview, and follow-up can reduce the rate of readmissions.

Methods: We conducted a randomized controlled multi-center study (Odense Pharmacist Trial Investigating Medication Interventions at Sector Transfer: OPTIMIST), enrolling 1467 patients from September 2013 to October 2015. The duration of follow-up was 6 month. Patients were 18 years or older, taking five drugs or more, admitted via an acute admission ward. The patients were randomized into three groups: usual care, basic intervention (medication review), and extended intervention (medication review, three motivational interviews, and post-discharge follow-up with the general practitioner, pharmacy, and nursing home).

Results: 498 patients were allocated to usual care, 493 to basic intervention and 476 to extended intervention. The extended intervention

had a significant impact on the numbers of patients who were readmitted within 30 days after inclusion (hazard ratio, [HR] 0.62, 95% confidence interval, [CI] 0.46-0.84) and 180 days after inclusion (HR 0.75, CI 0.62-0.90) and the number of patients who experienced the primary composite endpoint (HR 0.77, CI 0.64-0.93). The study also suggested a reduction in drug related readmissions within 30 days (HR 0.65, CI 0.39-1.09), and within 180 days (HR 0.80, CI 0.59-1.08) and for death (HR 0.83, CI 0.22-3.11). The number needed to treat for the extended intervention and the primary composite outcome was 12. The basic intervention had no material effect on any outcome.

Conclusions: Multifaceted clinical pharmacist intervention can reduce the rate of hospital readmissions.

824 | Impact of the new reimbursement limitations of palivizumab prophylaxis in Italy

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Background: Respiratory syncytial virus (RSV) is a common reason for hospitalization of infants, in particular for preterm babies. The risk of RSV hospitalization decreases according to increase in weeks of gestational age (wGA). Data from clinical trials showed that palivizumab reduces RSV hospitalization rates for premature infants (≤ 35 wGA). In October 2016 the Italian National Medicines Agency (AIFA), following the American Academy of Pediatrics recommendations, established new limitations for the reimbursement of palivizumab prophylaxis (≤ 29 wGA).

Objectives: To evaluate the impact of new reimbursement criteria regarding the use of palivizumab on the RSV hospitalization rates for infants under 2 years of age and the number of prescriptions of such drug in this target population.

Methods: This study is a retrospective sequential period analysis comparing the RSV hospitalization rates in patients under 2 years of age before and after the implementation of 2016 limitations for the reimbursement of palivizumab. Three RSV seasons (from October 1 to April 30) were defined: two before (2014/15; 2015/16) and one after (2016/17) the new AIFA reimbursement criteria. During these two periods, target population and hospitalization data were extracted from regional health systems (Lazio Region, 2016, 5 898 124 inhabitants and 47 595 live births). Furthermore, the number of palivizumab prescriptions recorded during RSV seasons and their cost for National Health System (NHS) were considered.

Results: In a population of 284 902 children under 2 years of age, the hospitalizations for RSV during the study period were 1729. RSV hospitalization rates showed a reduction after the new AIFA limitations, moving from 6.3/1000 (95% CI 6.0-6.7) to 5.5/1000 (95% CI 5.0-5.9). No differences in terms of gestational age for target population and in terms of age at the time of admission and RSV severity (supplemental oxygen or mechanical ventilations) for hospitalized infants were observed. After the new AIFA limitations a significant reduction in the number of prescriptions was detected (-48%) with a saving of around €750,000 by the NHS.

Conclusions: The implementation of the new palivizumab reimbursement criteria was not associated with an increase of RSV hospitalization for children younger than 2 years of age, despite a significant reduction in the number of palivizumab prescriptions.

825 | Systematic review of the applicability to real-world populations of randomised controlled trial evidence of treatments for physical health conditions

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Background: Guidelines and medicines regulators rely on randomised controlled trials (RCTs) of treatments to create evidence-based recommendations, but RCTs may lack applicability across the spectrum of patients seen in clinical practice.

Objectives: To examine the percentage of patients with a condition who would be eligible for RCTs of treatments for that condition.

Methods: Systematic review of studies examining the percentage of people in research or clinical cohorts who would have been eligible for RCTs of treatments for physical health conditions was conducted. Medline and Embase databases were systematically searched using a broad search strategy to identify studies. All title/abstract/full-text screening and data extraction was done independently by two reviewers. Risk of bias was assessed. Given study heterogeneity, analysis was limited to a descriptive/narrative review. The primary measure was the percentage of the comparison cohort who would have been eligible for each trial examined. Analysis was performed calculating percentages, medians and inter-quartile ranges, with differences between groups tested using the Wilcoxon rank test.

Results: 17 308 titles/abstracts screened, with 37 studies reporting data from 44 comparison cohorts. There were 291 trial-comparison cohort pairs across 25 conditions (8 cardiovascular, 3 respiratory, 6 cancer, and 8 others). Across all 291 trial-cohort pairs, median eligibility was 17.5% (interquartile range 7.2-40.2), ranging from 12.5% (IQR 5.0-24.0) for respiratory to 43.4 (IQR 29.6-45.4) for cancer studies. Eligibility was highest for HIV trials (32 trial-cohort pairs, median 58.0%, IQR 47.8075.3) eligible, and lowest for rheumatoid arthritis trials (62 trial-cohort pairs, median 8.4%, IQR 2.6-13.0). Median eligibility did not significantly differ between primary care and specialist cohorts (18.8 vs 16.9%, $p = 0.15$) or between older and newer trials (1967-2002 19.5%, 2003-2016 16.4%, $p = 0.07$).

Conclusions: Half of clinical trials examined excluded over 80% of patients with the physical condition studied, and 75% excluded at least 60%, most commonly based on age, comorbidity or coprescribing. Applicability needs more explicit consideration. Better evidence of treatment benefit and harm is needed in older, multimorbid populations.

826 | Comparative effectiveness of antibiotic therapy for the treatment of urinary tract infections

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Background: Urinary tract infection (UTI) is one of the most common indications for antibiotic prescriptions in otherwise healthy women, yet the comparative effectiveness of antibiotics for empirical therapy is not well-established. In addition, the clinical management of outpatient UTI has changed in recent years due to increasing prevalence of antibiotic-resistant uropathogens.

Objectives: To compare the effectiveness of guideline-recommended antibiotic agents for the treatment of UTI in premenopausal women in the United States.

Methods: Using data from a large, commercial insurance database, we conducted a retrospective cohort study of non-pregnant women aged 18-44 who received an outpatient diagnosis of UTI with an accompanying prescription for an antibiotic with activity against common uropathogens between July 1, 2006, and August 31, 2015. For each antibiotic, we estimated the daily cumulative risk and 95% confidence intervals (CIs) of treatment failure defined by a subsequent UTI-related antibiotic prescription since the index prescription. Patients were censored for end of insurance coverage, hospice enrollment, in-hospital death, or diagnosis of infection (excluding UTI). Propensity-score weighting was used to standardize the analysis to nitrofurantoin-initiators, accounting for demographic and geographic characteristics.

Results: Among 1 195 784 eligible women, the majority received first-line agents nitrofurantoin (24%) or trimethoprim-sulfamethoxazole (28%), or non-first-line fluoroquinolones (43%). Among initiators of first-line agents, the 7-day weighted cumulative incidence estimates of treatment failure were lower for nitrofurantoin (6.3%, 95% CI: 6.3-6.4%) than for trimethoprim-sulfamethoxazole (9.5%, 95% CI: 9.4-9.7%). Among non-first-line agents, treatment failure was lower among narrow-spectrum (6.1%, 95% CI: 5.8-6.3%) vs broad-spectrum β -Lactam/ β -Lactamase inhibitor combinations (6.9%, 95% CI: 6.5-7.3%). Patterns were similar for treatment failure within 30 days of the index antibiotic.

Conclusions: The risk of treatment failure differs widely by antibiotic agent, with substantial differences in two first-line antibiotics. Results interpretation is limited by absence of information on severity of index UTI. Understanding the effectiveness of antibiotic therapy is critical to guide clinical decision making, reduce suboptimal antibiotic prescribing, and reduce the risk of antibiotic resistance and other adverse events.

827 | Antidepressants use during pregnancy and the risk of gestational diabetes mellitus

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Background: Antidepressants (ADs) are increasingly being used in women of reproductive age. Their use during pregnancy has been linked to several maternal complications but their role in gestational diabetes remains unclear.

Objectives: To quantify the association between antidepressant classes, types and duration of use during pregnancy, and the risk of gestational diabetes mellitus (GDM).

Methods: Within the Quebec Pregnancy Cohort (1998-2015), we performed a nested case-control study. Pregnancies continuously covered by the public prescription drug plan for a minimum of 180 days prior to the beginning of pregnancy (first day of last menstrual period) and during pregnancy were eligible. Only pregnancies with gestational age over 20 weeks and ending with a delivery of a singleton were included; those with a history of diabetes, cystic fibrosis or obesity were also excluded. Cases were pregnancies with a diagnosis of GDM diagnosed after week 20 of gestation; index date was the calendar date of the diagnosis. For each case, up to 10 controls were randomly selected at index date and matched on gestational age and calendar year of pregnancy. Exposure was defined as having filled prescriptions for ADs between the first day of gestation and index date. We estimated crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) using conditional logistic regression models.

Results: Among the 20 905 cases and 209 050 matched controls, 9741 (4.2%) women were exposed to ADs during pregnancy. When adjusting for potential confounders including maternal underlying depression/anxiety, overall AD use (adjusted OR, 1.19 [95% CI, 1.08-1.30]; 1152 exposed cases) was associated with an increased risk of GDM. When looking at individual AD, venlafaxine (adjusted OR, 1.27 [95% CI, 1.09-1.49]; 230 exposed cases) and amitriptyline (adjusted OR, 1.52 [95% CI, 1.25-1.84]; 133 exposed cases) increased the risk of GDM. Moreover, the risk of GDM increased with longer duration of AD use, specifically for SNRI, TCA and combined use of two antidepressants classes. No statistically significant association was observed for SSRI.

Conclusions: Findings suggest that exposure to ADs, specifically amitriptyline and venlafaxine, was increasing the risk of GDM, even after adjusting for maternal depression.

828 | Prenatal paracetamol exposure and child neurodevelopment at 5 years

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Background: Paracetamol is one of the most widely used medications during pregnancy. Several recent studies have linked prenatal paracetamol exposure to neurodevelopmental disorders and ADHD in children. Even small increases in neurodevelopmental problems may have considerable implications for public health, and further investigation is needed.

Objectives: To determine whether prenatal paracetamol exposure is associated with neurodevelopmental problems in children 5 years of age, compared with unexposed children.

Methods: The Norwegian Mother and Child Cohort Study is a questionnaire-based prospective birth cohort that recruited pregnant women in Norway from 1999 to 2008. Women were categorized in 4 groups according to self-reported duration of paracetamol use: one, two, or three trimesters of use and non-users. Neurodevelopment was assessed using the Ages and Stages Questionnaire (ASQ), the Child Behavior Checklist (CBCL) and the Emotionality, Activity and Shyness Questionnaire (EAS). Linear and generalized linear models with inverse probability of treatment weights and robust standard errors were used to evaluate continuous and categorical outcomes.

Results: This study included 33 568 women, of which 45.9% reported using paracetamol at least once during pregnancy. Among users of paracetamol 55.3%, 32.8%, and 11.9% reported medication use in one, two, and three trimesters, respectively. Children born to mothers who used paracetamol in all three trimesters had increased risk of internalizing behavior (aRR 1.35, 95% CI: 1.03, 1.77), externalizing behavior (aRR 1.28, 95% CI: 0.98, 1.67) and communication problems (aRR 1.31 95% CI 0.97, 1.79) compared with unexposed children. Results from children born to mothers who used paracetamol in only one trimester compared with non-users were as follows: internalizing behavior: aRR 1.02, 95% CI: 0.93, 1.10, externalizing behavior: aRR 1.05, 95% CI: 0.96, 1.14, communication problems: aRR 0.96, 95% CI: 0.87, 1.06. Results were similar for children with prenatal paracetamol exposure in two trimesters.

Conclusions: Although the role of unmeasured confounding cannot be ruled out, paracetamol use in three trimesters was associated with greater internalizing behavior, and borderline associated with externalizing behavior and communication problems in preschool-age children.

829 | In-utero SSRI and SNRI exposure and the risk of long-term adverse mental and educational outcomes in children: A population-based retrospective cohort study utilizing linked administrative data

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Background: Few studies investigate the impact of untreated maternal depression versus in-utero antidepressant exposure on long-term effects on children. We delineate effects of these medications from untreated depression using a population-based sample of women

diagnosed with mood and anxiety disorder, thus restricting analysis to patients for whom pharmacotherapy is indicated.

Objectives: To investigate in utero SSRI and SNRI exposure on long term adverse mental and educational outcomes in children.

Methods: Using population-level linked administrative data from a universal health system, this study included all mother-newborn dyads in Manitoba (born 1996 to 2009, with follow-up through 2014). High Dimensional Propensity Scores and inverse probability treatment weighting were used to address confounding by indication and disease severity. The final trimmed cohort consisted of mothers who had a mood/anxiety disorder diagnosis between 90 days prior to conception until delivery ($n = 4995$); 16.8% had at least two dispensations of an SSRI or SNRI during pregnancy. Cox Proportional Hazard Regression models were used to estimate risk of mood and anxiety disorder in children and educational outcomes.

Results: Asymmetric trimming of the study cohort resulted in a total of 4998 mother-child dyads; 4159 children whose mothers did not use SSRIs/SNRIs during pregnancy and 839 children who were exposed to 2+ prescriptions in-utero. Use of SSRIs/SNRIs during pregnancy was not associated with an increased risk of mood/anxiety disorder in children HR 1.32 (95% CI 0.67 to 2.62). Initial results on the association between in-utero antidepressant use and early childhood development index (EDI) scores indicate no impact on school readiness (31.9% vs 29.3%), or scores on standardized tests of literacy and numeracy in Grade 3 (28.4% meeting expectation versus 31.4%) and in Grade 7 (68.8% versus 70.0%).

Conclusions: In a large population level sample, in utero exposure to serotonergic antidepressants compared with no exposure does not increase risk of the onset of mood and anxiety disorders and adverse educational outcomes in children later in life.

830 | Risk of early neurodevelopmental disorders associated with prenatal exposure to valproate: A nationwide cohort study based on the French health care databases

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Background: The association between prenatal exposure to valproate (VPA) and neurodevelopmental disorders (NDDs) is already known, but data related to trimester of exposure and dose are limited.

Objectives: To assess the association between prenatal monotherapy exposure to VPA and the risk of NDDs according to dose and trimester of exposure.

Methods: This cohort study was based on the French national health care databases and included children born alive between 2011 and 2014. Women were considered to be exposed to VPA during the 30 days following each dispensing and average daily doses were

calculated. Reference group included children born to women unexposed to antiepileptic drugs (AEDs) during pregnancy. NDDs were defined using long term diseases and hospital discharge diagnoses with ICD-10 codes F70 to F98. Pervasive developmental disorders (PDD, F84) and mental retardation (MR, F70-F79) were studied separately. Children were followed up until outcome, loss to follow-up, death or December 31, 2016. Hazard ratios (HRs) were calculated using Cox models adjusted for maternal (age, socioeconomic status, psychiatric history, comedications, ...) and infant (gender, gestational age and birth weight) characteristics.

Results: The cohort included 1,721,990 children, with a median follow-up of 3.6 years, and 991 were exposed to VPA used as an AED. Exposure to VPA was associated with increased risks of NDDs (HR = 3.7 [2.8-4.9]), PDD (4.6 [2.8-7.4]) and MR (5.1 [3.0-8.4]). A dose-response relationship was observed (NDDs: 1.8 [0.9-3.8] for doses <700 mg, 3.2 [2.1-4.8] for doses [700-1500 mg], and 8.2 [5.3-12.7] for doses ≥ 1500 mg). Exposure to VPA during the second or third trimester only (2.9 [1.3-6.6]) or in both first and second or third trimesters (5.4 [4.0-7.4]) was associated with an increased risk of NDDs, whereas exposure during the first trimester only was not (1.0 [0.4-2.6]). HRs were higher in mothers without psychiatric history (5.9 [4.1-8.4] for NDDs, 7.2 [4.0-13.0] for PDD, and 6.3 [3.1-12.6] for MR). A sensitivity analysis restricted to mothers with epilepsy, based on inverse probability of treatment weighting using the propensity score, and with exposure to lamotrigine as the reference group yielded comparable results.

Conclusions: Prenatal exposure to VPA was found to be associated with an increased risk of NDDs, with a dose-response relationship and differences according to trimester. A longer follow-up would be necessary to confirm the findings.

831 | Trivalent inactivated influenza vaccine (TIV) during pregnancy and risk for adverse infant neurodevelopment

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Background: Despite the demonstrated efficacy of the inactivated influenza vaccination in reducing influenza infections in pregnant women and their newborns, concerns over vaccine safety for the fetus remain a barrier to influenza vaccination during pregnancy.

Objectives: To assess the risk of trivalent influenza vaccination (TIV) during pregnancy on infant development at age 6 months.

Methods: We conducted a multi-site prospective cohort study of Kaiser Permanente Northern California and Northwest pregnant members during the 2010-2011 influenza season (12/2010-5/2011) and followed them and their newborns through 6 months of age. Eligible participants were identified through electronic health records (EHR) and recruited by telephone. Information on TIV during pregnancy

was ascertained from the EHR and self-report. The Ages and Stages Questionnaire-3 (ASQ) was completed by the mother to assess infant neurodevelopment when the infant was 6 months old.

Results: Of the 1616 women recruited into the study, 391 (24%) were excluded from the current analysis due to: missing vaccination status ($n = 16$), multi-gestation pregnancy ($n = 38$), lost to follow-up ($n = 171$), or the infant not being in the correct age range when the ASQ was completed ($n = 166$). This analysis includes 1225 mother-infant pairs. There were no significant differences between women who were and were not excluded from this analysis with regard to vaccination status, or influenza or other acute respiratory illness during pregnancy. Multivariate logistic regression analyses were conducted. 65% of women received TIV during pregnancy. No significant relationship was found between TIV during pregnancy and adverse infant development in the following domains: Communication (6.4% not on schedule vs 7.0%, $p = 0.658$) (vaccinated vs un-vaccinated, respectively) Gross Motor (10.8% vs 12.0%, $p = 0.52$), Fine Motor (8.9% vs 7.9%, $p = 0.56$) and Problem Solving (6.1% vs 7.0%, $p = 0.54$); these findings persisted after adjusting for confounders. There were significant differences in the Personal Social domain (10.0% vs 14.1%, $p = 0.03$); however, after adjusting for potential confounders the relationship was no longer statistically significant. Further, our findings did not differ by trimester of TIV exposure.

Conclusions: In our study, we did not observe an adverse effect on early childhood development, as measured by ASQ at age 6 months, associated with maternal TIV exposure during pregnancy. However, long-term follow-up and replication are needed.

832 | Abstract Withdrawn

833 | In utero drug exposure and hearing disorders in 2-year-old children: A case-control study using the EFEMERIS database

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Background: Literature is sparse about in utero drug exposure and hearing disorders.

Objectives: To assess the association between in utero drug exposure and the occurrence of hearing impairment in 2-year-old children, using the EFEMERIS database.

Methods: EFEMERIS includes all pregnant women administrated by the French Health Insurance System of Haute-Garonne from 2004 to 2015. It contains the dates of pregnancy, drugs dispensed during pregnancy (French Health Insurance Database) and births with the compulsory health certificates for child at 8 days, 9 and 24 months (Child Protection Centre Database). A case-control study was carried

out in EFEMERIS. Respectively, cases and controls were defined as children with an abnormal, or a normal hearing examination recorded on the 24-month certificate. Multivariable logistic regressions were adjusted on confounders ($p < 0.05$) from the descriptive analysis and known hearing loss risk factors: prematurity, recurrent otitis at 24 months, ...

Results: A total of 1245 cases and 28 046 controls were selected for analysis. Case and control mothers were comparable in terms of age ($p = 0.46$), level of education ($p = 0.43$) and congenital infection ($p = 0.6$). Cases and controls were comparable in terms of prematurity ($p = 0.75$), asphyxia ($p = 0.24$), and weight ($p = 0.81$) at birth. However, among cases, more ear deformities (0.6% versus 0.0%; $p \leq 0.001$) and more recurring otitis (11.3% versus 5.3%; $p \leq 0.0001$) were observed. Cases and controls were exposed to an average of 9.7 (± 6.3) and 9.4 (± 6.1) active substances, respectively. In adjusted logistic regressions, in utero drug exposures associated with hearing impairment were acetylsalicylic acid at low dosage <300 mg (OR 95% CI 1.5 [1.1-2.1]) and valproic acid (OR adjusted 95% CI 5.2 [1.9-14.0]). Conversely, exposure to systemic corticosteroids was associated with less ototoxicity (OR adjusted 95% CI 0.8 [0.6-0.9]). A sensitivity analysis excluding children with recurrent otitis at 24 months, found the same results.

Conclusions: This is the first study evaluating the risk of hearing disorders due to in utero exposure to drugs. Hearing disorders were associated with valproic acid and low-dose acetylsalicylic acid exposure during pregnancy. Conversely, children with normal hearing were more likely to have been exposed in utero to corticosteroids than children with hearing loss.

834 | Utilising the CPRD pregnancy register to examine the pattern of antiepileptic drug use during pregnancy in the United Kingdom

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Background: The management of epilepsy during pregnancy requires careful consideration to balance the risks of antiepileptic drugs (AED) and the potential adverse consequences of uncontrolled seizures. The teratogenicity of valproate (VPA) has been known since its licensing. In 2014, the European Medicines Agency (EMA) strengthened advice on the need to restrict VPA use in pregnancy and among women who can become pregnant due to the risks of neurodevelopmental disorders in children exposed in-utero.

Objectives: To examine the pattern of AED use during pregnancy over time in relation to the risk minimisation measures introduced for VPA.

Methods: The UK CPRD/LSHTM Pregnancy Register was used to detect pregnancies between 2010-2016 and estimate pregnancy start and end dates. The proportions of pregnancies who had a prescription for AEDs during pregnancy were calculated. Prescribing patterns for the most common AEDs were compared over time and rates before,

during, and after pregnancy calculated. Results will be updated to 2017 once data is available.

Results: Overall 506 243 pregnancies were detected in 332 478 women in the study period. The most commonly prescribed AED during pregnancy was lamotrigine throughout 2010-2016. By 2016, the 4 most common AEDs were lamotrigine (0.26% of all pregnancies), gabapentin (0.25%), pregabalin (0.23%), and levetiracetam (0.19%). Use of the latter 3 increased steadily during the study period (by 6-fold and 1.4-fold for levetiracetam). Use of VPA declined by 14% (from 0.07% to 0.06%) and carbamazepine by 33% (from 0.13% to 0.09%). Use of VPA decreases from 1 year prior to pregnancy, with lowest levels observed in the second trimester and prescribing rates reverting to pre-pregnancy levels post-partum.

Conclusions: The newly developed CPRD/LSHTM Pregnancy Register is a valuable addition to the CPRD database, enabling fast and reliable identification of pregnancies and pregnancy related dates. Use of VPA in pregnancy declined between 2010 and 2016 as use of newer AEDs, with seemingly better safety profiles, increased. While trends for decreasing use of VPA, including prior to pregnancy, are in line with NICE and regulatory recommendations for the treatment of epilepsy and bipolar disorders, use in pregnancy was still significant during this period. Continuously monitoring the effectiveness of the risk minimisation measures will be critical following recent recommendation from the EMA PRAC to implement a pregnancy prevention program for VPA.

835 | Genome-wide association study of asthma symptoms despite inhaled corticosteroids use in Dutch children

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Background: Inhaled corticosteroids (ICS) are the preferred first-line treatment for persistent asthma. However, approximately 25% of the pediatric asthma patients suffer from uncontrolled asthma despite regular use of ICS. Genetic variance has been associated with poor response to ICS. Most pharmacogenomics studies of asthma have considered lung function or exacerbations as the primary outcomes of poor response to ICS.

Objectives: To perform a genome-wide association study (GWAS) of poor asthma control.

Methods: We performed a GWAS in Caucasian children with a reported use of ICS included in the PACMAN cohort. Asthma control was assessed based on the Asthma Control Questionnaire (ACQ). Extreme phenotypes were considered for the analysis; patients were categorized to well-controlled ($ACQ \leq 0.75$) and uncontrolled asthma ($ACQ \geq 1.5$). Imputation of genetic variants

was performed using the Haplotype Reference Consortium as reference panel by means of the Michigan Imputation Server. Association testing of 7.5 million genetic variants with minor allele frequency $\geq 1\%$ was performed using logistic regression models with EPACTS. The model was adjusted for age, gender, and population stratification.

Results: From 495 asthmatic children (age: 4-12 years), 123 (24.8%) had poorly controlled asthma ($ACQ \geq 1.5$). Ten genetic variants were suggestively associated with poor asthma control despite ICS use ($p \leq 1 \times 10^{-6}$). The most significant association was found for variants located in chromosome 18 ($p = 1.3 \times 10^{-6}$).

Conclusions: This study identified new variants that are suggestively associated with asthma symptoms despite ICS use in Caucasian children. These novel markers will be validated in other studies participating in the multi-ethnic Pharmacogenomics in Childhood Asthma (PiCA) consortium.

836 | A pharmacoeconomic decision analytic model of multigene molecular diagnostics for colorectal cancer precision medicine

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Background: Two currently marketed tests, an 18 and 12 gene-expression classifiers for predicting disease relapse in early-stage colorectal cancer (CRC) are being used to guide adjuvant chemotherapy. Pharmacoeconomic evaluations are an important consideration in the evaluation of novel molecular technologies.

Objectives: To evaluate the outcomes and cost-effectiveness of using an 18-gene assay as compared with a 12-gene assay for treatment decisions for stage II colon cancer patients.

Methods: A 5-year Markov model was developed, and used to evaluate the costs and quality-adjusted-life-years (QALYs) associated with using two multigene assays for colon cancer treatment strategies. In modeling the costs and QALYs, we used data on the clinical validity of multigene assays, costs of treatments using multigene assays and adjuvant chemotherapy, costs associated with administration, adverse events, utilities; and generated estimates of the health care costs and QALYs, and the incremental cost-effectiveness ratio (ICER). Costs and QALYs were discounted at 3%.

Results: Analysis of 6064 patients for both multi-gene assays found that the recurrence score (RS) and microsatellite (MSI) status are the most reliable factors for prognosis of stage II CRC patients. For 5307 patients using the 12-gene assay, we found RS of 780 patients (14.69%) were in the low risk group, 990 patients (18.65%) in the intermediate risk group and 950 patients (17.90%) in the high-risk group. For 757 patients using the 18-gene assay, we found that the MSI status of 485 patients (64.06%) was in the low risk group and 272 patients were (35.93%) in the high-risk group. Use of the 12-gene assay for prognosis and treatment decisions, resulted in a 33% increase in expenditures in all costs related to CRC treatment as compared with use of the 18-gene expression assay ($p < 0.05$).

Conclusions: The 18-gene assay might be a more cost-effective strategy at a threshold willingness-to-pay of \$50,000 per QALY. This finding has important policy implications, particularly for health insurers.

837 | Pharmacogenomics of HIV in East Africa: Characterizing drug resistant mutations (DRMS) in the cross-border integrated health study, 2016

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Background: Effective antiretroviral therapy (ART) is necessary for patients to achieve viral suppression, which dramatically decreases the probability of HIV transmission. Drug resistance testing is integrated in the process of designing appropriate ART regimens, but this type of personalized medicine is costly and not possible in all settings. East African cross-border sites are visited by mobile and vulnerable populations, who may not benefit from HIV treatment and prevention interventions conducted at their place of residence.

Objectives: To identify and characterize the presence of DRMs in East African cross-border sites.

Methods: The USAID- and PEPFAR-funded MEASURE Evaluation project, led by the University of North Carolina at Chapel Hill, collected cross-sectional data using the Priorities for Local AIDS Control Efforts (PLACE) sampling method at 14 cross-border locations near or along the land and lake borders of Kenya, Rwanda, Tanzania, and Uganda from August 2016-January 2017. This bio-behavioral survey captured information from 11 428 individuals, 576 of whom were identified as HIV-positive. Data were weighted and analyzed using survey methods that accounted for the complex sampling design. We conducted HIV-1 *pol* gene sequencing for a subset of 125 people with unsuppressed HIV and detectable viral loads (>1000 copies/mL). Drug resistance mutations for nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors were identified using the Stanford HIVdb program. A phylogenetic analysis was conducted using the Bayesian Evolutionary Analysis by Sampling Trees (BEAST) package v1.8.4.

Results: Of the 125 people with sequence data, 18 had at least one DRM, and at least one mutation in each tested drug class was identified. Among ART-naïve individuals (*n* = 108), the weighted prevalence of DRMs is 12.0% (95% CI: 4.5, 19.6). The most common DRM was a K103N mutation that confers NNRTI resistance. Phylogenetic analysis demonstrated that putative transmission clusters (individuals with genetically similar viral sequences) were present.

Conclusions: The existence of DRMs in East African cross-border sites highlights the potential benefits of drug resistance testing. Such testing can inform treatment for mobile and vulnerable populations, to improve their health outcomes and reduce transmission.

838 | Multi-drug resistance protein 2 (MRP2) expression, adjuvant tamoxifen treatment and the risk of breast cancer recurrence in a Danish population-based nested case-control study

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Background: Adjuvant tamoxifen therapy approximately halves the risk of estrogen receptor-positive (ER+) breast cancer recurrence, but many women respond insufficiently to therapy. In vitro studies suggest that overexpression of multidrug resistance-associated protein 2 (MRP2) in tumor cells predicts tamoxifen resistance. However, this association is poorly investigated in vivo.

Objectives: To investigate the association of MRP2 expression in tumor cells with breast cancer recurrence, distinguishing MRP2's utility as a predictor of tamoxifen treatment effectiveness from its role as a breast cancer prognostic marker.

Methods: We conducted a case-control study nested in the Danish Breast Cancer Group clinical database. We included women aged 35-69 years diagnosed with stage I-III breast cancer 1985-2001, in Jutland, Denmark. We identified 541 recurrent breast cancers (cases) among women with ER+ disease treated with tamoxifen (TAM) for minimum 1 year (ER+/TAM+) and 300 cases with estrogen receptor-negative (ER-) disease, never treated with tamoxifen (ER-/TAM-). We matched one control to each recurrent case on ER/TAM status, year of surgery, menopausal status, stage and county. MRP2 expression was assessed using immunohistochemistry on tumor microarrays. We used a semi-quantitative histological score (H-score) to define MRP2 expression, where a H-score of >0 was considered positive and H-score = 0 was considered negative MRP2 expression, respectively. Odds-ratios (OR) and 95% confidence intervals (95% CI) associating MRP2 expression (positive vs negative) with breast cancer recurrence were calculated in conditional logistic regression models with adjustment for covariates of clinical or prognostic relevance.

Results: MRP2 expression was more prevalent in the ER+/TAM+ group, compared with the ER-/TAM- group. No predictive utility of MRP2 expression on breast cancer recurrence was found in the ER+/TAM+ group (OR_{adj} = 1.00, 95% CI 0.69, 1.45). MRP2 expression had also no prognostic utility, as no association between MRP2 expression and breast cancer recurrence was found in the ER-/TAM- group (OR_{adj} = 0.76, 95% CI 0.48, 1.21).

Conclusions: Our findings do not suggest that MRP2 is a predictive marker of tamoxifen effectiveness or a prognostic marker.

839 | Drug repurposing: Calcium channel blockers in psychiatric disorders?

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Background: The CACNA1C gene, encoding Cav1.2 of the L-type calcium channel has been implicated in the pathophysiological pathways of both schizophrenia and bipolar disorder and is involved in the pharmacological action of calcium channel blockers (CCBs) in treatment of cardiovascular disease (CVD).

Objectives: To investigate whether CCBs improve psychiatric hospitalizations and mortality in people with schizophrenia or bipolar disorder.

Methods: New user cohort study between 1996 and 2012 using Danish register data. Among all people with a diagnosis of schizophrenia or bipolar disorder, we 1:1 matched new users of L-type brain-penetrating (BP) and non-BP CCBs to betablocker (BB) users on a propensity score (PS) for receiving CCBs versus BBs, age and sex. We performed intention-to-treat analysis in the PS-matched cohorts and exposure time dependent analysis in unmatched models adjusted for PS, age, and sex. We estimated hazard ratios (HRs) with 95% confidence intervals (CIs) of any psychiatric hospitalization, hospitalization due to schizophrenia or bipolar disorder, all-cause and CVD mortality using (stratified) Cox regression by comparing rates in users of BP/non-BP CCBs versus (matched) BB users.

Results: We identified 4936 new users of non-BP CCBs, 1515 new users of BP CCBs, and 9755 new users of BB. We matched 2563/1019 non-BP/BP CCB users to 2563/1019 BB users. In matched analysis, the HR for psychiatric hospitalization was 1.08 (95% CI: 0.91-1.29) for non-BP CCBs and 1.03 (95% CI: 0.79-1.33) for BP CCBs. The risk of hospitalization due to schizophrenia was 1.27 (95% CI: 0.97-1.67) in non-BP CCBs, and 1.46 (95% CI: 1.17-1.82) in BP CCBs. There was no association between CCBs with hospitalizations due to bipolar disorder. The HR for all-cause mortality was 0.97 (95% CI: 0.83-1.13) for non-BP CCBs and 1.56 (95% CI: 1.28-1.91) for BP CCBs. The HR for CVD mortality was 0.74 (95% CI: 0.57-0.97) in non-BP CCBs and 2.08 (95% CI: 1.41-3.06) in BP CCB users. Unmatched time varying analyses overall corroborated results of the matched analyses but were attenuated in particular with regard to mortality risk in people using BP CCBs, which was down to 1.12 (95% CI: 0.83-1.51) for all-cause mortality and 0.92 (95% CI: 0.58-1.46) for CVD mortality.

Conclusions: The current approach did not detect a clear beneficial effect of CCB use compared with BB use regarding global outcomes such as hospitalizations in people with psychiatric disorders.

Non-BP CCBs were associated with a decreased risk of all-cause mortality, probably due to decreased CVD mortality.

840 | PD-L1 expression, EGFR mutations (EGFRm) and KRAS mutations (KRASm) in stage III unresectable non-small cell lung cancer (NSCLC) patients

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Background: Anti-PD-L1 therapy may improve prognosis in advanced NSCLC.

Objectives: To examine the relation of PD-L1 expression, KRASm and EGFRm, with survival in unresectable stage III NSCLC patients (pts) treated with chemotherapy.

Methods: We obtained data on unresectable stage III NSCLC pts (defined via AJCC staging, without surgery up to 120 days after diagnosis) diagnosed 2001-2012. We retrieved medical data from Danish population-based registries and paraffin-embedded tumor tissue from pathology archives. We tested PD-L1 expression using the Ventana IHC (SP263) validated assay. We genotyped KRAS and EGFR using PCR kits. Follow-up began at NSCLC diagnosis and continued to death, emigration, or 31/12/2014. We used Cox regression to compute hazard ratios for death (HRs) and associated 95% confidence intervals (95% CI) for each biomarker, adjusting for age, sex and histology.

Results: From 305 pts, 183 (60%) were men, 167 (55%) were >65 years at diagnosis. No pts used immunotherapy; 148 (49%) had adenocarcinoma, 117 (38%) squamous histology, 96 (31.5%) had PD-L1 positive tumors ($\geq 25\%$), 6 (2%) had EGFRm, and 69 (23%) had KRASm. Among PD-L1 positive tumors, 55% had stage IIIA, 45% IIIB disease; 1% had EGFRm and 34% had KRASm. Among PD-L1 negative tumors, 54% stage IIIA and 46% IIIB; 3% had EGFRm and 16% had KRASm. Median survival was similar in pts with KRAS wildtype (14.5 months, 95% CI = 11.4-16.8) and KRASm (13.8 months, 95% CI = 9.1-23.4). Pts with an EGFRm had a lower risk of death (HR = 0.75, 95% CI = 0.28-2.06). Tumor cell positivity for PD-L1 ($\geq 25\%$ versus $< 25\%$) yielded an HR = 0.80 (95% CI = 0.60-1.07). Immune cell positivity for PD-L1 $\geq 1\%$ and $\geq 25\%$ yielded HRs of 0.50 (95% CI = 0.39-0.66) and 0.45 (95% CI = 0.30-0.67), respectively. Tumor infiltration by immune cells with PD-L1 measured as a continuous variable yielded an HR = 0.96 (95% CI = 0.93-0.99).

Conclusions: Findings from this Danish registry-based study suggest that PD-L1 expression in tumors or tumor-infiltrating immune cells and *EGFR*, but not *KRAS*, may correlate with survival in unresectable Stage III NSCLC pts.

841 | The use of antimicrobial drugs has long-term impact on the human stool microbiota

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Background: The gut microbiota has increasingly been recognized to play an important role in health and disease. Its composition may vary due to several factors, including antimicrobial drugs, although little is known about the effects of specific antimicrobial drugs.

Objectives: To investigate the effects and the duration of these effects of different antimicrobial drug groups on the composition of the human stool microbiota.

Methods: Faeces samples were obtained from a community-dwelling cohort of middle-aged and elderly individuals (Rotterdam Study). Bacterial DNA was isolated, after which an OTU table was produced based on V3/V4 16S ribosomal RNA sequencing (Illumina MiSeq). The time between the last prescription of an antimicrobial drug and the day of sampling was categorized in 0-12 months, 12-24 months, 24-48 months, >48 months and was compared with no use of antimicrobial drugs at all. The effect of the specific antimicrobial drug groups (tetracyclines, beta-lactams, trimethoprim and sulphonamides, macrolides and lincosamides, quinolones, nitrofurantoin derivatives) on the Shannon alpha-diversity was studied with linear regression models, whereas a PERMANOVA-S analysis was used to study effects in Bray-Curtis beta-diversity. The analyses were adjusted for possible confounders such as sex, age, BMI, diabetes, technical covariates and the use of co-medication.

Results: Of 1413 individuals (57.5% female, median age 62.6 years) both stool microbiota and pharmacy data were available. The microbiota diversity was significantly lower up to 4 years after prescriptions of macrolides and lincosamides (β [95% CI] log alpha-diversity 0-12 months: -11.74 [-18.44, -5.03]; 12-24 months -7.33 [-14.62, -0.03]; and 24-48 months -8.59 [-14.24, -3.00]). Moreover, the diversity was lower in the first year after use of tetracyclines (β [95% CI] log alpha-diversity -6.29 [-12.20, -0.39]) and beta-lactams (β [95% CI] log alpha-diversity -7.02 [-12.13, -1.91]). Furthermore, the community structure of the stool microbiota was significantly different ($p < 0.05$) after use of tetracyclines, beta-lactams, macrolides and lincosamides, quinolones, and nitrofurantoin derivatives. These differences were present up to 4 years after use of antimicrobial drugs.

Conclusions: Antimicrobial drugs affect stool microbiota, and the effects differ by antimicrobial drug groups in effect and duration.

These findings need replication; if confirmed they may be important to take into account when prescribing antimicrobial drugs.

842 | The use of genetic risk scores in pharmacogenetics studies—A simulation study

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Background: Genetic risk scores (GRS) are increasingly used to measure individual responses to drugs in pharmacogenetics studies. However, the proper application of the GRS in these studies is sparse.

Objectives: We aimed to assess the methodological issues of the use of GRS or the genetic marker(s) in pharmacogenetics studies.

Methods: We considered several realistic scenarios, such as gene and environment interaction; gene and gene interaction; gene and exposure interaction; gene acts as confounders and instrumental variable; and replicated each scenario 1000 times with $n = 100\,000$ simulated observations. For simplicity, we considered continuous exposure, outcome and continuous and binary confounders. The genetic markers were simulated using the uniform distribution on the interval from 0.05 to 0.95 and the effect of the markers was generated using the lognormal distribution with mean zero and standard deviation one. We constructed the GRS using a sum of allelic count or using a weighted sum of allelic count where the weights being given by regression coefficients from the univariate regression model. The true exposure effect was $\beta = 1$. We used a linear regression model to simulate and analyze the data.

Results: Our analyses showed that when the gene(s) that was used for calculating GRS interacted with the exposure and if the analyses taking into account this interaction, the exposure effect similar with the true value ($\beta = 1$), 1.01 (confidence interval [CI]: 0.99-1.02), root-mean-square error (RMSE) = 0.01. However, a significant amount of bias (the exposure effect was far from the true value, $\beta = 1$) was present even after adjustment for the measured confounders (i) when the gene interacted with the unmeasured confounder, 1.05 (CI: 1.04-1.06), RMSE = 0.05 and this bias amplified, 1.12 (CI: 1.10-1.55), RMSE = 0.12, when the interaction effect was two times stronger; (ii) when the gene acts as a confounder, 0.59 (CI: 0.57-0.60), RMSE = 0.42; and (iii) when the gene acts as an instrumental variable 0.69 (CI: 0.68-0.71), RMSE = 0.31.

Conclusions: Our simulation study shows that the GRS can be used in pharmacogenetics studies to reduce the systematic bias or increase the precision of the exposure effects. Nevertheless, caution should

be taken and clinical knowledge should be applied to explain the results as some scenarios it induces bias in the association between exposure and outcome.

843 | Myelodysplastic syndrome and acute myeloid leukemia following use of chemo-immunotherapy and granulocyte colony-stimulating factors among elderly non-hodgkin lymphoma patients

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Background: Treatments for non-Hodgkin lymphoma (NHL) include both chemo-immunotherapy and granulocyte colony-stimulating factors (G-CSF) to prevent neutropenia. Myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) are rare but lethal therapy-related second primary cancers.

Objectives: Our purpose was to examine use of G-CSF in relation to risk of MDS/AML in a cohort of elderly patients with NHL.

Methods: We conducted a retrospective cohort study of adults ages 66 years and older diagnosed with first primary NHL between 2001 and 2011 using the SEER-Medicare linked database. Patients were included if they were alive and without second primary cancer at three months post-diagnosis. Using validated algorithms, we identified MDS/AML cases, primary NHL treatment received, and type and number of doses of G-CSF received (ie, filgrastim and/or pegfilgrastim). In cause-specific Cox proportional hazards models stratified by treatment, we estimated adjusted hazard ratios (HR) and 95% confidence intervals (CI) for risk of MDS/AML associated with G-CSF use.

Results: A total of 18 245 patients were included with a median follow up of 3.5 years. Most patients were diagnosed with diffuse large B-cell (34%) or follicular lymphoma (22%). Fifty-six percent of patients received chemo-immunotherapy, among whom most received rituximab-based chemotherapy (74%). G-CSF was most commonly used among those who received rituximab plus chemotherapy (77%). Subsequent MDS/AML was observed in 666 (3.7%) patients. Overall, we found a modest increased risk of MDS/AML with any use of G-CSF (HR = 1.28, 95% CI 1.01-1.62); although, a linear trend was observed with number of G-CSF doses ($P < 0.001$). Among patients receiving rituximab plus chemotherapy, risk of MDS/AML was highest in those receiving 10 or more G-CSF doses (HR = 1.64, 95% CI 1.14-2.37). Greater risk was consistently observed with filgrastim (HR = 1.67, 95% CI 1.25-2.23), but not pegfilgrastim (HR = 1.11, 95% CI 0.84-1.45).

Conclusions: We observed higher MDS/AML risk among those receiving G-CSF specific to filgrastim. The benefits of preventing therapy-related neutropenia in patients receiving highly myeloablative treatments likely outweigh the risk of this rare but serious secondary cancer. Further study of differential risk by type of G-CSF is warranted

given increasing use and FDA-approved biosimilar products newly available.

844 | Abstract Withdrawn

845 | Prognostic role of neutrophil-lymphocyte ratio in localized and metastatic renal cell carcinoma: A population-based cohort study

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Background: Inflammation is known to have an impact on several steps in tumor development and an elevated neutrophil-lymphocyte ratio (NLR) has been associated with a poorer prognosis in several types of malignancies.

Objectives: To examine the prognostic value of NLR in patients with localized or metastatic renal cell carcinoma (RCC) at time of diagnosis and at RCC recurrence.

Methods: Using prospectively collected data from Danish medical registries, we conducted a population-based cohort study including all patients above 18 years of age from the North and Central Denmark regions with a diagnosis of RCC and a NLR measurement within 30 days prior to diagnosis in the period from 1999-2015. Patients were categorized according to NLR levels (<3.0 and >3.0) and were followed until death, immigration, or up to 5 years. We estimated survival probabilities using Kaplan-Meier curves and hazard ratios (HR) with 95% confidence intervals using Cox proportional hazards regression. Results were adjusted for predefined, potential confounding covariates.

Results: We included 979 patients. Among these, 416 had at time of initial diagnosis a NLR <3.0 and 563 had a NLR >3.0 . The 5 year-survival rate was 35.2% in RCC patients with elevated NLR (>3.0) compared with 69.4% in patients with NLR <3.0 . The unadjusted HR was 3.1 (95% CI, 2.5-3.9) and when adjusted for all covariates, HR was 1.8 (95% CI, 1.4-2.2). In total, 76 patients had RCC recurrence and among these, 59 had NLR measured at time of diagnosis with RCC recurrence. Elevated NLR (>3.0) was associated with a poorer prognosis (adjusted HR = 2.1 [95% CI, 0.8-5.7]).

Conclusions: An elevated NLR at time of initial diagnosis of RCC is associated with a poorer prognosis. At time of RCC recurrence, an elevated NLR was similarly associated with an increased mortality. This information may be useful in risk-stratification of RCC patients and may help in guiding the development of new targets for cancer treatment.

846 | Association of exogenous hormone use with breast cancer subtype defined by Oncotype DX recurrence score

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Background: Hormone therapy (HT) and oral contraceptive (OC) use have been shown to affect breast cancer risk and prognosis. Recent studies have suggested that these exposures may also be associated with quantitative tumor genomic measures.

Objectives: To investigate associations between OC and postmenopausal HT use and 21-gene breast cancer Recurrence Score (RS) from Oncotype DX test, a prognostic and predictive clinical genomic assay.

Methods: We retrospectively reviewed the medical histories, pathology reports, and Oncotype DX results of patients with stage I or II estrogen receptor (ER) positive, HER2 negative breast cancer in the population-based Carolina Breast Cancer Study Phase 3 (2008-2013). We used linear binomial regression to estimate the prevalence differences (PD) of OC and HT use among tumors categorized as low (RS < 18), intermediate (RS 18-30), and high risk (RS > 30), adjusting for age, race, and stage. HT was examined only in postmenopausal women. We also examined use by duration, timing, and HT formulation.

Results: Of 603 total patients, 322 (53%) had low risk, 226 (37%) had intermediate risk, and 60 (10%) had high risk tumors. Median age at diagnosis was 51 years (range 28-74). 495 (82%) were ever OC users and 112 (19%) were never users. Of 346 postmenopausal women, 149 (43%) were ever HT users. Ever use of OC was not significantly associated with RS. 3-10 years of OC use was associated with significantly lower prevalence of high versus low risk tumors compared with never use (PD -13.3%; 95% CI -24.8%, -1.74%). Among postmenopausal women, ever HT use was associated with significantly higher prevalence of intermediate versus low risk tumors (PD 12.6%; 95% CI 1.0%, 24.2%). Compared with no HT use, unopposed estrogen was associated with significantly higher prevalence of intermediate risk tumors versus low risk tumors (PD 15.4%; 95% CI 1.89%, 28.8%); no significant association was found for combined estrogen and progestin use. No significant associations were found for recency of HT or OC use or HT duration.

Conclusions: Exogenous hormonal exposures, known to modulate estrogen metabolism, may impact the RS through ER gene expression, a component of the RS algorithm. Additional tumor data, such as quantitative ER, may help interpret these findings. Future research should evaluate whether these exposures modify the predictive value of RS. Interestingly, neither recency of use nor HT duration were associated with RS; however, small numbers in these categories may have limited power to detect associations.

847 | Use of antipsychotics and risk of breast cancer: A Danish nationwide case-control study

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Background: The use of some antipsychotics increases prolactin levels, which might increase the risk of breast cancer. Existing evidence is conflicting and based on sparse data, especially for the increasingly used second-generation antipsychotics.

Objectives: To assess the potential association between antipsychotic use and risk of breast cancer.

Methods: We conducted a nationwide case-control study based on Danish health registry data. We identified women with a first-time diagnosis of breast cancer 2000-2015 (n = 60 360). For each case, we age-matched 10 female population controls. Using conditional logistic regression, we estimated odds ratios (ORs) for breast cancer associated with cumulative use of antipsychotics. We stratified antipsychotics by first and second generation status and by ability to induce elevation of prolactin.

Results: 4951 cases (8.2%) and 47 643 controls (7.9%) had ever used antipsychotics. Long-term use ($\geq 10\ 000$ mg olanzapine equivalents) was associated with breast cancer, with an adjusted OR of 1.19 (95% CI, 1.07, 1.33). A weak dose-response pattern was seen, with ORs increasing to 1.27 (95% CI 1.02, 1.60) for $\geq 50\ 000$ mg olanzapine equivalents. Associations were similar for first- and second-generation antipsychotics (ORs 1.18 vs 1.12). An increased risk was also noted for non-prolactin inducing antipsychotics (OR 1.17; 95% CI 0.89, 1.56). Among second-generation antipsychotics, positive associations were found for prolactin-elevating but not for non-prolactin elevating antipsychotics.

Conclusions: Overall, our results do not suggest a clinically important association between antipsychotic use and risk of breast cancer. The importance of drug-induced prolactin elevation is unclear, but may be of relevance for second-generation antipsychotics.

848 | Direct-acting antivirals reduce the risk of non-hepatic cancers among hepatitis C virus-infected patients

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Background: Previous studies have shown that hepatitis C virus (HCV) infection increases the risk of non-hepatic cancers. However, it is unclear whether direct-acting antiviral (DAA) treatment for chronic HCV infection reduces the risk of non-hepatic cancers among HCV-infected patients.

Objectives: To examine the impact of DAA therapies on the risk of non-hepatic cancers among HCV patients in the U.S.

Methods: A retrospective cohort analysis of the Truven Health MarketScan Database (January 2008– August 2015) was conducted. We included adult patients with newly diagnosed HCV and without a history of cancer. We followed patients from the first HCV diagnosis to the end of enrollment or the occurrence of a composite outcome of non-hepatic cancers. To assess the association between DAA therapies and the risk of developing non-hepatic cancers, a time-varying exposure analysis was performed. We employed Cox proportional hazards models to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs). Baseline demographics and comorbidities such as cirrhosis, HBV, HIV, and drug abuse were adjusted in models. In secondary analyses, we evaluated incidence rates of specific non-hepatic cancers, including lung, breast, and gastrointestinal (GI) cancers, among DAA-treated patients and HCV non-treated patients, respectively.

Results: We identified a total of 46 361 HCV-infected patients (mean age = 52 yrs, 61% male), among which 4311 patients (9.3%) initiated DAA therapies whereas 42 050 (90.7%) patients did not receive any HCV treatment. Patients who received DAA therapies had a lower incidence rate of the composite non-hepatic cancer outcome compared with those without treatment (745 vs 1216 per 100 000 person-years). After controlling for covariates, DAA therapies were associated with a 63% decreased the risk of non-hepatic cancers (HR = 0.37, 95% CI = 0.23–0.57). For specific cancers, lower incidence rates of individual non-hepatic cancer were observed among DAA-treated patients compared with HCV non-treated patients, but the differences were not statistically significant. (lung: 196 vs 223 per 100 000 person-years; breast: 118 vs 163 per 100 000 person-years; GI: 118 vs 256 per 100 000 person-years; $p > 0.05$ for all comparisons).

Conclusions: DAA therapies are associated with a decreased risk of the composite non-hepatic cancer outcome among HCV patients in the United States.

849 | Incidence of hypothyroidism in women with breast cancer—A Danish population-based matched cohort study

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Background: Previous studies suggest an increased risk of hypothyroidism (HT) among women with breast cancer. However, the risk according to cancer-directed treatment is unclear.

Objectives: To estimate the incidence of HT in women with breast cancer, and in strata of chemo- and radiation therapy (RT), compared with cancer-free women from the general population

Methods: Using nationwide registries, we identified all Danish women aged ≥ 35 years with a first-time hospital diagnosis of breast cancer from 1996 to 2009 excluding women with prevalent HT or hyperthyroidism, and prior cancers. For each breast cancer case, up to five cancer-free women were matched with replacement on birth year and municipality at the date of breast cancer diagnosis. HT was ascertained using ICD-8 and 10 codes, or as ≥ 2 thyroxine prescriptions. Follow-up started on the date of diagnosis and continued until HT, hyperthyroidism, death, emigration, or July 1, 2016. We calculated incidence rates (IR) per 1000 person-years of HT and associated 95% confidence intervals (CI) for both cohorts. We used Cox regression to calculate hazard ratios (HR) for risk of HT adjusted for comorbidity and censored by death, hyperthyroidism and emigration.

Results: We identified 45 664 women with breast cancer and 219 302 matched controls with 408 626 and 2 372 812 person-years of follow-up, respectively. Women with breast cancer had higher incidence of HT than comparators, IR of 4.3 (95% CI: 4.1–4.5) and 0.9 (95% CI: 0.8–0.9), respectively, corresponding to an adjusted HR of 5.0 (95% CI: 4.7–5.3). Compared with the comparators, women assigned chemo and RT had an increased risk of HT (HR: 4.2, 95% CI: 3.1–5.7), RT without chemo (HR: 5.3, 95% CI: 4.6–6.1), chemo without RT (HR: 5.1, 95% CI: 4.5–5.8) and neither chemo nor RT (HR: 4.8, 95% CI: 4.3–5.4). Stratifying by years since diagnosis, calendar period, treatments, and comorbidity, and in combinations did not alter the results.

Conclusions: Women with breast cancer have substantially increased risk of HT compared with the general population. HT risk is especially elevated among those assigned chemo or RT.

850 | Hydrochlorothiazide use and risk of merkel cell carcinoma and malignant adnexal skin tumours

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Background: Hydrochlorothiazide use has convincingly been associated with a strongly increased risk of squamous cell carcinoma, likely induced by photosensitizing effects of the drug. No previous studies have investigated the association between hydrochlorothiazide use and the risk of rare types of non-melanoma skin cancer.

Objectives: To investigate the association between hydrochlorothiazide use and the risk of Merkel cell carcinoma or malignant adnexal skin tumours.

Methods: Using Danish nationwide demographic and health registries, we identified all patients with incident Merkel cell carcinoma or malignant adnexal skin tumours during 2004-2015 and individually matched cancer-free population controls. Using conditional logistic regression, we estimated odds ratios (ORs) associated with cumulative use of hydrochlorothiazide.

Results: We identified 97 cases of Merkel cell carcinoma and 132 cases of malignant adnexal skin tumours. The adjusted ORs of high-use ($\geq 50\,000$ mg) of hydrochlorothiazide were 2.3 (95% CI, 1.1-4.8) for Merkel cell carcinoma and 3.6 (95% CI, 1.9-7.0) for malignant adnexal skin tumours, increasing to 3.3 (95% CI 1.3-8.3) and 5.6 (95% CI 2.4-13.3) in the highest exposure category ($\geq 100\,000$ mg). Analyses restricted to individuals with no recorded use of photosensitizing drugs other than hydrochlorothiazide had little impact on the associations (Merkel cell carcinoma: OR 2.1, 95% CI 0.7-6.2; malignant adnexal skin tumours: OR 2.4, 95% CI: 0.9-6.1). We found no increase in risk of the tumours in analyses of drugs with similar indications as hydrochlorothiazide, except a tendency toward an increased risk of Merkel cell carcinoma associated with use of furosemide (OR 1.9, 95% CI 0.9-4.0).

Conclusions: Use of hydrochlorothiazide is associated with a markedly increased risk of Merkel cell carcinoma and malignant adnexal skin tumours.

851 | Identifying targets for pharmacovigilance in US children using a big data "Market Basket" analysis (The A Priori Algorithm)

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Background: Children are exposed to multiple medications in the ambulatory setting. Those with rarer conditions, eg, neurological impairment (NI) like epilepsy, may have use patterns different from the general population and may concurrently take drugs with the potential for drug-drug interactions (PDDIs). Pharmacovigilance requires an efficient, flexible approach to quantify exposures to medications and PDDIs in big data. The a priori algorithm has been used in marketing to analyze items that shoppers buy together and could be applied to prescription data to analyze exposure to concurrent medications on a daily basis.

Objectives: To use the a priori algorithm to (1) quantify exposure to the most common single and concurrent drugs and to (2) identify PDDIs in children overall and among those with NI specifically.

Methods: Longitudinal analysis of exposure to drugs by children 0-18 years old using subjects' most recent year from a 10% sample of

IMS Health LifeLink data. For each day, we identified the total number and identity of overlapping drugs by arraying claims using dispense date and days supplied. We excluded duplicate ingredients, topicals, and vaccines. NI status was based on ICD-9-CM codes. The a priori algorithm was used to identify the most frequent concurrent drug pairs. RxNorm's DrugBank interaction database was used to demonstrate identification of PDDIs, although any interaction database could be used.

Results: Of 95 269 total subjects, 42 489 had ≥ 1 claim; of those, 12% were exposed simultaneously to a maximum of 3 drugs, 6% to 4 drugs, and 2% to ≥ 5 drugs. In the subset of 6178 subjects with NI, 3064 had ≥ 1 claim; of those 16% were exposed to 3 drugs, 6% to 4 drugs, and 4% to ≥ 5 drugs. The ratio of exposures per 100 000 patients in the NI subgroup compared with all subjects was increased for anticonvulsants (26:1), antipsychotics (8:1), and antihypertensives (6:1). Among all subjects, there were 1,480 unique concurrent drug pairs (most common: diphenhydramine-ipratropium), and 42% were associated with PDDIs. For NI subjects, there were 141 drug pairs (most common: methylphenidate-risperidone), and 52% were associated with PDDIs.

Conclusions: Pharmacovigilance studies in the general population may obscure important patterns of use in children with rarer conditions. Children with NI are exposed to more and higher-risk drugs that may be involved in PDDIs. This flexible approach could be used for broad population-level surveillance and for more circumspect subgroup surveillance.

852 | Antipsychotic use among US commercially insured youth following implementation of state prior authorization monitoring policies

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Background: Emerging evidence shows decreased antipsychotic prescribing after many states implemented prior authorization (PA) policies to promote judicious psychotropic use among Medicaid-insured youth. PA policies can influence providers' overall prescribing practices, and thus it is possible that antipsychotic prescribing also would decrease among commercially insured youth.

Objectives: To evaluate trends in the prevalence of antipsychotics, antidepressants and mood stabilizers among US commercially insured youth prescribed psychotropic medications.

Methods: Commercially insured youth living in 17 US states that implemented PA in 2011 and 2012 and who met the age criteria of the PA at the time of dispensing were identified using IMS Pharmetrics Plus pharmacy claims. From 2006-2015, we estimated the monthly prevalence of antipsychotics (the primary focus of PA programs), mood stabilizers (a potential antipsychotic substitute), and antidepressant (which should be unaffected by PA policies). The denominator was the number of youth each month treated with any

psychotropic. The 10-year study period was divided into 3 segments; pre-PA (2006-2010), implementation (2011-2012) and post-PA (2013-2015). We used segmented regression of interrupted time series analysis to estimate pre- to post-PA change in monthly prevalence of each targeted psychotropic class. Autocorrelation was corrected using Yule-Walker estimation method.

Results: Antipsychotic monthly prevalence increased 0.01% (95% CI: -0.01, 0.04) per month during the pre-PA period. Immediately following PA implementation, we observed a non-significant decrease (coefficient = -0.48; 95% CI: -2.30, 1.35) in antipsychotic prevalence, but the overall post-PA trend had a significant 0.09% (95% CI: -0.15, -0.03) decline per month. Pre-PA mood stabilizer use decreased significantly per month (coefficient = -0.03; 95% CI: -0.04, -0.03), but post-PA, the prevalence significantly increased 0.04% per month (95% CI: 0.02, 0.05). There was no significant trend in the monthly prevalence of antidepressant use pre-PA and post-PA.

Conclusions: The observed decrease in antipsychotic use among U. S. commercially insured youth mirrored trends among Medicaid-insured youth following PA policy implementation. The significant increase in mood stabilizer use following PA may suggest substitution effects, since the overall prescribing of antidepressants did not change.

853 | Predictors for pharmacological and psychotherapeutic treatment in children newly diagnosed with ADHD

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Background: Predictors for the use of evidence-based treatments in routine care of children newly diagnosed with attention-deficit/hyperactivity disorder (ADHD) over several years are unknown.

Objectives: To investigate predictors for use of medication and psychotherapy within five years after a first ADHD diagnosis in Germany.

Methods: This cohort study was based on the German Pharmacoepidemiological Research Database and included 12 250 treatment-naïve children aged 5-12 years with an incident ADHD diagnosis in 2010 and a minimum follow-up of five years. Children were categorized into treatment groups based upon dispensations of ADHD drugs and billed codes for psychotherapy within five years following the first ADHD diagnosis. Multivariable logistic regression was used to estimate associations between children's characteristics at the first diagnosis and the chosen treatment approach.

Results: Within 5 years after the incident ADHD diagnosis, 37% of the children received medication; 11% only psychotherapy; 52% no treatment. Of those receiving medication, 27% had additional psychotherapy. Boys (adjusted odds ratio [aOR] 1.41, 95% CI 1.28-1.55), children

with an ADHD diagnosis "with hyperactivity" (aOR 5.64, 95% CI 4.94-6.44), and those with comorbid conduct disorders (aOR 1.35, 95% CI 1.21-1.51) were more likely to receive medication than no treatment. Male sex (aOR 1.18, 95% CI 1.02-1.35) and comorbid neurotic and somatoform (aOR 1.38, 95% CI 1.12-1.70), conduct (aOR 1.45, 95% CI 1.23-1.71), and emotional disorders (aOR 1.60, 95% CI 1.33-1.92) were associated with only psychotherapy. Comorbid depression (aOR 1.41, 95% CI 1.13-1.77), neurotic and somatoform (aOR 1.31, 95% CI 1.02-1.68), conduct (aOR 1.52, 95% CI 1.29-1.78), and emotional disorders (aOR 1.48, 95% CI 1.21-1.81) increased the odds of receiving both treatments than medication only; conversely, higher age (aOR 0.73, 95% CI 0.59-0.90) and mental retardation (aOR 0.48, 95% CI 0.28-0.83) decreased the odds. Children who were initially diagnosed by a non-specialist were more likely to receive no treatment than medication, whereas diagnosis by a psychotherapist increased the odds of receiving medication, only psychotherapy, or both.

Conclusions: This study is the first to show patterns of two main ADHD treatment approaches in newly diagnosed children and to identify several patient characteristics as predictors.

854 | Off-label systemic drug utilization in a large US pediatric population

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Background: Medicines are commonly used off-label in children. Most research on off-label drug utilization has come from Europe or focused on individual drug classes or inpatient settings.

Objectives: To describe usage of systemic drugs that are off-label based on age in a US-representative outpatient pediatric population.

Methods: We performed a cross-sectional study using the National Ambulatory Medical Care Surveys (NAMCS, 2006-2014), annual population-representative surveys of US outpatient physician visits. We examined usage patterns of prescription and non-prescription systemic medicines provided to children under age 18, stratified by age group. Off-label drugs were defined as being given at an age not approved by the FDA for any indication. We evaluated relative and absolute rates of off-label usage in children by drug class and used multivariable logistic regression to examine factors related to off-label utilization. All analyses were weighted to account for the complex sampling design.

Results: The study population consisted of 63 522 surveyed pediatric visits, representing 1.6 billion pediatric encounters over the 9-year study period. Physicians gave a systemic drug at 43% of visits. Overall, 8.4% of systemic drugs were given off-label, based

on FDA-approved age. Prevalence of off-label drug usage varied by age group (<2y: 14.1% [95% CI 12.5, 15.9]; 2-5y: 7.8% [95% CI 6.9, 8.9]; 6-11y: 5.9% [95% CI 5.2, 6.7]; 12-17y: 8.0% [95% CI 7.2, 9.0]). Proportion of off-label usage by class ranged from 2.0% for anti-microbial drugs to 33.9% for gastrointestinal (GI) drugs and 42.4% for psychotropic drugs. Across all visits and in absolute terms, off-label usage was highest for respiratory drugs (14.3 [95% 12.3, 16.7]/1000 visits), psychotropic drugs (11.9 [95% 10.1, 14.0]/1000 visits), and GI drugs (9.7 [95% 8.3, 11.4]/1000 visits); these rates, as for other classes, varied considerably by age group. In multivariable models, off-label usage was more common at visits with infants under 2, with public insurance, and with medical subspecialists. Pediatric off-label drug usage did not change over time or relate to sex or race.

Conclusions: Off-label utilization of systemic drugs varies considerably by age and by drug class in a large outpatient US pediatric population. In absolute terms, respiratory, psychotropic, and GI drugs are given most commonly off-label to children. More research is needed to clarify the appropriateness of drug utilization by clinical indication in this population.

855 | Adverse drug reactions of statins in a paediatric population: A descriptive analysis of individual case safety reports from Vigibase

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Background: Statins are lipid-lowering drugs used in children with familial hypercholesterolemia. However, their benefits must be weighed against their potential risks. In paediatric populations, safety of statins in 'real-life' is not known.

Objectives: Our objective was to review, in paediatric populations, adverse drug reactions (ADRs) to statins spontaneously reported and recorded in the World Health Organization drug safety Database, Vigibase®.

Methods: We extracted reports in the paediatric population (<18 years) associated to statins (C10AA ATC class) as "suspected" drug until July 18, 2017. Reports involving infants (1-27 months), "anomaly congenital" for seriousness and "Congenital disorders" for ADRs were excluded. Characteristics of children (age groups, gender), type of ADRs (System Organ Class (SOC) and Preferred Term (PT) according to MedDRA classification), and ADRs seriousness were described.

Results: A total of 311 reports was identified for 8 statins corresponding to 712 ADRs (atorvastatin [110 reports, 35.4%], simvastatin [80, 25.7%], lovastatin [47, 15.1%], pravastatin [36, 11.6%], rosuvastatin

[34, 10.9%], fluvastatin [6, 1.9%], cerivastatin [4, 1.3%], pitavastatin [1, 0.3%]; one report may have several statins). Age mean was 11.5 years $\pm$ 5.0 with 182 (58.5%) adolescents (12-17 years) and 129 (41.5%) children (2-11 years). Girls accounted for 54.3% (169) of reports. Overall, 42.8% (133) of reports were "serious." The most frequently reported SOC classes were "Musculoskeletal and connective tissue disorders" (76 [24.4%] reports including 36 [11.6%] "myalgia" and 11 [3.5%] "rhabdomyolysis"); "General disorders and administration site conditions" (67 [21.5%] reports with 10 [3.2%] "asthenia," 7 [2.3%] "fatigue" and 6 [1.9%] "pain") and "Injury, poisoning and procedural complications" (67 [21.5%] reports with 9 [2.9%] "off label use," 9 [2.9%] "accidental exposure to product by child," 9 [2.9%] "intentional overdose," 8 [2.6%] "accidental exposure to product" and 8 [2.6%] "intentional product misuse").

Conclusions: As far as we know, this study is the first one assessing statins safety in "real-life" paediatric populations. As expected, statin-related ADRs mainly concern musculoskeletal and general disorders. More interesting, a significant number of accidental exposure and intentional misuse was observed in this population.

856 | Quantifying prevalence and mortality associated with neonatal enteroviral sepsis (NES) using inpatient data in FDA's Sentinel System

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Background: Neonatal enteroviral sepsis (NES) is a severe enterovirus (EV) infection in the neonate that may include hepatic necrosis and coagulopathy (HNC) with or without myocarditis. Currently no FDA-approved medical product exists for the treatment of NES, although reports indicate intravenous immune globulin (IVIG) is sometimes administered. Limited data are available regarding the epidemiology of the condition. Observational data on NES prevalence and mortality rates could inform planning for future clinical trials to evaluate investigational treatments.

Objectives: To describe NES prevalence and mortality rates among hospitalized neonates.

Methods: We identified potential NES cases using inpatient data from a Sentinel System data partner from 7/1/2012-3/31/2016. Patients aged <60 days on admission were considered eligible for inclusion. As laboratory confirmation of EV infection was not available, potential NES cases were identified using a combination of diagnostic code-based case definitions denoting sepsis and EV infection, as well as bleeding, liver, and/or cardiac dysfunction. Codes for EV infection, sepsis plus one or more of the organ dysfunctions were required to

satisfy the NES case definition. We characterized patient demographics (age in days, sex), hospitalization characteristics (admission year, length of stay, discharge disposition), and IVIG use. In addition, potential cases with antimicrobial or antifungal use extending beyond 48 hours at any time were excluded.

Results: Among all eligible hospitalized patients during the study period, there were 16 patients with EV infection and sepsis; of those, 9 met the NES case definition criteria. One patient received IVIG. NES prevalence was 0.12 per 100 000 neonate inpatient stays. At admission, the majority (89%) of the patients with NES were <30 days old. Median length of stay (LOS) among EV infected patients without organ dysfunction was 10 days (range, 2-28 days); EV infected patients with organ dysfunction had longer LOSs (median LOS ranged from 81-346 days, depending on specific organ dysfunction). No fatalities were observed.

Conclusions: This is the first assessment focused on NES case identification using inpatient data from the Sentinel System. Future work may include validation of potential NES cases with medical record review. Additional data are needed to characterize factors that might impact clinical outcomes among NES patients to inform the design of future clinical trials.

857 | Factors associated with antibiotic prescribing for common childhood diseases: A population-based study

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Background: The appropriate use of antibiotics can reduce the antibiotics resistance and likelihood of childhood death due to common childhood diseases such as acute respiratory infection (ARI), diarrheal diseases and fever, in developing countries including Bangladesh. However, no previous representative studies in Bangladesh have investigated the factors associated with antibiotics prescription for these childhood diseases.

Objectives: We aimed to explore the associations between prescription of antibiotics by qualified doctors and socioeconomic characteristics of the children under 5 years with ARI or/and diarrhea or/and fever.

Methods: We used a most recent data from the nationally representative Bangladesh Demographic and Health Survey conducted in 2014. Mothers of the children were asked the name of antibiotic drugs (ie, Beta Lactum, Macrolides, Quinolone, Cephalosporin, Cotrimoxazole, Gentamycin & Metronidazole) for ARI, diarrheal diseases and fever used during 2 weeks prior to the survey. If the mothers did not know the name of the drug, they were asked to show the drug or the

packaging of the drug. Moreover, mothers were asked whether the antibiotics prescribed by a qualified doctor or not and sources of the antibiotics. We considered several potential factors such as parent's education, occupation and economic condition, place of residence, source of drug, mass media access, religion etc. Data were analyzed using a survey logistic regression.

Results: Out of 8092 children under 5 years of age, 3135 (38.7%) were suffering from ARI or fever or diarrhea and among them, 8.5% or 9% or 8.7% were treated by antibiotics, respectively. The antibiotics prescribed by a qualified doctor was only 14.2% and about 42% drugs were collected from the pharmacy, odds ratios (OR) = 1.38 (95% confidence interval [CI]: 1.06-1.79). Factors like parent's higher education, OR = 1.65 (CI: 1.06-2.57), wealthy economic condition, OR = 2.00 (CI: 1.46-2.75) and living in urban area, OR = 1.51 (CI: 1.15-1.99), influenced the antibiotics prescription.

Conclusions: Our study shows that the antibiotics prescription by a qualified doctor is very low level in Bangladesh. To increase the appropriate use of antibiotics including prescription by a qualified doctor and avoid the risk of antibiotic resistance, we recommend to an emphasis on better regulation of the use of antibiotics, education and improvement of socioeconomic conditions.

858 | Clinical effectiveness of high-dose versus standard-dose influenza vaccination among veterans health administration patients: A crossover study

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Background: Each influenza season is unique, but the 2011-2012 and 2012-2013 seasons, by some of the most important measures from the Centers for Disease Control and Prevention (CDC) such as predominant strain (both A [H3N2]) and vaccine effectiveness (47% and 49%, respectively), were remarkably similar. They also coincided with the introduction of a high-dose influenza vaccine (HD) in adults aged 65 or older, while the standard-dose vaccine (SD) remained mainstream.

Objectives: In this study, we assessed the relative vaccine effectiveness (rVE) of HD vs SD in a Veterans Health Administration (VHA) population.

Methods: We conducted a crossover observational study of veterans aged 65 or older who received HD vaccine in one season and SD vaccine in another during the 2011-2012 and 2012-2013 seasons. Using this self-controlled design, we were able to effectively control for confounders that were stable over time, even those unmeasured or unknown. VHA electronic medical records and Medicare claims data were used to capture as completely as possible the study exposure

(HD/SD), outcome (hospitalizations due to pneumonia or influenza, cardio-respiratory hospitalizations, and all-cause hospitalizations), patient demographics and clinical characteristics. We applied a Generalized Estimating Equations (GEE) Poisson model for repeated measures, accounted for clustering at both the patient and facility levels. An autoregressive of first order correlation structure was applied. Estimates of rVE were obtained from the GEE model, and confidence intervals (CI) were calculated using a robust covariance estimator for the estimated effects.

Results: 14 190 patients switched between SD and HD from one season to the next; 5121 patients received HD in 2011-2012 season and then switched to SD in the following 2012-2013 season; and 9069 patients received HD in 2012-2013 season, but selected SD in the prior 2011-2012 season. Patients who received HD vs SD were similar in demographic characteristics (age, sex, race, and regions), morbidity profiles and health care utilization. The multivariate adjusted rVE estimate of HD was 22% (95 CI, 11%-31%) against hospitalizations due to pneumonia or influenza, 10% (95 CI, 2%-17%) against cardio-respiratory hospitalizations, and 11% (95 CI, 8%-15%) against all-cause hospitalizations.

Conclusions: Among elderly veterans, HD is more effective than SD in protecting against hospitalizations, especially those due to pneumonia or influenza.

859 | Advance system testing: Vaccine benefit studies using multi-country electronic health data: An example on pertussis vaccination

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Background: The Accelerated development of vaccine benefit-risk collaboration in Europe (ADVANCE), a private-public consortium, implemented and tested a distributed network system for the generation of best evidence on the benefits-risks of marketed vaccines in Europe.

Objectives: We tested the system by estimating the incidence rate (IR) of pertussis and complications following pertussis in children vaccinated with acellular (aP) and whole cell (wP) pertussis vaccine.

Methods: Data from 7 electronic databases from 4 countries (Denmark: AUH and SSI, Spain: SIDIAP and BIFAP, UK: THIN and RCGP and Italy: Pedianet) was included in a retrospective cohort analysis. The exposure was defined as any pertussis vaccination (aP or wP). The exposure time started 14 days after the first dose. All children receiving any pertussis vaccine were eligible except those switching from one type to the other, or with unknown type. The study period was January 1990 to December 2015. The outcomes of interest were confirmed or suspected pertussis and complications such as pneumonia and generalized convulsions within 30 days and death within 90 days of disease onset.

Results: The cohort comprised of 2 938 973 children ≤ 5 years of age for the period of 1990-2015. Data on aP vaccination was available in all databases while only 4 databases could provide data on wP vaccination. The IR (per 100 000 person-years) for pertussis ranged between 0.15 (95% CI: 0.12; 0.19) and 1.15 (95% CI: 1.07; 1.23), and the trend over time was consistent with those observed from national surveillance databases for confirmed pertussis. IR of pertussis decreased with the number of doses of vaccines received: eg: the incidence rate after one dose of aP ranged from 0.40 to 2.83 vs post-dose 3 from 0.03 to 0.68. Complications of break-through cases were rare (93 pneumonia, 8 generalized convulsions, and no death) and their relative risk (vs non-pertussis) could not be reliably estimated.

Conclusions: The study demonstrated the feasibility of ADVANCE data distributed system to estimate the IRs of pertussis and its complications. The trends over time were coherent with those from national surveillance databases showing external validity. Larger sample sizes and inclusion of more data sources would provide additional power.

860 | Physicians' intention to prescribe the HPV vaccination later than recommended: A systematic review and meta-analysis

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Background: Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide and is the primary cause of cervical cancer, as well as several other cancers. An effective vaccine is

available that prevents the majority of HPV strains, and the CDC recommends routine vaccination beginning at age 11 or 12 years.

Objectives: The main objective of this study was to synthesize (and assess heterogeneity within) the existing evidence regarding the reported proportion of physicians who intended to prescribe the HPV vaccine.

Methods: The MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines were used throughout the design, execution and reporting of this study. A systematic search of EMBASE, PsycInfo, Medline, PubMed, and Google Scholar was performed using relevant medical subject heading (MeSH) terms.

Proportions were abstracted and reviewed independently by three reviewers, with disagreements settled by consensus. All meta-analyses used random effects models with restricted maximum-likelihood (REML) to estimate between study variance. Subgroup analysis and meta-regression analysis were performed to investigate and reduce heterogeneity.

Results: There were six studies (providing a total of 10 data points) on physician endorsement or recommendation of the HPV vaccine. The proportion of physicians who intended to prescribe the HPV vaccination ranged from 66% to 97%. However, there was a high degree of heterogeneity (overall $I^2 = 96.4\%$) between studies. A significant amount of heterogeneity could be attributed to the age of intended recipient, with physicians more likely to recommend vaccination to older girls: 73% (95% CI: 68%-78%), 89% (95% CI: 76%-95%), and 95% (95% CI: 84%-98%) for recipients aged <14 years, 14-17 years, and greater than 17 years, respectively ($p = 0.0014$). Still, heterogeneity was high within these age categories and specific estimates of pooled effects should be used with care.

Conclusions: Our findings show that physicians are very likely to recommend the HPV vaccine overall and less likely to recommend the vaccine for those aged less than 14 years, which is contrary to the CDC recommendations. This could potentially lead to reduced intention to vaccinate and reduced adherence to vaccination schedule. Furthermore, studies have shown that catch-up vaccinations later in life may have a reduced utility.

861 | Varicella vaccine safety surveillance using a tree-based scan statistic

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Background: National childhood varicella immunization program in Taiwan was initiated in 2004, providing one dose of varicella vaccine to children aged 12-15 months. Postlicensure safety surveillance primarily focused on spontaneous reports of adverse events.

Objectives: To explore acute medical events during risk windows after varicella vaccination by the tree-based scan statistics.

Methods: This nationwide study was conducted with the linkage of the Taiwan National Health Insurance data and National Immunization Information System from 2004 January through 2014 September. The study population was 12- to 36-month children who received varicella vaccine, excluding those coadministered with other vaccines on the same day. We evaluated incident ICD-9-CM diagnoses occurring 1-56 days after the first dose of varicella vaccination, and classified them in hierarchical levels (nodes) by the Multi-Level Clinical Classifications Software (MLCCS). We used a data mining tool, TreeScan, in conditioned self-controlled tree-temporal scan to examine MLCCS groups and temporal risk windows that were 2-28 days in length, starting in 1 to 28 days, and ending in 2 to 49 days after vaccination. The comparison period consisted of days in the 56-day follow-up period that were not in the risk windows. We categorized nodes with the same third level into a single set as a signal.

Results: Of the 2 150 135 varicella vaccinees, 1 277 535 (59.4%) received single varicella vaccine on the same day. Among them, TreeScan identified 13 alerting nodes with significant clustering features. The nodes were categorized into five signals: fever at day 1-4 (ICD 780.6, relative risk (RR) 1.31, $p = 0.001$), acute gastritis at day 1-2 (ICD 535.00, RR 1.79, $p = 0.001$), varicella infection without mention of complication at day 1-9 (ICD 052.9, RR 4.99, $p = 0.001$), other upper respiratory infections at day 1-6 (Node 8.1.5, RR 1.42, $p = 0.001$), and nausea and vomiting at day 1-2 (Node 17.1.6, RR 1.55, $p = 0.011$). All these signals and their risk windows have been identified in previous clinical trials and surveillance studies. No alerting nodes were observed 2 weeks after vaccination.

Conclusions: Unexpected acute medical events were not observed in cluster after varicella vaccination in Taiwan.

862 | Where do people get vaccinated? Trends in influenza immunization by provider setting

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Background: Traditionally, vaccinations have been administered in the primary care setting. However, since the passage of laws allowing pharmacists to immunize, the subsequent impact on changes in where vaccines are given remain unknown.

Objectives: To describe trends in influenza vaccination by provider setting among adults in the United States.

Methods: We identified adult influenza vaccinations in the Optum Clinformatics™ Data Mart. Influenza vaccinations were identified from procedure codes between 2010 and 2015. Enrollees were categorized as covered under either a commercial plan or a Medicare Advantage plan. Secular trends of administration rates were assessed by provider setting with joint point analyses. Geographical variations were also assessed.

Results: Among the commercially-insured population, we identified 5 552 997 influenza vaccine administrations (36% pharmacy, 64%

primary care) among 3 400 173 enrollees. The total number of vaccination increased by 316 862 (46% change) from 2010 to 2015. Over the study period, the rate of pharmacy-based influenza vaccination increased significantly from 20% in 2010 to 42% in 2015 (slope 4.3 ± 0.8 , $p = 0.005$). In Nevada and Arizona, pharmacy-based vaccination was as common as vaccination in the primary care setting (pharmacy-based, 51% in both states). Whereas, vaccination in the primary care setting was almost universal in other states, such as North Dakota (95%) and Minnesota (95%). Among Medicare Advantage enrollees, we identified 3 792 217 vaccinations (3% pharmacy, 97% primary care) among 1 901 766 enrollees. The total number of vaccinations increased by 186 730 (35% change) from 2010 to 2015. While the number of administrations increased in the primary care setting (91% to 99%, slope 1.4 ± 0.4 , $p = 0.03$), pharmacy-based vaccinations declined (9% to 1%, slope -1.4 ± 0.4 , $p = 0.03$). Four states and the District of Columbia had greater than 90% of administrations in the primary care setting (Hawaii 99.6%, Minnesota 99%, South Dakota 99%, and North Dakota 99%). Pharmacy-based administrations only exceeded 10% in Puerto Rico (20%), California (18%), and Nevada (12%).

Conclusions: While pharmacy-based immunization increased significantly among commercially-insured adults, the opposite trend was observed among older adults enrolled in a Medicare Advantage plan. Additionally, substantial geographic variation in pharmacy-based immunization was observed, even though influenza immunization by pharmacists has been allowed in all states since 2010.

863 | Developing the infrastructure to assess pregnancy outcomes following vaccination: Influenza vaccines and spontaneous abortion as a use case

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Background: Because data on the safety of vaccine use during pregnancy are limited and clinical trials typically exclude pregnant women, post-market surveillance is needed.

Objectives: To assess the feasibility of assessing pregnancy outcomes following vaccination with Sentinel by (1) validating algorithms for spontaneous abortion (SAB) and gestational age in pregnancies ending in live births and (2) developing a case-time control (CTC) approach to study influenza vaccines and SAB.

Methods: The study population included pregnant women ages 18-34 from two claims-based Data Partners who received influenza vaccine in the 2008-2009 or 2010-2011 seasons. Pregnancies ending in a

SAB or live birth were identified using algorithms. Because we intended to match controls (live births) to cases (SABs) by pregnancy start in the CTC, an algorithm was used to identify pregnancy start in controls. Algorithms were validated with medical record review.

Using the same cases and controls, a CTC design was implemented to examine risk of SAB following influenza vaccine in (1) the 1-28 days post-vaccination or (2) any time after vaccination occurring from -4 through 4, 2 through 5, or 6 through 11 weeks gestation.

Results: Of the 140 potential SAB cases identified in claims data, 97 had charts available and 53 (55%) met case confirmation criteria (ie, documentation of intrauterine pregnancy and pregnancy loss). The positive predictive value (PPV) did not vary by maternal age, code type (procedure vs. diagnosis code), or medical care setting. Of the 185 potential controls identified in claims data, 133 had medical charts available to confirm pregnancy start. The algorithm to assign pregnancy start in pregnancies ending in live births was accurate within ± 14 days in 95% of pregnancies. For the exploratory CTC design, we observed an odds ratio of 0.49 (95% CI 0.15 to 1.60) for occurrence of SAB within 1-28 days of vaccination. The odds ratios associated with vaccination from -4 through 4, 2 through 5, and 6 through 11 weeks gestation were 0.42 (95% CI 0.05, 3.61), 0.84 (0.19, 3.79), and 1.74 (0.46, 6.63), respectively.

Conclusions: Although the PPV of the pregnancy start algorithm was excellent, the moderate PPV of the SAB algorithm suggests that rigorous validation is needed to study pregnancy outcomes with Sentinel. Using a CTC approach, we successfully implemented a use case (influenza vaccines and SAB), further supporting the feasibility of conducting surveillance of pregnancy outcomes.

864 | Post-authorization safety study (PASS): Cohort event monitoring for CYD-TDV dengue vaccine

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Background: Dengue is a major public health concern in many tropical and subtropical regions of the world. CYD-TDV, a live, attenuated, tetravalent dengue vaccine, is indicated for the prevention of dengue caused by serotypes 1, 2, 3, or 4 in individuals 9 up to 60 years of age living in endemic areas.

Objectives: Our post-authorization safety study (PASS) aims to evaluate the safety profile of CYD-TDV when used in real-world immunization settings, as part of the global Risk Management Plan of the vaccine.

Methods: We report initial progress of this non-interventional, prospective, multinational cohort event monitoring study. Active safety surveillance occurs over 5 years after receipt of the first dose of CYD-TDV. It is based on follow-up contacts with all study participants, at least quarterly, and up to every 6 weeks (for the first 4.5 months after each vaccine dose). Our interim results are based on quarterly descriptive analyses of collected safety data at individual level. For selected AEs that may occur during the first 4.5 months after each vaccine dose and for which a risk period may be defined (eg, allergic reactions), self-controlled case series methods will allow to measure any association with vaccination at population level.

Results: As of December 7, 2017, 12 573 vaccinees have been enrolled: 10 222 in the Philippines (including 10,037 children vaccinated in a public campaign in Cebu); 2,291 in Brazil (including 2,170 9-45 year-olds vaccinated in a public program in the State of Parana, 58% of whom are male); and 60 in Mexico (private market). About half of the participants are 9 to 11 years old (average: 14.5 years), 72.4% of the participants had at least one follow-up contact and 48.4% at least 2 follow-up contacts after the first vaccination; 2.7% of the participants have received 2 doses. Overall, the study identified: 1.3% off-label use (inappropriate age); 3.2% misuse (non-compliance to vaccination schedule); 7 allergic reactions (including anaphylactic reactions); 6 dengue cases (non-severe based on WHO 2009 criteria); 3 cases of seizures (with an alternative etiology); and 49 other SAEs (including 36.7% from "Infections and Infestations" System Organ Class, and, among the 2170 participants from Parana campaign, no SAEs related to vaccination at individual level).

Conclusions: As of December 7, 2017, our study has not shown any new safety signal as compared with the known profile of the vaccine.

865 | Near real-time safety surveillance of three seasonal influenza vaccines in Europe during influenza season 2017/18

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Background: As influenza vaccine compositions may change annually, pharmacovigilance systems must rapidly detect and evaluate potential new safety concerns at the start of each influenza season. This is especially important for new vaccines, such as the quadrivalent influenza vaccine where post-market safety needs to be confirmed. As per the European Medicines Agency requirement, rapid assessment of safety data for influenza vaccines was conducted within two months.

Objectives: To estimate reporting rates of suspected adverse reactions (ARs) following routine influenza vaccination with Intradermal Trivalent Inactivated Influenza vaccine thiomersal free (TIV-ID), Trivalent Inactivated Influenza vaccine thiomersal free (TIV), or Quadrivalent Inactivated Influenza vaccine thiomersal free (QIV).

Methods: Enhanced passive safety surveillance (EPSS) was implemented at the start of the Northern Hemisphere (NH) 2017/18 influenza season in the United Kingdom and Ireland. Individuals were vaccinated according to national recommendations. Vaccinees who received TIV-ID (from 60 years), TIV (from 6 months), or QIV (from 3 years) in routine practice were eligible to participate. For each vaccine brand, real-time data on usage was collected at the site level. Vaccinators provided a safety report card (SRC) to vaccinees to report suspected ARs, with an emphasis on those occurring in the 7 days post-vaccination, via a dedicated phone number. Reporting was stimulated but remained spontaneous in nature. Vaccinee and AR reporting rates were derived and compared with those from the NH 2016/17 EPSS when possible.

Results: A total of 979 TIV-ID, 1005 TIV, and 957 QIV SRCs were distributed in 18, 42, and 43 days, respectively. Among TIV and QIV vaccinees, only 2.6% and 1% were younger than 18 years. The majority of suspected ARs reported occurred within 7 days post-vaccination. Overall vaccinee reporting rates were 2.9% (95% confidence interval [CI]: 1.82%, 3.90%), 1.4% (95% CI: 0.67%, 2.11%), and 2.1% (95% CI: 1.18%, 3.00%) with associated suspected AR reporting rates of 7.9%, 4.0%, and 5.9% for TIV-ID, TIV, and QIV, respectively. Only 2 (0.2%) serious suspected ARs occurred with TIV-ID. Vaccinee and AR reporting rates were in line with those reported from the NH 2016/17 EPSS.

Conclusions: The reported suspected ARs and frequencies observed were consistent with the safety profiles of the 3 vaccines. These data provide further reassurance to stakeholders on the safety of each vaccine, particularly for QIV.

866 | Anticoagulant treatment in combination with antiplatelet therapy in patients with coronary artery disease and atrial fibrillation: A comparative effectiveness and safety study in Valencia Spain

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Background: There is not certainty about the optimal long-term anti-thrombotic therapy of patients diagnosed with atrial fibrillation (AF) and coronary artery disease (CAD), but commonly, an antiplatelet agent (APT) is added to oral anticoagulation.

Objectives: To compare the effectiveness and safety of treatment with oral anticoagulants (OAC) alone and in combination with APT in patients with AF and CAD who had not previously taken OAC.

Methods: This is a population-based retrospective cohort study using electronic health records from the Valencia Region, Spain (covering 5 million inhabitants, ~12% of the Spanish population). We included all new users of OAC from November 2011 to December 2015, with diagnoses of AF and myocardial infarction (MI) or unstable angina. We used inverse probability of treatment weighted Cox regression models to compare OAC vs OAC + ACT for mortality and

hospitalization for acute coronary syndrome (ACS), ischemic stroke, gastrointestinal (GI) bleeding, major GI bleeding and intracranial hemorrhage.

Results: We included 4119 new users of OACs with AF and CAD, 45.6% were treated with OACs alone. The weighted incidence of mortality was 130 per 1000 person-years for patients treated with OAC, and 111.9 for patients treated with OAC + APT. The weighted incidences of GI and major GI bleeding for patients treated with OAC were 11.9 and 6.0, while for patients treated with OAC + APT were 14.3 and 6.8, respectively. The weighted incidence for intracranial hemorrhage was 5.9 for patients treated only with OAC and 6.7 for patients treated with OAC + APT, while that of ischemic stroke was 14.8 for patients treated with OAC and 24.2 for patients treated with OAC + APT. The weighed incidence of ACS was 31.6 for patients treated with OAC and 60.3 for patients treated with OAC + APT. Compared with patients that were treated with OAC alone, patients treated with OAC + APT had an increased risk of ACS (HR: 1.6; 95% CI: 1.2-2.2). We did not find statistically significant differences in risks for the rest of the outcomes studied.

Conclusions: In this population-based study, patients with AF and CAD, treated with both OAC and APT showed a higher risk of ACS. Despite our attempt to reduce bias, residual confounding (eg, disease severity) could explain the results of this study. Further research is needed to assess treatment options with their clinical implications in patients with AF and CAD.

867 | Statin use at the time of intra-abdominal surgery is associated with reduced risk of post-operative adhesion-related complications

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Background: Adhesion-related complications (ARCs), including small bowel obstruction (SBO) and need for lysis of adhesions (LOA), are common complications of intra-abdominal surgery. Statins have been shown to inhibit adhesion formation in murine models. This has not been assessed in humans.

Objectives: To assess the impact of statin use on post-operative adhesion-related complications.

Methods: Design and setting: We performed a retrospective cohort study using The Health Improvement Network (THIN), a population-representative dataset with >11 million patients and 75 million person-years of data. THIN has been previously validated for medical comorbidities, medications, smoking, surgeries, SBOs, and LOAs. Individuals 18 or older with an incident intra-abdominal surgery were eligible for inclusion. Those with inflammatory bowel disease or an ARC outcome prior to incident surgery were excluded. Exposures: The primary exposure was statin use at the time of surgery. Main

Outcome: The primary outcome was an ARC, consisting of a diagnostic code for SBO, LOA, or adhesions occurring after surgery. Statistical Analyses: Cox proportional hazards models were used to measure the association between statin use and adhesion-related complications, adjusting for gender, age, surgery type, hypertension, hyperlipidemia, tobacco use, obesity, or primary or metastatic cancer involving the peritoneum. We utilized backwards elimination of non-significant covariates not modifying the HR for statin use by >10%. Sensitivity analyses examined pre-operative statin discontinuation and fibrates use.

Results: 148 601 individuals met inclusion criteria. 2060 (1.4%) experienced an adhesion-related complication, of which 1489 were SBOs. Statin use at the time of surgery was associated with a decreased risk of ARCs (adj. HR 0.84, 95% CI 0.73, 0.96) and SBO (adj. HR 0.83, 95% CI 0.72, 0.96). Increasing age, tobacco use, bowel-specific surgery, and malignancy were associated with an increased risk of ARC, while obesity was associated with a decreased risk. Statin use prior to but not at the time of surgery (adj. HR 1.13, 95% CI 0.85, 1.50) and fibrates use (adj. HR 1.10, 95% CI 0.65, 1.87) were not associated with ARCs.

Conclusions: In this study, statin use at the time of intra-abdominal surgery was associated with a reduced risk of adhesion-related complications. Future studies are warranted to explore the role of statins in reducing the rate of these complications.

868 | Clinical events after discontinuation of β -blockers in patients without heart failure optimally treated after acute myocardial infarction: A cohort study on the French health care databases

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Background: β -blockers have been among the first medications shown to improve outcomes after acute myocardial infarction (AMI). With the advent of reperfusion therapy and other secondary prevention medications, large-scale experience after AMI in the contemporary era is lacking.

Objectives: To evaluate the impact of β -blocker discontinuation beyond the acute stage in a cohort of patients without heart failure, revascularized and optimally-treated after AMI.

Methods: Using the French Healthcare databases, 73 450 patients (<80 years of age), admitted for AMI in 2007-2012, without acute coronary syndrome (ACS) in the previous 2 years and no evidence of heart failure, having received optimal treatment with myocardial revascularization and all recommended medications in the 4 months following index admission and not having discontinued β -blockers before 1 year, were followed for 3.8 years on average. β -blocker discontinuation was defined as 4 consecutive months without

exposure. If β -blocker treatment was resumed later on, follow-up was stopped. Both the risk of the composite outcome of death or admission for ACS and the risk of all-cause mortality were assessed in relation with β -blocker discontinuation over follow-up. Adjusted hazard ratios (aHR) were estimated using marginal structural models accounting for time-varying confounders affected by previous exposure. A similar analysis was performed with statins.

Results: Of 204 592 patient-years, 12 002 (5.9%) discontinued β -blocker treatment. For β -blocker discontinuation, the aHR for death or ACS was 1.17 (95% confidence interval 1.01-1.35); for all-cause death, the aHR was 1.13 (0.94-1.36). In contrast, for statin discontinuation, the aHR for death or ACS and for all-cause death were 2.31 (2.01-2.65) and 2.57 (2.19-3.02), respectively. The estimated effect of β -blockers discontinuation was modified by the type of AMI and the presence of asthma/chronic obstructive pulmonary disease at baseline.

Conclusions: In routine care of patients without heart failure, revascularized and optimally-treated after AMI, discontinuation of β -blockers beyond 1 year after AMI was associated with an increased risk of death or readmission for ACS, while statistical significance was not reached for the association with all-cause mortality. A contemporary randomized clinical trial is needed to precise the role of β -blockers in the long-term treatment after AMI.

869 | Comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on overall mortality and major cardiovascular diseases in primary prevention: Population-based nationwide cohort study based on French health insurance data (SNIIRAM)

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Background: Both American and European guidelines stated that angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are suitable and recommended, among other drugs, for the initiation of antihypertensive treatment. However, data available raised question when comparing ARBs with ACEIs.

Objectives: To compare overall mortality in hypertensive new users of ARBs and ACE inhibitors in a primary prevention setting.

Methods: Design - Population-based nationwide retrospective cohort study with at least 5 years of follow-up. Setting - Comprehensive French Health Insurance Data (SNIIRAM/DCIR) linked to data from French hospital discharge database (PMSI), France. Participants - Subjects aged 50 or above, identified as ARB or ACE inhibitor new users in 2009 (at least one delivery during the year and no such delivery in 2008). Exclusion criteria included history of cancer, cardiovascular

disease or chronic renal insufficiency. Main outcome measure concerned overall mortality. Secondary outcome included cause of death, as well as major cardiovascular non-fatal events (myocardial infarction, ischemic stroke, intracranial hemorrhage, heart failure).

Results: Out of 407 815 eligible subjects, 233,682 (57%) were ARB users; two-third had no previous exposure to antihypertensive drug. Based on SITPW Cox model with ITT-like principle, ARB new user group had a better survival (HR: 0.878, 95% CI, 0.875 to 0.880); analysis of causes of death is planned for second quarter of 2018. ARB new user group was at lower risk for major cardiovascular events (HR: 0.886, 95% CI, 0.885 to 0.888). Statistically significant quantitative interactions were detected in almost all subgroups (for instance diabetes, lipid-lowering drug use and cardiovascular risk level). Different ways in handling propensity score led to very similar estimates. On-treatment (censure at the time of stop or switch the initial drug) based analyses showed lower risk estimates.

Conclusions: Considering subgroups analyses, ARBs were better than ACE inhibitors in non-diabetic subjects and in those subjects with a low/medium cardiovascular risk profile. <!--EndFragment-->

870 | Anticoagulants in patients with atrial fibrillation after intracranial hemorrhage

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Background: Patients with non-valvular atrial fibrillation (NVAF) who survive an intracranial hemorrhage (ICH) have an increased risk of ischemic stroke and systemic emboli (IS/SE).

Objectives: We investigated whether starting oral anticoagulants (OAC) among older NVAF patients after an ICH was associated with a lower risk of IS/SE and mortality, but offset by an increase in major bleeding.

Methods: Cohort study assembled from administrative data from the Quebec RAMQ and Med-Echo databases. We identified older adults (>65 years) with NVAF from 1995 to 2014 who were discharged alive. All patients with incident ICH were included. Patients were categorized as no, partial or continuous OAC exposure (Mean Possession Ratio (MPR) $\geq 90\%$). Outcomes included IS/SE, all-cause mortality, recurrent ICH and other major bleeding after a quarantine period of 6 weeks. Crude events rates were calculated at 1-year of follow-up, and Cox proportional hazard models were used to assess adjusted hazard ratios (AHRs). We conducted analyses by calculating propensity scores (PS) to better match patients and assemble cohorts that would be balanced on specific baseline characteristics.

Results: Cohort of 703 NVAF patients with ICH aged 82.8 years on average. The rate (per 100 person-years) for IS/SE, mortality, ICH and major bleeding were 2.4, 36.2, 10.6 and 1.9, respectively, for the no OAC group; and 1.1, 3.2, 1.1 and 2.2 for continuous exposure to OAC. The AHR for IS/SE and death was 0.11 (0.05-0.28), 0.09 (0.01-0.63) for recurrent ICH and 0.93 (0.19-4.5) for major bleeding comparing continuous exposure to OAC to non-exposed. Similar results were also observed for the propensity-matched analyses.

Conclusions: Initiating OAC after ICH in older individuals with NVAf is associated with a reduction of IS/SE and mortality as well as recurrent ICH supporting its use after ICH. However because of the observational nature of the study and the residual risk for unmeasured confounding future randomized controlled trials are required to confirm our results.

871 | Statins for the primary prevention of cardiovascular disease in low cardiovascular risk Koreans

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Background: Although statin therapy has been considered an important strategy for the primary prevention of cardiovascular diseases (CVDs), various unanswered questions remain regarding its efficacy in low-risk populations. Since Koreans belong to a low ischemic mortality group, studies on the use of statins for the primary prevention of CVD in low-risk Korean populations could offer a novel perspective on this issue.

Objectives: To investigate whether statin use protects against CVD in relatively low-risk Korean populations.

Methods: Using the Korean National Health Insurance Health Examination Cohort, subjects aged between 40 and 65 with total cholesterol level more than 240 mg/dL without any history of CVD were divided into statin users and non-users. Primary outcome was the major adverse cardiovascular event (MACE) and secondary outcome was all cause mortality and the occurrence of new onset diabetes mellitus (DM). We performed three different types of hazard ratio to minimize potential confounding and immortal bias.

Results: Among 25 253 subjects, 4231 (16.75%) experienced a MACE, and the incidence of MACEs was higher (HR 1.31, 95% confidence interval [CI] 1.24-1.38), all-cause mortality was lower (HR 0.69, 95% CI 0.53-0.89), and the occurrence of new-onset DM was higher among statin users (HR 1.80, 95% CI 1.71-1.88) than among non-users. Additionally, the HRs from the three types of Cox models were similar to the HR from the unadjusted model.

Conclusions: Statin therapy in relatively low-risk Korean populations may not be beneficial for the primary prevention of CVD.

872 | Comparative effectiveness of statin and renin-angiotensin-aldosterone system blocker combination therapy in patients with coronary heart disease: A nationwide population-based cohort study

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Background: Patients with coronary heart disease (CHD) frequently have hypertension and hyperlipidemia concurrently. Thus, it is reasonable to assess statin-renin-angiotensin-aldosterone system (RAAS) blocker combination therapy and compare different RAAS blockers simultaneously.

Objectives: To evaluate whether angiotensin II receptor blockers (ARBs) are associated with reduced risk of major adverse cardiovascular and cerebrovascular events (MACCEs) compared with angiotensin-converting enzyme inhibitors (ACEIs) when used in combination with statins in patients with established CHD.

Methods: We conducted a population-based cohort study utilizing Korean National Health Insurance Service-National Sample Cohort. Statin-ACEI and statin-ARB cohorts were matched using propensity-score model. Incidence and incidence rate were calculated to estimate differences between two cohorts. Hazard ratios (HRs) and 95% confidence interval were estimated using Cox proportional hazard model.

Results: A total of 6577 adult patients (1870 in the statin-ACEI and 4707 in the statin-ARB cohorts) were identified from the database. After the matching, 1838 patients remained in the each cohort. The incidences of MACCE were 19.9% and 14.7% and the incidence rates were 11.7 and 8.1 per 100 person-years in the statin-ACEI and statin-ARB cohorts, respectively. The risk of MACCE was significantly lower in the statin-ARB cohort (adjusted HR 0.69; 0.59-0.81).

Conclusions: In patients who received statin-ARB, MACCE was less likely to occur. Similar trends were seen in cardiovascular mortality and recurrent MI, but not in stroke. Further research is warranted to validate our findings and to address whether a particular statin-ARB combination is more effective than other combinations.

873 | Comparative effectiveness and safety of non-vitamin K oral anticoagulants and acenocoumarol in patients with atrial fibrillation: A propensity-weighted cohort study

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Background: Acenocoumarol is a vitamin-K-antagonist (VKA) primarily used as oral anticoagulant in several countries. Differences between coumarinics might theoretically affect effectiveness and safety, but there is a paucity of studies assessing non-vitamin K oral anticoagulants (NOAC) in relation to VKAs different to warfarin.

Objectives: To compare the effectiveness and safety of NOAC and acenocoumarol in patients with non-valvular atrial fibrillation (NVAf) in real-world clinical practice.

Methods: Population-based retrospective cohort study. All new users of OAC from Nov 2011 to Dec 2015 with NVAf were included (N = 42151). Data were obtained by linking several health electronic records of the Valencia Region, Spain. Incidence rates were estimated.

We used inverse probability of treatment weighted cox analysis to overcome biases when assessing the risk of several outcomes on effectiveness and safety of each NOAC compared with acenocoumarol. Sensitivity analyses stratifying on age, sex and risk according to scores were performed. Furthermore, we did a sub-analysis switching the index date from prescription to dispensation.

Results: The weighted incidence of ischemic stroke was 10.26, 16.82, 10.57, and 11.14 per 1000 person-years for acenocoumarol, apixaban, dabigatran and rivaroxaban, respectively. Regarding mortality, the incidence was 76.48, 80.15, 63.1, and 78.56 per 1000 py; that of gastrointestinal (GI) bleeding was 8.05, 5.74, 8.31, and 7.65 per 1000 py and that of major GI bleeding was 4.35, 2.51, 3.15, and 3.67 per 1000 py. Intracranial haemorrhage had an incidence of 7.17, 4.67, 2.17 and 3.93 per 1000 py. We did not find significant differences in risk of mortality, ischemic stroke or major GI bleeding. However, we found an increased risk of GI bleeding for apixaban (HR: 0.55, 95% CI: 0.31-0.97) and a decreased risk of intracranial haemorrhage for dabigatran (HR: 0.32, 95% CI: 0.19-0.54) and rivaroxaban (HR: 0.54, 95% CI: 0.35-0.85) as compared with acenocoumarol. Results were consistent in all sub-analyses.

Conclusions: In this large population-based cohort, no differences were found in the effectiveness and safety profiles of NOAC compared with acenocoumarol, overall. However, apixaban showed a higher risk of gastrointestinal bleeding, while dabigatran and rivaroxaban showed lower risk of intracranial haemorrhage as compared with acenocoumarol.

874 | Reductions in death, stroke, and myocardial infarction: The comparative effectiveness of 4th line antihypertensive drugs in resistant hypertension

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Background: Clinical trial evidence now exists to support the use of aldosterone antagonists (AA) as a 4th line antihypertensive treatment in resistant hypertension, although clinical outcomes have not been assessed in any trials to date.

Objectives: To compare the effect of 4th line antihypertensive drugs, on clinical outcomes, in a routine care population with resistant hypertension.

Methods: We conducted a population based cohort study using the Clinical Practice Research Datalink: a repository of electronic health records from UK primary care. In patients concurrently using ace-inhibitors/angiotensin receptor blockers, calcium channel blockers and a diuretic we identified those who were prescribed a 4th line antihypertensive drug (AA, beta-blocker, alpha-blocker, amiloride + other). We compared the primary outcome (composite of death, stroke and myocardial infarction) between patients on different 4th line drugs, using AA as the reference group. Secondary outcomes included heart failure, stroke, myocardial infarction, end stage renal disease and

death. Adverse events were gynecomastia and hyperkalaemia. We used Cox proportional hazards models, adjusted with propensity scores, to calculate hazard ratios and 95% confidence intervals (HR, 95% CI).

Results: Overall, 18 694 patients were included. Mean age was 68.4 years (SD 12.0) and 48.3% were female. In propensity score adjusted analyses, the primary outcome was reduced for users of alpha-blockers (HR 0.82, 95% CI 0.71-0.94), beta-blockers (HR 0.89, 95% CI 0.79-1.00) and amiloride + others (HR 0.85, 95% CI 0.74-0.98) versus AA. For some cardiovascular secondary outcomes there was a non-significant trend towards increased hazard for users of alpha-blockers, beta-blockers and amiloride + other versus AA. In contrast, a protective effect remained for all-cause death: HR 0.67 (95% CI 0.60-0.75) for alpha-blockers; HR 0.75 (95% CI 0.68-0.83) for beta-blockers; and HR 0.82 (95% CI 0.71-0.95) for amiloride + other versus AA. There was a protective association for hyperkalaemia and gynecomastia for users of alpha-blockers, beta-blockers and amiloride + others versus AA.

Conclusions: For some individual cardiovascular outcomes, AA tended towards a beneficial effect compared with other treatments. By contrast, AA users had an increased hazard for the primary outcome, driven by all-cause death; suggestive of confounding. Further analyses will focus on increased control for confounding.

875 | Effect of evidence-based combination pharmacotherapy for the secondary prevention of cardiovascular disease: Systematic review and meta-analysis

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Background: The combination pharmacotherapy of antiplatelet agents, Angiotensin converting enzyme (ACE) inhibitors, beta-blockers and lipid-modifiers are recommended by international guidelines. However, the information of effectiveness and safety for the Evidence-Based Combination Pharmacotherapy (EBCP) is limited.

Objectives: To determine the effect of EBCP on mortality and Cardiovascular (CV) events in patients with Coronary Heart Disease (CHD) or cerebrovascular disease.

Methods: A systematic review and meta-analysis of observational studies were undertaken in Medline and Embase databases up to October 2017. The reviews were conducted by two people. Cohort and case-control studies were selected that reported on EBCP for secondary prevention in patients with established CHD (defined as myocardial infarction or angina) or cerebrovascular disease (defined as stroke or transient ischaemic attack). EBCP was defined as being

prescribed two or more of the following classes of drug: antiplatelet agents, ACE inhibitors, beta-blockers and lipid-lowering drugs. The main outcomes were all-cause mortality and major CV events (fatal or non-fatal myocardial infarction, angina, stroke or transient ischaemic attack). Meta-analyses were performed based on random effects models.

Results: Of 10 358 studies reviewed, 21 studies (17 cohort studies and 4 case-control studies) met the inclusion criteria, of which 20 were included in the meta-analysis. Comparing EBCP, to either monotherapy or no therapy, the pooled risk ratios were 0.60 (95% confidential interval 0.55 to 0.66) for all-cause mortality, 0.70 (0.62 to 0.79) for vascular mortality, 0.73 (0.64 to 0.83) for myocardial infarction and 0.79 (0.68 to 0.91) for cerebrovascular events. Optimal EBCP (all 4 classes of drug prescribed) had a risk ratio for all-cause mortality of 0.50 (0.40 to 0.64). This benefit became more dilute as the number of different classes of drugs comprising EBCP was decreased—for 3 classes of drug prescribed the risk ratio was 0.58 (0.49 to 0.69) and for 2 classes, the risk ratio was 0.67 (0.60 to 0.76).

Conclusions: EBCP reduces the risk of all-cause mortality and CV events in patients with CHD or cerebrovascular disease. The different classes of drugs comprising EBCP work in an additive manner, with optimal EBCP conferring the greatest benefit.

876 | The effect of indapamide versus bendroflumethiazide for primary hypertension—A systematic review

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Background: Thiazide and thiazide-like diuretics are used to treat arterial hypertension with the aim of reducing the risk of cardiovascular events. In the United Kingdom, the thiazide bendroflumethiazide and the thiazide-like indapamide are the most commonly used. However, the comparative effectiveness of these two drugs is unclear.

Objectives: The primary objective of the review was to compare efficacy of bendroflumethiazide monotherapy versus indapamide monotherapy in primary hypertension. The primary outcomes were all cause mortality and major cardiovascular outcomes. The secondary outcome was effect on blood pressure.

Methods: MEDLINE, EMBASE, CINAHL, The Cochrane Library, HTA Database, ClinicalTrials.gov, EU Clinical Trials Register and Google Scholar were searched. Two review authors independently screened search results, assessed risk of bias and extracted data from included trials using a pre-piloted form. When there was disagreement, a third reviewer was consulted. Randomized trials of hypertension of at least one-year duration were selected. Risk ratio (RR) and mean difference were used in direct and indirect comparisons, which used network meta-analysis.

Results: Only three trials satisfied the inclusion criteria, two comparing bendroflumethiazide against placebo and one comparing indapamide with placebo. Furthermore, there were no long-term studies directly comparing the two drugs. Three short follow-up randomised trials comparing indapamide and bendroflumethiazide were included in a separate analysis with blood pressure as an outcome. No statistically significant difference was found between indapamide and bendroflumethiazide for all deaths (RR 0.82; 95% CI 0.57, 1.18), both cardiovascular and non-cardiovascular deaths (RR 0.82; 95% CI 0.55, 1.20 and 0.81; 95% CI 0.54, 1.22) or all cardiovascular events (RR 0.89; 95% CI 0.67, 1.18). However, indapamide performed worse for stroke (indirect RR 2.21; 95% CI 1.19, 4.11), even though a reduction in RR compared with placebo was observed in both groups. There was no statistically or clinically significant difference between indapamide and bendroflumethiazide in blood pressure reduction (mean absolute difference <1 mmHg).

Conclusions: This review highlights a lack of studies to answer the review question but also a lack of evidence of superiority of one drug over the other. Therefore, there is a clear need for new studies directly comparing the effect of these drugs on the outcomes of interest.

877 | Incidence of effectiveness and safety outcomes in hemodialysis patients with atrial fibrillation on warfarin

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Background: Evidence for long term warfarin use for stroke prophylaxis in hemodialysis (HD) population with atrial fibrillation (AF) has been controversial. Current observational studies using claims database do not reflect use of low cost generics paid out of pocket, anticoagulation levels or the high competing risk of death typical in HD patients. International normalized ratio (INR) is a more sensitive measure of warfarin use than pharmacy claims data alone.

Objectives: To estimate the cumulative incidence of ischemic stroke (IS), hemorrhagic stroke (HS), bleeding and mortality by levels of achieved INR in a cohort of HD patients with AF.

Methods: We conducted a retrospective cohort study of HD patients with incident AF initiating warfarin using linked data from the US Renal Data System and clinical data from a large US dialysis provider (2007-2011). Adult patients with continuous Medicare part A, B, and D coverage and no warfarin use in a 6-month baseline period prior to incident AF diagnosis were included. Patients were followed from the first INR measurement post-warfarin initiation to end of study period, death or administrative censoring. The first INR measurement was categorized as low (<2.0), target (2.0-3.0) or high (>3.0). Crude cumulative incidence curves accommodating for death as a competing risk and Gray's test were used to evaluate differences in the cumulative incidence function (CIF) of outcomes between INR groups.

Results: We identified 1896, incident AF patients initiating warfarin and having at least 1 INR measurement post warfarin prescription. First measured INR was low for 60%, in target range for 23%, and high for 17% of patients. Overall, the cumulative incidence at 6 months for the entire cohort was 12.4% for IS, 1.8% for HS, 22.1% for bleeding, and 15.3% for mortality. Patients with low INR had the lowest incidence of HS (1.3% vs 2.9% target INR vs 1.9% high INR) and mortality (12.3% vs 18.6% target INR vs 21.1% high INR) at 6 months after the first INR measure. There was strong evidence of difference in the CIF for HS (Gray's test $p = 0.0087$) and mortality ($p = 0.0003$). The crude incidence of ischemic stroke ($p = 0.4033$) and bleeding ($p = 0.3990$) did not differ by anticoagulation levels.

Conclusions: Although the overall incidence of HS was low, it was higher among patients with INR >2.0 . Mortality incidence consistently increased with increasing INR categories. While the overall incidence of IS and bleeding is high, no difference in crude estimates were observed by INR.

878 | Comparative effect of statins on the risk of incident Alzheimer's disease

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Background: Over the last years, statins have been evaluated as potential agents for the prevention and treatment of Alzheimer's disease (AD)

Objectives: Investigate whether fungus derived statins are associated with a lower risk of incident Alzheimer's disease (AD) compared with synthetic statins using real-world clinical practice data

Methods: We identified a population-based retrospective cohort of patients aged ≥ 60 years newly prescribed a statin between January 1, 1994 and December 31, 2012 and followed until March 31, 2015, using the UK Clinical Practice Research Datalink (CPRD). Statins were consecutively classified according to their type, lipophilicity, and potency. For each group, we calculated the crude AD incidence rates per 1000 person-years. Time-dependent Cox proportional hazards models adjusted for propensity scores deciles were used to estimate hazard ratios (HRs) with 95% CIs of incident AD associated with different statin categories

Results: Over the 18-year study period we identified 465 085 statin users, including 7669 patients who developed AD during 2 891 268 person-years of follow-up (incidence rate 2.65 [95% CI: 2.59-2.71] per 1000 person-years). Compared with synthetic, fungus derived statins were associated with an increased risk of AD (HR 1.09, 95% CI: 1.03-1.15). Lipophilic statins also were associated with higher AD risk (HR 1.18, 95% CI: 1.09-1.27) compared with hydrophilic statins, while statin potency did not modify the risk of AD (adjusted HR 1.03, 95% CI: 0.98-1.08). The risk was further reduced in sensitivity analyses

Conclusions: Fungus derived and lipophilic statins were not associated with decreased incidence of AD compared with synthetic and hydrophilic statins. The modest variations in the risk of incident AD observed between statin characteristics needs to be evaluated in future studies on their possible heterogeneous neuroprotective effect

879 | Detection of drug interaction between warfarin and antimicrobial agents based on administration routes and antimicrobial susceptibility to *Bacteroides Fragilis*

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Background: The concomitant use of antimicrobial agents increase the risk of enhancement warfarin anticoagulation ability and bleeding event. To date, the impact of concomitant use of antimicrobial agents according to category, administration route and antimicrobial spectrum on warfarin anticoagulation ability and bleeding event have not been fully clarified in clinical settings.

Objectives: The aim of this study was to evaluate the risk of excessive anticoagulation ability and bleeding associated with concomitant use of antimicrobial agents according to administration route and to susceptibility to *Bacteroides fragilis* in patients receiving warfarin.

Methods: This retrospective study included the patients co-treated with warfarin and antimicrobial agents at Hamamatsu University Hospital (HUH; 613 beds, 1270 outpatients per day) between 2011 and 2015. The PT-INR and bleeding events after the concomitant use of antimicrobial agents were searched from all in- and out-patients using a medical information database developed at HUH, which was called D*D. The warfarin-treated patients were grouped according to concomitant β -lactams or fluoroquinolones that has susceptibility (BL_{sus} or FQ_{sus}) and non-susceptibility (BL_{non} or FQ_{non}) to *Bacteroides fragilis* and that is administrated orally (BL_{po} or FQ_{po}) or intravenously (BL_{iv} or FQ_{iv}). Warfarin-treated patients not receiving antimicrobial agents were grouped as the control group. The prolonged PT-INR was defined as G2 $>1.5 \times$ baseline and G3 $>2.5 \times$ baseline. The comparison of each grade of prolonged PT-INR and bleeding risks between in each groups were statistically analyzed using Fisher's exact test.

Results: A total of 1,185 patients was included. In prolonged PT-INR, the incidence of G2 was higher in BL_{sus} than BL_{non} (29% vs 7.8%, $p < 0.05$). FQ_{sus} has higher incidences of G2 and G3 than FQ_{non} (32% vs 13%, $p < 0.001$ and 13% vs 0%, $p < 0.05$). FQ_{iv} has higher incidences of G2 and G3 than FQ_{po} (35% vs 20%, $p < 0.001$ and 15% vs 5%, $p < 0.05$), respectively. The bleeding risk rate of FQ_{sus} was higher than the control (13% vs 2%, $p < 0.05$).

Conclusions: In conclusion, patients co-treated with antimicrobial agents has susceptibility to *Bacteroides fragilis* in warfarin therapy potentially has the higher risk of excessive anticoagulation ability.

880 | Preventive effect of statins, metformin, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on age-related macular degeneration in the elderly: A nested case-control study

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Background: Statins, metformin, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are drugs used for treating cardiovascular diseases. Recently, the possibility of repositioning these drugs has been suggested for treatment of age-related macular degeneration (AMD) by their pleiotropic effects.

Objectives: To investigate the preventive effect of statins, metformin, ACE inhibitors, ARBs and their combinations on AMD.

Methods: We conducted a nested case-control study using the National Health Insurance Service-Senior Cohort data in Korea between 2002 and 2013. Our cohort included the patients who were diagnosed with diabetes mellitus or cardiovascular diseases in 2002 (Cohort entry = T₀). Within cohort, cases were defined as AMD those who were diagnosed with degeneration of macular and posterior pole (ICD-10 code: H35.3) after cohort entry, and the first date of that diagnosis was defined as index date. One control per case was matched on age, sex, cohort entry and follow-up duration with risk-set sampling method. The exposure was defined as the use of drugs of interest within one year prior to the index date. We used conditional logistic regression to estimate adjusted odds ratios (aORs) and their 95% confidence intervals (CIs) of AMD in drug users compared with non-users. Furthermore, we observed the duration response relationships between these drugs and the occurrence of AMD.

Results: Our study included 26,240 cases and their matched 26,240 controls within a cohort of 228,452 patients with diabetes mellitus or cardiovascular diseases. The aORs for the occurrence of AMD among users with statins, metformin, ACE inhibitors, ARBs and their combinations were 1.19 (95% CI: 1.10-1.27), 1.00 (95% CI: 0.92-1.09), 0.96 (95% CI: 0.89-1.04), 1.10 (95% CI: 1.04-1.17), and 1.09 (95% CI: 1.03-1.15), respectively. The long-term use of ACE inhibitors seems to have preventive effect on AMD (aOR: 0.85, 95% CI: 0.75-0.97 in the use for 300-365 days, aOR: 0.96, 95% CI: 0.85-1.08 for 90-299 days, aOR: 1.12, 95% CI: 0.96-1.30 for 1-89 days; *p* for trend: 0.0058).

Conclusions: We found no preventive effect on the occurrence of AMD for the use of statins, metformin, ACE inhibitors, or ARBs in the elderly, while the long-term use of ACE inhibitor might be.

881 | Comparative outcomes of treatment initiation with brand-name versus generic warfarin: A medicare cohort study

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Background: Warfarin is a narrow therapeutic index (NTI) anticoagulant used for the prevention of stroke and venous thromboembolism. Generic versions of warfarin were approved based on bioequivalence with the brand version (Coumadin). Post-marketing studies comparing brand and generic products can help us evaluate therapeutic performance of generic NTI drugs.

Objectives: To compare clinical outcomes between generic and brand initiators of warfarin

Methods: Using US Medicare claims (2007-2013) linked to electronic medical records (EMRs) from the Partners Healthcare system in Boston and US Census Bureau data, we identified a cohort of patients newly initiating brand or generic warfarin after 180-day continuous Medicare enrollment. Patients were followed for the primary composite effectiveness outcome of ischemic stroke, systemic embolism, pulmonary embolism, or deep vein thrombosis and primary safety outcome of a major hemorrhage. Patients were censored at warfarin discontinuation, switching between generic and brand versions, Medicare disenrollment, or administrative censoring (Dec 31, 2013). As a secondary outcome, we evaluated 1-year all-cause mortality. Propensity score (PS) fine-stratification weighting was used to account for 109 confounding variables derived from Medicare claims (demographics, indications, comorbid conditions, co-medications), EMRs (smoking, obesity, kidney function), and Census data (socioeconomic status). As a secondary approach, we used high dimensional (hd)-PS to adjust for 200 empirical confounders. PS weighted Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results: A total of 33 645 warfarin initiators (mean age, 77 years) were included in our analysis with 755 (2%) initiated on the brand version. In this study population, % of patients who were initiated on brand vs. generic warfarin for atrial fibrillation, valve disorders, and venous thromboembolism were 73% vs 57%, 21% vs 15%, and 19% vs 30%, respectively. The PS-weighted HRs (95% CI) for the primary effectiveness, primary safety, and all-cause mortality outcomes for brand versus generic were 0.95 (0.63-1.43), 0.92 (0.64-1.33), and 0.82 (0.61-1.12), respectively. Estimates from the hdPS analyses were consistent with the primary analyses.

Conclusions: Comparable effectiveness, safety, and risk of all-cause mortality were observed between initiators of brand and generic warfarin products in a cohort of Medicare patients.

882 | Effectiveness of statins according to cardiovascular risk in the elderly

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Background: While there is clear consensus on the benefit of initiating statins in elderly with cardiovascular disease, the benefit of starting these treatments in patients without such history remains debated.

Objectives: To evaluate, in real life, the effect of initiating statins in the elderly, according to cardiovascular risk.

Methods: This cohort study was performed using data of the random representative sample of the French health care system database for the 2008-2014 period. Patients were eligible for the study if they were aged 75 years and above during the study inclusion period (2009-2012). Every trimester during this period, new users of statin were dynamically included in the cohort. New users of statin were defined as a first identified statin dispensing without statin dispensing in the previous year. To each statin new-user, one statin non-user was matched on age, gender, numbers of different drugs dispensed and medical consultations, and history of cardiovascular diseases or use of cardiovascular drugs. Patients were classified as high (history of previous coronary heart disease), moderate (diabetes or use of cardiovascular medications), or low cardiovascular risk (none of the above). Effect of cumulative use of statins on occurrence of acute coronary syndrome or all-cause death was analysed by using multivariable time-dependent Cox models stratified on cardiovascular risk at inclusion.

Results: 3642 new statin users matched 1:1 with statin non-users, for a total of 7284 patients were included in the study, 4.8% of whom were at high cardiovascular risk, 84.9% at moderate risk, and 10.3% at low risk. Over the study follow-up (median: 4.7 years), the cumulative use of statins was associated with a lower risk of outcomes in the high-risk group (adjusted hazard ratio (HR) 0.75 per year of use; 95% confidence interval (95% CI) 0.63-0.90), in the moderate-risk group (HR 0.93 per year of use; 95% CI 0.89-0.96), but not in the low-risk group (HR 1.01 per year of use; 95% CI 0.86-1.18).

Conclusions: This study confirms the benefit of initiating statins in elderly treated for secondary cardiovascular prevention or at identified cardiovascular risk. However, in primary prevention, outcomes were

similar regardless of statin use for older adults with no identified cardiovascular risk factors.

883 | Clinical effectiveness and safety of clopidogrel co-administered with statins and proton pump inhibitors in patients undergoing percutaneous coronary intervention

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Background: Insufficient antiplatelet effectiveness of clopidogrel, in part, has been associated with drug-drug interaction (DDI). Simultaneous competition with clopidogrel for CYP2C19 and CYP3A4 access might occur clinical exacerbation with CYP3A4-metabolized statins and proton pump inhibitors (PPIs).

Objectives: To evaluate whether the concurrent administration of CYP3A4-metabolized statins and PPI individually and jointly attenuate effectiveness of clopidogrel to increase the risk of major thrombotic events

Methods: We identified acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) with stenting using Korean Health Insurance Review and Assessment Service database. We confirmed an initiation of clopidogrel, statins, and PPIs within 30 days after index stenting, and classified subjects into 4 groups according to concomitant use of PPI and/or CYP3A4-metabolized statin. The primary endpoint was major thrombotic events consisting of acute myocardial infarction, ischemic stroke, and coronary revascularization procedure up to 12 months. We used inverse probability of treatment weighted Cox proportional hazard models to examine the independent association between concurrent CYP3A4-metabolized statins and/or PPIs with clopidogrel and the risk of adverse outcomes.

Results: The risk of major thrombotic events was significantly increased in PPI concurrent group compared with others (HR 1.23; 95% CI 1.09-1.39), and such difference was not shown between CYP3A4-metabolized statins and other statins (HR 1.02; 95% CI 0.97-1.06). Both of multiplicative (HRR 0.92; 95% CI 0.78-1.08) and additive interaction (RERI -0.10; 95% CI -0.29-0.09) were not statistically significant between the impact of CYP3A4-metabolized statins and PPI on clopidogrel.

Conclusions: Co-administration of PPI with clopidogrel and statin was associated with the risk of major thrombotic events in ACS patients undergoing PCI with stenting, and CYP3A4-metabolized statin did not be synergized to further increase the risk due to concurrent PPI.

884 | Comparative effectiveness of statins in cardiovascular secondary prevention

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Background: Simvastatin, pravastatin, fluvastatin, rosuvastatin and atorvastatin are the five statins used in secondary prevention of acute coronary syndrome (ACS) in France.

Objectives: To compare effectiveness of each statin in overall population and according to sex and age.

Methods: This cohort study was performed using data of the French health care system database, SNDS, for the 2009-2014 period. Patients were included if they were hospitalized for a first ACS in 2010. They were followed until the occurrence of a new ACS, death or the December 31, 2014. Exposure to statins was considered daily. Each day of treatment, patient cumulated a dose of a statin, expressed in defined daily dose (DDD). This accumulation decreased when the patient was not exposed to the statin. Exposure took into account of switches between different statins and overlaps of a same statin. It was considered as time-dependent variable in models to reduce information and confounding bias. Effectiveness of each statin was assessed by multivariate time-dependent Cox models adjusted on confounders such as demographic and first ACS characteristics, comorbidities and other medications. Analyses were also stratified on sex and age of patients.

Results: 31 136 patients were included in the cohort. Median follow-up duration was 4 years. Effectiveness for reduction of morbi-mortality in secondary prevention was demonstrated for each statin except fluvastatin (adjusted hazard ratio [HR] varied from 0.88 per year of cumulative use for rosuvastatin to 0.95 for atorvastatin). Rosuvastatin was the most effective drug in all populations (for total cohort: HR 0.88, 95% confidence interval (95% CI) 0.85-0.91). Stratified analysis on sex showed better effectiveness of statins in women than in men (HR 0.82, 95% CI 0.76-0.88, in women against HR 0.91, 95% CI 0.87-0.95 in men, for rosuvastatin). Stratified analysis on age showed lack of effectiveness for simvastatin in patients older than 75 (HR 0.97, 95% CI 0.89-1.07) and for pravastatin in patients younger than 75 (HR 1.00, 95% CI 0.93-1.07).

Conclusions: This population-based study confirmed the best effectiveness of rosuvastatin in cardiovascular secondary prevention. Differences of effectiveness between statins according to sex and age should be considered for the prescription.

885 | Postponement of death by heart failure treatment: A meta-analysis of randomized clinical trials

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Background: Outcome postponement has been proposed as an effect measure for preventive drug treatment. Using this measure has been shown to be in better agreement with patient understanding and values than conventional outcome measures, including the "number needed to treat." We have previously demonstrated that statin treatment postpones all-cause mortality during the trials' running time with an average of 13 days in a meta-analysis of 16 trials.

Objectives: To conduct a meta-analysis of modelled outcome postponement for the following heart failure treatments (Beta-blockers, ACE-inhibitors, Angiotensin II receptor blockers [ARB], ARB among users of ACE-inhibitors, Aldosterone-antagonists, Ivabradine, Renin-antagonist, Neprilysin inhibitors).

Methods: We calculated the outcome postponement by modelling the area between survival curves. The outcome postponement was modelled on the basis of the hazard ratio or relative risk, the cumulative risk of outcome among the placebo group and the trial's duration. The modelled outcome postponement was subjected to a meta-analysis.

Results: We identified 13 eligible trials involving heart failure treatment, with 52 014 patients randomized. The results in terms of postponement of all-cause mortality was; Beta-blockers 43.7 days (Postponement interval [CI], 20.8-66.5), ACE-inhibitors 37.4 days (CI, 2.3-72.6), ARB 24.8 days (CI, 5.9-43.7), ARB among users of ACE-inhibitors 9.4 days (CI, -12.1-30.1), Aldosterone-antagonists 41.3 days (CI, 14.3-68.4) and Ivabradine 3.8 days (CI, -11.8-19.3). All results were standardized to 3 year of trial running time to achieve comparability between treatments.

Conclusions: Based on modelled outcome postponement estimates, the investigated heart failure treatments provided much larger gains in postponement of all-cause mortality than statin treatment during the trials' running time.

886 | Association between adherence to renin-angiotensin-aldosterone-system (RAAS) inhibitors and renal function among patients with type 2 diabetes: A population based study using real world data

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Background: Renin-angiotensin-aldosterone system (RAAS) inhibitors are indicated for hypertension, heart failure and chronic kidney

disease. Randomised controlled trials showed that RAAS inhibitors were beneficial for renal function especially in high dosages or when renal function was reduced. The effect of RAAS inhibitors on renal function among patients with a normal renal clearance is less clear. Especially in type 2 diabetes mellitus (T2DM) patients, who are at risk for renal damage, adherence to RAAS inhibitors is important.

Objectives: To determine if a higher adherence to RAAS inhibitors is associated with improvement of the renal function among T2DM patients using real world data.

Methods: A cohort study was conducted using data from the PHARMO Database Network, a population-based network in the Netherlands combining data from different health care settings. T2DM patients with data available in the Out-patient Pharmacy Database and availability of estimated glomerular filtration rate (eGFR) values were selected between 1999-2015. Of these patients, new users of RAAS inhibitors were included. Adherence to RAAS inhibitors was determined by the medication possession ratio (MPR) as well as persistence during a fixed period of 15 months after initiation of RAAS inhibitors (index date). To assess the association between renal function over time and adherence to RAAS inhibitors, mixed-effect model repeated measures were performed (adjusted for age, gender, number of eGFR measurements and a chronic disease score) by modelling the eGFR over time, separately for patients with low (<80%) and high ($\geq 80\%$) MPR, as well as for patients with long (≥ 6 months) and short (<6 months) persistence.

Results: In total, 8950 patients were included in the study cohort (57% male, mean $\pm$ SD age at index date 66 ± 11 years); 74% of the patients with a high MPR and 84% with a long persistence. During the 15 months after index date, the mean eGFR declined about 2.5 mL/min/1.73m² in patients with a low MPR or a short persistence; for patients with a high MPR or long persistence this was about 4 mL/min/1.73m².

Conclusions: In a real world setting, a higher adherence to RAAS inhibitors was not associated with an improvement of the renal function among T2DM patients.

887 | Bone marker CTX-1 as an indicator of osteoporosis treatment initiation and adherence in clinical practice

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Background: Collagen type I C-telopeptide (CTX-1), a bone resorption marker, has been proposed as a surrogate of osteoporosis treatment efficacy. Clinical trials have shown that its serum levels significantly decreases 3 months after antiresorptive therapy (ART) initiation. A decrease of 30-60% in CTX-1 has been considered as an indicator of

ART efficacy. Risedronate (Ri) and alendronate (Al) are oral ART with similar kinetic effect on CTX-1.

Objectives: To assess the changes in CTX-1 levels from baseline to 6 and 12 months according to exposure to Ri/Al and adherence level.

Methods: We gathered clinical data of a prospective cohort of women and men recruited from 2010-2013 in a Fracture Liaison Service and followed for 1-year after a fragility fracture. CTX-1 levels (ng/mL) were measured at baseline, 6 and 12 months. From 422 patients with complete 1-year coverage of administrative data, we selected patients who filled at least two prescriptions of Ri/Al at two different times to define exposure; 3 months before 6-month CTX-1 and 3 months before 12-month CTX-1. Patients switching to other ART were excluded. Patients without ART dispensation during the study period formed the unexposed group. Adherence level was measured using PDC between the 3-month dispensation and last CTX-1 measurement ($PDC \geq 80\%$ = adherent, $PDC < 80\%$ = non-adherent). The outcome was the change in CTX-1 levels between baseline and 6 and 12 months according to exposure and adherence level. Multilevel models adjusted for variables measured at baseline (age, gender, body mass index [BMI], spine bone mineral density [SBMD], prior use of ART) were used.

Results: From 130 exposed and 125 unexposed patients ($n = 255$), more than 84% were female. Mean age was 65.6 years in the exposed group and 57.1 years in the unexposed group ($p < 0.001$). PDC was $>80\%$ in 115 (88.5%) exposed patients. Significant predictors of CTX-1 were SBMD and BMI. Mean changes of CTX-1 from baseline were more important in exposed than unexposed patients (baseline-6 months: -0.173 [-48.3%] vs -0.098 [-29.1%], $p = 0.012$; baseline-12 months: -0.183 [-51.1%] vs -0.091 [-27%], $p = 0.002$). Mean changes of CTX-1 from baseline were more important in adherent than non-adherent patients (baseline-6 months: -0.189 (-51.6%) vs -0.033 (-8.9%), $p = 0.020$; baseline-12 months: -0.194 (-53%) vs -0.030 (-8.1%), $p = 0.038$).

Conclusions: Our results show that the CTX-1 bone resorption marker may be an indicator of oral osteoporosis treatment initiation and adherence level in clinical practice.

888 | Risk of osteoporotic fractures in new users of denosumab compared with new users of alendronate: A Danish population-based cohort study

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Background: Head-to-head randomized controlled trials (RCT) have compared efficacy of denosumab versus alendronate in relation to bone mineral density. No RCT has been designed and conducted to compare the anti-fracture efficacy of denosumab and alendronate.

Objectives: We compared the effectiveness of denosumab versus alendronate, measured by clinically manifested fracture risk, using data from population-based Danish health registries.

Methods: We included new users of denosumab or alendronate (with a one year wash-out period with no anti-osteoporosis dispensation/s) aged 50 years or older who started either therapy between May 10, 2010 and December 31, 2015. To control for measured confounding, we used inverse probability of treatment weights. Using the Cox regression and the intention-to-treat approach, we calculated adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) separately for any fracture, hip fracture, vertebral fracture, and non-vertebral non-hip fracture.

Results: There were 3734 new users of denosumab (median follow-up time: 3.24 years) and 67 765 new users of alendronate (median follow-up time: 3.27 years) sustaining 10.9% and 10.3% any fractures, respectively. Initiation of denosumab versus alendronate was associated with aHRs of 0.94 (CI: 0.84-1.04) for any fracture, 1.07 (CI: 0.90-1.27) for hip fracture, 0.77 (CI: 0.57-1.03) for vertebral fracture, and 0.91 (CI: 0.79-1.05) for non-vertebral non-hip fracture. Similar aHRs were observed after stratification by sex and fracture history. Among patients older than 80 years, aHRs were 1.21 (CI: 0.92-1.48) for hip fracture and 1.17 (CI: 0.92-1.48) for non-vertebral non-hip fracture.

Conclusions: Overall, initiation of denosumab and initiation of alendronate were associated with similar risks of any fracture. Denosumab was associated with a 23% lower risk of vertebral fracture than alendronate. Among patients ages 80 years or older, denosumab was associated with higher risks of hip fracture and non-vertebral non-hip fracture than alendronate. Head-to-head RCT(s) are needed to compare the efficacy of denosumab and alendronate.

889 | Factors influencing treatment maintenance of SC and IV tocilizumab (TCZ) in patients with rheumatoid arthritis (RA) in real life

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Background: Phase III study SUMMACTA shown that SC TCZ was non-inferior to IV TCZ. However, effectiveness of the SC TCZ formulation has not been evaluated in real life.

Objectives: This analysis assessed the factors associated to the maintenance of SC TCZ 12 months after switching from IV to SC formulation in patients (pts) with RA in real-life.

Methods: All RA pts of the shared medical file "RIC Nord de France" with at least 1 DAS28-ESR 3 months before inclusion, treated with TCZ, switching or not from IV to SC TCZ, between April 2015 and

January 2016 were analyzed. The survival time was defined as the time between the first injection at inclusion date and last reported injection/infusion in the same route of administration and was estimated using the Kaplan-Meier method. Comparisons between Switch and No-switch groups were tested using log-rank test. Factors associated with treatment maintenance were determined using Data-Mining techniques: Survival Trees (STs) and Random Survival Forests (RSFs).

Results: From the 314 pts included, 30% switched from IV to SC TCZ after the first injection. At baseline, there were 77.7% females and mean RA duration was 14.9 ± 9.2 years. Mean IV TCZ duration before inclusion was 35.0 ± 23.1 months in Switch and 26.8 ± 22.1 months in No-Switch pts. Treatment maintenance at 12 months in Switch and No-switch pts was observed in 78% (95% CI [68%-85%]) and 80% (95% CI [74%-85%]) of pts respectively, with no significant difference ($p = 0.555$). Overall, 79 pts (25%) stopped TCZ before the database extraction (May 15, 2017). Associated factors with treatment maintenance using STs and RSFs techniques were the DAS28-ESR at inclusion and TCZ duration before inclusion. Three distinct groups of pts defined by these 2 parameters were identified:- Group A (lower maintenance, $n = 77$): TCZ duration before inclusion < 9.5 months (with 31 [40%] treatment discontinuation in this group)

- Group B (higher maintenance, $n = 88$): TCZ duration before inclusion ≥ 9.5 months & DAS28 < 1.8 (with 10 [11%] treatment discontinuation)

- Group C (medium maintenance, $n = 149$): TCZ duration before inclusion ≥ 9.5 months & DAS28 ≥ 1.8 (with 38 [26%] treatment discontinuation).

Conclusions: In real life population, similar therapeutic maintenance rates were observed for Switch and No-switch pts. The therapeutic maintenance was mainly related to patient's condition including the DAS28 value at inclusion and the TCZ duration before inclusion.

890 | Acute pharmacological management after spinal cord injury: A secondary analysis of clinical trial data

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Background: Spinal cord injury is often immediately coupled with various secondary health conditions including infections, spasticity, and the development of neuropathic pain. These conditions necessitate the administration of a range of medications (eg, antibiotics, analgesics). To date, a comprehensive evaluation of the drugs administered in the acute phase of spinal cord injury is missing.

Objectives: To determine the types of drugs commonly administered, alone or in combination, in the acute phase of spinal cord injury.

Methods: We completed a secondary analysis of a cohort of adult patients with traumatic spinal cord injury who participated in the multi-centre randomized controlled clinical trial (Sygen). Concomitant medication use (non-randomized medications), including dosage,

timing, and reason for administration, was tracked through the duration of the 1-year trial. Descriptive statistics (means, percentages, standard deviation, confidence intervals, etc.) were used to describe the drugs administered. Patterns of poly-pharmacy was determined using a hierarchical cluster analysis. R Statistical Software was used for all statistical analyses and to create plots for data visualization.

Results: Of 797 patients included in our analysis (mean age at injury: 34 years; 83% male), 75% were injured at the cervical level. A total of 640 drugs from 49 different drug classes were administered within 90 days after injury. The average number of drugs given to one patient in the first month was 46.4. The highest prevalence was found for analgesics (acetaminophen [92.6%], morphine [75.4%]), coagulants (heparin [68.3%]), and antibiotics (cefazolin [52.4%]). The most frequent drug-combination was acetaminophen and heparin [68.4%]. The drug exposure patterns ranged from single (ie, drug was given once), to intermittent, to continuous exposure (ie, drug was administered for 90 days).

Conclusions: Our study reveals important findings regarding the types and prevalence of drugs administered (alone or in combination) to patients sustaining a traumatic spinal cord injury.

891 | Real-world persistence and effectiveness of conventional systemic therapies in the treatment of psoriasis: A systematic review

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Background: The effectiveness and persistence of biologic therapies is better understood than more commonly prescribed conventional systemic therapies in clinical practice.

Objectives: To evaluate large-scale observational studies investigating the persistence and effectiveness of acitretin (AC), ciclosporin (CIC), fumaric acid esters (FAE) or methotrexate (MTX) in ≥ 100 adult patients with moderate-severe psoriasis, exposed to therapy for ≥ 3 months.

Methods: A literature search was conducted using Medline, Embase, the Cochrane Library and PubMed. Outcomes of interest were persistence (therapy duration or the proportion of patients discontinuing therapy) and effectiveness (improvements in Psoriasis Area and Severity Index [PASI] or Physician Global Assessment [PGA] at 3, 6, or 12 months), including patients who achieved a reduction of $\geq 75\%$ in their PASI score from baseline (PASI75). Study characteristics and results were extracted and the risk of bias was assessed using the Cochrane tool.

Results: Of the ten articles reviewed, the risk of bias was high in seven and medium in three; therefore, a meta-analysis was not conducted. *Persistence:* Three studies investigated AC, CIC and MTX; the first study investigated FAE and MTX, whilst the second and third studies investigated FAE and MTX only. Two of the 3 studies investigating

AC, CIC and MTX reported median durations of 0.7, 0.4, and 1.0 years, and 0.5, 0.5, and 1.0 years, respectively. The third study only reported a mean duration of 20 weeks exposure to MTX. The study investigating FAE and MTX reported 69% and 74% patients discontinued during follow-up, respectively. The remaining studies reported mean durations of 28 and 50 months for FAE and 1 year for MTX, with 2 studies reporting median MTX durations of 7.7 and 17.2 months. *Effectiveness:* Three studies reported 76% (FAE), 53% (MTX) and 59% (MTX) patients achieving PASI 75 at 12 months, with 1 study reporting 76% FAE-exposed patients with markedly improved/clear PGA at 12 months. No studies investigating the effectiveness of AC or CIC were identified.

Conclusions: Few data were available for AC and CIC, and the time to discontinuation was generally not provided. This review highlights the need for registry-based studies to explore the real-world persistence and effectiveness of conventional systemic treatments in clinical practice.

892 | Creation of a real-world cohort of hyperkalemia patients using Danish health care data to simulate the control population of a single arm clinical intervention trial

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Background: Some of the recent long-term clinical trials for potassium binders do not include a control arm due to concerns about denying patients hyperkalemia (HK) treatments for up to 1 year.

Objectives: To explore the feasibility of constructing a real-world reference population of HK patients similar to that included in the ZS-005 clinical trial.

Methods: The ZS-005 clinical trial was a Phase 3 multicenter, international, multi-dose, open-label maintenance study to investigate the long-term safety and efficacy of Sodium Zirconium Cyclosilicate (formerly known as ZS-9) an oral sorbent, in 751 subjects with HK over 52 weeks. We utilized rich health care data from Northern Denmark together with a dataset of de-identified individual patient level data of the ZS-005 trial to develop a reference cohort. We first applied the inclusion and exclusion criteria from the ZS-005 trial to the health care data. The reference cohort consisted of 122 128 patients, eligible at all time points when they had a HK event (blood K⁺ level ≥ 5.1 mmol/L) and fulfilled trial inclusion criteria (total of 404 261 HK events). We then used logistic regression to estimate the propensity score of each Danish real-world HK patient existing in the ZS-005 trial population, based on the characteristics (eg, age, gender, comorbidity history, drug use, potassium levels, eGFR) of the ZS-005 trial patients.

Results: Prior to the matching, patients in the real-world reference cohort were older than those in the ZS-005 trial, had slightly lower mean baseline K⁺ levels (5.4 versus 5.6 mmol/L), similar eGFR values,

but less presence of heart failure, diabetes and RAASi use. Nearest neighbor 1:1 propensity score matching resulted in a real-world reference cohort of 751 patients, and increased similarity between the trial and real-world patients. After matching, mean (SD) age was 64 (15) in real-world patients and 64 (13) in trial patients, mean baseline K⁺ 5.7 (0.6) versus 5.6 (0.4), mean eGFR 47 (32) versus 47 (32), with similar prevalence of chronic kidney disease (65% and 68%), heart disease (37% and 38%), diabetes (61% and 63%), and RAASi use (67% and 70%) in the two cohorts, respectively.

Conclusions: We found it feasible to create a real-world reference cohort of HK patients, highly similar to the trial population of the recent ZS-005 interventional clinical trial, using propensity score matching of Danish health care data, to better understand the real-world management and outcomes of HK patients.

893 | Clinical outcomes of adding xanthines to ICS and LABA combination in patients with chronic obstructive pulmonary disease

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Background: Theophylline and related xanthine derivatives have been found to induce histone deacetylase activity (HDAC), a potential mechanism for regulating inflammatory gene expression and corticosteroid resistance in chronic obstructive pulmonary disease (COPD).

Objectives: This study aimed to evaluate whether adding xanthine to long-acting β -agonist (LABA) and inhaled corticosteroids (ICS) combination can improve the outcomes of COPD patients.

Methods: In this retrospective cohort study, patients with a diagnosis of COPD were identified from the National Health Insurance Research Database of Taiwan. New users of ICS/LABA combination with xanthine derivatives (xanthine group) or without (control group) during 2004-2013 were enrolled. Propensity score matching was performed to balance baseline characteristics between two groups. The outcomes of interest were the rate of acute exacerbation (AE) during the follow-up period, and time to first AE and all-cause mortality. Cox and Poisson regression modeling were utilized to estimate the association between xanthine use and risk of adverse outcomes. We further examined the effect of different equivalent daily dose of theophylline in different age groups.

Results: After propensity score matching, 1685 patients were identified in both groups. The xanthine group and control group, in general, were not significantly different with regard to incidence rate of AE, time to first AE, and all-cause mortality. However, adding low-dose theophylline (≤ 200 mg/day) was associated with a lower risk of mortality (HR 0.39, 95% CI 0.22-0.67), and theophylline in a usual dose (> 200 mg/day) was associated with a higher risk of AE (incidence rate ratio [IRR] 1.38; 95% CI 1.01-1.90), compared with non-users in the control group. Reduced risk of AE (IRR 0.53, 95% CI 0.31-0.92) and all-cause mortality (HR 0.37, 95% CI 0.19-0.72) with low-dose theophylline were both found in patients aged 75 years and older.

Conclusions: Although adding xanthines to ICS/LABA, as a whole, did not improve the outcomes of COPD patients, heterogeneity of treatment effect exists. The present study provides evidence that low dose of theophylline may lower the risk of mortality, the beneficial effect of which was more prominent in the elderly. The increased risk of AE with usual dose of theophylline, especially in younger patients, warrants further investigation.

894 | Effectiveness of ranibizumab intravitreal injections in visual impairment due to macular edema secondary to retinal vein occlusion: Final results at 24 months from the French boreal cohort

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Background: The French Health Technology Assessment agency requested information on the ranibizumab (RBZ) usage and impact in real-world setting

Objectives: To assess the effectiveness and patterns of use of RBZ intravitreal injections (IVI) for patients with visual impairment due to macular edema secondary to branch (B) or central (C) retinal vein occlusion (ME-RVO) for up to 24-month follow-up

Methods: This is a real-world, post-authorization, observational cohort study in adult patients with RBZ IVI initiation for best-corrected visual acuity (BCVA) loss due to ME-RVO, followed-up for up to 24 months by their ophthalmologist. The primary endpoint was BCVA evolution from baseline to Month 6. BCVA, central subfield thickness (CSFT) evolution from baseline to Month 24, treatment exposure to ranibizumab and safety were also assessed

Results: Between December 2013 and April 2015, for B/C cohorts, 226/196 patients were enrolled, and 162/139 (71.7/70.9%) completed the 24-month follow-up. Patient characteristics were mean (SD) age of 70.9 (11.1)/70.4 (14.3) years, 48.7/51.5% of men, mean baseline BCVA of 52.2 (18.7)/40.4 (25.6) letters, mean CSFT of 550 (175)/643 (217) μ m. The BVCA mean change from baseline was

+14.1 (11.7 to 16.5)/+9.5 (5.5 to 13.5) letters at 6 ± 1.5 months. The vision is maintained at Month 12 and 24 with a mean change in BCVA from baseline of +13.0 (10.2 to 15.9)/+9.2 (4.5 to 13.9) letters at 12 ± 1.5 months and +11.4 (7.7 to 15.2)/+8.3 (3.7 to 12.8) letters at 24 ± 1.5 months, with 53.1/ 38.9% of patients having a BCVA >70 letters. The CSFT mean change was -223(-254 to -192)/-267 (-314 to -220) µm at 6 ± 1.5 months, -225 (-260 to -191)/-284 (-334 to -233) µm at 12 ± 1.5 months and -211 (-251 to -170)/-305 (-356 to -255) µm at 24 ± 1.5 months. At the end of 24 months of follow-up, the mean number of IVI was 7.2 (4.3)/7.1 (4.4) with 85.8/ 85.6% patients who had at least one interruption of RBZ IVI, 72.6/ 62.5% for improvement of the pathology and 15.2/26.7% for lack of efficiency. At 24 months, 69.8/62.6% of studied eyes received only ranibizumab and 30.2/37.4% received another intravitreal treatment. No new safety findings were identified

Conclusions: Effectiveness of RBZ in daily practice at 24 months is close to the results at 6 months, but limited compared with the results of the preregistration randomized clinical trial at 24 months, probably due to the fewer number of IVI

895 | What is real-world data? A review of definitions based on literature and stakeholder interviews

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Background: Health Technology Assessment (HTA) agencies increasingly require robust evidence on relative effectiveness of products. Randomised controlled clinical trials (RCT's) provide robust evidence on efficacy, but not on effectiveness. Real-World Data (RWD) may provide an alternative source for effectiveness data. However, despite increasing recognition of the value of real-world data (RWD) for drug assessment, consensus on the definition of RWD is lacking.

Objectives: In order to shed light on similarities and differences between available RWD definitions, we aimed to review definitions for RWD from the perspective of different stakeholders.

Methods: A literature review and stakeholder interviews were used to compile data from 8 groups of relevant stakeholders. Outputs from documents and interviews were pooled and subjected to coding analysis. Definitions identified were classified into one of four pre-defined categories: 1-Data collected in a non-RCT setting, 2-Data collected in a non-interventional/non-controlled setting, 3-Data collected in a non-experimental setting (ie, not based on a pre-established study protocol), and 4-Other (ie, do not fit into three categories above). The frequency of definitions identified under each category was recorded.

Results: In total 52 documents and 20 interviews were assessed. 38 definitions were identified: 20 out of 38 definitions (53%) were category 1 definitions, 9 (24%) were category 2 definitions, 5 (13%) were

category 3 definitions and 4 (11%) were category 4 definitions. Differences were identified both between, and within, definition categories. For example, opinions differed on the aspects of intervention (treatment assignment, patient selection, and patient follow-up) with which non-interventional/non-controlled settings should abide. No definitions were provided in 2 interviews or identified in 32 documents.

Conclusions: The majority of definitions assessed defined RWD as data collected in a non-RCT setting. However, a considerable number of alternative definitions diverged from this concept. Moreover, a significant number of authors and stakeholders did not have an official, institutional definition for RWD. Persisting variability in stakeholder definitions of RWD may lead to confusion among different stakeholders when discussing the use of RWD in decision-making.

896 | "Real-World" evidence for drugs and devices: 2017 literature reviewed

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Background: The term "real-world evidence" (RWE) has become increasingly common in recent years. Yet little is known about what constitutes RWE in published literature and whether RWE is similar across therapeutic interventions, such as drugs and devices.

Objectives: We evaluated RWE in 2017 publications overall and for drugs and devices separately.

Methods: Pubmed and Embase were reviewed for English language 2017 titles and abstracts in which the term "real world" appeared. The following were extracted based on information in the title/abstract: therapeutic area, exposure type, study design, primary outcome, timing of outcome, country and data source. Descriptive analyses were performed.

Results: There were 1045 hits for "real world" publications in 2017. Of these, 315 were excluded because they lacked an abstract (n = 93) or were not related to provision of health care (n = 222); 730 remained in the analysis. Overall, most studies were retrospective (67%) vs prospective (31%); used a data source of medical records (32%), primary data collection (28%), administrative or pharmacy data (12%), registries (10%), and other/not reported (19%); and, were focused in 3 therapeutic areas (TAs): cardiovascular (CV, 23%), oncology (19%) and infectious disease (ID, 14%). Eight percent focused on short-term outcomes (<30 days). Real-world data from over 50 countries were analyzed in the studies, with the US most frequently noted. Most studies assessed RWE of drugs (67%); 15% assessed devices and 18% other interventions. Drug RWE studies were mostly retrospective (72%) vs prospective (26%); used a data source of medical records (34%), primary data collection (23%), or administrative/pharmacy data (14%); evaluated efficacy (56%) or treatment patterns (13%); and were focused in one of 4 TAs (oncology [22%], ID [20%], CV [15%], or metabolic [10%]). Drug studies also tended to focus on longer term

outcomes (5% <30 days). Device RWE studies were split between retrospective (52%) and prospective (47%); used a data source of primary data collection (34%), medical records (31%) or a registry (17%); evaluated efficacy (53%) or safety (19%); were most often focused on CV TA (63%). Device studies also assessed shorter term outcomes more often than drug studies (19% <30 days).

Conclusions: In 2017, the published literature on RWE studies reported using a wide variety of outcomes and methods, with important differences between drugs and devices. Efforts to standardize reporting of RWE studies should cover this breadth and apply across therapeutic interventions.

897 | Discontinuation of first biologic drug for rheumatoid arthritis: What happens next? A descriptive drug utilization study in Tuscany, Italy

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Background: Discontinuation of biologic disease-modifying antirheumatic drugs (bDMARDs) is frequent in clinical practice. However, evidence on prescribing patterns of bDMARDs following first discontinuation event is poor.

Objectives: To describe prescribing patterns following first treatment discontinuation in new users of bDMARDs.

Methods: Administrative health care data from one Italian region, Tuscany, were used. Patients with ≥ 1 dispensing of a bDMARD between 2010 and 2013 were selected. The date of first dispensing was the cohort entry date. Patients were included in the study cohort if they had: at least 2 years of look-back, a diagnosis of rheumatoid arthritis (RA) recorded before or on the entry date, 3 years of observation time. On the basis of the first bDMARD received, patients were classified in two exposure categories: (1) anti-TNF α (ie, infliximab, adalimumab, golimumab, certolizumab, etanercept) and (2) non anti-TNF α (ie, abatacept, anakinra e tocilizumab). Patients were followed up for 3 years and classified as *switchers*, when they changed bDMARD from an anti-TNF α to a different anti-TNF α , or *swapper*, when they start using a bDMARD with a different mechanism of action (eg, from an anti-TNF α to a non anti-TNF α). *Discontinuation* was defined as ≥ 90 days not covered by the index bDMARD. Defined Daily Doses were used to calculate days covered by bDMARDs. The first event occurred among discontinuation, switch/swap, end of follow-up (ie, patients persistent to the index drug) was observed. Patients who discontinued were further followed up to the re-inization of a bDMARD, (ie, index drug, switch or swap) or the end of follow-up, whichever occurred first.

Results: A total of 1180 new users of a bDMARD were selected. Mean age was about 50 years and female/male ratio was 3:1. About 90% of patients started with an anti-TNF α . Patients persistent to the index drug during 3 years were 27%. Those who changed bDMARD

without discontinuation were 18% (n = 208) and most of them were switchers (n = 150). Those who discontinued the index bDMARD where 55% (n = 651). Among the latter, patients who re-started a bDMARD before the end of follow-up were 62% (n = 403). Patients who re-started a bDMARD continued to receive the index drug in 70% of cases (n = 283).

Conclusions: The majority of new users of a bDMARD who re-started the treatment following the first discontinuation continued to use the index drug. Sustained disease remission is likely to explain the observed prescribing pattern.

898 | Pain relief medicines: Availability for outpatients

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Background: Necessary analgesics are not always available in the low- and middle-income countries.

Objectives: The objective of this work was to study availability of medicines for pain treatment in Armenia.

Methods: Data on availability of 2 tracer medicines - diclofenac (tablets, 50 mg) and paracetamol (syrup, 120 mg/5 mL) were collected in 60 pharmacy outlets from all 11 regions of Armenia. Study was implemented in May-June 2015. Availability of opioids at community pharmacies in Yerevan and regions was identified by interviewing key informants. The List of registered medicines for 2016 was analyzed to identify medicines for pain relief which are authorized in Armenia.

Results: Tablets of diclofenac were available at all the community pharmacies studied; originator brand (OB) of diclofenac was identified at 70.0% of outlets and lowest-priced generic (LPG)—at 30.0%. Syrup of paracetamol was available at 97.0% of all outlets; OB and LPG were found at 76.7% of community pharmacies. In Yerevan (the capital of Armenia) morphine was available only at 1 pharmacy outlet. Analysis of all the medicines registered in the country showed that in 2016 the following numbers of medicines for pain relief were authorized: 5 opioids (1 combination), 24 other analgesics and antipyretics (19 combinations) and 7 antimigraine preparations (5 combinations).

Conclusions: Non-opioid analgesics are mainly available at pharmacy outlets in Armenia, while opioids are less accessible. The list of registered analgesics is limited.

899 | Identification of medication discrepancies on medication reconciliation during hospital admission

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Background: Medication discrepancies often occur during care transitions, such as hospital admission or discharge, which are likely to cause patients at risk for medication errors and adverse outcomes.

Objectives: To identify medication discrepancies which occurred when patients were admitted to the hospital.

Methods: A prospective study was conducted among the patients aged 20 and older who were prescribed with more than one medications and admitted to the internal ward in National Cheng Kung University Hospital, Taiwan, during 2017/1/1-2017/9/30. Pharmacists conducted medication reconciliation services, including visiting patients at ward, retrieving patients' medication records from pharmacy claims data (ie, PharmaCloud), comparing medication history with current orders, and resolving potential medication discrepancies. Medication discrepancies were defined as the differences in medication profiles before and after hospital admission. The medication discrepancies and the reasons for medication discrepancies were identified. Patient characteristics were described and compared using independent *t* test for continuous variables and chi-square tests for categorical variables by the SAS Enterprise Guide 6.1 software.

Results: Sixty-four inpatients were enrolled in this study, with mean age of 73.04 (± 12.95) years and 53.13% as male. Thirty-eight patients (59.38%) had at least one medication discrepancies, with total 103 prescriptions of medication discrepancy (16.29%) identified. Most of the medication discrepancies were explainable (ie, "problems solved": 58.25%, "medication regimen change": 18.44%). 10.68% ($n = 11$) medication discrepancies were unexplainable. The common chronic medications with discrepancies were "antihypertensive agents" ($n = 20$, 19.41%), "antidiabetic agents" ($n = 11$, 10.67%), and "antithrombotic agents" ($n = 6$, 5.82%). Older patients (aged ≥ 75 vs aged < 75 , $p = 0.07$) and patients used more medications (6.11 ± 2.95 vs 4.65 ± 3.55 , $p = 0.08$) tend to have more medication inconsistency during hospital admission.

Conclusions: This study results highlight an important role for pharmacists in medication reconciliation at hospital admission, especially for the elderly (≥ 75 years) and used more medications for their chronic diseases.

900 | Characteristics of women initiating conjugated estrogens/bazedoxifene

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Background: Conjugated estrogens/bazedoxifene (CE/BZA) is approved in the United States for the treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of post-menopausal osteoporosis. CE/BZA became available in the United States in 2014, and there has been a lack of information on the type of patients using the medication.

Objectives: The objective of this analysis was to describe patient characteristics among CE/BZA initiators.

Methods: As part of an ongoing study, the HealthCore Integrated Research Database was used to identify patients with ≥ 1 dispensing of CE/BZA between May 1, 2014 and April 30, 2016. We identified CE/BZA initiators as patients with no dispensings of any hormone therapy in the 12 months prior to the index date, defined as the first dispensing date of CE/BZA. We excluded patients with prior hysterectomy, diagnosis of cancer and less than 1 year of eligibility prior to the index date. The baseline period was defined as the period prior to the index date. We described patient demographics, baseline medication dispensings, and medical history among CE/BZA initiators.

Results: We identified 958 CE/BZA initiators. Seventy-six percent were in the 40 to 55 year age group, while 24% were older than 55 years. The median length of the baseline period was 53 months. At baseline, 68% had a diagnosis of vasomotor symptoms, 85% had a screening for malignant neoplasm of breast, 54% had cervical screening, 20% had a family history of cancer and 50% had a diagnosis of joint pain. Medications commonly used in the past were antimycobacterials (52%), antidepressants (46%), and oral corticosteroids (43%).

Conclusions: We observed that nearly half of CE/BZA initiators had received anti-mycobacterials, antidepressants and oral corticosteroids and had a diagnosis of joint pain in the past. More than two-thirds had been diagnosed with vasomotor symptoms.

901 | A data-driven methodology to define and visualise line of therapy for real-world data epidemiology of cancers

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Background: European and American guidelines recommend systemic anti-cancer therapy (SACT) in patients with advanced or metastatic cancers. There is significant interest in better understanding of the epidemiology of disease and clinical characteristics of patients with such cancers in real-world clinical practice. With the increase in availability of observational real-world data (RWD), a robust approach is needed to define and visualize complex SACT data in relation to line of therapy (LoT).

Objectives: A pilot study to explore the feasibility of building a generic clinically-relevant data-driven framework to define and visualise LoT in RWD epidemiology of cancers.

Methods: A review of clinical guidelines and published observational studies was undertaken with the support of oncology experts in order to shape the generic strategy for defining LoT. Based on the review, generic rules for LoT were defined, a pilot framework developed, and assumptions tested by using observational data. To describe distribution of treatments, the applicability of Sankey diagrams was explored as a data visualisation tool for summarising complex data relationships.

Results: Methodological considerations identified during the application of the framework on observational data included defining relevant time periods between SACT sequences when data are incomplete or not collected. Another consideration was to set a time gap (between start dates of two consecutive SACT cycles) to define advance in LoT. Finally, all aggregated counts were extracted to compile a summary dataset for data visualization in Sankey diagrams. Within these plots, LoT sequencing was shown by colour coding and incident counts by the width of each flow.

Conclusions: As the availability of RWD sources for observational research in oncology continue to grows, more efficient procedures for reporting and visualizing summary data are needed. This pilot study showed that a generic clinically-relevant data-driven framework can be compiled to define and visualise SACT treatment sequencing. Next steps include validation of the framework against any information that directly corresponds to LoT, where available.

902 | Tramadol use in Norway: A register-based population study

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Background: Increasing use of tramadol for chronic non-cancer pain (CNCp) is of concern, since tramadol users may be at risk of developing problematic opioid use.

Objectives: Therefore, we investigated the pattern of drug use by following a complete national cohort of tramadol users in a 4 years' period.

Methods: The analyses were based on 154 042 individuals from the adult Norwegian population (approximately 4 million individuals), who had at least one tramadol prescription in 2012. Patients were stratified into four study population groups according to their opioid use in a 2 years' period before their first tramadol prescription in 2012 and followed until December 2016. All dispensed items of tramadol, other opioid analgesics, and benzodiazepines (BZDs) were retrieved from the Norwegian Prescription Database (NorPD) for analyses of drug use.

Results: Six percent of opioid naïve tramadol users became recurrent users and doubled their mean opioid consumption from 66 to 108 defined daily doses (DDD). Strong opioid users for CNCp developed a prescription pattern like the pattern of patients in palliative care with a high, consistent and increasing mean consumption of strong opioids (125 to 222 DDD, 283 to 379 DDD, respectively); 61% and 70% became recurrent users, respectively, half of them used BZDs or Z-hypnotics, and one-quarter used both drugs. Twenty-three % of opioid naïve tramadol users and 19% of former weak opioid users proceeded to strong opioid use during follow-up.

Conclusions: These findings indicate that the use of tramadol requires the same attention and follow-up as other opioids.

903 | Challenges and issues in drug utilization research identified from the Latin American and African regions

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Background: Despite advancements in drug utilization research (DUR), these have not been universal. Some regions such as the Latin America (LatAm) and African regions are facing challenges that are impeding the development of DUR.

Objectives: To identify the main challenges and issues for DUR in the LatAm and African regions. **Methods:** A collaborative initiative by the International Society of Pharmacoepidemiology Global Development Committee in partnership with the Latin America Drug Utilization Group and the Medicines Utilization Research in Africa Group was undertaken. A comprehensive literature review was conducted to identify local and international DUR publications. A core group of investigators and experts in DUR reviewed the publications and identified the main methodological challenges and issues. Subsequently, the group exchanged materials, participated in WebEx discussions, and reviewed the draft document.

Results: Main issues: (1) Socioeconomic: high unemployment rate with poor standard of living, socioeconomic inequalities, low literacy levels, urban segregation, high migration rates, high rates of violent crime including drug trafficking and possession. (2) Health care-related: Disparities of social determinants of health, differences in the quality of public and private health sectors; and epidemiologic transition from communicable diseases to non-communicable diseases. Most health care systems are fragmented with variable access to medical care and medicines, and substandard record keeping. (3) Drug utilization-related: Inappropriate use of medicines including the elderly; limited infrastructure to reliably collect DU data; over-prescription of antimicrobials; polypharmacy; high rates of self-medication; and poor patient adherence (eg, HIV/AIDS, diabetes mellitus and hypertension). Planning for DUR is affected by the multiplicity of drug distribution channels; trading in sub-standard, counterfeit medicines and insufficient quality control centers. Some publications are generated by local investigators, often suffering of methodological issues such as lack of representativeness of the population, limited data validity, and small sample sizes.

Conclusions: There are common challenges for DUR when working within the LatAm and African regions. Based on our findings, the group is developing Guidance on Good Practices of Drug Utilization Research in those regions to assist researchers with issues pertaining to the planning, conduct, and evaluation of DUR.

904 | Prevalence and correlates of pharmacy closures in the United States, 2009-2015

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Background: Despite the central role that pharmacies play in the pharmaceutical supply chain, little is known regarding the prevalence and correlates of pharmacy closure.

Objectives: To quantify trends in pharmacy closures and to identify pharmacy, community, and market factors associated with such closures in the United States.

Methods: Serial, cross-sectional analysis of pharmacy data from the National Council for Prescription Drug Programs (2009-2015), IQVIA LRx LifeLink and the American Community Survey. We performed ecological analysis at the census-tract level to examine associations between pharmacy closure and pharmacy (eg, chain, independent, food store), community (eg, racial/ethnic composition, uninsured rates), and market (eg, prescription volume) characteristics.

Results: From 2009 to 2015, the total number of pharmacies increased by 7.8% from 62 815 to 67 721. During this period, 9564 (12.7%) of the 74 921 pharmacies in operation during the observation period had closed by 2015. After adjustment for potential confounders, the hazard of closure was greater among independent pharmacies (cumulative hazard 24% vs 8%; hazard ratio [HR], 2.38; 95% confidence interval [CI] 2.24, 2.53) and pharmacies located in predominantly black neighborhoods (19% vs. 13%; HR, 1.21; CI 1.11, 1.31).

Pharmacies located in neighborhoods with uninsured rates $\geq 20\%$ (18% vs 13%; HR 1.08; CI 1.01, 1.14) and experiencing a decline in prescription volume (16% vs 14%; HR 1.18; CI 1.13, 1.22) were also at increased risk for closure.

Conclusions: Despite growth in US pharmacies between 2009 and 2015, nearly one in eight pharmacies closed during this time period, disproportionately impacting people using independent pharmacies and living in underserved communities.

905 | Physicians as a source of medicine information for patients

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Background: Physicians provide patients with appropriate medicines information (MI) for achieving safe and effective use of medicines. To ensure providing the most beneficial MI it is important to know attitudes of patients to MI provided by physicians, as well as particular needs of patients.

Objectives: The objectives of this study were to evaluate importance of information provided by doctors for patients and identify specific topics of MI which patients expect to receive from physicians.

Methods: Face-to-face interviews were conducted with patients and care givers (n = 1059) in Armenia (10 regions and Yerevan). Previously developed questionnaire was used for interviewing patients. The results were analysed with the SPSS statistical software, version 22.0.

Results: 71.5% of respondents reported that they "always" or "often" use MI received from physicians; 84.0% of them noted that they trust the information received. 79.6% of participants are "completely" and "mainly" satisfied with MI they receive from physicians. More than three quarters of all the participants acknowledged importance of receiving from doctors information on dosage and method of administration (95.6%), therapeutic indications of pharmaceuticals (94.7%), duration of treatment (92.5%), adverse reactions (87.0%), contraindications (86.8%), type of activity (83.6%) and medicine's common name (76.4%). Information on manufacturer was the only topic that is important for less than half of respondents. Participants' acknowledgement of information on certain categories of users (children, pregnant women, the elderly and others) is decreasing with age increasing ($p < 0.001$).

Conclusions: Patients appreciate receiving medicines information from physicians. The most of them trust the information received and are satisfied with it. The majority of patients are interested in getting information on various specific topics from doctors. As not all the patients are satisfied with MI they receive from physicians it seems important to introduce courses of continuing education leading to increasing knowledge of medical professionals about medicines as well as their motivation to provide information patients need.

906 | A population-based description of chronic polypharmacy by sex and age

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Background: Polypharmacy, the use of multiple medications, could be described using health care databases in population regardless of age and patient characteristics.

Objectives: To describe chronic polypharmacy and patterns of encountered medications in France, according to age and sex.

Methods: All subjects alive at January 1, 2015, from the representative sample of the French health care database were included in this cohort study and followed until December 31, 2015, or date of death. Drug exposure started at dispensing date and treatment durations were estimated from mean duration of prescription of the drug. A drug presenting with a continuous exposure lasting ≥ 6 months was defined as chronic medication. Polypharmacy, ie, simultaneous exposure of ≥ 5 chronic medications, was assessed daily. Polypharmacy drug patterns were described by exposure density using ATC and by one-to-one combinations of level 1 of ATC. Description was stratified on sex and age (≤ 75 years and > 75 years).

Results: In 2015, over 584 862 subjects included in the cohort, 32 723 (5.6%) subjects presented with prevalent chronic polypharmacy including 6217 (1.1%) incident for this condition. While prevalence and incidence of polypharmacy were similar in men and women, these were higher in elderly people (eg, prevalence was 26.7% in ≥ 75 y vs 3.3% in subjects < 75 y). Overall, cardiovascular drugs were the most involved in polypharmacy (C level of ATC, 44.7% of polypharmacy). However, at a drug level (level 5 of ATC), acetylsalicylic acid (B01AC06) was the most encountered drug (5.2% of polypharmacy). Cardiovascular drugs were more frequent in men than in women (46.9% vs 42.5%) contrary to nervous system drugs (N level of ATC: 9.6% vs 15.6%). Compared with subjects aged 75 and over, youngers were more exposed in polypharmacy to drugs used in diabetes (A10 level of ATC, 10.0% vs 5.4%) to lipid lowering agents (C10 level of ATC, 11.0% vs 9.2%) and to psycholeptics (N05 level of ATC, 5.9% vs 4.1%). Cardiovascular drugs were often associated with both alimentary tract and metabolism drugs (ATC A, 26% of them in polypharmacy) and nervous system drugs (ATC N, 13% of them in polypharmacy).

Conclusions: Polypharmacy, which is mainly studied in elderly population, appeared also as a concern in the youngers where its prevalence exceeded 3%. Polypharmacy patterns varied with sex or age consistently with the admitted differences in comorbidities in these populations.

907 | Self-management of medication use by the Brazilian population: Results from the National Survey On Access, Use, And Promotion Of Rational Use Of Medicines (PNAUM)

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Background: Interest in how patients manage their illnesses and pharmacological treatments has grown in importance.

Objectives: To analyze three behaviors related to the use of medications in the Brazilian population: self-medication, intentional non-adherence, and alterations of the prescribed doses.

Methods: The data analyzed are part of the National Survey on Access, Use and Promotion of Rational Use of Medicines (PNAUM). The PNAUM was a cross-sectional survey performed in 245 Brazilian municipalities. Data from 31 573 individuals aged 20 or higher were analyzed. The sample represents the urban Brazilian population recorded by the 2010 Brazilian Census. In the search to explore and understand the behaviors related to the use of medications, three variance-adjusted Poisson regression models were constructed. The dependent variables of each model were the use of non-prescription medications (self-medication), non-adherence to the medical prescription (intentional non-adherence), and increasing or decreasing the doses (alteration of prescribed doses). All the analyses took the complex sampling plan and weighting into consideration.

Results: In the adjusted regression models, the variables of gender, age and self-assessment of health revealed themselves as being associated with self-medication and intentional non-adherence. Changes in dose appear associated with age, income, and self-assessment of health. More than half of the respondents reported an instance of self-medication, while 38% reported intentionally not taking their prescribed medication at least once. As for changes in prescriptions, 8.8% of the interviewees reported increasing the dose of their medications, and over 21% reported decreasing the dose.

Conclusions: A significant percentage of the Brazilian population do not use medications exclusively as prescribed by their physician. People, many times, cease taking medications or adapt usage schemes with the aim of better-adjusting them to their life styles. Seeking to address these different situations, we proposed the term “self-management of medication use” to designate the medications use practices, both prescribed and non-prescribed, which the individuals undertake in their daily routine. We also stress the necessity of adopting of other paradigms in health care, such as collaborative care and the “lived body,” inasmuch as the use of medications is not strictly bounded by medical prescriptions.

908 | Utilization of prescribed topical antipsoriatics in Denmark: A nationwide study

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Background: Psoriasis is a chronic inflammatory skin disease that presents a wide clinical spectrum and fluctuates through periods of flare-ups and remissions. The reported real-life use of prescribed topical antipsoriatics is conflicting and based on heterogeneous data sources.

Objectives: To describe the utilization of topicals among psoriasis patients in Denmark.

Methods: We conducted a nationwide drug utilization study based on Danish health registry data. We identified patients who received a first-time hospital diagnosis of psoriasis and had redeemed at least one topical antipsoriatic 2005-2015 ($n = 7720$). Patients were followed for 3 years from time of diagnosis. Using descriptive statistics we analyzed utilization parameters of topicals divided on type and amount. We further assessed regional differences, skewness in use, distribution of patients' number of redemptions of topical antipsoriatics, and use of methotrexate within 1 year after diagnosis.

Results: The total use of topicals during the study period were divided by (2005 vs 2015 percentages) corticosteroids with calcipotriol (27% vs 36%), calcipotriol (18% vs 2%), very potent corticosteroids (17% vs 29%), potent corticosteroids (33% vs 34%), moderate corticosteroids (7% vs 8%), and corticosteroids with antimicrobials (2% vs 1%). There was a 20% reduction in the total use of all topicals during the study period, mainly driven by a 39% decrease in the use of calcipotriol-containing preparations. Regional differences in total use of topicals (between regions with lowest to highest use) varied with a factor 1.5 in the 2013-2015 period. The distribution of topicals was skewed, with 25% of patients using 70% of the total amount of topicals. The majority of patients redeemed more than 2 packages of topicals during the first year after being diagnosed; 10% redeemed 0 packages, 23% redeemed 1 package, 39% redeemed 2-4 packages and 28% redeemed 5 or more packages. There was an increase in the prescription of methotrexate from 9.6% in the 2005-2008 period to 16.4% in the 2013-2015 period - corresponding to an increase of 70%.

Conclusions: Our study provides further evidence that use of topical antipsoriatics shows considerable heterogeneity.

909 | Patterns of hormonal contraceptive use in the self cohort

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Background: Switching contraceptive methods is common. However, no data are published on lifetime patterns of hormonal contraceptive use among U.S. black women. The Study of Environment, Lifestyle and Fibroids (SELF) is the first prospective, ultrasound-based study for the assessment of fibroid incidence and growth. SELF includes black women, aged 23-34 years, living in Detroit, Michigan (2010-2016).

Objectives: To examine lifetime patterns of hormonal contraceptive (HC) use in the SELF cohort.

Methods: Lifetime history of HC use for SELF was collected via telephone interview as part of the enrollment questionnaire. Participants were asked if they had ever used each of the following types of contraception: birth control pills, implant, patch, vaginal ring, shot, hormonal intrauterine device (IUD), and emergency contraception. Brief descriptions and examples of common brand names were provided. Contraceptive biographies were constructed for each participant ($n = 1,693$).

Results: Ever use of HCs was common in this cohort ($n = 1494$, 88%). Most women had tried two or more HCs (53%), and 55% tried both estrogen-containing and progestin-only formulations. Combined oral contraceptives (COC) were the most common HC ever used, with 70% of the cohort reporting ever use and 17% reporting current use. Ever use of other HCs were as follows: injectable progestin (IP): 43%, emergency contraception (EC): 24%, patch: 18%, vaginal ring: 13%, IUD: 11%, progestin-only pills: 6%, implant: 2%. The most frequent trajectories of HC use were COC only ($n = 315$, 21%), COC followed by IP ($n = 191$, 13%), IP only ($n = 138$, 9%), and COC followed by EC ($n = 83$, 6%). Majority of women reported using COC as their first or only HC ($n = 1058$; 71% of ever HC users; age at first use [mean, SD] = 18[3]). This was most often followed by IP ($n = 326$; 31%), patch ($n = 142$; 13%), or EC ($n = 126$; 12%). Among women who started with COC and switched to IP ($n = 326$), the most frequent third line HCs were patch ($n = 44$, 13%), EC ($n = 36$, 11%), and IUD ($n = 31$, 10%). IP was the first or only HC for 258 (17% of ever HC users; age at first use: 18[4]). This was most often followed by COC ($n = 65$, 25%) or EC ($n = 16$, 6%).

Conclusions: Oral contraception and injectable progestin were common first line hormonal contraceptives in the SELF cohort. Many women tried both estrogen-containing and progestin-only hormonal contraceptives. Knowledge of these patterns will give meaningful context to findings from pharmacoepidemiologic studies of hormonal contraception using SELF data.

910 | Time trends among new users of osteoporosis drugs over 20 years: Considerations for pharmacoepidemiologic study design

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Background: Oral bisphosphonates entered the market in 1996 and are the main osteoporosis drugs prescribed in Canada. Introduction of new therapeutic options, updates to practice guidelines, and health care policy changes may make studies examining new-users of bisphosphonates susceptible to time-varying biases.

Objectives: To compare characteristics of first-time bisphosphonate users in Ontario, Canada over time.

Methods: The Ontario Drug Benefit (ODB) program covers prescription drugs listed on the ODB formulary for residents aged 65 or more years. We identified first dispensation of an oral bisphosphonate (alendronate [10 and 70 mg], etidronate [400 mg and 500 mg calcium], and risedronate [5, 35, and 150 mg]) among residents of Ontario, from 1996/04 to 2015/03. We excluded patients taking other osteoporosis drugs, with health conditions known to impact bone, and residents of long-term care facilities. We also excluded patients aged younger than 66 years to ensure at least 1 year of drug plan eligibility. Medical and pharmacy claims within the year prior to first bisphosphonate dispensation were used to characterize patients. Descriptive statistics were used to summarize and compare patient characteristics by fiscal year.

Results: We identified 523 210 eligible seniors starting bisphosphonate therapy in Ontario from 1996 to 2015 (mean age 75 years; 5.0% rural). A larger proportion of men (6.2% to 29.0%) and diabetics (8.7% to 17.8%) initiated therapy over time. History of benzodiazepines decreased (26.6% to 11.5%), while prior statin use (9.5% to 42.8%), oral corticosteroid use (10.6% to 14.7%), and prior bone mineral density testing (46.7% to 68.0%) increased. A shift in prescriptions from etidronate to alendronate and risedronate was documented, consistent with drug policy changes.

Conclusions: Characteristics of new initiators of oral bisphosphonates among Ontario seniors changed over time, reflecting changes in health care delivery and osteoporosis management. Consideration must be given to time-trends when designing pharmacoepidemiologic studies in this population, including those using interrupted time series analysis, matching, propensity scores, or self-controlled designs.

911 | Over 63 700 Ontario seniors have initiated denosumab: User characteristics and persistence with therapy

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Background: Denosumab was added to the Ontario Drug Benefit formulary for patients at high risk for osteoporotic fracture in February 2012. Each injection covers 6-months of therapy.

Objectives: We sought to describe new denosumab users and estimate persistence with therapy.

Methods: We identified Ontario seniors (aged ≥ 66 years) initiating denosumab therapy from 2012/02 to 2016/03. Patient characteristics were summarized based on medical and pharmacy claims, and stratified by residence in the community or long-term care (LTC). Persistence with therapy and return to therapy after discontinuation (>90 -day gap) were summarized.

Results: We identified 63 780 (97% female, 13% LTC, 79% in urban areas) new users of denosumab; with an average of 1300 (SD = 183.0) patients initiating therapy per month. Denosumab users residing in the community had a higher prevalence of bone mineral density testing (63% vs 5%), yet were younger (mean age = 78.3 years vs 87.6 years), and had a lower proportion of hospitalizations (14% vs 31%), or hip fractures (3% vs 9%) compared with LTC patients. Prior osteoporosis drug use was high in both groups (78% community, 82% LTC) as was persistence with denosumab therapy. Patients persisted with therapy for an average of 1.7 years (SD = 1.0). Overall, 70% persisted ≥ 1 year, 35% ≥ 2 years, and 15% ≥ 3 years. Of those that discontinued therapy, 17% returned within 4 years.

Conclusions: New exposure to denosumab is increasing at a steady rate among Ontario seniors. Patients persisted with therapy for an average of 1.7 years, and more than a third persisted for at least 2 years.

912 | Prevalence and duration of skeletal muscle relaxant treatment among commercially insured adults in the United States: 2005 to 2015

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Background: Skeletal muscle relaxants (SMR) are a commonly prescribed group of medications indicated for relief of acute and painful musculoskeletal conditions, but secular trends and longitudinal patterns of their use are poorly described in the current literature.

Objectives: To examine the annual prevalence and duration of SMR treatment among commercially insured US adults aged 18 to 64 years.

Methods: In this retrospective cohort study, the Truven MarketScan Research Database was used to identify eligible patients with musculoskeletal disorders and 11 years of continuous enrollment between 2005 and 2015. Using a repeated cross-sectional design and direct standardization to the 2015 source population, we estimated the age-adjusted annual prevalence of SMR treatment use. Using the Kaplan-Meier method, we derived median survival times of treatment duration. Analyses were stratified by sex, age groups, and individual agents.

Results: A total of 1.25 million patients were included. The prevalence of SMR use increased slightly by 7% (prevalence rate ratio [PRR] and 95% confidence interval [CI]: 1.07 [1.05-1.09]) from 152.7 per 1000 patients in 2005 to 163.2 in 2015. Cyclobenzaprine was the dominant agent accounting for more than half of the use (from 66.9 to 82.4 per 1000 patients, PPR: 1.23 [1.20-1.26]). The considerable growth in the use of baclofen (PPR: 3.04 [2.74-3.37]), tizanidine (PPR: 2.18 [2.07-2.30]), and methocarbamol (PPR: 2.08 [1.97-2.19]) was in parallel with a decline in the use of metaxalone (PPR: 0.31 [0.30-0.33]), orphenadrine (PPR: 0.52 [0.46-0.57]) and carisoprodol (PPR: 0.64 [0.60-0.68]). The use of SMR was more prevalent among females, and age groups 35 to 44 and 45 to 54 years. Overall, the median duration of treatment was 15 days with 8.4%, 4.1%, and 2.1% of patients used treatment for more than 90, 180, and 365 days, respectively. The treatment duration increased with age and was slightly higher for females. Compared with cyclobenzaprine, patients initiated on baclofen (HR: 1.75), tizanidine (HR: 1.64), and carisoprodol (HR: 1.33) had longer duration of treatment.

Conclusions: While the trend varies between individual agents, the overall utilization of SMRs among patients with musculoskeletal disorders remains stable in recent years. Despite limited evidence to support efficacy, a sizable number of patients are long-term users. Further study is needed to understand determinants of treatment as well as outcomes associated with long-term SMR use.

913 | Prescribing variation in English primary care following a regulatory safety warning on mirabegron

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Background: Safety issues detected after marketing of medications can trigger regulatory action such as direct health care professional communications (DHPC). DHPC can be effective in changing prescribing behaviour, however the extent to which prescribers vary in their response to DHPC is unknown.

Objectives: To explore changes in prescribing following a DHPC on mirabegron's safety, and variation in prescribing among GP practices.

Methods: This is an interrupted time series study of English GP practices from 2014-2017. The Health and Social Care Information Centre provided monthly statistics on aggregate practice-level prescribing and

practice characteristics (practice staff and registered patient profiles, Quality and Outcomes Framework indicators, and deprivation of the practice area). The primary outcome was monthly mirabegron items as a proportion of all overactive bladder (OAB) drug items. The exposure was a DHPC issued by the Medicines and Healthcare products Regulatory Agency in September 2015. Between-practice variation in prescribing before and after the DHPC was assessed using the systematic component of variation (SCV). Multilevel segmented regression with random effects quantified the change in level and trend of prescribing after the DHPC, and practice characteristics were assessed for their association with a reduction in prescribing.

Results: This study included 7408 practices. Pre DHPC, 87.6% of practices prescribed mirabegron in August 2015 and mirabegron composed a mean of 7.9% (SD 6.66) of OAB items. Variation between practices was classified as very high and mean SCV did not change significantly in the 6 months after the DHPC (12.4) compared with before (11.6). Before the DHPC, there was a monthly trend of 0.294 (95% CI 0.287, 0.301) percentage points increase. There was no significant change immediately after the DHPC (0.0157, 95% CI -0.079, 0.111) however there was a significant reduction in trend (-0.038, 95% CI -0.051, -0.025). Deprivation, lower proportion of older patients, and fewer registered patients were associated with a practice significantly reducing the level of mirabegron prescribed immediately post-DHPC.

Conclusions: Variation in mirabegron prescribing was high and did not change following a DHPC. There was no immediate prescribing change post-DHPC, although the monthly growth did slow. Knowledge of the degree of variation in and determinants of response to safety communications may allow those that do not change prescribing to be provided with additional supports.

914 | Patterns of drug utilization and spontaneous adverse drug reactions reporting of oral anticoagulants in the Czech Republic between 2007-2016

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Background: Mostly warfarin had been used until direct oral anticoagulants (DOACs) were approved; therefore, some changes are expected in the field of drug utilization and pharmacovigilance reporting.

Objectives: The aim was to explore drug utilization patterns and to evaluate reported adverse drug reactions (ADRs) of oral anticoagulants (OACs) in the Czech Republic (CR) between 2007-2016.

Methods: A retrospective study was conducted using data from the State Institute for Drug Control (SUKL) database containing reports on drug supplies from distributors to pharmacies, health care facilities, vendors of selected pharmaceuticals, and veterinarians. The OACs approved in the CR during the study period were included and their

utilization was calculated as a ratio of the number of defined daily doses per thousand inhabitants per day (DDD/TID). Furthermore, the OACs related expenditures analysis was performed. Secondly, the preliminary quantitative analysis of the SUKL database of spontaneously reported suspected ADRs to OACs was conducted. In the CR, reporting is obligatory for health care professionals (HCPs) and marketing authorisation holders, yet also is received from patients. Only the reports from HCPs and patients were included. Descriptive statistics was used to describe utilization and ADRs patterns. Cross-correlation was applied to assess DOACs and warfarin utilization relationship ($p < 0.05$).

Results: The DOACs utilization grew from 0.002 to 5.26 DDD/TID between 2008-2016, while warfarin utilization slightly decreased after DOACs approval, from 10.03 to 8.36 DDD/TID between 2007-2008. However, after a small increase, its current utilization almost stagnates (in average 11.46 DDD/TID between 2012-2016), showing that the increasing use of warfarin was halted along a significantly rising use of DOACs. OACs expenditures obviously increased, due to higher costs of DOACs. First results showed that in the given period the ADRs were reported mostly to warfarin (43.83%), dabigatran (32.34%), and rivaroxaban (18.30%), however much less to apixaban (5.53%) of total 235 ADRs. Ongoing ADRs analysis is still in progress.

Conclusions: The results reflected a growing utilization of DOACs. Warfarin utilization does not decrease in relation to DOACs, so the total OACs utilization is increasing. Outcomes of drug utilization and ADRs should be interpreted in relation to the time of approval. *The study was supported by Charles University grant (SVV 260 417).*

915 | Characteristics and treatment patterns of new users of fluticasone furoate/vilanterol: A cohort study set in UK primary care

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Background: Fluticasone furoate/vilanterol (FF/VI) is an inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) approved in the EU in 2013 for the treatment of asthma (two strengths 100/25µg or 200/25µg) and Chronic Obstructive Pulmonary Disease (COPD, 100/25µg only).

Objectives: This study aimed to describe patient characteristics and drug utilisation in new users of FF/VI in the post approval period.

Methods: A retrospective cohort study using the UK Clinical Practice Research Datalink (CPRD). Patients newly prescribed FF/VI between 1Jan2014-31Dec2015 were identified using prescription records. New users were required to have recorded data for at least 12 mths prior to and 12 mths post the index FF/VI prescription date. To

account for both approved indications, new users were assigned to mutually exclusive diagnosis groups based on recorded codes for: (1) COPD (with/without asthma history), (2) asthma (without COPD) or (3) other (neither COPD/asthma). Patient characteristics including medical history, past and concomitant respiratory medications, FF/VI treatment patterns and adherence (proportion of days covered [PDC]) were described by diagnosis group and FF/VI strength.

Results: Among this new user cohort, 77% (n = 3380) initiated FF/VI 100/25 (29% COPD with asthma history, 36% COPD without asthma history, 31% asthma, 4% other) and 23% (n = 993) initiated FF/VI 200/25 (25% COPD with asthma history, 20% COPD without asthma history, 51% asthma, 4% other). The COPD groups (both strengths) had a mean age of 68-69 yrs and about half were female; the asthma group was younger (mean age 49-53 yrs) and two-thirds female. About half of COPD patients were also taking a long-acting anti-muscarinic drug at the index date. COPD patients were more likely than asthma patients to augment or switch medication over 12 months follow-up. Median PDC was slightly higher among COPD patients (0.74, IQR 0.41-0.99) compared with asthma (0.66, IQR 0.25-0.90) and lowest in the other group (0.25, IQR 0.08-0.74).

Conclusions: While two-thirds of FF/VI 100/25 initiators had a recorded diagnosis of COPD, FF/VI 200/25 was more evenly prescribed over the two indications. Differences in demographics and treatment patterns were observed across diagnosis group and strength prescribed. These findings suggest that when conducting drug utilisation studies, both product strength and indication should be considered to capture the diversity in prescribing patterns in a real-world setting. GSK funded study: RJ2214

916 | Use of bisphosphonates before and after hip fracture surgery: A Danish population-based prevalence study, 2005-2015

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Background: Despite availability of effective pharmacotherapy, international research suggests that less than one-third of hip fracture patients receive treatment for secondary fracture prevention.

Objectives: To conduct a series of Danish nationwide cross-sectional analyses of bisphosphonate use before and after hip fracture surgery over several calendar periods.

Methods: We included patients aged 65+ with an incident hip fracture in 2005-2015 registered in Danish population-based health registries, who were alive one year after surgery. Bisphosphonates use was defined as ≥ 1 bisphosphonate prescription in the year before or after hip fracture. Incident users were previously treatment-naïve patients with ≥ 1 bisphosphonate prescriptions in the year after hip fracture. We calculated the proportion of

bisphosphonate users before and after hip fracture. Using log-binominal regression, we calculated prevalence ratio (PR) with 95% confidence interval (CI) for being incident user after hip fracture for sex and age groups.

Results: Among the 46 513 hip fracture patients surviving 1 year (1-year mortality = 29%), the proportion of bisphosphonate use before hip fracture varied between 8% and 12%, increasing slightly from 2005 to 2015. After hip fracture, the proportion of any bisphosphonate use within one year decreased from 17% in 2005 to 14% in 2011, whereupon it increased to 22% in 2015. The proportion of incident bisphosphonate use decreased from 4% in 2005 to 2% in 2010, whereupon it increased to 4% in 2015. A slightly lower proportion (range: 1-4%), but same pattern was seen for incident use before restricting to survivors. The PR for incident bisphosphonate use was 0.8 (95% CI: 0.7-0.9) for men compared with women, and 0.9 (95% CI: 0.8-1.0) and 0.5 (95% CI: 0.4-0.5) for patients age 75-84 years and ≥ 85 years, respectively, compared with patients age 65-74 years.

Conclusions: Less than one-third had bisphosphonate after hip fracture. We observed only a slight increase in bisphosphonate user following hip fracture over the study period, and initiation of bisphosphonate depended on sex and age of the patients.

917 | Drug use among Canadian seniors

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Background: On average, seniors use more drugs than any other age group. Although using multiple prescription medications is an important part of managing many chronic conditions, it is associated with an increased risk of adverse drug events, highlighting the need for continued focus on improving prescribing practices

Objectives: This report measures the average number of drugs used by Canadian seniors, and the proportion of seniors meeting various thresholds of drug use (eg, 10+ drugs) between 2011 and 2016. It also identifies the drugs classes most commonly prescribed to seniors in the community and in long-term care facilities. Finally, it examines variations in the number of drugs used, and potentially inappropriate drug use by sex, age, neighbourhood income, and geographic location.

Methods: This reports analyzes data from the Canadian Institute for Health Information's National Prescription Drug Utilization Information System, which holds drug claims data from Canadian public drug programs, including data for over 5 million seniors, roughly 90% of the Canadian seniors' population. Information on drugs dispensed in hospitals, or drugs not covered by public drug programs, is not included. Potentially inappropriate drug use was defined using the American Geriatrics Society's 2015 updated Beers criteria.

Results: There was little change in the number of drugs prescribed to between 2011 and 2016. Approximately one-quarter of seniors

on public drug programs used 10 or more drug classes in both years. Statins were most commonly prescribed drugs among seniors. Proton pump inhibitors (PPIs) and several classes to treat cardiovascular disease were also among the most commonly prescribed drugs. Almost one-half of seniors had a potentially inappropriate prescription, most commonly PPIs or benzodiazepines. The use of benzodiazepines decreased during the study period; which may be related to ongoing initiatives to reduce the use of these drugs in seniors. However, the use of PPIs, which have also been the focus of such initiatives, increased. Seniors living in low-income neighbourhoods and rural/remote areas were prescribed more drugs overall, and more potentially inappropriate drugs, as did women and older seniors.

Conclusions: The need to reduce the number of drugs, the number of potentially inappropriate drugs and adverse drug events among seniors is a topic of increasing concern. Some initiatives focused on improving prescribing to seniors have shown promising results; however, their overall impact on the number of drugs used has been minimal.

918 | Availability of essential medicines for newborns in health care institutions of Bangladesh

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Background: Assessment of the availability of essential medicines for the newborn in health care facilities in developing countries is scarce particularly in Bangladesh. The demand for the essential medicines for newborns is very high. This study aimed to assess the availability of essential medicines for newborns in health facilities of Bangladesh.

Objectives: This study aimed to assess the availability of essential medicines for newborns in health facilities of Bangladesh.

Methods: We used data from the nationally representative 2014 Bangladesh Health Facility Survey. The availability of essential medicines within the facility was measured using the methodology proposed by World Health Organization (WHO) and United States Agency for International Development (USAID). Information on four essential medicines for newborn care (Antibiotic eye ointment for newborn, Injectable gentamicin, Ceftriaxone powder for injection, and Amoxicillin syrup/suspension) was collected if the facility had the medicine on the day of the survey. Data was collected from 1548 public, private, and non-governmental (NGO) health facilities throughout Bangladesh.

Results: Eight out of ten facilities that offer normal delivery care (78% excluding Community Clinic [CCs]) had amoxicillin syrup or suspension available. The Amoxicillin syrup or suspension was more available at Union level public facilities (87%), CCs (85%), and

district and Upazila level public facilities (79%) as compared with private hospitals (55%) and NGO facilities (71%). Only a smaller proportion (28% or less) of the facilities that offer delivery services had the other three essential medicines for newborn care available at the service site on the day of the survey. Availability of antibiotic eye ointment varied from 19% to 29% across different health care facilities.

Conclusions: Availability of essential medicines for the newborn in most of the primary and the secondary care institutions was satisfactory. On average, the private hospitals were somewhat better supplied with all essential medicines.

919 | Use of prescription medications with boxed warnings in the United States, 2003-2014

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Background: The Food and Drug Administration mandates the use of boxed warnings for prescription medications with serious or life-threatening risks.

Objectives: This study will examine hitherto sparsely studied trends in the use of medications with boxed warning among US children, adolescents, and adults.

Methods: Medications with boxed warnings were identified via Truven Health Analytics Micromedex. Use of these medications was estimated over a 12-year period using nationally representative data from the National Health and Nutrition Examination Survey (NHANES). Five consecutive 2-year NHANES cycles were included (2003-2004 to 2013-2014). Our sample includes US children, adolescents, and adults as represented by 50 865 non-institutionalized participants of NHANES.

Results: In 2013-2014, 35.5% (33.7%, 36.8%) of Americans report using at least one medication with a boxed warning. Eight percent (8.2% [6.7%, 9.9%]) of children and adolescents (ages 0-19) report using a medication with a boxed warning in 2013-2014. Older age groups use these medications at progressively higher rates; 25.1% (21.9%, 28.5%) of adults ages 20-39, 48.5% (44.5%, 52.0%) of adults ages 46-64 years, and 74.5% (70.3%, 78.4%) of adults 65 years of age or older report using a medication with a boxed warning. Use of medications with a boxed warning in aggregate remained stable in every age group in the period examined. Among children and adolescent who used a medication, the most commonly used therapeutic classes of medications with boxed warnings in 2013-2014 were central nervous system stimulants (16.6%), sex hormones (6.1%), antidepressants (5.9%), analgesics (5.5%), antipsychotics (4.5%), and bronchodilators (1.7%). Among adult medication users, antidepressants (23.8%), analgesics (18.1%), antidiabetics (15.0%), β -blockers (12.7%), thyroid hormones (12.3%), and sex hormones (8.9%) were the most prevalent therapeutic classes. Analgesics and sex hormones experienced declines

in use among adults between 2003-2004 and 2013-2014 (from 25.8% to 18.1% and 12.3% to 8.9% respectively; $p < 0.001$), while use of antidepressants, antidiabetics, and CNS stimulants increased (from 17.8% to 23.8%, 9.5% to 15.0%, and 0.3% to 1.8%, respectively; all $p < 0.01$).

Conclusions: More than one-third of Americans use at least one medication with a boxed warning, despite growing drug safety concerns. The majority of these medications are psychotherapeutics and central nervous system agents, which may be over-prescribed in the United States.

920 | A comparison of drug utilization metrics for six drug classes with nationally projected sales and patient-level data from the Sentinel database

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Background: Obtaining medication use estimates is a vital component of postmarketing surveillance. Nationally projected sales data and patient-level data from population-based administrative claims databases are widely used to estimate medication use. However, it is unclear whether these estimates are comparable.

Objectives: To compare US drug utilization estimates of relative percent market share for six drug classes between nationally projected sales data from IQVIA National Sales Perspectives (NSP) database and patient-level data from the Sentinel Distributed Database (SDD).

Methods: We conducted a study using IQVIA NSP database and SDD from 2011-2015 for selected medications from six drug classes, three of which had relatively standardized dosing (1. Statins, 2. Angiotensin converting enzyme inhibitors [ACEI], 3. Beta blockers [Bb]) and three of which had more complex dosing (4. intravenous [IV] iron products, 5. Granulocyte Colony Stimulating Factors [GCSF], 6. Tumor Necrosis Factor inhibitors [TNFI]). From NSP, we extracted the amount sold of each medication using three different metrics: (1) *Eaches*-number of vials/bottles; (2) *Extended Units (EU)*-number of tablets/capsules/milliliters, and (3) *Kilograms (Kg)*-amount of active ingredient. For each sales-based and patient-level estimation, we calculated the percent market share across all sales distribution channels by calendar year for selected products within the six drug classes. We compared each sales-based metric with patient-level data in SDD using different agreement metrics, including standardized mean differences and correlation.

Results: For statins, ACEI, and Bb, EU showed the closest agreement compared with other sales-based metrics when compared with patient-level data. The Kg sales-based metric had the closest agreement with patient-level data for both IV iron products and GCSF. None of the sales-based metrics consistently agreed with the

patient-level data for TNFI. Among the selected medications within the six drug classes, *Eaches* showed the least agreement relative to other sales-based metrics when compared with SDD patient-level data.

Conclusions: Nationally projected sales data and their agreement with patient-level data can vary considerably between selected metrics, in part driven by product characteristics. When comparing nationally projected sales to patient-level data, it may be useful to evaluate multiple sales data metrics to better understand medication use.

921 | Trends and drivers of immunosuppressants' expenditure in Brazil

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Background: The costs of immunosuppressants pose a growing burden on health care systems worldwide. A comprehensive understanding of how procurement is being carried out provides strong support for the development of effective policies.

Objectives: This study analyzes the spending trends of immunosuppressants in general and by therapeutic subgroups in Brazil, from 2010 to 2015, and identifies the main factors that contribute to the increase in expenditure.

Methods: All data regarding drug purchases were retrieved from the Federal Procurement System database (SIASG). The purchases were grouped by volume (number of packages purchased) and by expenditure (number of packages purchased multiplied by unit price) for each year. Data on price and expenditure was adjusted according to inflation of December 31, 2015. In order to study the immunosuppressants responsible for 90% of expenditure, DC90% methodology was applied. A model of decomposition analysis was used to evaluate the impact of price, quantity purchased and therapeutic choice on immunosuppressive expenditures.

Results: From 2010 to 2015, the Brazilian Federal Government spent USD 3.4 billion on the acquisition of 623.7 million drug packaging units of immunosuppressants. TNF- α inhibitors were responsible for the largest expenditure, accounting for 67% of total spending (USD 2 billion). During the period, over 331 million units of calcineurin inhibitors were purchased, accounting for 53% of total purchases in volume. Spending on immunosuppressants increased 1.49 times over the period. The quantity acquired was the main contributing factor to the increase in expenditure. The therapy choice has contributed to the increase in the expenditure for the following therapeutic groups: selective immunosuppressants, calcineurin inhibitors and other immunosuppressants. Only ten drugs were responsible for 90% of total expenditure. Adalimumab was responsible for one third of the costs (USD 1.1 billion) while Eculizumab, that was not

registered by the Brazilian regulatory agency at that time, ranked sixth in the list (USD 217 million).

Conclusions: Introduction of new products has significantly influenced spending growth. Adopting new technologies into Brazilian health care system should be done cautiously, considering the therapeutic values and financial impact of each new drug to ensure the system sustainability.

922 | Overall decreasing trend in polypharmacy over 12 years, but still unresolved in pediatric patients in South Korea

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Background: Polypharmacy is associated with adverse drug reactions (ADR) and is an economic burden on the health insurance system. Little is known about both the long term polypharmacy trends and the distributions of polypharmacy according to age groups or socioeconomic status in South Korea.

Objectives: To assess longitudinal time trend in polypharmacy and its associated factors in South Korea.

Methods: Our time-series study used a nationwide sampled database. Our study subjects were outpatient of all ages who received at least one prescription between January 1, 2002, and December 31, 2013. Polypharmacy was defined as the concomitant prescription of ≥ 6 distinct medications. The yearly prescribing trends were calculated and plotted. The distributions of polypharmacy were examined according to patient economic status (0 = most deprived and 10 = most affluent). We conducted logistic regression to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for polypharmacy.

Results: The yearly prevalence of polypharmacy decreased from 53.6% in 2002 to 43.4% in 2013. Of 920 951 outpatients in 2012-2013, 55.5% ($n = 510\ 806$) were exposed to polypharmacy. Pediatric patients one to 10 years of age had the highest association with polypharmacy (aOR = 6.71; 95% CI = 6.35-7.10). Pediatric patients 1 to 4 years of age had the highest numbers of medications among all age groups (mean: 4.14 ± 0.75 years), followed by children aged 5 to 9 (mean: 4.05 ± 0.75 years), and elderly aged 80-84 (mean: 3.90 ± 1.37 years). A strong association between multimorbidity and polypharmacy was also observed (aOR = 4.41; 95% CI = 4.36-4.46). The most deprived subjects had higher odds of polypharmacy compared with those in the most affluent subjects (aOR = 1.49; 95% CI = 1.45-1.54).

Conclusions: Polypharmacy prescriptions have decreased over 12 years in South Korea. The most deprived group had more morbidities and were more exposed to polypharmacy. The high level of polypharmacy in pediatric patients is a public health concern that warrants policymaker attention.

923 | Factors related to intentional non-initiation of bisphosphonate treatment in osteoporosis patients in primary care

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Background: Adherence to osteoporosis treatment is crucial for good treatment effects. However, adherence has been shown to be poor and a substantial part of the patients do not even initiate treatment.

Objectives: To gain insight into the considerations of both osteoporosis patients and general practitioners (GP) concerning intentional non-initiation of bisphosphonate treatment.

Methods: Osteoporosis patients and GPs were recruited from the SALT Osteoporosis Study and a transmural fracture liaison service, both carried out in the Netherlands. Using questionnaires, we identified non-starters and starters of bisphosphonate treatment. Semi-structured interviews were conducted to gain a detailed overview of all considerations until saturation of the data was reached. Starters were asked to reflect on the considerations that were brought forward by the non-starters.

Results: 16 non-starters, 13 GPs, and 10 starters were interviewed. Three main themes were recognized: information to patients, medication, and disease awareness. Some non-starters indicated to be insufficiently or ambiguously informed by the GP. Aversion towards medication, fear of side effects, and a low risk perception also contributed to not starting the medication. Concerns about osteoporosis treatment and its side effects were confirmed by several GPs. Some GPs had a limited understanding of the current osteoporosis guidelines and the indications for treatment. Starters were properly informed, or they collected information themselves. They were aware of their fracture risk and were confident in the outcome of the treatment.

Conclusions: Insufficient information to patients, and attitudes towards medication use including concerns about side effects, and a low risk perception were primary factors. Our findings suggest that primary care might be improved by increasing patients knowledge as well as addressing expected barriers and discussing possible solutions, in order to increase the rate of patients who start using osteoporosis medication, thereby preventing future fractures.

924 | Incident use of proton pump inhibitors in France, 2015

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Background: Proton pump inhibitors (PPIs) are indicated in the treatment of gastric acid-related diseases and for the prevention of nonsteroidal anti-inflammatory drugs (NSAIDs)-induced gastro-intestinal lesions in patients at risk. Due to high effectiveness, relative safety and low cost, their use has widespread dramatically. To date, in France, most studies on the use of PPIs have been limited to specific populations.

Objectives: To describe the nationwide incident use of PPIs in France in 2015, based on the French national health insurance reimbursement and hospitalisation databases (National System of Health Data, SNDS).

Methods: A longitudinal, retrospective observational study was conducted using the SNDS, which covers almost the entire French population (66 million inhabitants). The included population comprised new PPI users in 2015, ie, with no reimbursement for PPI in the past year. Only prescribed PPIs, accounting for approximately 97% of PPIs dispensed in pharmacies, are recorded in the SNDS. The date of the first reimbursement for PPI in 2015 was the study entry date. Individual information on concomitant medications, hospital diagnoses and medical and laboratory procedures was available. Follow-up ended at any treatment discontinuation of >30 days or, in the absence of treatment discontinuation, one year after study entry.

Results: Among the 15 837 416 subjects with a reimbursement of PPIs in 2015, 7 776 032 (49.1%) were new users: 43.7% of PPIs initiators were men, mean age was 48.8 years and 20.7% (n = 1 606 587) were aged over 65 years old. PPI treatment was initiated by a general practitioner in 73.9% (n = 5 745 155), and 78.2% (n = 6 077 832) received only one PPI reimbursement. Mean PPI treatment duration was 40.8 days overall, with higher duration among individuals aged >65 years (65.0 days). Long-term users (>6 months) accounted for 4.0% (n = 309 983) of PPIs initiators overall, and 10.2% (n = 164 058) among individuals aged >65 years. Overall, more than half (52.0%, n = 4 042 269) PPIs initiations occurred in patients with a co-prescription of NSAID, among whom 90.7% (n = 3 664 566) initiated PPI and NSAID simultaneously. In addition, 33.9% (n = 2 634 700) of PPIs initiators did not have any identified concomitant medication, medical/laboratory procedure or hospital discharge diagnosis supporting the use of PPI.

Conclusions: Almost 8 million patients initiated a PPI treatment in France in 2015, mostly in association with NSAID. In view of such a widespread use, the appropriateness of PPI treatments should be questioned.

925 | Supply of drugs for the treatment of psoriatic arthritis in the Brazilian public health system

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Background: Psoriatic arthritis (PsA) is a chronic arthritis that affects axial and peripheral joints and is associated with psoriasis. In the Brazilian Public Health System (SUS), the treatment consists mainly of Disease-Modifying Antirheumatic Drugs conventional synthetic (csDMARD) and biological (Anti-TNF).

Objectives: To evaluate the profile of drugs solicitations and the time spends to obtain these drugs in the SUS.

Methods: A cross-sectional study was conducted in a Specialized Pharmaceutical Center in Belo Horizonte, Brazil. All the drugs solicitations in the period between November 2014 and December 2016 were evaluated. The period among the physician prescription until the delivery of the drug for the patients by pharmacy was considered for time analysis for drug supply. Categorical variables were described by the frequency distribution and the continuous variables by the median (Interquartile Range [IQR]).

Results: A total of 217 solicitations were analyzed, which contained 250 drugs. Anti-TNF drugs were the most requested (68%), being 40% for adalimumab, 20% for etanercept and 8% for infliximab. Among the csDMARD (28.4%), the drugs methotrexate (13.6%) and leflunomide (12%) were the most requested. However, 87% of all solicitations were attended. The median age of the patients was 52.8 years (IQR 23.9-29.9) and most requests were for female patients (57.2%). Rheumatologists were the doctors who most requested some drug (74.2%). As for the health establishment of origin, 42.4% of solicitations were made from private practices and 31.3% from hospitals. Most of the establishments that did do solicitations were private (60.8%) and did not attend the SUS patients (62.2%). The median time between the physician prescription and the first dispensation of the drug by pharmacy was 64 days (IQR 44-88), and there was no difference between anti-TNF and csDMARD.

Conclusions: Optimize the time spent on access to medicines is important. In this sense, to inform and guide the patient, decrease the bureaucracy for process analysis, increase interaction between prescribers and the State, and computerize of documents and processes can be important tools for the efficiency of public management.

926 | Depression treatment in primary care: Do prescribers account for weight modulating effects of antidepressants?

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Background: Certain antidepressants (AD) are obesogenic, and patients with excess weight may be less responsive to treatment with AD, leading to increased prescribing volumes. These effects may form a vicious circle contributing to the high prevalence of treatment resistant depression in obese and overweight patients in primary care. It is important to evaluate how primary care providers prescribe AD known to modulate body weight.

Objectives: Using a national primary care practice database, to evaluate frequency of AD prescribing to patients of different weight groups, with a focus on AD known to modulate body weight.

Methods: Study sample was extracted from the national Canadian Primary Care Sentinel Surveillance Network (CPCSSN) for 2014-2016. Patients aged 18-65 with a history of depression were included. Measures were AD group, AD type, body mass index (BMI). BMI was classified as underweight (<18.5 kg/m²), normal weight (18.5-24.99 kg/m²), overweight (25-29 kg/m²), or obese (≥30 kg/m²). Data were analyzed with descriptive and Chi-square statistics; 95% Confidence Intervals (95% CI) were calculated by Newcomb-Wilson method.

Results: Of 48 525 patients with a history of depression, 23 468 (48.4%) were prescribed AD. Compared with normal weight patients, 3.8% (95% CI [2.7, 4.9]) more obese, and 1.6% (95% CI [0.5, 2.7]) more overweight patients received AD. Bupropion, a norepinephrine-dopamine reuptake inhibitor (risk for weight loss), was prescribed to 1.4% more (95% CI [0.9, 2.9]) obese and 0.9% more (95% CI [0.3, 1.4]) overweight than to normal weight patients. Underweight patients received 1.1% (95% CI: [0.1, 2.1]) more norepinephrine- and specific serotonergic AD mirtazapine (risk for weight gain), compared with normal weight patients. In contrast, another AD known for its risk for weight gain, amitriptyline (tricyclic group), was prescribed to 1.3% (95% CI [0.9, 1.7]) more obese and 0.8% (95% CI [0.4, 1.2]) more overweight patients.

Conclusions: Our results suggest that primary care prescribers account for weight modulating impact of mirtazapine and bupropion, but not for obesogenic effect of amitriptyline. In addition, the proportion of patients with AD prescriptions was higher in the excess weight groups than in the normal weight group. These findings support the hypothesis that obesogenic effects of AD may contribute to the high prevalence of treatment resistant depression in patients with excess weight and highlight the importance of accounting for these effects when prescribing.

927 | Estimating probability of refills after initial opioid analgesic prescriptions for acute pain in primary care settings

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Background: In response to rising opioid overdose deaths, several stakeholders in the US have implemented upper limits on initial opioid analgesic prescribing for acute pain. The impact of such limits for

patients with acute pain conditions presenting to primary care settings has not previously been assessed.

Objectives: To estimate opioid use, including need for refills, by opioid-naïve adults presenting to primary care settings with common pain conditions.

Methods: Using 2014 data from a large US national commercial insurer, we identified opioid-naïve adults who filled an opioid analgesic prescription of <30 days duration within 7 days of an initial visit for any of 10 common acute pain conditions presenting to a primary care setting (back pain with radiculopathy, back pain without radiculopathy, neck pain, joint pain, tendon/bursal pain, muscle strains/sprains, musculoskeletal injury such as ligamentous tears, urinary calculus, headache, and dental pain). Patients were followed for 30 days following the index opioid fill; any additional fill for opioids during this period was considered a refill. We generated descriptive statistics concerning the days' supply, number of tablets dispensed, and morphine milligram equivalents (MME) of the index dispensing. A generalized additive logistic model (GAM) was used to estimate the probability of refill (PR) as a smooth function of days' supply of the index dispensing. This model was used to estimate the PR using an initial days' supply of 7 (PR₇) as a threshold of interest, as this represents the Centers for Disease Control and Prevention recommended upper-limit of prescribing for acute pain.

Results: Of 176 607 patients with a primary care visit for an acute pain complaint, 7.6% obtained at least one opioid prescription. The median initial days, tablets and MME supplied across all 10 conditions ranged from 4-7 days, 20-30 tablets, and 100-150 MME. PR₇ for 9 out of 10 conditions was ≤ 0.25 (headache 0.11, back pain without radiculopathy 0.15, muscular strains 0.15, tendonitis 0.18, joint pain 0.20, dental pain 0.20, nephrolithiasis 0.21, radicular back pain 0.21, neck pain 0.22). PR₇ for musculoskeletal injury was 0.41.

Conclusions: A seven-day supply on initial opioid analgesic prescriptions may be appropriate for most patients with acute pain presenting to primary care settings, though adequate treatment for all patients will depend on the ability of health systems to generate timely refills for those with additional requirements.

928 | Prescription drug coverage for treatment of low back pain among US Medicaid, Medicare Advantage, and Commercial Insurers

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Background: Despite unprecedented injuries and deaths from prescription opioids, little is known regarding medication coverage policies for the treatment of chronic, non-cancer pain among US insurers.

Objectives: To assess coverage policies for 62 pharmaceutical products commonly used to treat low back pain, including prescription opioids (n = 30), non-steroidal anti-inflammatory drugs (NSAIDs) (10), anti-depressants (10), muscle relaxants (6), anticonvulsants (4) and topical analgesics (2).

Methods: We conducted a cross-sectional study of publicly available documents for year 2017, derived from 15 Medicaid, 15 Medicare Advantage and 20 commercial health plans based in 16 states representing over half the US population. Our primary outcomes were formulary coverage, utilization management and patient out-of-pocket costs. Documents were reviewed and abstracted by a single reviewer; a second reviewer validated a 20% data sample with inter-rater agreement exceeding 95%. To supplement the data extraction and aid interpretation, we conducted 20 key informant interviews with senior medical and pharmacy health plan executives from representative plans.

Results: Medicaid and Medicare Advantage plans covered fewer opioids (medians 63% and 57%, respectively) and non-opioids (69%, both) examined than commercial plans (77% opioids, interquartile range [IQR] 70-84%; 81% non-opioids, IQR 74-85%). Utilization management strategies were common for opioids (91% Medicaid; 100% Medicare Advantage; 74% commercial), generally relying upon 30-day quantity limits, and non-opioids (52% Medicaid; 45% Medicare Advantage; 35% commercial), most commonly using quantity limits and prior authorization. Step therapy was especially uncommon. Among commercial plans, the median plan placed most opioids (74%) and non-opioids (81%) on Tier 1, with a median copayment of \$10 (IQR \$9-\$10) per 30-day supply. Key informant interviews revealed an emphasis on increasing opioid utilization management and identifying high-risk prescribers and patients, rather than promoting comprehensive strategies to improve treatment of chronic pain.

Conclusions: Given the effect of coverage policies on drug utilization and health outcomes, these findings provide an important opportunity to evaluate how formulary placement, utilization management, copayments and integration of non-pharmacologic treatments can be optimized to improve pain care while reducing opioid related injuries and deaths.

929 | Coverage of non-pharmacologic treatments for lower back pain among public and private insurers in the United States

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Background: There are epidemic rates of addiction and deaths from prescription opioids in the United States. While non-pharmacologic treatments are an important therapeutic alternative to opioids for chronic, non-cancer pain, little is known regarding payers' coverage policies for these approaches.

Objectives: To assess coverage policies for several non-pharmacologic approaches commonly used to treat low back pain among commercial, Medicaid, and Medicare Advantage insurance plans.

Methods: We conducted a cross-sectional study of publicly available documents for the 2017 calendar year among 15 commercial, 15 Medicaid, and 15 Medicare Advantage health plans in 16 diverse US states. We focused on 5 treatments (physical therapy, occupational therapy, chiropractic care, acupuncture, and therapeutic massage) across insurers and 6 additional treatments for Medicaid beneficiaries. Main outcomes of interest were medical necessity, formulary coverage, utilization management and patient out-of-pocket costs. Documents were reviewed and abstracted by a single reviewer; a second reviewer validated a 20% data sample with inter-rater agreement exceeding 95%.

Results: Commercial and Medicare insurers consistently regarded physical and occupational therapy as medically necessary for low back pain, but policies varied regarding the medical necessity of acupuncture, steroid injections, facet injections and transcutaneous electrical nerve stimulation (TENS) units. Physical therapy, occupational therapy, and chiropractic care were most commonly covered across all payers, while TENS and steroid injections were the most commonly covered among the therapies examined for Medicaid plans only. Despite evidence to support use of acupuncture and psychological therapies, we did not find evidence of coverage of these therapies for the plans that we examined. Utilization management tools, such as prior authorization, were common, but varied greatly across plans with respect to which conditions and what quantity and duration of services were covered.

Conclusions: Wide variation in coverage and management of non-pharmacologic treatments for low back pain suggests an important opportunity to improve the accessibility of services, reduce opioid use and ultimately, improve the quality of care for individuals with chronic, non-cancer pain.

930 | Impact of Florida's prescription drug monitoring program and pill mill law on high-risk patients—A comparative interrupted time series analysis

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Background: In response to unprecedented levels of death and injuries from prescription opioids, states have increasingly implemented prescription drug monitoring programs (PDMPs) and "pill mill" laws.

The effects of these measures on opioid utilization are not well understood.

Objectives: To quantify the effects of Florida's prescription drug monitoring program (PDMP) and pill mill law on high-risk patients.

Methods: We used QuintilesIMS LRx Lifelink data to identify patients receiving prescription opioids in Florida (intervention state, N: 1.13 million) and Georgia (control state, N: 0.54 million). The pre-intervention period was from July 2010 to June 2011, the policy implementation period extended from July 2011 (pill mill law) to September 2011 (PDMP), and the post-intervention period ranged from October 2011 through September 2012. We identified three types of high-risk patients: concomitant users; chronic users; and opioid shoppers. Measures and outcomes of interest were average morphine milligram equivalent (MME) per transaction, total opioid volume across all prescriptions, average days supplied per transaction; and total number of opioid prescriptions dispensed. We used a comparative interrupted time series approach to quantify the impact of Florida's laws on our outcomes while accounting for secular trends as well as the autocorrelated nature of the data.

Results: Among opioid-receiving individuals in Florida, 6.62% were concomitant users, 1.96% were chronic users and 0.46% were opioid shoppers. Following policy implementation, Florida's high-risk patients experienced relative reductions in: MME (opioid shoppers: -1.08 mg/month, 95% confidence intervals [CI] -1.62 to -0.54), total opioid volume (chronic users: -4.58 kg/month, CI -5.41 to -3.76), and number of dispensed opioid prescriptions (concomitant users: -640 prescriptions/month, CI -950 to -340). Low-risk patients generally did not experience statistically significant relative reductions.

Conclusions: Compared with Georgia, Florida's PDMP and pill mill law were associated with large relative reductions in prescription opioid utilization among high-risk patients.

931 | Evaluating the impact of delisting high strength opioids on opioid use in Ontario

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Background: As part of Ontario's Opioid Strategy, high-strength fentanyl, hydromorphone, and morphine were delisted from the public drug formulary for non-palliative care on January 31, 2017. We assessed the policy's effect on opioid use stratified by prescriber palliative care status, opioid, and strength.

Objectives: To examine the impact of delisting high-strength opioids on opioid prescribing in Ontario.

Methods: We conducted a population-based cross-sectional study among individuals who were dispensed long-acting fentanyl, hydromorphone, or morphine through the Ontario Drug Benefit Program between January 1, 2014 and July 31, 2017. We reported the

total number of recipients stratified by prescriber type (palliative vs. non-palliative), and the total volume of each drug dispensed stratified by strength, monthly. We used interventional autoregressive integrated moving average models to assess the policy's impact. In a secondary analysis, we compared a cohort of non-palliative care patients receiving high-strength opioids at time of policy implementation to a historical cohort, to assess changes in patterns of access.

Results: We observed a 98% decrease in the number of publicly funded high-strength opioid recipients between December 2016 and July 2017 (5930 to 133 recipients) among all prescribers. The policy led to a significant decline in the total volume of all long-acting opioids dispensed; hydromorphone from 20 374 621 to 16 952 097mg ($p < 0.01$), morphine from 40 644 190 to 33 555 480 mg ($p = 0.03$), and fentanyl from 9 604 913 to 5 842 405 mcg/h ($p < 0.01$). This reduction generally corresponded with an increase in use of low-strength formulations. In our secondary analysis, 5.4% of people in the intervention cohort ceased to receive publicly-funded opioids compared with 0.7% in the historical cohort ($p < 0.01$). Similarly, the intervention cohort was much more likely to obtain high-strength opioids through cash or private insurance compared with the year prior (32.5% vs 0.2%; $p < 0.01$).

Conclusions: The delisting of high-strength opioid formulations in Ontario has substantially changed the landscape of opioid use in this province, by reducing the number of high-strength opioid recipients and overall volume of publicly-funded fentanyl, morphine and hydromorphone dispensed. These changes in opioid access occurred among non-palliative care patients and the results of this study may be useful for other jurisdictions considering similar policy changes.

932 | Opioid Prescriptions in Older Medicare Beneficiaries Following the 2014 Hydrocodone Rescheduling

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Background: Recent research on privately insured and younger populations has shown a varying impact of the October 2014 federal hydrocodone rescheduling law on opioid prescribing patterns and outcomes.

Objectives: Our objective was to examine how this law has affected older adults, who are among the largest consumers of prescription opioids in the United States.

Methods: **Design:** Retrospective cohort study **Setting:** United States **Participants:** A 20% sample of Medicare Part D beneficiaries ≥ 65 from 2013 through 2015 ($>2\,500\,000$ beneficiaries in each year) **Measurements:** From January 2013 to December 2015, we calculated the monthly prevalence of opioid prescriptions and the prevalence of patients who received prescriptions for a ≥ 90 -day supply ("prolonged"), as well as hospitalizations related to opioid toxicity in 2013 and 2015. **Statistical analysis:** We analyzed the monthly trend

of any opioid prescription using an interrupted time-series model by piecewise linear regression. In addition, modified Poisson regression models—adjusted for the fixed effect of states, patient and regional characteristics, months of follow up, and clustering effect within patients—were constructed to evaluate the prevalence ratio in the prescriptions measured and also hospitalizations for opioid toxicity between 2013 and 2015.

Results: From 2013 to 2015, the proportion of Medicare Part D enrollees who received a hydrocodone prescription in a year decreased from 21.9% to 18.3%. Monthly rates for hydrocodone prescriptions declined significantly in 2014. The risk of receiving prolonged opioid prescriptions decreased by about 7.0% in the multi-variable analyses comparing 2015 to 2013 (prevalence ratio = 0.93, 95% CI: 0.93-0.94). Medicare enrollees with an original entitlement due to disability or with Medicaid eligibility had smaller decreases in prolonged prescriptions and, unexpectedly, small increases in high-dose prescriptions. Opioid-related hospitalizations did not change significantly, but opioid-related hospitalizations without a documented opioid prescription increased (OR: 1.24, 95% CI: 1.03-1.50).

Conclusions: The 2014 change in hydrocodone from schedule III to schedule II was associated with modest decreases in rates of opioid use in the elderly. The unexpected increase in opioid-related hospitalizations without documented opioid prescriptions may represent an increase in illegal use.

933 | Incorporation of unlicensed medicines by the Brazilian Unified Health System, 2012-2016

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Background: Licensing is an essential tool in assessing quality, safety and efficacy of medicines. In Brazil, the current regulatory framework prohibits the incorporation of any technology by the Brazilian Unified Health System (SUS) without prior licensing by the Brazilian Health Surveillance Agency (ANVISA). The National Health Technology Incorporation Committee (CONITEC) advises the Brazilian Ministry of Health (MoH) on which health technologies should be incorporated.

Objectives: To investigate the incorporation of unlicensed medicines carried out by CONITEC, from January 2012 to June 2016, and their purchases by the Brazilian Federal Government before and after CONITEC's recommendations.

Methods: Descriptive retrospective study focusing on new medicines incorporated between 01/01/2012 and 06/30/2016. CONITEC's recommendations were obtained from the Committee website. Licensing status of medicines on the date of purchase were verified with ANVISA, based on drug nonproprietary name and dosage form.

Unlicensed medicines were those that did not have an active license on date of incorporation decision published in the National Gazette. Public purchases of unlicensed drugs were obtained from the General Services Administration System (SIASG).

Results: Among the 93 medicines incorporated in the period, six were unlicensed (6.5%), in 8 different dosage forms: biotin 10 mg and 10 mg/mL; hydrocortisone cypionate 10 mg and 20 mg; chloramphenicol palmitate 125 mg/5 mL; hydroxocobalamin hydrochloride 5 mg; doxycycline 100 mg, and hydroxyurea 100 mg. Two medicines had been licensed for the same indication: spotted fever. Only two of the decisions were submitted to public consultation. The main justifications for incorporation were severity of disease, minor adverse events, and low budgetary impact. In 50% of the cases, medicines for the approved indications were already present in SUS, but in dosage forms inappropriate for pediatric or severe case use. 3 159 085.96 BRL (Brazilian reais) were spent on the purchases.

Conclusions: The incorporation of unlicensed medicines is contrary to current Brazilian legislation regulating CONITEC and the public procurement of medicines. While highlighting the importance of incorporating drugs for the health system that address relevant therapeutic gaps, the evaluation and incorporation of unlicensed medicines raises questions about the safety and efficacy of products to which users are exposed.

934 | Challenges in development, market authorisation and commercialisation of advanced therapy medicinal products in Europe: A cohort study

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Background: Recent advances in biomedicine have brought about innovative therapies for diseases with high unmet medical need, such as gene therapies, cell-based therapies and tissue-engineered products. In the European Union these therapies are defined as advanced therapy medicinal products (ATMPs). Considerable developmental activity is observed across Europe, with more ATMPs reaching late development stages. So far only eighteen marketing authorization applications were submitted.

Objectives: To assess factors associated with advancement of advanced therapy medicinal products (ATMPs) through the medicines life-cycle, from first-in-human testing to market authorization and commercialisation.

Methods: We conducted a cohort study among commercial ATMP developers. Clinical trial database searches, industry associations member lists and an open call via industry association websites and media, were used to identify all commercial ATMP developers in Europe with at least one product in clinical development stage. An online survey was used to collect developer and product characteristics and challenges experienced in development (pre-

and post-authorisation). Information was collected on a product level and specified per development stage. Perceived individual challenges were grouped by domain (Clinical, Financial, Human Resource Management, Regulatory, Scientific, Technical and Other challenges) and scored by occurrence. A descriptive analysis was performed.

Results: We included 271 ATMP developers (response rate 38%). General characteristics did not differ between responders and non-responders. Of products in development 40% were gene therapies, 59% cell-based therapies and 1% combined ATMPs. Most developers were small, medium-sized enterprises (65%) and most products were in early clinical development (64%). We identified 243 challenges in total, of which most were in the regulatory (34%), technical (30%) and scientific (14%) domain. Most common specific challenges were meeting country specific requirements (16%), product manufacturing (15%), and clinical trial designs (8%).

Conclusions: The European ATMP field is still in early stages of development, with a high percentage of SME's. Addressing the identified challenges experienced by developers may accelerate European ATMP development. It is important to follow the cohort as they reach market authorisation, and continue post-authorisation.

935 | Survey of regulations related to the use of dietary supplements in hospitalized patients in the Czech Republic and New Zealand: Pilot study

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Background: The prevalence rates of complementary and alternative medicine (CAM) use are 76% in the Czech Republic and 74% in New Zealand. In view of the relatively high percentage of the population using DS, a question arises as to whether there is a hospital policy in place on DS use by hospitalized patients and if so, what its quality is.

Objectives: The aim of this survey was to assess and compare the quality of regulations and rules applicable to DS use by hospitalized patients in the Czech Republic (CR) and New Zealand (NZ).

Methods: In 2017 (January to May), an observational, cross-sectional study was conducted using an e-questionnaire survey in hospitals of the CR and NZ. The hospitals were contacted at their e-mail addresses available on the websites of the National Registry of Health Service Providers and then were invited repeatedly to complete the questionnaire after 4 and 8 weeks. Setting: Hospital facilities in the CR and NZ. Exposures or interventions: There were no exposures or interventions in this study. Main outcome measures: Quality assessment of the regulations and rules applicable to DS use by hospitalized patients based on the 10-criteria HPPQS score (HPPQS according to Gardiner et al, 2007) (score range 0-10, higher score indicating higher quality). Descriptive statistics was used. Differences between groups were tested by parametric tests at a

significance level of $p = 0.05$. Statistical analysis was performed using SPSS version 18.0.

Results: Of 162 hospitals addressed in the CR, 34 took part in the survey (a response rate of 21%) and of 27 hospitals addressed in NZ, six took part in the survey (a response rate of 22%). The mean HPPQS scores did not differ between the CR and NZ (CR: 6.71 [SD 1.96, range 2-10] vs NZ: 5.67 [SD = 0.82, range 5-7]; $p = 0.21$). Seventy-nine percent of the participant hospitals in the CR and 50% of those in NZ met more than 50% of the criteria. More than 73.5% and more than 50% of hospitals in the respective countries ($p = 0.34$) had specific recommendations on DS use by pre-surgical patients.

Conclusions: A policy on DS use by hospitalized patients was lacking in more than 80% of hospitals in CR and in 50% of hospitals in NZ. The development of hospital policies on DS use by hospitalized patients or improvements to the existing ones are strongly recommended in order to ensure patient safety in hospitals in both countries. The validity of the results needs to be tested on a larger sample of respondents, particularly in view of the low response rates.

936 | Representative survey on Czech physicians awareness of generic drugs and substitution

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Background: Generic drugs and generic substitution (GS) belong among the tools by which health care costs may be reduced. However, the knowledge and various attitudes on the behalf of health care professionals, as well as of patients play essential role in the rational use of GS.

Objectives: The present study aimed to analyse, in the Czech Republic (CR), physicians' opinions and attitudes towards generic drugs and GS, as well as their experience in this field.

Methods: The representative national cross-sectional survey was conducted during 2 weeks in November and December 2016 by face-to-face structured interviews. Using random allocation, 1551 physicians practicing in the CR were asked to participate in the study inquiring their opinions on 10 statements, related to brand name drugs, generic drugs and GS, attitudes towards performing GS in pharmacies, understanding of legislative rules for GS, as well as previous experiences with drug-related problems of generic drugs and providing GS to patients. Data on socio-demographic characteristics and medical specialties were also collected. Descriptive statistics were performed expressed either as absolute and relative frequencies. Categorical variables were analysed by Pearson Chi-Square test.

Results: Out of total 1237 (79.8%) physicians who agreed to participate, 28.5% were general practitioners, 17.8% paediatricians, 53.7% obstetricians and other medical specialists. The respondents were 43.6% male; median age 48 ± 11.6 years and 51.9% private health care providers. Slightly more physicians (53.5%) agreed that generic drugs are bioequivalent to the respective original brand name drugs. Physicians from outpatient facilities agreed more often with this statement ($p < 0.05$). Hence, 67.5% physicians needed more information on bioequivalence results. The opinions that generic drugs have more adverse effects than brand name drugs was reported by 28.5% physicians, especially those with specialised qualification ($p < 0.01$). However, most physicians have not experienced any negative issue with generic drugs and GS in their patients within last 3 months. Reported examples were allergic reactions, adverse drug effects, or duplicity. Physicians without specialised qualification evaluated rather positively the possibility of providing GS in pharmacy ($p < 0.01$).

Conclusions: The study results has shown, among Czech physicians, insufficient awareness of issues related to generic drugs and GS which is necessary to raise in order to ensuring patient safety.

937 | Availability of pharmacies participating in the 340B Drug Pricing Program, 2016

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Background: Despite significant growth in the number of 340B covered entities, little is known about the availability of pharmacies that participate in 340B program across the United States.

Objectives: (1) To estimate the availability of 340B pharmacies and (2) to examine the community characteristics associated with 340B pharmacy availability.

Methods: Cross-sectional analysis of pharmacy data from the National Council for Prescription Drug Programs, the Health Resources and Services Administration data on active 340B pharmacies and Medically-Underserved Area (MUA) status, and the American Community Survey (2011-2015) to derive community characteristics (eg, urban, poverty level, uninsured rates). We estimated the number of 340B pharmacies per capita for all communities in the United States. We used logistic regressions to examine community characteristics associated with the availability of 340B pharmacies in communities.

Results: In 2016, one in four community pharmacies in the United States participated in the 340B program ($n = 16\,397$). While chain and independent pharmacies account for 58.7% of 340B pharmacies, only 14.4% of independent pharmacies participated in the program. The number of 340B pharmacies per 1000 peoples (per-capita) was 5.2; this ranged considerably between and within counties. Medically Underserved Areas (MUA) (20.3% vs 18.9%; $P < 0.01$) and communities with higher prevalence of public insured

(Q1: 15.5% vs Q5: 22.2%; $P < 0.01$) and poverty (Q1: 14.5% vs Q5: 21.5%; $P < 0.01$) have higher availability of at least one 340B pharmacy. Communities with the highest uninsured rates have lower availability of 340B pharmacies than all other communities (Q1-Q4 average: 14.5% vs Q5: 21.5%; $P < 0.01$). After adjustment for potentially confounding covariates among urban communities with at least one pharmacy, being a MUA (OR: 1.13 [CI 1.05-1.20]; $P < 0.01$) and higher poverty (Q1 vs Q5 OR: 1.39 [CI 1.23-1.57]; $P < 0.01$) is positively associated with 340B availability. Community prevalence of no insurance (Q1 vs Q5 OR: 0.79 [CI 0.68-0.92]; $P < 0.01$) is negatively associated with 340B pharmacy availability.

Conclusions: One in five communities in the United States have a 340B pharmacy. Community availability of 340B pharmacies is more common in poor communities. Despite the program's aim of improving access to health care and medications for uninsured patients, communities with higher proportion of uninsured residents are lacking 340B pharmacies.

938 | Recent initiatives in Scotland to improve the quality and efficiency of prescribing: Findings and implications

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Background: Changing demographics with an increase in chronic disease prevalence coupled with more aggressive management targets, and the continued launch of new premium priced products, has put considerable strain on health care systems to continue providing universal, high quality health care. High appropriate use of generics in a class where care is not compromised by prescribing generics versus patented products, combined with quality measures, can help with providing quality health care.

Objectives: Assess the utilisation and costs of lipid lowering therapies (C10), Proton-Pump Inhibitors (PPIs) (A02BC), and Selective Serotonin Reuptake Inhibitors (SSRIs) (N06AB) in ambulatory care in Scotland between 2001 and 2015 alongside reforms to provide future guidance.

Methods: Utilisation measured in the number of items dispensed to assess prescriptions and reimbursed expenditure captured in GB pounds from NHS Scotland national database. National and regional initiatives to improve the quality and efficiency of prescribing were captured using standard methodologies (4Es—education, engineering, economics and enforcement). No time series analyses analysis was conducted as multiple interventions over time.

Results: Lipid lowering therapies (statins predominantly): multiple initiatives including identifying patients with CHD, encouraging preferential prescribing of generics, reducing ezetimibe prescribing as little evidence of benefit, and encouraging the prescribing of higher dose

statins in line with recommendations, resulted in statin expenditure falling by 56% in 2015 vs 2001 despite a 4.03 fold increase in utilisation. High dose statins now account for 71.3% of total prescriptions, up from 17.3% in 2001. PPIs: similar multiple initiatives resulted in a 68% reduction in expenditure despite a 2.91 fold increase in utilisation. High dose prescribing reduced to 20.3% of all PPIs in 2015, down from 25.8% in 2009, following concerns. SSRIs: similar initiatives and encouraging citalopram vs escitalopram resulted in expenditure falling by 60.1% despite a 2.12 fold increase in utilisation. Concerns with citalopram in 2012 saw its prescribing fall in recent years while the prescribing of sertraline has grown. The prescribing of paroxetine continually fell from 2002 onwards as a result of concerns.

Conclusions: Multiple strategies have been successful with improving the quality and efficiency of prescribing in Scotland. These will continue.

939 | Abstract Withdrawn

940 | Point prevalence survey of antibiotic use and resistance at the biggest national referral hospital in Kenya: Findings and implications

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Background: A substantial amount of antibiotic use in hospitals may be inappropriate, leading to an increase in antibiotic resistance, adverse effects, mortality and increased costs. This can be reduced by documenting and understanding current utilisation patterns to instigate appropriate measures

Objectives: To assess antibiotic use patterns and prevalence of antibiotic resistance in the biggest national referral hospital in Kenya; subsequently identify opportunities for quality improvement

Methods: A point prevalence survey (PPS) was carried out with data abstracted principally from patient medical records supplemented by interviews from physicians, using the global PPS data collection tool and methodology. Patients were selected using universal sampling. Descriptive analysis was used to describe the pattern of antibiotic use. Differences in antibiotic use and indications between the selected wards were compared using the Chi-square test or Fisher's exact tests

Results: Among the patients surveyed (n = 269), 67.7% (n = 182) were on antibiotics. The most common classes of antibiotics prescribed were third generation cephalosporins (55%), imidazole derivatives,

eg, metronidazole (41.8%), and broad spectrum penicillins (41.8%). Most common indication for antibiotic use was medical prophylaxis (29%). Dosing of antibiotics was seen as typically optimal when assessed against current recommendations. Among gram positive organisms, *Staphylococcus aureus* isolates were resistant to cotrimoxazole (90%), amoxicillin (69%), co-amoxyclov (67%) and cefaclor (67%). Among gram negative bacteria, *Escherichia coli* isolates were resistant to piperacillin (90%). *Pseudomonas aeruginosa* isolates were resistant to imipenem (100%)

Conclusions: While the dosing of antibiotics seemed adequate, there was high use of antibiotics, exacerbated by the high proportion being prescribed without reference to current guidelines. Antibiotic resistance also seems to be very high especially against the broadest spectrum antibiotics, which is a real concern and imposes severe negative clinical implications. Programmes are currently being instigated to address these concerns.

941 | Comparison of zidovudine and tenofovir based regimens With regard to quality of life and prevalence of symptoms in HIV patients in Kenya

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Background: Zidovudine and tenofovir form the backbone of antiretroviral therapy in Kenya, with sub-Saharan Africa having the highest prevalence of HIV worldwide. However, they have side effects which may adversely affect health related quality of life (HRQoL) and adherence. More women than men have HIV in sub-Saharan Africa; consequently, crucial to conduct studies in Africa

Objectives: Compare the Health Related Quality of Life of adult patients on tenofovir versus zidovudine based regimens in a leading referral hospital in Kenya to guide future management decisions

Methods: Comparative cross sectional study conducted on adult out-patients on either tenofovir or zidovudine at Kenyatta National Hospital between 2015 and 2016. The Medical Outcome Study HIV Health Survey (MOS) was administered. Linear regression analysis was performed to identify determinants of HRQoL

Results: Of the total 501 patients included, participants on zidovudine (39.9%, n = 200) had a higher median Physical (PHS) and Mental Health Scores (MHS) (61.9, IQR: 59.5, 62.8) compared with those on tenofovir (60.1, IQR: 55.1, 62.3). Presence of any symptom of disease and stated inability to cope were negatively associated with PHS whilst having regular source of income improved PHS. Being on tenofovir, symptom of illness (β -1.24, 95% CI: -2.253, -0.226), absence of pain (β 0.413, 95% CI: 0.152, 0.674) and patient stated inability to cope with HIV (β -1.029, 95% CI: -1.441, -0.617) affected

the MHS. Patients on tenofovir and second line regimens also had more signs and symptoms of illness

Conclusions: Participants on zidovudine based regimens had a better performance across all aspects of HRQoL, and should be actively considered in the future where pertinent

942 | Mapping antibiotic use in a newly founded emergency department

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Background: The emergency department of the University Hospital opened in the second half of 2014. The Level I department is providing care for all adult emergencies and major paediatrics trauma. The head of department initiated to set-up a multidisciplinary antibiotic stewardship team and programme. As a first step an antibiotic utilisation study was performed to identify problematic areas.

Objectives: The aim of the present study is to map antibiotic use in emergency department (ED) inpatients.

Methods: Data was collected on systemic antibiotics delivered from the central pharmacy to the ED between 2015 and 2017. Antibiotics prescribed for outpatient cases are not included. Antibiotics were classified according to the Anatomical Therapeutic Chemical (ATC) index. Consumption was analysed by the WHO Defined Daily Dose (DDD) method (version 2017). Consumption data in DDD was standardized for 100 admissions. Quality was assessed by the DU90 method (drugs that account for the 90% of the prescribed volume).

Results: The total antibiotic use in DDD per 100 admissions has crept up from 49.4 in 2015 to 70.5 in 2017. Mainly parenteral agents were used (2015: 89.5%, 2017: 98.4%). In 2017 a total of 13 different antibacterial agents were used at the ED of which only 5 antibacterial agents were responsible for the DU90% segment. Fluoroquinolones (ciprofloxacin and levofloxacin) were the most extensively used antibiotics (DDD per 100 admissions: 2015: 37.1; 2017:39.4) with a relative use above 50% for all years. Third generation cephalosporin (ceftriaxone) use increased more than three-fold (DDD per 100 admissions: 2015: 2.1; 2017: 9.1) and was the top 3 agent in 2017. Narrow spectrum beta-lactamase sensitive penicillins (ATC code: J01CE) use has disappeared while the use of all other antibiotic classes (except carbapenems) increased between 2015 and 2017.

Conclusions: Our study showed a high and increasing antibiotic exposure at the ED. The homogenous antibiotic use, the disappeared use of narrow spectrum penicillins along with the extensive use of fluoroquinolones and an increased use of third-generation cephalosporins require specific interventions.

943 | Pattern and predictors of antibiotics use among adults in the rural and urban communities, Oyo State, Nigeria

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Background: Antibiotics are lifesaving drugs and the most important weapon against life-threatening infections. Indiscriminate use of antibiotics is the main driver of selection pressure increasing Antimicrobial Resistance (AMR) globally.

Objectives: To determine the pattern, and predictors of antibiotics use among adults in the rural and urban communities, Oyo State, Nigeria.

Methods: A cross-sectional study was carried out among 999 adults aged 18 years and above, in Oyo State, selected by multistage sampling. The questionnaire, pretested and interviewer-administered, was used to elicit information on respondents' socio-demographic characteristics, the pattern of antibiotics use, prescribers, sources of drug acquisition, and perception of drug risk. Univariate, bivariate and multivariate analyses were done with SPSS version 22, at 5% level of statistical significance.

Results: The mean age of the respondents was 38 ± 15 years, and 501 (50.2%) represented the rural communities' dwellers. The respondents' lifetime use of antibiotics was 474 (47.4%), while the current and past uses were 217 (21.7%) and 254 (25.4%) respectively. The commonly used antibiotics were Ampicillin/Cloxacillin 220 (48.6%), Amoxicillin (11.0%), Metronidazole 43 (9.3%) and Cotrimoxazole 31 (6.8%). The initiation of use was mostly by self-medication and outside the health facilities, 280 (55.5%). The commonest source of drug acquisition was patent medicine stores, 307 (65.3%). Residence of respondents did not significantly affect antibiotics use ($\chi^2 = 0.02$, $p = 0.5$). The predictors of antibiotics use were education level (OR = 2.0 [95% CI: 1.4-2.6], $p < 0.0001$) and gender (OR = 0.62 [95% CI: 0.41-0.9], $p = 0.02$).

Conclusions: The prevalence of antibiotics and outside health facilities use was high among adults in Oyo State, Nigeria. Effective legislative strategies including the prohibition of sales of antibiotics without prescription should be considered, while educational interventions aiming at behavioural modification should be designed for the public.

944 | Utilisation of medicines for treatment of multiple myeloma in Australia

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Background: Multiple myeloma (MM) is a plasma cell malignancy. Approximately 1600 new cases are diagnosed in Australia each year. Although there is no cure, various treatment options are available.

Objectives: To determine prevalence and duration of treatment with medicines for MM in Australia.

Methods: A retrospective study was undertaken using patient level Pharmaceutical Benefits Scheme data from 1 Jul 2013 to 31 Dec 2016. The dataset contain information on all subsidised medicines dispensed in Australia. The prevalence rates and clinical pathways for thalidomide, bortezomib, lenalidomide and pomalidomide were determined. A cohort study was also conducted to investigate duration of the first treatment episode (to cessation or switch) in people who initiated a medicine for MM in 2014 (after no dispensing for such a medicine in the previous 6 months). The initiators were followed for 24 months. The duration was determined using Kaplan-Meier survival analysis.

Results: The prevalence rate per 100 000 Australian residents receiving treatment for MM increased from 9.4 in Jul 2013 to 11.8 in Dec 2016 (Chi-square, $p < 0.0001$). Clinical pathways including first, second and third line therapy showed that 61% of people received one therapy only, with 42% receiving bortezomib only, 14% thalidomide only, and 5% lenalidomide only. Where people did require a second line therapy, the most common pathway was from bortezomib to thalidomide, and thalidomide to lenalidomide. The median duration of the first episode on bortezomib for stem cell transplant was 3 months (95% CI 84-92 days), it was 3.5 months for other bortezomib (95% CI 98-112), 5 months for thalidomide (95% CI 137-167) and 9.5 months for lenalidomide (95% CI 227-400).

Conclusions: Utilisation of MM medicines was mostly consistent with guideline recommendations and PBS restrictions in Australia. The use outside subsidy or PBS restrictions was for lenalidomide as first line therapy, even though it was recommended as second and subsequent therapy at the time of the study period.

945 | Appropriateness of use of low-molecular-weight heparins prescribed in patients discharged from emergency departments: A drug utilization study based on administrative health databases

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Background: Even if Low-Molecular-Weight Heparins (LMWH) are generally considered safe and effective, different authors pointed out a possible inappropriate use of these medications in several clinical settings. So far, little is known about the appropriateness of the prescription of LMWH in patients who are discharged

from Emergency Departments (ED), a high risk setting for medical errors.

Objectives: To assess the appropriateness of use of LMWH prescribed in patients discharged from ED in an Italian Region.

Methods: In this population-based study, administrative data from Piedmont (4.4 million inhabitants) were used. All prescriptions of LMWH (ATC B01AB*) dispensed for outpatient consumption and reimbursed by the National Health Service were analyzed. Patients included in the study met all the following inclusion criteria: (1) resident in Piedmont; (2) at least an admission to ED during 2014; (3) at least a LMWH prescription at the discharge from ED, or in the following week. Subjects were excluded if they already received any type of anticoagulant therapy before the admission to ED (1 year of look-back). For each patient, we used the discharge diagnoses from ED to evaluate whether the prescription of LMWH was likely to be appropriate or not. According to the approved indications of these drugs in Italy, we considered as appropriate the prescriptions following a diagnosis belonging to one of these diagnostic groups: diseases of the circulatory system (ICD-9-CM: 390-459), diseases of the musculoskeletal system and connective tissue (ICD-9-CM: 710-739), injuries (ICD-9-CM: 800-959).

Results: We included in the study 16 570 patients. In about 80% of cases, the discharge diagnosis belonged to the diagnostic groups reported above. The remaining 20% of cases were related to a miscellaneous of diagnoses for which there was not a clear indication for the use of LMWH.

Conclusions: Our study suggests that in Italy ED can constitute a high risk setting for inappropriate prescription of LMWH. Future studies based on clinical records are warranted to confirm these results and to identify predictors of inappropriate prescribing.

946 | Quality of anticoagulation control in patients with atrial fibrillation in Valencia, Spain: A real-world, population-based study

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Background: Efficacy and safety of oral anticoagulation for stroke prevention in atrial fibrillation (AF) patients using vitamin K antagonists (VKA) are closely associated with the quality of anticoagulation control. Therapy with VKA can be challenging and must be tightly controlled and maintained within a narrow therapeutic index of International Normalised Ratio (INR). VKA used in Spain is acenocoumarol instead of warfarin, for which most of the evidence of INR control is based on.

Objectives: To assess Time in Therapeutic Range (the most commonly used measure of INR control) of AF patients treated with acenocoumarol in the region of Valencia, Spain, in 2015, using different calculation methods and thresholds, and to identify factors associated with poor anticoagulation control.

Methods: Population-based cross-sectional study including all AF patients' prevalent users of acenocoumarol in the region of Valencia in December, 2015. Data were obtained from several electronic health records of the Valencia Health Agency, covering 5 million inhabitants. We described patient characteristics, and we calculated TTR during 2015 using Rosendaal and % of INR in range (PINRR) methods. We used two definitions for poor control: TTR <65% (NICE) and TTR <70% (European Society of Cardiology). We used logistic multivariate regression to identify factors associated to poor control.

Results: 24 402 AF patients were treated with acenocoumarol in 2015, mean age was 77 years and mean CHADS₂-VASC and HAS BLED scores were 4.11 and 3.52, respectively. Average number of INR values per patient in 2015 was 14. Mean TTR was 62.55%. Considering a threshold of TTR <65%, and using the Rosendaal method, 51.76% of patients had poor INR control during 2015 (62.36% patients using PINRR). When applying a threshold of 70%, poor control affected 62.05% to 70.59% of patients, depending on the calculation method used. Being female, comorbid conditions as diabetes, depression, dementia, heart failure, renal and vascular disease, use of NSAIDs and ER visits were associated to an elevated risk of poor INR control. Being older than 65 years old and higher income were associated to optimal INR control.

Conclusions: we found that quality of INR control in the region of Valencia is suboptimal, with a half to more than two thirds of patients below the acceptable TTR threshold and thus at increased risk of bleeding or ischemic events. Women and high-risk patients were more likely to have poor INR control.

947 | Use of preoperative aspirin in patients undergoing elective isolated CABG in Japanese Nationwide Registry

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Background: Preoperative use of aspirin is recommended for patients undergoing coronary artery bypass graft surgery (CABG) in major US and European clinical practice guidelines. However, use of aspirin under the present Japanese medical system is not well documented.

Objectives: To assess the frequency of use for pre-CABG aspirin in Japanese patients and describe factors associated with its use pattern using a nationwide surgical registry

Methods: This was a cohort study enrolling patients undergoing elective isolated CABG throughout Japan in 2013-2016, using Japan Cardiovascular Surgery Database. We assessed the use of preoperative aspirin within 5 days of surgery in the whole cohort, as well as for each hospital. Factors associated with aspirin use were identified from fitting a hierarchical logistic regression model with patient and hospital level covariates as fixed effects and hospital specific random intercepts. Intraclass correlation coefficient (ICC)

was calculated as the proportion of total variation attributable to the hospital level.

Patients undergoing CABG at 578 hospitals during the study period. Aspirin was used in 15 337 (33.6%) of the cases. The percentage varied greatly across the hospitals with median of 21.8% and first and third quartiles of 6.3% and 54.2%; at 69 (11.9%) hospitals, none of the patients were given pre-CABG aspirin. Factors such as kidney dysfunction (Odds ratio [OR] 0.89), off pump procedure (OR 1.31), record of preoperative warfarin use (OR 0.24), malignancy (OR 0.79), past PCIs (OR 1.45) and hospital case-volume (OR 0.66 for yearly average <50 vs ≥50) were identified as strong predictors of aspirin use/non-use. ICC suggested that 78.6% of the variation in aspirin use was attributable to the hospital level after differences in patient and case volume across hospitals are accounted for.

Conclusions: Evaluation of pre-CABG aspirin use from a nationally representative clinical registry suggests possible underutilization of this preoperative medication in Japan. Great variability in its use was mostly attributable to hospital level, and warrant further investigation on the causes of practice pattern variation, as well as on the effectiveness of the medication in routine care in Japan.

948 | evaluating a risk evaluation and mitigation strategy designed to prevent use of dronedarone in patients with permanent atrial fibrillation

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Background: In December 2011, the US Prescribing Information for dronedarone was updated to include a contraindication to permanent atrial fibrillation (AF). The dronedarone Risk Evaluation and Mitigation Strategy (REMS) was subsequently modified in June 2012 to include the evaluation of practice patterns and adherence to the prescribing information as requested by the FDA.

Objectives: To evaluate the timing and frequency of cardiac rhythm monitoring (CRM) in dronedarone users, to determine the prevalence of permanent AF in dronedarone users, and to characterize decisions and outcomes in patients with permanent AF.

Methods: A medical chart review study was conducted in 2 waves to collect data on patients treated with dronedarone during 2 eligibility periods, 11/19/2012-2/19/2013 and 4/1/2013-6/30/2013. Prescribing physicians were invited to participate through a random selection stratified by specialty. Each physician could only participate in one wave. A maximum of 8 eligible charts per physician was reviewed. For physicians with more than 8 patients, 8 charts were randomly selected to avoid selection bias. A patient's first routine visit in the eligibility period was defined as the index visit. Treatment related data were abstracted in an observation period from the index visit to 5/19/2013 or 3/31/2014 in the first or second wave, respectively.

Results: In the first and second waves of the study, 88 and 105 physicians participated, respectively; and 400 and 525 medical charts were reviewed in each respective wave. The mean dronedarone treatment periods were 4.1 and 9.5 months in each respective wave. In the observation period, 63.0% (n = 252) of patients in Wave 1 and 70.3% (n = 369) in Wave 2 had at least 1 CRM. Among the 45 and 71 patients for whom dronedarone was first prescribed in the index visit in Waves 1 and 2, respectively, 64.4% (n = 29) and 46.5% (n = 33) had CRM performed on or within 3 days prior to the index visit. In the pooled study population, 1.3% (n = 12) had permanent AF at the index visit and 0.8% (n = 7) developed permanent AF during the observation period. Among these patients, dronedarone was discontinued in 10 (52.6%) patients. No patients with permanent AF died during the observation period.

Conclusions: Dronedarone users commonly underwent CRM. Considering that permanent AF accounts for 30-50% of all AF cases, its low prevalence in dronedarone users shows that dronedarone, in accordance with revised prescribing information, was used infrequently in permanent AF.

949 | Evaluating statin utilisation in clinical practice in Scotland: Impact of Statin intensity on adherence and persistence to therapy

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Background: Based on recent clinical trial evidence, updated treatment guidelines in the United Kingdom recommend high-intensity statin therapy (atorvastatin 80 mg) for secondary prevention of cardiovascular disease. However, with this high statin dose, there are concerns about a potential increase in the incidence of statin-related side effects, which might affect patients' adherence and, in turn, clinical outcomes. Hence, this study aimed to evaluate the effect of statin intensity on adherence and persistence to therapy.

Objectives: To evaluate adherence, discontinuation, and persistence to high-intensity statin in comparison to moderate and low-intensity in Scotland.

Methods: Retrospective cohort study using linked health records. The study population included patients (≥18 years) initiated on statins between Jan 2010 and Dec 2015. Statin treatment was stratified into high, moderate, and low-intensity based on the current National Institute for Health and Care Excellence classifications. Treatment discontinuation and persistence were evaluated using the refill-gap and anniversary methods, respectively; adherence was assessed by calculating the proportion of days covered (PDC).

Results: A total of 73 716 patients (mean age 62 years [SD 12.6]) initiated statins during the study period: high-intensity $n = 7163$ (9.7%), moderate-intensity $n = 65\,125$ (88.3%), and low-intensity $n = 1428$ (1.9%). High-intensity therapy was more common among males (10.7%) than females (8.6%), and most common (17.1%) in the youngest age group (18–24 years). The majority of patients initiating high-intensity treatment received either atorvastatin 20 mg (43.1%) or 40 mg (32.3%), while 22.8% received atorvastatin 80 mg. Crude discontinuation rates (50.9% high vs 75.5% low-intensity) and 1-year persistence (74.7% high vs 53.1% low-intensity) differed significantly between intensity levels; crude adherence (PDC $\geq 80\%$) was highest among high-intensity patients with 63.7%, compared with 51.6% and 40.5% in moderate and low-intensity, respectively.

Conclusions: Increasing the intensity of statin therapy does not seem to negatively impact adherence and persistence to treatment, although findings could be due to confounders (eg, primary vs secondary prevention) and/or the low proportion of patients using the recommended high dose statin. Further analysis is ongoing to adjust for confounders, and to evaluate clinical outcomes associated with high-intensity statin therapy.

950 | Migraine cocktails sold by pharmacies in South Africa

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Background: Pharmacists are often the first health care providers patients consult when they experience symptoms of a migraine. Many pharmacies in South Africa sell “migraine cocktails” (migraine kits) over-the-counter that include various components to treat migraine attacks. There is a paucity of information in the literature about these migraine cocktails.

Objectives: The primary aim was to determine the number and content of these migraine cocktails sold by pharmacies.

Methods: A questionnaire survey was conducted during 2014 under community pharmacists in Port Elizabeth, South Africa. The focus was on the number and types of active ingredients in the migraine cocktails, and the cost. Data were analysed with Microsoft Excel. Basic descriptive statistics were calculated.

Results: Fifteen of the 18 pharmacists who completed the survey indicated that they sell migraine cocktails. An average of 30 (SD = 21) migraine cocktails were reported to be sold by the pharmacies per month. Fourteen pharmacists were willing to indicate what medications were included in their migraine cocktails. Migraine cocktails were generally comprised of three to five medications. Medications with the highest possibility of being included in a migraine cocktail were anti-inflammatory agents (85.7%), anti-emetics (85.7%), combination analgesics (57.1%), α_2 -adrenergic agonists (42.9%), single-component analgesics (35.7%), vitamin supplements (35.7%), antispasmodics (28.6%), an ergot alkaloid (21.4%) and a dopamine antagonist 7.1%). The combination analgesics included in migraine cocktails, all

contained codeine phosphate. The price of a migraine kit varied from R8.00 to R30.00 (the average price was R18.40 [SD = R6.42]).

Conclusions: It was evident that each pharmacy had their own combination of medications. A migraine kit is useful adjunct service that pharmacists can provide to migraineurs, since the patient does not have to buy the individual medications, and theoretically the migraine kit contains the correct dosage and combination of medications for a single dose.

951 | Prescribing patterns of oxycodone in a private health care setting in South Africa

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Background: Oxycodone is classified as a Schedule 6 medicine in South Africa, which means it is strictly controlled. It is an opioid analgesic indicated for moderate to severe pain. Similar to other opioid analgesics, it has the potential to be abused.

Objectives: The primary aim of the study was to determine the prescribing patterns of oxycodone (ATC code N02AA05) in a private health care setting in South Africa.

Methods: A retrospective drug utilisation study was conducted on 2016 medical insurance scheme data. All prescriptions for ATC code N02AA05 were extracted and analysed according to prescription frequency and cost. A total of 338 patients received 1059 prescriptions for oxycodone during 2016. Microsoft Excel was used for data and statistical analysis.

Results: The average age of patients was 46.96 (SD = 14.29) years (56.21% male patients). Patients received an average of 3.13 (SD = 6.74) oxycodone prescriptions over the year, with 39.94% of patients receiving a single oxycodone prescription and 75.74% of patients receiving three or less prescriptions during the year. Two tradenames of oxycodone were available on the market: a prolonged-release tablet (26.82% of prescriptions accounting for 75.39% of the amount claimed for oxycodone) and a capsule (73.18% of prescriptions accounting for 24.61% of the amount claimed). Most prescriptions were dispensed by private hospitals (90.75%). Just over 75% (76.80%) of the amount claimed for these products were reimbursed to patients by the medical insurance schemes. A third of the prescriptions (34.37%) were dispensed under the chronic benefit option of members. Where the referred provider was indicated in the database, most prescriptions originated from general medical practice, orthopaedics, oncology, and obstetrics and gynaecology. Of the 13.91% of patients ($n = 47$) who used more than one dosage form or dosage strength of oxycodone during the year, only 17 patients were prescribed both the tablet and capsule formulation during the course of the year (not simultaneously). The DDD for oxycodone is 75 mg orally. In this study, the average DDD per prescription was 1.12 DDDs.

Conclusions: It was not possible to detect abuse or overuse of oxycodone in this study. It will be important to conduct a qualitative study to determine the perceptions of pharmacists and prescribers regarding

possible overuse or abuse of oxycodone in the private health care setting in South Africa.

952 | Disparities in the appropriateness of anticholinergic drug use: Analysis of the regards study

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Background: Anticholinergic drug (ACHD) use is linked with falls and delirium and is considered to be potentially inappropriate in older adults. Health disparities in ACHD use may exist.

Objectives: To assess the association between demographics and socioeconomic status (sex, race, income, education, and rural or urban areas) and ACHD use among older adults.

Methods: The analyses included 14 857 black and white US adults with age ≥ 65 years from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study (recruited 2003-2007). The ACHD use was measured by the presence of these drugs in the patients' medication list using the 2015 Beers Criteria. Multivariable logistic regressions were used to assess the association of disparity parameters with ACHD use. The full model included interaction terms between race and other disparity variables. Similar analyses were applied for individual classes of ACHDs.

Results: Approximately 13% of the participants used at least one ACHD listed in the Beers Criteria. Most frequently appearing ACHDs were antidepressants (4.3%), antihistamines (4.2%), and antimuscarinics (3.4%). ACHD use was significantly associated with income ($< \$20,000$ vs $\geq \$75,000$: OR = 1.71, 95% CI 1.32-2.20; $\$20,000$ - $\$34,000$ vs $\geq \$75,000$: OR = 1.48, 95% CI 1.17-1.88; $\$35,000$ - $\$74,000$ vs $\geq \$75,000$: OR = 1.27, 95% CI 1.01-1.61). A significant sex-race interaction ($p < 0.01$) illustrated that ACHD use was higher among both black and white females (blacks: OR = 1.36, 95% CI 1.14-1.63 and whites: OR = 2.0, 95% CI 1.74-2.29). Similar relationships were observed among female antidepressant (blacks: OR = 1.50, 95% CI 1.08-2.08 and whites: OR = 1.91, 95% CI 1.52-2.39) and antimuscarinic (blacks: OR = 1.53, 95% CI 1.10-2.13 and whites: OR = 2.46, 95% CI 1.87-3.24) users. White females also had higher odds of having antihistamines (OR = 1.45, 95% CI 1.15-1.82), skeletal muscle relaxants (OR = 1.88, 95% CI 1.13-3.12), and antispasmodics (OR = 2.31, 95% CI 1.41-3.80) than white males. Education level also was a significant predictor of antidepressant use ($< \text{high school}$ vs $> \text{college}$: OR = 1.54, 95% CI 1.16-2.05; $< \text{high school}$ vs some college : OR = 1.39, 95% CI 1.06-1.82) and antispasmodics use among blacks ($< \text{high school}$ vs some college : OR = 3.15, 95% CI 1.10-8.98; high school vs. some college : OR = 2.93, 95% CI 1.06-8.09).

Conclusions: Demographic and socioeconomic disparities in ACHD use exist, and future studies should seek to better understand factors contributing to the disparities to help develop interventions.

953 | The prevalence of chronic antidepressant drugs prescriptions in the province of Bologna, Italy

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Background: Antidepressant drugs (ADs) are used as acute and maintenance treatment phases in depression. Maintenance phase should usually last between 6 and 12 months and the need for a longer treatment is rarer and should be clinically motivated (ie, high risk of relapse, chronic treatment-resistant depression). Nevertheless, aggregate data of ADs consumption in Italy suggest that prescription patterns may differ from guidelines.

Objectives: To measure the prevalence of chronic use of ADs, defined as a use longer than two years, in a cohort of incident patients of ADs in 2013 in the province of Bologna, Italy.

Methods: We conducted a retrospective claims-based cohort study using prescription claims from the Bologna Local Health Authority in the years 2013-2016. We selected a cohort subjects having claimed at least one prescription of an AD in 2013 and without any ADs prescriptions claimed in the previous year. DDDs of ADs and other drugs claimed were calculated for the entire period. Socio-demographic variables were collected at the time of the first AD prescription. Chronic use was defined as having claimed at least 1 prescription in each year of the three-year follow-up. Factors associated with chronic ADs use were identified by logistic regression.

Results: Among the 18 307 subjects newly treated with ADs in 2013, 5448 (29.8%) claimed at least one prescription for ADs in every year of follow-up (2013-2016), with a mean number of prescriptions claimed of 6.4 in the first, 5.3 in the second and 5.2 in the third year after the first prescription, corresponding to 257, 235, and 232 DDDs (Defined Daily Doses), respectively. Chronic users were more frequently women (68%) and in the age group 70-79 years old (20.4%). Compared with those aged ≥ 89 years, younger subjects were less likely to be chronic users (OR < 18 = 0.59, 95% IC [0.37-0.95], OR 19-29 = 0.67, 95% IC [0.43-1.06]). Women and those having claimed more than 5 concomitant prescriptions were more likely to be treated chronically (OR = 1.08, 95% IC [1.01-1.07] and OR = 1.57, 95% IC [1.46-1.69], respectively).

Conclusions: Chronic use of ADs is very common in our population. As treatments longer than two years should be clinically motivated, these results may indicate potentially inappropriate prescriptions.

954 | Claims database study of utilization patterns of dimethyl fumarate in Germany

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Background: Dimethyl fumarate (DMF) is indicated for the treatment of relapsing-remitting multiple sclerosis (MS) in adult patients. In Germany, fumaric acid ester is used to treat psoriasis. To satisfy EU risk management regulatory requirements, an assessment was required of off-label use of DMF in patients without an MS diagnosis and/or <18 years old in Germany.

Objectives: To estimate the proportion of DMF use that is prescribed “on-label” versus “off-label” in Germany.

Methods: The study was a non-interventional, retrospective cohort study using a German sick fund claims database collected by Arvato Health Analytics from Sep 2013 to Dec 2015. This database contains sick fund claims data for 3.5 million insured citizens, and accounts for ~4% of the sick fund population in Germany. Patients were included if they initiated DMF (Anatomical Therapeutic Chemical classification system code N07XX09) on/after 1 Mar 2014, the date DMF became available for MS treatment in Germany, without previous DMF use in the 6 months prior to the index date. “On-label” prescriptions were those for patients ≥18 years old and diagnosed with MS (≥1 medical inpatient and/or ≥2 outpatient claims with an International Classification of Diseases 10-GM diagnosis code G35.x). Off-label prescriptions were defined as those for adult patients without an MS diagnosis or for patients <18 years of age with MS. Statistical analyses were descriptive.

Results: Overall, 714 patients in the database received DMF between March 2014 to the end of 2015. Only 1.4% (10/714) of cases were deemed off-label. Patients treated with on-label DMF had a mean age of 41.4 years (Standard Deviation (SD) 10.8) and were predominantly female (73.4%). Off-label patients were on average 4 years younger (37.9 years, SD 11.5), and 70.0% were female. Of the 10 off-label patients, one patient with MS was 17 years old at treatment initiation and one patient had psoriasis. Eight other patients had an MS diagnosis at some time during the period but did not meet the MS definition per protocol at treatment initiation. Also, per current German guidelines, DMF was mostly prescribed by physician specialists denoted as “neurologist” or “neurology, psychiatry and psychotherapy.”

Conclusions: Two patients were either <18 years old or had a non-MS diagnosis, while 8 others had an MS diagnosis code, but did not satisfy the MS algorithm requirements of the study. Therefore, based on this analysis of a large claims database, this study demonstrated that DMF is infrequently prescribed off-label in Germany.

955 | The safety of fentanyl patch initiation in Australian clinical practice: A population-based study

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Background: Safety concerns regarding transdermal (TD) fentanyl initiation have been raised in Australia and internationally due to increasing reports of unintentional fatal overdose resulting from inappropriate prescribing. Although guidelines caution against initiation of TD fentanyl among people who are opioid naïve, there is concern that some patients are not receiving adequate prior opioid exposure in clinical practice.

Objectives: To determine the proportion of people in Australia that are opioid naïve at the time of transdermal (TD) fentanyl initiation; examine the strengths initiated; and determine the characteristics associated with being opioid naïve.

Methods: This was a retrospective population-based cohort study representing a 10% sample of Pharmaceutical Benefits Scheme concessional beneficiaries initiating TD fentanyl between 29 September 2009–31 December 2013. Individuals were deemed to be opioid naïve if they had no opioid dispensings in the previous 90-days. Socio-demographic characteristics, likely comorbidities and previous analgesic use were compared among those opioid naïve/opioid exposed. Logistic regression was used to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) to determine characteristics associated with being opioid naïve.

Results: A total of 13 166 people initiated TD fentanyl; 60.4% were female and 76.2% were aged ≥65 years. Three in ten (30.4%) were opioid naïve and 63.2% initiated the 12 mcg/hour patch. Those who were opioid naïve were more likely to be female (adjusted odds ratio (aOR) 1.35; 95% CI 1.25–1.46), older (aOR 1.85; 95% CI 1.54–2.28 for those ≥85 years) and previously dispensed medicines for dementia (aOR 1.37; 95% CI 1.04–1.80). People previously dispensed medicines for cancer were less likely to be opioid naïve (aOR 0.57; 95% CI 0.48–0.67).

Conclusions: Three in ten Australians initiating TD fentanyl are opioid naïve. Our findings suggest that specific patient sub-populations already at increased risk of opioid-related adverse events are not receiving prior opioid treatment before initiation, highlighting the need for greater adherence to current treatment guidelines.

956 | A database study of antipsychotic polypharmacy in the treatment of schizophrenia in China and Japan

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Background: Although monotherapy is consistently recommended for the treatment of schizophrenia, antipsychotic polypharmacy (APP) is not rare in practice. However, longitudinal data on APP in schizophrenia treatment are limited.

Objectives: To estimate the rates of APP in schizophrenia treatment in China and Japan.

Methods: This is a longitudinal database study, utilizing electronic medical records databases of one mental health center and one general hospital in China and one insurance claims database (JMDC) in Japan, and data from January 2010 to December 2014 were retrieved for the analysis. Schizophrenia patients with continuous health care (having had at least three consecutive outpatient or inpatient visits with gaps of at least 14 days but no longer than 45 days) and at least one prescription of first-generation antipsychotic (FGA) or second-generation antipsychotic (SGA) medications were selected. Patients were identified using ICD-10 codes (ICD-10 F20.x), and drugs were selected and classified based on generic names. Initial therapy was defined as the first antipsychotic medication(s) identified after January 2010, and switching or adding of new antipsychotic medications during follow-up were captured. APP was defined as having more than one antipsychotic medication overlapping for at least 60 days.

Results: The study cohorts comprised 8571 from the mental health center and 3,390 from the general hospital in China, and 25 034 from JMDC in Japan. Mean ages were 38.6 years, 28.6 years, and 39.0 years, respectively, and there were slightly more females than males in all three cohorts. Most patients were initially prescribed monotherapy with oral SGA as the majority (78.9% in China and 65.8% in Japan). The prevalence rate of APP during initial treatment was lower in China (12.7%) than that in Japan (19.9%), and the most common combinations were two oral antipsychotic medications. Among patients started with monotherapy, 11.8% (12.6/100 person-years) in China and 11.0% (9.6/100 person-years) in Japan progressed to APP during follow-up. In both countries, APP progression rates were similar in men and women, and more likely in younger patients, in all study cohorts.

Conclusions: The APP rates were lower than those reported in previous publications in Asia. It is probably due to the longitudinal approach to exclude transient overlapping or drug titrations. Most schizophrenia patients can be well-maintained on monotherapy and those who were younger were more likely to progress to APP.

957 | Generic substitution patterns of levothyroxine and escitalopram in subgroups of US Medicare beneficiaries

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Background: Branded levothyroxine and escitalopram are commonly used among Medicare populations with alternative generics available.

Objectives: To analyze generic substitution patterns overall and in subgroups (by age, sex, and race) of Medicare beneficiaries.

Methods: Study population (n = 5 million) included a 5% random sample of Medicare administration claims data plus oversampled data in southern states in 2013-2015. Two new user cohorts (washout period of 6 months) of fee-for-service Medicare beneficiaries who initiated oral brand or generic levothyroxine (n = 32 083; 33.2% brand users) or escitalopram (n = 23 076; 11.7% brand users), were included. Mutually exclusive outcomes including substitution (brand to generic or vice versa), therapeutic switch (switch to another drug in the same therapeutic class), discontinuation (gap >90 days), and death/loss of follow up were recorded using pharmacy claims data in up to 12 months of follow-up period. Descriptive analyses (Chi square tests) were used to compare: (1) proportions of brand and generic new users switching to different outcomes and (2) proportions of brand new users switching to outcomes among subgroups (by age, sex, and race).

Results: Overall, about half of brand and generic levothyroxine users stayed on their original treatment during follow-up period. Higher proportions of brand levothyroxine users encountered substitution (19.1% vs. 11.6%) and therapeutic switch (1.4% vs 0.9%) compared with generic users ($P < 0.0001$). In addition, 14.5% of brand and 23.3% of generic escitalopram users stayed on treatment. Higher proportions of brand escitalopram users encountered substitution (20.5% vs 3.3%) compared with generic users while higher proportions of generic escitalopram users discontinued treatment (30.3% vs. 24.6%) compared with brand users ($P < 0.0001$). Among brand levothyroxine users, racial minorities (vs white) were less likely to substitute (15.3% vs 19.5%) but more likely to discontinue (28.6% vs 19.7%); females were more likely to switch (1.7% vs 0.8%); younger beneficiaries (<65 vs ≥ 65) were more likely to discontinue (25.7% vs 19.9%). Among brand escitalopram new users, racial minorities were less likely to switch treatment but more likely to discontinue; younger beneficiaries were more likely to switch. All $P < 0.05$.

Conclusions: Different generic substitution and switch patterns observed in subgroups of Medicare beneficiaries ascertain the need to closely monitor treatment outcomes among these subgroups.

958 | The impact of potentially inappropriate medication use on mortality and hospitalization in nursing home residents

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Background: Association of potentially inappropriate medication (PIM) use with outcomes such as mortality and hospitalization in the community-dwelling older population, was demonstrated in previous studies.

Objectives: The aim of this study is to confirm these findings in the setting of a nursing home (NH) population.

Methods: Data from the observational prospective Ageing@NH study, based on a inception cohort of newly admitted NH residents (65+) was used. Information about socio-demographic, clinical and functional characteristics, as well as medication use, was collected. The PIM use was assessed by applying a set of PIM criteria originating from three lists (EU-7 PIM list, Beers 2015 and STOPP/START 2014).

Results: Medication chart and clinical information was available for $n = 281$ residents (mean age 83.6, 63.6% female). The mean number of total medications was 8.2 (range 1-23). Polypharmacy (≥ 5 medications) was 86.1%, with extreme polypharmacy (≥ 10 medications) in 24.9%. The prevalence of PIM use was high (93.2%) with mean number of 4.5 medications per resident (range 0-13). Underuse was 81.9%, with 50.6% ≥ 4 underused medications. Misuse was 60.9%, with 2.9% ≥ 4 misused medications. After adjustment, the risk of mortality for underuse was approaching significance (OR = 1.12, 95% CI 1.00, 1.24). Association between misuse and mortality was not significant, neither the associations misuse and underuse with hospitalization.

Conclusions: In the setting of a NH population, the association between misuse and underuse with mortality and hospitalization could not be confirmed despite the high PIM use. Future studies in NH setting should focus more on the associations of PIMs with factors related to the quality of life (pain, alertness, sleep).

959 | Evaluation of level of adherence and deviation from the standard hospital antibiotic policy: A cross-sectional study

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Background: Antibiotic guidelines are generally based on scientific evidence. Therefore, the best results can be achieved when they are followed in clinical practice. Usually, lower degree of adherence to antibiotic guidelines will leads to poor therapeutic outcomes

Objectives: To check appropriateness of antibiotic therapy for cases with antibiotics and to investigate reasons for deviation from antibiotic guideline if present so

Methods: Data regarding antibiotic use were collected from 110 patients admitted in medicine wards of a tertiary care hospital during

40 days period. Inclusion criteria were patients (more than 18 years of age) receiving one or more antibiotics during the course of their hospital stay. Antibiotic usage pattern was compared with antimicrobial policy of the hospital

Results: Indications for antibiotics used were definite in 33 (36%) cases, prophylaxis in 15 (13.6%) cases and empirical in 62 (56.4%) cases. Antibiotic use in 62 (56.4%) cases were found to be deviated from the guidelines. Most common reasons for deviation is "not rational according" to guidelines, that accounts 38 (34.5%) of cases. 48 (43.6%) of cases deviates from the guidelines. The reason for absence of deviation is according to guidelines in 34 (30.9%) cases, according to culture-sensitivity reports in 10 (9.1%) cases and acute febrile illness in 4 (3.6%) cases, where, empirical monotherapy given. 76(69.1%) cases antibiotics were given despite culture being negative. However, 25 (22.1%) cases antibiotic given were sensitive. 4 (3.6%) cases antibiotic given were resistant. Most common empirical therapy for respiratory illness were ceftriaxone plus azithromycin, which accounts for 11 (10%) cases.

Conclusions: Irrational use of antibiotics are very common. Antibiotics were prescribed in some cases where there is no indication of the use. Strict adherence to the treatment guidelines is necessary to improve positive clinical outcome. The study highlights the need of antibiotic stewardship program in the health care system.

960 | Pharmacoepidemiological study on over-the-counter (OTC) medicines' use from people in Alexandroupolis

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Background: The Greek legislation permits people buying OTC medicines without prescription. However, we still have no knowledge of how people are informed about their use and whether this might be a public health issue.

Objectives: The purpose of this pharmacoepidemiological study is to evaluate the use of OTC medicines and people's habits in supplying them. Prior hypothesis was that people are not informed enough and their last initiation may be wrong or even dangerous.

Methods: Questionnaires were distributed inside Greek community pharmacies to those people who had just supplied an OTC medicine. The statistical analysis was conducted using the SPSS statistic program. There were no exclusion criteria, except for people's unwillingness to answer the questionnaire. Matching and selection was under Chi-Square Tests evaluation. The main questions were whether they asked the pharmacist and if this medicine had any side-effects.

Results: In this study we evaluated 198 unique questionnaires. Participants' mean age was 40.76 years (men:women 42 and 58% respectively). The main reason of OTC consumption was headache (31%), while

cold, flu and any kind of pain were also among the most frequent reasons. Although, they knew exactly the use of the medicine they bought (100%) they weren't aware of medicine's side effects or even worse they had no idea of any side-effects (86.4%). Almost 50% of the participants prefer to use OTC medicines based on their own previous experience and thus, they have been supplied OTC upon their own decision without asking physicians or pharmacists. Only of the participants have 15% seem to be influenced on their OTC decision by the pharmacist.

Conclusions: It seems that people usually consume significant quantities of OTC medicines but they are not sufficiently informed about the right use and probable dangers of this medicine.

961 | A description of the national claims database in Ghana

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Background: The Ghana National Health Insurance Scheme's (NHIS) claims database is a combination of manually (from 2004) and electronically submitted (from 2013) claims for reimbursement of health care services delivered by accredited providers. The Ghana NHIS electronic claims database is the first of its kind in West Africa and provides an opportunity to study the health care utilization and quality delivered in Ghana.

Objectives: To describe the NHIS database and demonstrate how it can be leveraged to measure the utilization of commonly prescribed medicines.

Methods: The 2015 electronic claims data were analyzed. This represents the most comprehensive and stabilized data capture since the implementation of the electronic processing system. We evaluated the database structure for the presence of standardized data domains required for drug utilization research (DUR) by using the Mini Sentinel Common Data Model (MSCDM) v2.1 as a referent guide. In a DUR case example, we identified the commonly prescribed medicines in 2015 and their distribution by patient demographics and the most prevalent disease diagnoses. Medicines were identified using the NHIS medicines list based on anatomical and therapeutic classification (ATC) codes. Defined daily doses (DDD) were calculated to measure overall medication consumption.

Results: The Ghana NHIS database structure includes 9 out of the 10 data domains specified in the MSCDM, cause of death data and out of hospital death data were not available. Some notable coding differences exists between the NHIS and the MSCDM, for example, medicines are coded with ATC compared with NDC in the MSCDM. There were 1.43 million unique patients in the data representing patients treated by 81 providers located in 9 out of 10 regions in Ghana. The mean age of the sample was 31 (standard deviation, 22) years, a third of whom were aged <18 years old. Women represented two-thirds of the sample. Overall, analgesics, antibiotics, multivitamins, antimalarial, and antihypertensives were the 5 top most prescribed drugs across all ages, gender, and geographical regions in Ghana. The top 3 most prescribed medicines across all demographic groups were paracetamol (4.38 million DDD), diclofenac (3.28 million DDD), artemether/lumefantrine (319,249 DDD).

Conclusions: This study demonstrates that the Ghana NHIS database can be leveraged for DUR. To further improve the utilization of this database for other health research, researchers will need to transform the NHIS database into one of the existing standardized common data models prior to analyses.

962 | Clinical experience with oxytocin quality used by health care providers in Lagos, South-West Nigeria: A cross-sectional study

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Background: Obstetric haemorrhage especially postpartum haemorrhage (PPH) is a leading cause of maternal mortality in Nigeria and most low-income countries. The WHO strongly recommends Oxytocin as an effective and the safest drug of choice in the management of PPH at the dose of 10IU. However, surveillance studies have shown high prevalence of poor quality oxytocin especially in Africa and Asia. Excessive, inappropriate indication for use, and inconsistent dosage administration of oxytocin is also common in low resource settings.

Objectives: To assess the clinical experiences with the quality of oxytocin used by healthcare providers in Lagos State Nigeria.

Methods: A descriptive cross-sectional study done in 2017. Multistage sampling technique was used to select 195 health care facilities (public and registered private facilities) that provide obstetrics and gynaecological services within the health system across the State. 705 respondents (doctors and nurses) who use oxytocin were selected from these facilities. The main outcome measures were proportion of health care providers (HCP) with good knowledge of oxytocin storage, pattern of oxytocin usage and dosing by HCP, the proportion of oxytocin perceived to be ineffective by HCP. Data collection was quantitative using a pretested self-administered questionnaire. Data analysis was done using IBM SPSS version 21 and presented in frequency tables, simple proportions. Inferential statistics was done with chi-square to test for association and statistical significance set at $p < 0.05$. Ethical approvals were obtained. Funding support was provided by the USAID-funded PQM program implemented by USP.

Results: 52% of the respondents knew oxytocin should be stored at 2-8°C. 80% of the respondents used oxytocin for Augmentation of labor; 68% for induction of labor and 78% for management of PPH. About 41% used 20IU for management of PPH and as much as 10% used doses ranging between 30IU to 60IU for management of PPH. About 13% of the respondents have experienced use of an ineffective brand of oxytocin in their practice.

Conclusions: There was poor knowledge of proper storage of oxytocin; oxytocin was highly inappropriately used intrapartum, with excessive and inconsistent dosing for the indications. These could be contributors and proxies to quality of oxytocin as doses above recommended 10IU were used to achieved desired result. Continued training of HCP on drug safety monitoring and the availability of a heat-stable oxytocin is recommended.

963 | Adherence to inhaled corticosteroids before and after an asthma-related hospitalisation: Distinct trajectories

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Background: Despite proven efficacy of inhaled corticosteroids (ICS) in asthma, many patients are not adherent to their regular use.

Objectives: To analyse trajectories of adherence to ICS in patients with an asthma-related hospitalisation.

Methods: Patients hospitalised for asthma in 2013 and with data available between 2012 and 2014 were included from the EGB (*Echantillon Généraliste de Bénéficiaires*, 1/97e random sample of the French claims database SNIIRAM). Continuous Measure of Medication Acquisition (CMA7) for ICS were computed for each quarter of the 12-months periods before and after hospital admission (HA). Trajectories of CMA7 were analysed using Ward's minimum-variance hierarchical clustering, and the number of clusters was determined with the analysis of the CCC, pseudo F and pseudo T2 criteria.

Results: 343 patients were included in the cohort (51.6% females; 23.7 mean age), representing 0.07% of patients recorded in the database. Three distinct trajectories were of particular interest: T1: 37.3% of patients did not adhere to ICS (CMA7 < 10%) during the 12 months before HA, and 47.7% remained in this cluster after; T2: 16.0% of patients steadily increased their adherence during the 12 months before HA (from 30% in Q1 to 70% in Q4), and 51% remained adherent (CMA7 ≥ 80%) during the following year; T3: 12.2% of patients had a CMA7 ≥ 90% before HA, and 88% remained adherent following HA.

Conclusions: In this cohort of patients with a HA for asthma, distinct trajectories of adherence to ICS could be distinguished before and after the event. HA modifies the level of adherence in the majority of patients.

964 | Deciphering patterns of respiratory medication use in Ireland to target interventions appropriately: A focus on COPD

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Background: Ireland has the highest rates of hospitalisations for COPD of all the OECD countries, double the OECD average. In 2016, the age standardised rate of hospitalisations was 411 and

347/100 000 population for males and females, respectively. While high hospitalizations rates are multifactorial, non-adherence to inhaler therapy plays a significant role.

Objectives: We sought to identify patterns of respiratory medication use in Ireland in 2016 to inform interventions for prescribers and patients to improve adherence to drug therapy in COPD.

Methods: We used a publically insured cohort (GMS), which covered approx 40% of the Irish population in 2016 (including over 70% of all residents aged over 70 years), and restricted to those with full eligibility for the year. We firstly examined the distribution of all respiratory medications dispensed, and then patterns of medication use in those likely to have a diagnosis of COPD. Group 1: those aged >45 years who received at least one LAMA (+/- LABA). Group 2: those >45 years who received at least one LAMA (+/- LABA), or an ICS and LABA combination, or a SAMA (+/- SABA).

Results: 1. Of those with full eligibility in 2016 (1.53m), 20% filled at least one prescription for a respiratory medication; 25% of those >55 yrs did so. 14% of those eligible received at least one SABA, and almost one-third of these received no alternative respiratory medication during the year. 11% of eligible patients received at least one ICS (7% an ICS_LABA combination), increasing to 20% in those aged 65+ years, with 13% receiving at least one ICS_LABA. 2. The age and sex specific trends in COPD were evident. In those aged 45-54 yrs, 3% of males and 3% of females received a LAMA (+/- LABA) (group 1), and 7% of males and 10% of females received at least one LAMA (+/- LABA) OR a SAMA (+/- SABA) (group 2). In those over 65 years, the numbers increased to 11% (m) and 9% (f) in group 1 and 19% (m) and 18% (f) in group 2. 3. Of those newly initiated a LAMA (+/- LABA), 25% did not receive another within 90 days, and 17% never filled a second dispensing for any LAMA (+/- LABA).

Conclusions: There is significant respiratory medication use in the GMS population, and the age and sex specific patterns in COPD are clear. Several patterns raise concern, most notably the increasing prevalence of ICS use with age, and the non-adherence with LAMA therapy. Further analysis is necessary to explore these patterns and identify the characteristics of those less likely to adhere, to target interventions appropriately.

965 | Real life data on COPD treatment

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Background: Adherence to controller therapy in chronic obstructive pulmonary disease (COPD) has been associated with a reduced risk of COPD exacerbations. The controller to total COPD medications ratio (CTR) can be used as a measure of treatment adherence.

Objectives: To describe, in a real life setting, respiratory drug use in COPD patients. Next to describe the CTR and compare characteristics in patients with high vs. low CTR.

Methods: A retrospective cohort study (2007-2016) in COPD patients ≥ 40 years was conducted in two primary care databases; IPCI (NL) and THIN (UK). COPD was defined as the presence of ≥ 1 COPD disease code in combination with ≥ 2 prescriptions of respiratory drugs in 1 year. Respiratory drug use was retrieved by ATC code from prescription records and expressed as number of users/1000 person-years (PY). Baseline patient characteristics were compared between patients with a high (≥ 0.5) and a low CTR (< 0.5).

Results: In IPCI 40 746 patients with a mean age of 68.3 contributed to 47 461 431 person-days, and in THIN 127 234 patients with a mean age of 68.8 contributed to 190 156 330 person-days. In IPCI, user prevalence rates ranged between 0.15/1000PY and 558/1000PY with the highest use for long-acting β_2 -agonists (LABA) (558/1000PY) followed by long-acting muscarinic antagonist (LAMA) (466/1000PY), inhaled corticosteroids (ICS) + LABA (441/1000PY), short-acting β_2 -agonist (SABA) (278/1000PY), short-acting muscarinic antagonist (SAMA) (129/1000PY) and ICS (122/1000PY). In THIN, user prevalence rates ranged between 0.14/1000PY and 851/1000PY with the highest use for SABA (851/1000PY) followed by LABA (635/1000PY), ICS + LABA (562/1000PY), LAMA (562/1000PY), ICS (131/1000PY), and SAMA (114/1000PY). The median and interquartile range of CTR was 0.88 (0.59-1.00) and 0.60 (0.43-0.75) in IPCI and THIN, respectively. In IPCI 80% of patients had a high CTR whereas this was 63% in THIN. In both databases, patients with a high CTR were significantly younger, more often male and suffered less frequently from diabetes, depression and heart failure at baseline compared to patients with a low CTR.

Conclusions: Differences in drug use and CTR were observed between the 2 countries. Whether a low CTR results in a higher incidence of COPD exacerbations needs to be investigated in future research.

966 | Utilization of antibiotics for patients with acute upper respiratory tract infections at community health care institutions in Beijing

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Background: Inappropriate antibiotic prescribing contributes to the subsequent drug resistance worldwide and is particularly common in China.

Objectives: Our aim was to examine the prevalence, quantity, and factors of antibiotic and non-antibiotic prescriptions to acute upper respiratory tract infections (AURIs) of community health care institutions (CHCIs) in Beijing.

Methods: We conducted a retrospective observational study, deriving data on diagnoses, prescriptions, and demographic characteristics of doctors and patients from the electronic health records collected from 65 CHCIs in Beijing in 2016. Eligible patients were adults aged 18 years or more who attended a CHCIs as an outpatient and were given a prescription following a primary diagnosis of AURIs and with no other infectious diseases. Four outcomes regarding antibiotic

prescribing were the antibiotic, multiple, broad-spectrum, and intravenous antibiotic prescription rate; three outcomes regarding non-antibiotic prescribing were the antiviral, glucocorticoid, and traditional Chinese medicine (TCM) prescription rate. Seven outcomes were analyzed from the perspective of patients' and doctors' characteristics, and inter-cluster variability was assessed with χ^2 test. Ethics approval obtained from PUIRB (No. IRB00001052-17016).

Results: We included 164 575 AURIs prescriptions over the study period and 12.1% of prescriptions were treated with antibiotics, 55.8% with TCMs, none with antivirals or glucocorticoids. Broad-spectrum, intravenous, and multiple antibiotics were prescribed in 84.3%, 1.6%, and 0.6% of antibiotic prescriptions, respectively. Second-generation cephalosporins dominated prescribing (60.2%), followed by macrolides (16.2%) and fluoroquinolones (8.7%), narrow-spectrum penicillin preferred by the guidelines were not used. Patients were more likely to receive antibiotics if they aged 18-50 years, diagnosed with acute tonsillitis, paid fully out-of-pocket; or if their responsible doctors had higher educational level or higher title ($P < 0.05$).

Conclusions: This detailed insight in antibiotic prescribing of adult AURIs patients shows targets for improvement strategies: (i) prevent antibiotic abuse for AURIs and (ii) reduce the use of broad-spectrum antibiotics and TCMs. Furthermore, pragmatic interventions on antimicrobial stewardship based on guidelines targeting primary health care providers should be normalized.

967 | Treatment guidelines: Adherence and use among type 2 diabetes mellitus providers and their patients

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Background: The American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), and European Association for the Study of Diabetes (EASD) publish treatment guidelines for managing patients with type 2 diabetes mellitus (T2DM). It is useful to understand if these recommendations are applied in practice, by which type of HCPs, and if HCP adherence to these guidelines impacts patient outcomes.

Objectives: To understand HCP adherence to and use of treatment guidelines in their management of patients with T2DM based on evidence available in published literature.

Methods: A systematic literature review was conducted to identify articles examining (1) a relationship between guidelines and real-world treatment patterns, (2) a description of characteristics of patients with T2DM and of HCPs treating such patients, or (3) any evidence describing the decision-making process of the prescribing HCP to adhere to guidelines or choose alternate therapies. A search combining terms for T2DM; ADA, AACE, or EASD; and guideline/treatment patterns was executed in PubMed and EMBASE in February 2018. Only articles published since 2012, in English, focusing on human subjects were included. Study selection was accomplished

through two levels of screening using exclusion and inclusion criteria. Relevant data were extracted for further evaluation and to determine generalizability.

Results: Of the 584 abstracts identified, 34 papers did not contain an exclusion criterion. Upon full text review, 17 articles met inclusion criteria. All studies referenced ADA treatment guidelines; AACE and EASD guidelines were referenced in 2 and 5 studies, respectively. The majority of HCPs studied was primary care providers and endocrinologists working in varied healthcare settings. A single study addressed the HCP decision-making process for selecting treatment. A comparison of patient test values, such as HbA1c, blood pressure, and lipid levels, against recommended targets was provided in 13 articles; all of which reported that patients did not meet at least one of the targets. HCP knowledge of lab value goals, treatment inertia or appropriate drug combinations was described as inaccurate or lacking as evaluated by survey, interview, and chart review.

Conclusions: Documented departures from recommended treatment could be attributed to patient or HCP nonadherence. Further research is needed to investigate any relationship between HCP guideline knowledge and the gap between patient targets and real-world results.

968 | Medical home enrollment and quality of care: Population estimates from the US Medical Expenditure Panel Survey

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Background: The Patient Centered Medical Home (PCMH) emphasizes the use of a primary care physician to provide patient centered, comprehensive, and coordinated care that is accessible to patients and enhances health care quality and safety.

Objectives: The objective of this study is to examine the effect of having a usual source of care and medical home enrollment on preventative and medication specific quality of care metrics among a nationally representative sample of the US ambulatory population.

Methods: The newly released Medical Organization Survey (MOS) of the 2015 Medical Expenditure Panel Survey (MEPS) was used to examine cross-sectional medical home and usual source of care (USC) status. MEPS captures respondent health care use, spending, demographics, insurance status, and health related information on more than 35 000 patients with weighting to allow estimation in the entire US ambulatory population. Among patients 18 and older, we constructed cohorts of 3951 respondents reporting no USC, 2998 respondents with a USC not recognized as a PCMH, and 2059 respondents with a USC recognized as a PCMH. Chi-squared and multivariable logistic regression will be used to compare validated HEDIS quality measures across cohorts.

Results: Compared with having no USC, respondents with a USC had higher rates of screening for cervical (93 vs 87%, $p < 0.001$), breast (82 vs 58%, $p < 0.001$), and colon cancer (4.8 vs 2.7%, $p = 0.024$) and inappropriate screening for prostate cancer (86 vs 62% $p = 0.002$). Among patients reporting a USC, there was no difference in screening

by PCMH status. In a subset of patients with diabetes, respondents with a USC had better annual foot screening (71 vs 58%, $p = 0.008$), eye exams (66 vs 43%, $p < 0.001$), hemoglobin A1C testing (93 vs 87%, $p = 0.040$), and cholesterol screening (97 vs 90%, $p < 0.001$) than respondents with no USC. Having a USC also led to better rates of flu vaccination (63 vs 45%, $p = 0.004$) and preventative statin medication use (59 vs 47% 0.034). PCMH enrollment had little effect on diabetes quality metrics with the exception of better rates of annual foot screening (78 vs 66%, $p = 0.004$) and poorer rates of annual cholesterol screening (93 vs 98%, $p = 0.019$).

Conclusions: Our initial results suggest little benefit to PCMH standards beyond improved access to a usual source of care. Steps are under way to confirm these findings using multivariable logistic regression controlling for demographics, insurance status, comorbidity, and disease severity.

969 | Inappropriate medication prescribing among elderly patients in Italy

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Background: Pharmacological intervention is an essential step in health promotion. However, lots of drugs are often used in inappropriate ways, especially in elderly patients. The assessment of inappropriate prescribing is commonly based on explicit criteria, which require each prescription to be compared with a set of published standards. Such indicators are useful to summarize the performance of a system and to monitor the effectiveness of policy measures.

Objectives: To retrospectively evaluate indicators of appropriate prescribing in an elderly population using Regional administrative prescription databases.

Methods: This analysis was based on the baseline data of the EDU.RE. Drug project (funded by the Italian Medicines Agency). A set of explicit criteria, including a list of inappropriate drugs (ERD) in elderly (based on validated Beers, STOPP and EU-(7)-PIM criteria), a list of drugs with high anticholinergic burden (ACB) and with elevated sedative load (SL), has been selected, updated, and adapted to Italian context. The study population was composed by all patients over 65 years followed by a general practitioner (GP) of four local health units (LHUs) in Lombardy and Campania. These criteria were applied to the administrative databases of the outpatient drug prescriptions (reimbursable by the NHS) in 2016.

Results: The number of GPs for the four LHUs involved (Lecco, Bergamo, Napoli1 Centro and Napoli2 Nord) were 205, 661, 744 and 794, with a mean of 369, 324, 225, 170 patients over 65 for each GP, respectively. For LHUs in Lombardy, the percentages of elderly who received at least an ERD drug were 37.6% for Lecco (median 37.2; IQR 33.9-40.6) and 43.0% for Bergamo (median 42.7; IQR

38.6-47.5). For LHUs in Campania, more than 60% of patients were involved in the ERD list. In all LHUs, the most inappropriate drug prescribed was diclofenac. A high anticholinergic burden (ACB score ≥ 3) was found for 6.0%, 8.0%, 6.7%, and 7.0% of patients belonging to the four LHUs, while an elevated sedative load (SL score ≥ 3) was observed in less than 1% of patients.

Conclusions: These results show that the prescription of potentially inappropriate drugs in elderly patients is widespread, with some remarkable geographical differences. Therefore, it is necessary to implement local strategies to improve the rational use of drugs, including information/education for healthcare professionals and for the public from independent sources. This will enhance safe prescribing practices, reducing costs associated with inappropriate/unnecessary prescribing.

970 | Medicines for malaria: An exploration of practices at retail medicines outlets in urban and rural Ghana

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Background: Medicines play a major role in protecting, maintaining and restoring people's health. In developing countries like Ghana, medicines form about 30-40% of health expenditure but most of these medicines are bought by individuals for self-medication and rarely bought on prescription; yet as technical products their uncontrolled use could be dangerous to health.

Objectives: As part of a bigger research that uses anti-malarials as a lens to explore the realities surrounding the global pharmaceutical market in developing countries, this study describe and analyse the retail practices of operators and users of medicines outlets and implications for public health by looking at (a) what is the range of medicines that are sold and dispensed in private drug outlets? (b) Do drug outlets follow essential regulations and principles of appropriate dispensing? (c) What is the extent of purchasing by clients through self-medication?

Methods: Qualitative ethnographic case study using observations and semi-structured interviews at retail drug outlets located in urban and rural areas in Greater Accra and Central regions of Ghana, respectively. Four hours per session observations twice weekly were done in each retail outlet for 4-6 months. Excel was used to analyse preliminary quantitative data. Apart from demographic characteristics main outcome measures include national health insurance status, median price and range of products and the therapeutic classes of medicines purchased.

Results: Preliminary results show that majority of clients were male (55%) and adolescents of 15 to 19 years (42%). The use of formal prescriptions was very few (4%). The median price of product purchased was twice in urban to rural. The top three products sold were analgesic/antipyretic (25%), anti-malarial (10%) and vitamin preparations (8%) and also included herbal preparations (4%).

Conclusions: Medicines sales pattern confirm "the commodification of health care," in which health care is bought and sold in a market and has implications for rational drug use and drug resistance. There is need to find innovative ways to educate and improve drug sales practices for providers and consumers in private drug outlets.

971 | Self-medication practices and associated factors among undergraduate medical students in St Paul Hospital Millennium Medical College

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Background: Self-medication is a common practice worldwide with serious global implication. It has a special significance among medical students in developing countries as they are expected to have knowledge about diseases/drugs and prescriptions are not well controlled. There is no current data available regarding the self-medication practice among undergraduate medical students in Ethiopia.

Objectives: To assess the magnitude of self-medication practices and associated factors among under graduate medical students in St Paul Hospital Millennium Medical College (SPHMMC)

Methods: This is a descriptive cross-sectional study. The study population consisted of randomly selected regular undergraduate medical students of SPHMMC. This study was conducted from 30 March 2017 to 15 April 2017. Sample size was calculated based on 10% contingency of non-response rate with expected prevalence from previous study. A total of 279 students were included. A pretested self-administered questionnaire was used to collect data and data were summarized using counts and percentages.

Results: Among 270 students, 58.5% practiced self-medication. Disease conditions for which they self-medicated included headache 52 (19.3%), cough and common cold (8.5%), dyspepsia (8.1%), and dysmenorrhea (6.3%). The classes of drugs that were commonly used for self-medication were analgesics (27.8%), antibiotics (11.5%), and anta-acids (6.7%). The reasons for self-medication were quick relief 59 (21.9%), prior experience 51 (18.9%), and mildness of the illness 32 (11.9%). The major sources of the drugs used for self-medication were the pharmacies 87 (40%), friends/relatives 55 (20.4%), leftover drugs from previous prescriptions 14 (5.2%), and kiosks 2(07%). Information about drugs were obtained from self-decision 75 (27.6%), family and friends 30 (11.1%), and reading material 30 (11.1%).

Conclusions: Self-medication is practiced by a majority of undergraduate medical students. This practice could potentially cause serious harm, not only to students themselves but also to those whom they suggest medication; hence, restriction of sale of drugs with potentially harmful effects should be implemented effectively with monitoring systems between the physicians and pharmacist.

972 | Medication prescribing practices of eating disorder consultants for the treatment of young people with anorexia nervosa: A questionnaire study

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Background: Anorexia nervosa (AN) is a condition that onsets in young people (YP). First-line treatment consists of psychological interventions; however, psychotropic medications are sometimes prescribed if there is a less than optimal treatment response.

Objectives: This study aimed to describe contemporary prescribing practices of consultant child and adolescent eating disorder (CAED) psychiatrists, including the most common medications they prescribe and their process of continuing pharmacotherapy among individuals with AN.

Methods: We developed a self-administered questionnaire which was distributed among all 71 child and young people eating disorder services (CYP EDS) in England during the Health Education England national training days.

Results: From 71 CYP EDS, 40 teams represented by an ED consultant responded (response rate 56%). Most (40%) consultants estimated <10% of patients with AN to be on psychotropic medications. 38% of consultants reported olanzapine as their most commonly prescribed medication for AN, followed by fluoxetine (29%) and sertraline (10%). The minimum olanzapine initiation dose was at 2.5 mg for 2-4 weeks, reaching a maximum dose of 5 mg. 38% ED consultants met their patients once every 2 weeks on average, whereas 30% and 22% met once weekly and once monthly, respectively. Over 40% of consultants reported to continue olanzapine prescribing with the ED service teams, in contrast to the 30% who transferred prescribing to general practitioners.

Conclusions: The study showed that despite a lack of evidence, psychotropic medications are still prescribed, most commonly olanzapine. Further evidence is needed on which patients may potentially benefit from pharmacotherapy as an adjunct to psychological interventions.

973 | Use of medicines in adults with autism spectrum disorder

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Background: Use of psychotropic medicines like antipsychotics, antidepressants, and anxiolytics is common in children with autism spectrum disorder. Currently, very little is known about medicine use in adults with Autism Spectrum Disorder (ASD).

Objectives: This pilot project aimed to characterise medicines use in adults with ASD.

Methods: We conducted a retrospective analysis of deidentified mental health care plan records for adults (aged 18 years or over) with ASD who attended a psychology practice in metropolitan Adelaide, South Australia, and who received a mental health care plan between June 2012 and November 2017. Medicines data were extracted from the mental health care plans and a descriptive analysis of medicines use was conducted. Ethics approval was received from UniSA Human Research Ethic committee.

Results: Currently, care plans have been reviewed for 86 adults with ASD. The median age of patients was 26 years (interquartile range 20-40 years) and 60.5% were male. Twelve patients (14.0%) had no regular medications recorded on their care plan. Thirty-three patients (38.4%) were prescribed an antidepressant at the time of their care plan, most commonly escitalopram (8% of participants) or sertraline (8%); and use of amitriptyline was also common (5% of patients). Nine percent of patients were prescribed an antipsychotic at the time of their care plan, most commonly quetiapine; and 7% had been prescribed a benzodiazepine. Use of asthma medicines was also common, with 19.8% prescribed at least one type of inhaler at the time of care plan.

Conclusions: Preliminary results of this pilot study, which is ongoing, have provided some insight into the types of medicines used by adults with autism spectrum disorder. Future work will explore the appropriateness of medicines use in this population and assess whether there is a link between psychotropic medicines use and cognitive impairments in adults with ASD.

974 | Risk of drug-drug interactions in out-hospital drug dispensings in France: Results from the drug-drug interaction prevalence study (drug-DIPS)

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Background: Drug interactions could account for 1% of hospitalizations in the general population and 2-5% of hospital admissions in the elderly. However, few data are available on the drugs concerned and the potential severity of the interactions encountered.

Objectives: To estimate, within drug out-hospital dispensings performed in France, the prevalence of codispensing of drugs Contraindicated or Discommended because of Interactions (CDI codispensings), and to identify the most frequently involved drug pairs in these codispensings.

Methods: This cross-sectional study was carried out using a random sample constituted from all drugs dispensings registered in the database of the *Echantillon Généraliste des Bénéficiaires* (EGB), a 1/97th sample of all affiliates to the French Health Insurance System between 2010 and 2016. The prevalence of CDI codispensings was estimated in terms of number and proportion. The risk of CDI

codispensings for each drug pair was studied using an ad hoc developed codispensing indicator. This indicator (DIPS-Score) compares, for a given drug pair, the observed frequency of codispensing to its expected probability, estimated from the observed frequency of dispensing of the individual drugs involved. The DIPS-Score consists in the ratio of these observed and expected frequencies. A value exceeding one could indicate the codispensing was sought, a value lower than one that it was avoided. DIPS-Score estimates were provided with 95% confidence interval.

Results: We analyzed 6 908 910 dispensings: 13 196 (0.2%) involved contraindicated codispensings (CCs), and 95 410 (1.4%) discommended codispensings (DCs). The drug pair involved in the most frequent CCs ($n = 5036$) was "bisoprolol + flecainide." The drug pair involved in the CC with the highest score value was "citalopram + hydroxyzine" (DIPS-Score: 3.7; 2.9-4.6); that with the lowest score was "clarithromycin + simvastatin" (DIPS-Score: 0.2; 0.2-0.3). DIPS-Score median value was 0.4 for CCs and 0.6 for DCs.

Conclusions: The prevalence of CDI codispensings appeared high, indicating an important risk of interactions and the need for further risk-prevention actions regarding drug-drug interactions. In this perspective, the use of the developed DIPS-Score could ease the identification of interactions that are poorly considered by clinicians/pharmacists and help targeting the intervention.

975 | Monitoring of Italian pharmaceutical administrative databases: An assessment of prescriptive performance

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Background: Monitoring of pharmaceutical prescription is an effective indicator of quality of care. The single pharmaceutical prescription is a list of drugs and prices, while a full record set of prescriptions represents a rich information base providing complex and useful data about public health.

Objectives: The aim of this study is to evaluate the prescriptive behavior in two Italian regions (Campania and Lombardy).

Methods: The study design was a non-randomised controlled trial. Data were retrieved from administrative databases of Campania (Naples 1, Naples 2, Avellino, and Caserta) and Lombardy regions (Bergamo, Mantova, Lecco, and Monza) regarding all adults (over 40 years) assisted by National Health Service (NHS). The analysis of prescriptions was restricted to eight specific therapeutic categories related with the following ATC codes: A02BC; J01; R03; C10AA; C09AA; C09CA; N06AB; N06AX. The study population percent of persons using at least one prescription drug for one of these categories, in age groups 40-64 years and ≥ 65 years during the years 2014, 2015, and 2016 in the Local Health Units (LHUs) involved.

Results: Out of 3 294 735 residents in the LHUs involved in Campania Region: 924 849 (27%) was in 40-64 age groups; 572 125 (17%) was in ≥ 65 age groups. Out of 2 233 697 residents in the Local Health Units involved in Lombardy Region: 1 566 603 (57%) was in 40-64 age group; 564 680 (21%) was in ≥ 65 age group. In the age group 40-64 years, the most prescribed drug were the antibiotics. The percentage of patients that using antibiotics ranging from 50.3% in Naples 1 to 55.7% in Naples 2 for Campania region and ranging from 19.2% in Mantova to 29.2% in Monza for Lombardy region. In the age group ≥ 65 years, the most prescribed drug were the antibiotics for Campania region ranging from 71% in Naples 1 to 73.7% in Naples 2. In Lombardy region, for the same age group, the most prescribed drug were the proton pump inhibitors, ranging from 32.5% in Lecco to 43.1% in Mantova. Finally, antidepressant drugs was the less prescribed in 40-64 and ≥ 65 age groups both in the Campania and Lombardy Region.

Conclusions: The regional variability observed in our study can be explained by different prescribing patterns among physicians and different local health policies. The high rates of medication prescription increases the complexity and cost of healthcare. Therefore, interventions that aim to reduce disparities in prescriptions practices among physicians of different regions can decrease total health system costs.

976 | Feasibility of using point prevalence surveys to assess antimicrobial utilisation in public hospitals in South Africa; a pilot study and implications

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Background: Antimicrobial resistance (AMR) is a serious world-wide health concern and a direct threat to future patient safety, with the misuse and overuse of antimicrobials increasing AMR rates. Consequently, it is imperative to measure current antibiotic utilisation within hospitals to guide future quality initiatives. However, data on antimicrobial utilization among public hospitals in South Africa (SA) is currently lacking and needs to be addressed.

Objectives: Determine antimicrobial consumption in a leading public hospital in South Africa using a point prevalence survey (PPS) methodology.

Methods: A point prevalence study was conducted in Dr George Mukhari Academic Hospital (DGMAH) between February to March 2017 using tested data collection instruments developed with the help of the WHO. Data were collected by trained pharmacist interns. All patient files in one single in-patient ward were completely surveyed during a single day. The number of patients who were on antimicrobials served as the numerator and the denominator comprised the total number of patients in the ward.

Results: Patients in 39 in-patient wards were surveyed, resulting in 512 patient files assessed of which 400 were adults, with 175 (44%) males and 225 (56%) females. 193 patients received at least one antimicrobial (38%). The highest utilisation was in the ICUs including the neonatal ICU (70.8%, 95% CI: 52.6, 89.0) and lowest in obstetric and gynaecology wards (3.3%, 95% CI -1.7, 8.3). Broad spectrum penicillins (J01CA) - 34.1%, cephalosporins (J01D) - 17.9% and antimicrobials for TB (J04AB02/AM and others) - 12.0% - were the most prescribed antimicrobials. 83% of antibiotic treatment was modified following culture and sensitivity results (n = 72) and 12 (17%) were not modified. The remainder of the patient's files had no culture and sensitivity tests results recorded. Encouragingly, 98% of antimicrobials prescribed complied with the national EML. There was also low use of restricted antibiotics, which is also encouraging. However, there were concerns with the lack of IV to oral switching where possible.

Conclusions: The PPS method offers a standardized tool that can be used to identify targets for quality improvement programmes in hospitals. In DGMAH, this includes encouraging greater use of oral antimicrobials where possible. Concerns with the time taken on PPS studies is being addressed with the development of an APP.

977 | Use of ADHD medication, antipsychotics, antidepressants, and melatonin in children and adolescents with autism spectrum disorder: A Danish drug utilization study

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Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social communication and interaction, and unusually restricted, repetitive behavior and interests. There is no evidence based pharmacological treatment of ASD core symptoms. Nevertheless, children with ASD have a substantial use of psychotropic drugs.

Objectives: To describe the use of ADHD medication, antipsychotics, antidepressants, and melatonin in children and adolescents diagnosed with ASD in Denmark during the period 2010-2016.

Methods: Based on data from the Danish Psychiatric Central Research Register, we defined a cohort of children born between 1992 and 2010 with a recorded diagnosis of ASD after the age of three. From the Danish National Prescription Registry, we extracted data on all prescriptions of ADHD medication, antipsychotics, and antidepressants to our cohort between 2010 and 2016. We extracted data on melatonin prescriptions from 2012 to 2016. For each calendar year, we reported the 1-year prevalence proportion for the use of these drug classes (≥ 2 prescription per year) according to age group (3-5 years, 6-11 years, and 12-17 years).

Results: We identified 19 096 children born between 1992 and 2010 with a recorded ASD diagnosis. Of these children, 76% were male, 30% had comorbid ADHD, 16% had comorbid mental retardation, and 57% had other comorbid psychiatric disorders. The use of ADHD medication, antipsychotics, and antidepressants varied between age groups, with negligible use in the youngest age group. In 2016, the prevalence of use of ADHD medication, antipsychotics, antidepressants, and melatonin was 16%, 3%, 1%, and 13% for children aged 6-11 years and 18%, 8%, 7%, and 13% for children aged 12-17 years. The use of ADHD medication, antipsychotics, and antidepressant was generally stable during the study period for all age groups, while the use of melatonin increased (from around 7 to 13% for children aged 6-17 years).

Conclusions: The use of ADHD medication, antipsychotics, and antidepressants in Danish children and adolescents with ASD was stable from 2010 to 2016, while melatonin use increased. Except for ADHD medication use, the reported prevalences were generally low compared with what was reported in a recent systematic review, most likely due to our conservative criteria of requiring at least two prescriptions filled within a given year.

978 | Slow adoption of new evidence into clinical practice and associated factors: The case of duplicate therapy with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

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Background: New evidence emerged in 2008 that duplicate therapy with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) increased the risk of hypotension and renal dysfunction with no benefit on clinical outcomes. Little is known about how quickly this information was incorporated into practice.

Objectives: (1) Estimate the prevalence and examine the time trend of duplicate ACEI/ARB therapy, (2) assess whether duplicate therapy prescriptions were written by the same prescriber and/or filled at the same pharmacy, and (3) identify predictors of ACEI/ARB duplicate therapy.

Methods: Medicare fee-for-service claims were used to identify a cohort hospitalized for a myocardial infarction (MI) from 2008-2010. Patients were ≥ 66 years old, had 1 year of continuous enrollment pre-MI, and filled an ACEI and/or ARB prescription within 30 days after hospital discharge (index Rx). Patients were followed for 120 days after the index Rx to measure duplicate therapy. The percent of duplicate therapy fills written by the same prescriber and/or filled at the same pharmacy was assessed. Relative risks (RRs) and 95% confidence intervals (CIs) of duplicate

therapy predictors were calculated with a modified Poisson regression model.

Results: A total of 137 906 patients met eligibility criteria, with 3955 (2.9%) receiving duplicate therapy. The prevalence of duplicate therapy did not decrease over the study period. Of the duplicate therapy prescriptions, 58.6% were written by the same prescriber and 90.6% were filled at the same pharmacy. After multivariable adjustment, patients dually enrolled in Medicaid were more likely to receive duplicate therapy (RR 1.12; CI: 1.05-1.20); Black (RR 1.34; CI: 1.22-1.46) and Hispanic (RR 1.28; CI: 1.12-1.46) patients were also more likely to receive duplicate therapy compared with White patients.

Conclusions: The prevalence of duplicate therapy did not decrease over time. A majority of duplicate therapy prescriptions were written by the same prescriber, and nearly all were filled at the same pharmacy, suggesting new clinical evidence was not being incorporated into practice. Vulnerable populations had a higher risk of receiving duplicate therapy.

979 | The association of domperidone use and ventricular arrhythmia in the elderly

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Background: Domperidone, a dopamine antagonist, is used for increasing gastrointestinal motility since the 70s. However, issues of domperidone related cardiac side effects were raised.

Objectives: To investigate the association of domperidone use and ventricular arrhythmia in the elderly.

Methods: We used the National Health Insurance Service-Senior cohort (2002-2013) which contains 558 147 elderly patients to perform a case-crossover study. The ventricular arrhythmia was defined as first hospitalization with primary diagnose of ventricular arrhythmia (ICD-10 code: I47-I49) or cardiac arrest (I46) during 2003-2013. Exposures to domperidone were assessed during the 14 days prior to the date of ventricular arrhythmia. We set four control periods with same lengths as the hazard periods, and we selected 180 days as washout period. For sensitivity analysis, we applied 7, 30 days as length of periods. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated by conditional logistic regression. Use of fluoroquinolone, typical antipsychotic, and monoamine reuptake inhibitors which were related with QT-prolongation were adjusted.

Results: Of 7739 patient of ventricular arrhythmia (mean age 76.4 ± standard deviation 7.1, 59.7% is female), 478 patients were exposed to domperidone in hazard period. The adjusted OR for ventricular arrhythmia was 2.14 (95% CI 1.82-2.50), and when applying 7, 30 days of hazard periods, the OR was 2.01 (95% CI 1.69-2.38), 1.79 (95% CI 1.53-2.08).

Conclusions: We found the association of increased risk of ventricular arrhythmia and domperidone use in elderly patients.

980 | Intensive monitoring (IM) of new glucose lowering drugs (GLD): Results from an inception cohort study in Portugal using patients as a source of information

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Background: New GLD are being used in large numbers of patients in Portugal, though little is known about its use and time related information about adverse drug events (ADE) in daily practice.

Objectives: To determine ADE profile (frequency, time course, and factors potentially associated) and to estimate the frequency of hypoglycaemic events, using patients as a source of information.

Methods: Eligible population was recruited at pharmacies and consisted of T2DM patients initiating one dipeptidyl peptidase-4 inhibitors (DPP-4), glucagon-like peptide-1 (GLP-1) or sodium-glucose co-transporter 2 inhibitors (SLGT2). Data were collected through a baseline questionnaire (demographic and clinical data) and telephone-questionnaires conducted 2 weeks, 3 and 6 months after the index date (ADE, hypoglycaemic events and reasons for drug stopping). Kaplan-Meier curves and log-rank were computed to compare the time with ADE onset. Cox models were used to explore potential factors associated with ADE.

Results: 1328 eligible patients were recruited. A total of 1118 ADE were reported by 41.40% patients. A higher proportion (47.94%; $p < 0.0001$) of prevalent new users (PNU) (patients who used in the past/recruitment at least one GLD of the monitored drug classes, but not the inception drug) reported an ADE compared with the proportion among incident new users (INU) (patients who used for the first time one of the monitored GLD and had no current/prior experience with DPP-4, GLP-1 and SLGT2). Decreasing age, increasing body mass index, and insulin usage were significantly associated with reporting an ADE. The median latency time of ADE reported in $\geq 1\%$ patients was 0-2 days. A total of 328 inception GLD were withdrawn, of those more than half due to an ADE. One fifth experienced, at least, one hypoglycaemic episode.

Conclusions: New monitored GLD were generally safe. The most prominent reported AE were nausea, diarrhea, dizziness, pollakiuria, and constipation, which occurred very early in the treatment. IM can play an important role in the frame of real-world practice evidence generation data, since it can generate other type of information as compared with spontaneous reporting and other methodologies used in clinical practice.

981 | GLP-1RAs and risk of diabetic retinopathy: Analysis of the FDA Adverse Event Reporting System database

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Background: Glucagon-like peptide 1 receptor agonists (GLP1RAs) are increasingly being used as treatment for type 2 diabetes. Recent large trials indicated that GLP1RAs may be associated with diabetic retinopathy (DR); however, the results are conflicting and effect of GLP1RAs on DR remained uncertain.

Objectives: To assess the association between GLP-1RAs and DR using US Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: DR is defined as diabetic retinopathy, retinopathy, macular edema, retinopathy proliferative, retinopathy haemorrhagic, blindness, and vitreous haemorrhage. By running a query on AERSMINE (an open access web data mining tool), we obtained the number of DR events and all other adverse events in GLP1RAs, each GLP1RA drug (exenatide, liraglutide, albiglutide, and dulaglutide) and all other (non-GLP1RA) drugs from 2005 Q3 to 2017 Q3. We calculated proportional rate ratio (PRR) using 2×2 tables and 95% confidence interval (CI) and repeated analysis in patients with diabetes indication, patients without limiting indication, and patients with diabetes indication and without using insulin, respectively. We also downloaded the FDA AERS database and identified DR cases involved GLP1RA use up to 2017 Q3 by SAS software v9.4 (Cary, NC).

Results: In patients with diabetes indication, exenatide (2.52/1000p) had a PRR of 0.25 (95% CI 0.21-0.30; $P < 0.001$), liraglutide (3.56/1000p) had a PRR of 0.41 (95% CI 0.32-0.52, $P < 0.001$), albiglutide (1.58/1000p) had a PRR of 0.21 (95% CI 0.11-0.40, $P < 0.001$), and dulaglutide (1.17/1000p) had a PRR of 0.17 (95% CI 0.08-0.33, $P < 0.001$). In patients without limiting indication, the PRR of DR for GLP1RAs was 0.76 (95% CI 0.68-0.85, $P < 0.001$); in patients with diabetes indication and without using insulin, the PRR is 0.37 (95% CI 0.30-0.44, $P < 0.001$). Overall, PRRs are consistent (PRR < 1) across different population groups. A total of 267 GLP1RAs associated DR cases were extracted from FAERS, 175 cases involved exenatide and 64 cases involved liraglutide. On average, patients were 63.7 year-old and majority of the cases involved blindness (52.8%) and diabetes retinopathy (31.8%).

Conclusions: Our analysis based on FAERS database indicated that there was no significant association between GLP1RA and DR. This study is limited by reporting bias and further studies are warranted to assess the potential DR risk associated with GLP1RAs.

982 | Sitagliptin and the risk of heart failure hospitalization: Comparisons of different designs of case-only studies

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Background: Sitagliptin is a commonly used dipeptidyl peptidase-4 inhibitors, a new class of anti-diabetics in treating type 2 diabetes mellitus (DM). Recent observational studies have suggested that sitagliptin may increase, decrease, or have no effect on heart failure hospitalization (HFH). However, the potential influence from temporal trends in exposure prevalence has not been well studied.

Objectives: To evaluate the risk of HFH associated with sitagliptin and examine the influence from exposure-time trend using different types of case-only studies.

Methods: We conducted four types of case-only studies of DM patients who experienced HFH between 2006 and 2012 in a population-based Taiwanese database, including (1) case-crossover design, (2) case-time-control design using controls sampling from DM patients without HFH, (3) case-case-time-control design using controls sampling from DM patients experiencing HFH in the future, and (4) case-time-control design using disease risk scores (DRS)-matched controls sampling from DM patients without HFH. We defined the case period and the control period as 1-30 days and 91-120 days before the date of experiencing HFH, respectively. To determine the association between sitagliptin and HFH, we compared the occurrence of HFH between two periods and estimated odds ratios (OR) and 95% confidence intervals (CIs) with conditional logistic regression models after controlling for potential time-varying covariates.

Results: The eligible cohort comprised 793 920 diabetes patients; 12 146 experienced HFH (3.0% and 2.3% used sitagliptin in the case and control periods, respectively). ORs were 3.72 (95% CI, 2.26-6.13) for the case-crossover design, 1.56 (95% CI, 1.06-2.29) for the case-time-control design, 4.15 (95% CI, 0.40-42.81) for the case-case-time-control design, and 1.28 (95% CI, 0.63-2.60) for the case-time-control design using DRS-matched controls.

Conclusions: The case-time-control design using DRS-matched controls may facilitate to evaluate the safety issue of sitagliptin and mitigate a potential influence from exposure-time trend.

983 | Cardiovascular (CV) safety of phentermine and topiramate in a US claims database

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Background: Increased heart rate was seen in clinical trials for Qsymia (Q, phentermine [P] and topiramate [T]), an oral medication for weight management, but the effect on major adverse CV events (MACE) is unknown.

Objectives: This study compared MACE incidence among current users of P, T, and P + T (including unbranded and Q) with former users of any of these medications.

Methods: A retrospective cohort study was conducted in MarketScan Commercial Claims and Medicare Supplemental data. Entry criteria were age ≥ 18 years and enrollment duration ≥ 6 months before the index date. Current use periods began at the first prescription dispensing date after a ≥ 180 -day clean period (initial entry) or after a gap of >60 days (subsequent use). Unexposed periods began after 60 days without exposure to any study medication. MACE comprised hospitalization for acute myocardial infarction (AMI) or stroke and in-hospital CV-related death as determined via ICD-9-CM diagnoses. MACE incidence rates (IR) and IR ratios (IRR) with 95% confidence intervals (CIs) were estimated for P, T, P+T, and Q current vs unexposed time in former users. Cohort trimming and stratification by propensity score were used to adjust for confounding.

Results: Current users of P + T (n = 19 184 people) contributed 3245 person-years (py) (including 2587 py with Q); current P (n = 124,334) contributed 24 107 py; and current T (n = 316 388) contributed 64 607 py. Former users (n = 386 136) contributed 310 665 py. MACE and its components were generally increased in patients who were older, male, and who had prior CV events. As expected, AMI and stroke IR were higher than IR of in-hospital CV death.

Crude MACE IR/1000 py (95% CI) were 0.92 (0.19-2.70) for P + T; 0.39 (0.01-2.15), Q; 0.91 (0.57-1.38), P; 3.37 (2.94-3.85), T; and 2.00 (1.85-2.17), unexposed. Adjusted IRR (95% CI) vs unexposed were 0.57 (0.19-1.78) for P + T; 0.24 (0.03, 1.70), Q; 0.56 (0.34-0.91), P; and 1.58 (1.33-1.87), T. Results were quantitatively similar when limiting the comparison of current to former users within each specific medication cohort (eg, current vs former P + T use), although the point estimates were closer to the null.

Conclusions: Unexpectedly, MACE risk was lower with current P and higher with current T vs unexposed. MACE risk in current P + T (including Q) users was lower than that among former users; however, the small number of events produced considerable statistical uncertainty, and results are consistent with a range of effects from a strong negative association to a modest positive association.

984 | Association between PPI use and risk of cardiovascular events

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Background: Proton pump inhibitors (PPIs) are the most commonly prescribed drugs for the management of upper gastrointestinal disorders. The beneficial effects even after short-term therapy, together with a good tolerability profile, lead to an overutilization of PPIs. However, recent studies have suggested the potential association between PPI use and even serious adverse events, like cardiovascular disease.

Objectives: To evaluate the risk of hospitalization for cardio/cerebrovascular (CV) events in a cohort of incident PPI users.

Methods: A nested case-control study was carried out, using the health care utilization databases of Italian Lombardy region. All residents (age: 18-70 years), with a first prescription (index date, ID) of PPIs from 2003/01/01 to 2007/12/31, were selected and followed until the event, death or migration, or 2010/12/31. Patient with antithrombotic therapy or hospitalization for any CV event during 3 years before the ID, or <57 days of follow-up, were excluded. For each case, defined by hospitalization for non-haemorrhagic CV event, up to five controls were matched by gender, age, and ID. Exposure was estimated as recency of therapy (defining *current*, *recent*, and *past* users) and number of days covered (based on defined daily doses). Conditional logistic regression was used to estimate association between the exposure and outcome, adjusting for several confounding variables. The same design was applied to a cohort of H2-receptor antagonist users.

Results: In our cohort, 17 832 cases and 89 160 controls were identified (males 64.9%; mean age 58.9 years). Cases showed a significantly higher prevalence of diabetes, hypertension, and hypercholesterolemia than controls. In the multivariate-adjusted regression analysis, risk of event was significantly higher for *current* (OR 1.61; 95% CI 1.55-1.68) and *recent* users (OR 1.15; 95% CI 1.06-1.26) compared with *past* users, regardless of the type of PPIs. Analogous results were found separately for cardiovascular (OR_{current} 1.72; 95% CI 1.63-1.81) and cerebrovascular events (OR_{current} 1.43; 95% CI 1.34-1.54). Risk was confirmed in strata by antithrombotic or statin use, or by exposure duration. The analysis on H2-receptor antagonist use showed no significant results.

Conclusions: Consistent with the evidence that PPIs may adversely impact vascular function, in this study, current PPI use was independently associated with an increased risk of first-time CV event in the general population. These results underline the need to promote appropriate prescribing of these drugs.

985 | The effect of proton pump inhibitors on cognition and brain volume in the Rhineland Study

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Background: Proton pump inhibitor (PPI) use has been associated with an increased risk of cognitive decline and dementia. This could however not be confirmed by others.

Objectives: We aimed to assess the associations between PPI use and cognition and brain volume.

Methods: We used data from the Rhineland Study, a population based cohort in Bonn Germany that includes people aged ≥ 30 years. PPI use (interview based) was classified as regular use of PPIs. Participants using PPIs as needed were excluded. All participants underwent cognitive testing and eligible participants were scanned on Siemens 3 Tesla Prisma MRI scanners. We assessed the effect of PPI use on cognitive domains (processing speed, executive functioning, working memory, and long-term memory) and brain volumetric measures (total brain volume, cortical grey matter volume, and ventricle volume) using multivariable linear regression models controlled for age, body mass index, diabetes, hypertension, antithrombotic use, statin use, and NSAID use. In models with brain volumetric outcome measures, we additionally controlled for head size. Processing speed and ventricle volume were log transformed. All outcome measures were z-standardized.

Results: The analysis to determine the effect of PPI use on cognition was based on 1130 participants (mean age 55, standard deviation [SD] 13.5; 57% women; 81 PPI users). We observed no effect on processing speed with a mean SD difference (95% confidence interval [CI]) of 0.02 (−0.18; 0.22). We observed a trend towards a negative effect of PPI use with a mean SD difference (95% CI) for executive functioning of −0.13 (−0.35; 0.10), for working memory of −0.12 (−0.36; 0.11) and for long-term memory of −0.17 (−0.39; 0.06). Effect sizes were comparable with a 5- to 9-year increase in age for executive functioning, working memory, and long-term memory. We had MRI data in a subset of 640 participants (mean age 54, SD 13.2; 56% women; 28 PPI users). Brain volume measures were smaller in PPI users compared with non-users, but these effects were far from significant with a mean SD difference (95% CI) for total brain volume of −0.05 (−0.23; 0.12), for cortical grey matter volume of −0.03 (−0.23; 0.17), and for ventricle volume of −0.06 (−0.37; 0.25).

Conclusions: Given our small sample size and relatively young population, these results suggest a possible effect of PPI use on brain structure and function and warrant further investigation in larger samples.

986 | Glucagon-like peptide-1 receptor agonists and the risk of incident diabetic retinopathy

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Background: Previous studies, including randomized controlled trials, suggested that glucagon-like peptide-1 receptor agonists (a class of antidiabetic drugs) may initially worsen and possibly increase the risk of diabetic retinopathy. However, data on this possible association remain limited.

Objectives: To determine whether use of GLP-1 receptor agonists is associated with an increased risk of incident diabetic retinopathy in patients with type 2 diabetes.

Methods: Using the UK Clinical Practice Research Datalink, we conducted a cohort study among 77 115 patients initiating antidiabetic drugs between January 2007 and September 2015. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of incident diabetic retinopathy were estimated using time-dependent Cox proportional hazards models, comparing use of GLP-1 receptor agonists overall and by duration of use (≤ 6 , 6.1–12, or > 12 months), with current use of ≥ 2 oral antidiabetic drugs. We conducted several sensitivity analyses, including stratification on high-dimensional disease risk score deciles and accounting for competing risk due to death.

Results: During 245 825 person-years of follow-up, 10 763 patients were newly diagnosed with diabetic retinopathy (crude incidence rate: 43.8 per 1000/year). Compared with current use of ≥ 2 oral antidiabetic drugs, use of GLP-1 receptor agonists was not associated with an increased risk of incident diabetic retinopathy overall (crude incidence rates, 40.4 versus 49.0 per 1000/year; adjusted HR, 1.00; 95% CI, 0.85–1.17). However, a statistically significant association was observed with durations of use between 6.1 and 12 months (crude incidence rates, 56.6 versus 45.9 per 1000/year; HR, 1.44; 95% CI, 1.06–1.95), while no associations were observed with shorter (≤ 6 months, crude incidence rates, 38.2 versus 51.3 per 1000/year; adjusted HR, 0.94; 95% CI, 0.76–1.17) and longer (> 12 months, crude incidence rates, 33.2 versus 47.4 per 1000/year; HR, 0.83; 95% CI, 0.60–1.15) durations (p for heterogeneity 0.07). The results remained consistent in sensitivity analyses.

Conclusions: Use of GLP-1 receptor agonists was not associated with an overall increased risk of incident diabetic retinopathy. However, there was a suggestion of a transient increased risk with durations of use between 6 and 12 months.

987 | Safety of colonoscopy bowel cleansers when combined with the stimulant laxative, bisacodyl: A CNODES multi-centre, population-based cohort study

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Background: Concerns have been raised about the safety of commonly used bowel cleansers when combined with higher doses of the stimulant laxative, bisacodyl. At the request of Health Canada,

we quantified the risks of ischemic colitis (IC) and other commonly-reported electrolyte disturbances associated with hyperosmotic bowel preparations, alone vs combined with bisacodyl.

Objectives: To describe patterns of use of colonoscopy bowel cleansers in the United States and Canada and to quantify the risks of IC and electrolyte disturbances associated with bowel cleansing.

Methods: We undertook a retrospective cohort study of adult new users of polyethylene glycol (PEG) and sodium picosulfate (PICO) bowel cleansers from 2007 to 2015 captured in the prescription claim databases of the Canadian provinces of British Columbia (BC), Manitoba and Ontario and a large database of public- and privately-insured Americans, MarketScan. We tabulated the annual number of new uses of each cleanser alone vs combined with bisacodyl, excluding those dispensed both cleansers and prescriptions apparently for other indications. The primary outcome was hospitalization with a primary diagnosis of IC in the 30 d following cleanser dispensation, excluding those with a secondary diagnosis of *C. difficile* enteritis, non-infectious gastroenteritis/colitis, or inflammatory bowel disease. Secondary outcomes were hypokalemia, hyponatremia, hypomagnesemia, and acute kidney injury (AKI). Secondary analyses excluded patients who may have received colonoscopy for other than screening.

Results: We identified over 1.7 million new uses of bowel cleansers, approximately 2/3 in MarketScan and 1/3 in Ontario. BC and Manitoba had few bowel cleanser claims due to lack of coverage by the provincial drug plans. Overall, 72% of patients received PEG and 10% received bisacodyl, although both PICO and bisacodyl use rose over the study period. We consistently observed higher adverse event rates with PICO relative to PEG, higher rates of hyponatremia or AKI when bisacodyl was added to PEG, and higher rates of IC when bisacodyl was added to PICO or PEG (9.3 [95% CI 7.92-10.84] vs 18.8 [95% CI 13.94-25.28] events per 100 000). Secondary analyses were consistent with the primary, but with lower absolute risks.

Conclusions: Addition of bisacodyl to commonly used colonoscopy bowel cleansers approximately doubled the risk of ischemic colitis, although the absolute risk was low.

988 | Time between laboratory tests and acute liver and kidney injury diagnosis codes in CPRD: Are we doing it right?

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Background: A 3-month time window around time of diagnosis, commonly used in database studies to validate acute kidney injury (AKI) and acute liver injury (ALI), is based on clinical criteria that define chronic liver disease and chronic kidney disease (CKD), rather than on timing of acute events.

Objectives: To evaluate the validity of the 3-month time window used as a first step to validate ALI and AKI in the Clinical Practice Research Datalink (CPRD).

Methods: Two cohorts (ALI and AKI) of adult new users of specific oral glucose-lowering drugs (OGLD) for type 2 diabetes were identified in the CPRD, UK (August 2014-October 2016). Patients with a previous diagnosis of ALI, AKI, or CKD were excluded, while those with previous abnormal laboratory values were not excluded. ALI and AKI cases were identified using diagnosis codes. Lab criteria were based on the Food and Drug Administration (FDA) definition for ALI or the adapted Risk, Injury, Failure, Loss, End-stage (RIFLE) definition for AKI. We evaluated the period extending from 3 months before to 3 months after diagnosis. In addition, we evaluated the number of patients that fulfilled the lab criteria for ALI and AKI, irrespective of the presence of a diagnosis code.

Results: In the ALI cohort, among 14 805 new users, 64 potential cases were identified based on diagnosis codes; 6 of them fulfilled the lab criteria. Of the 6 patients, 5 fulfilled the lab criteria within 7 days after diagnosis and 1 within 31-90 days. Seven patients fulfilled the lab criteria but did not have a diagnosis code for ALI. In the AKI cohort, among 12 346 new users, 23 potential cases were identified based on diagnosis codes; 7 patients fulfilled the lab criteria. Of the 7 patients, less than 5 fulfilled the lab criteria within 7 days after diagnosis, 1 within 16-30 days. Two patients had a diagnosis code and fulfilled the lab criteria beyond the 3-month criterion (more than 120 days). While not having a diagnosis code suggesting AKI, 151 patients fulfilled the lab criteria.

Conclusions: In the CPRD database, most cases (69%) fulfil the lab criteria within 1 week of the diagnosis code questioning the relevance of using a 3-month time windows in such studies. A higher number of patients fulfilled the lab criteria suggesting AKI without a diagnosis code. These patients may have chronic liver or kidney disease where CKD was defined only by diagnosis codes.

989 | Proton pump inhibitor use and risk of hip fractures among community-dwelling persons with Alzheimer's disease—A nested case-control study

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Background: Hip fractures are a major health concern among older persons with Alzheimer's disease, who usually use many concomitant drugs for several diseases. Evidence of the association between proton pump inhibitor use and risk of hip fracture is contradictory.

Objectives: Objective of this study was to investigate whether the long-term use of proton pump inhibitor (PPI) is associated with risk of hip fractures among community-dwelling persons with Alzheimer's disease.

Methods: Design: Nested case-control study, including 4818 (mean age 84.1) community-dwelling persons with Alzheimer's disease who

encountered hip fracture. For each hip fracture-case at the date of hip fracture, 19 235 controls (1:4, mean age 84.0) without hip fracture were matched.

Setting: Study participants were extracted from nationwide register-based MEDALZ cohort, which consists of all community-dwelling persons who received clinically verified diagnosis of Alzheimer's disease between 2005 and 2011 (N = 70 718). The study was restricted to new hip fractures, and thus, persons with previous hip fracture were excluded.

Exposures: Cumulative PPI use was investigated during 10 years before the hip fracture. Additionally, we investigated current (0-30 days before event), duration of current and past (31-90 days before event) PPI use. Long-term use was defined as >1 year of current use. Drug use periods, describing when continuous drug use started and ended, were modelled by PRE2DUP-method from Prescription Register.

Main outcome measures: Incident hip fractures according to Hospital Discharge Register.

Statistical analysis: Conditional logistic regression was used to investigate the association between PPI use and hip fracture.

Results: Long-term or cumulative PPI use were not associated with an increased risk of hip fracture. Short-term current PPI use (<1 year) was associated with an increased risk of hip fracture compared to non-use (adjusted OR 1.23, 95% CI 1.10-1.37). Differences between drug substances and risk of hip fracture was not found.

Conclusions: The increased risk of hip fracture was evident only on short-term PPI use but no association was found for long-term or cumulative use among persons with Alzheimer's disease.

990 | Use of proton pump inhibitors and risk of acute kidney injury among patients with rheumatoid arthritis

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Background: Recent observational studies have indicated that use of proton pump inhibitors (PPIs) may be associated with increased risk of adverse renal events, including acute kidney injury. Proton pump inhibitors are widely used among patients with rheumatoid arthritis (RA). Importantly, patients with RA may be at already increased risk of renal events, due to chronic inflammation and drug exposure in RA treatment.

Objectives: To investigate whether use of PPIs increases the risk of acute kidney injury among patients with RA.

Methods: The study was conducted as a historical prospective cohort study in Denmark, 2004-2015. Patients with RA, 30-84 years of age were identified from the Danish National Patient Registry. Among these, episodes of use and non-use of PPIs (control episodes) were identified and matched 1:4 on the propensity score. The primary outcome was a first diagnosis of acute kidney injury and the secondary outcome was any serious renal event (a first diagnosis of acute kidney

injury or chronic kidney disease), as identified from hospital admission and cause of death records. The primary time point for analysis was 120 days after study entry. The analyses were conducted using proportional hazards regression.

Results: The incidence rate of acute kidney injury was 2.2 per 1000 person-years during episodes of use of PPIs (n = 24 579) and 0.9 during control episodes (n = 98 230). Use of PPIs was associated with a significantly increased risk of acute kidney injury (hazard ratio [HR] 2.30, 95% confidence interval [CI] 1.26-4.20). The absolute risk difference was 40 (95% CI 8 to 99) events of acute kidney injury per 100 000 episodes of use of PPIs. Use of PPIs was also associated with a significantly increased risk of the secondary outcome any serious renal event (incidence rate 5.9 per 1000 person-years during episodes of use of PPIs and 2.3 per 1000 person-years during control episodes; HR 2.61, 95% CI 1.80-3.80).

Conclusions: This study among patients with RA found the risk of acute kidney injury to be significantly increased during episodes of use of PPIs, compared with episodes of no use of PPIs. These findings may help inform clinical decision making when the benefits and risks of PPI treatment in RA are considered.

991 | The use of multiple antidiabetic medications and its association with hypoglycaemic event: A case-crossover study

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Background: The use of multiple antidiabetic medications is found to be associated with serious and potentially life-threatening adverse events, specifically hypoglycaemia.

Objectives: To investigate the association between the use of multiple antidiabetic medications and hypoglycaemic events.

Methods: We conducted a case-crossover study in Amman, Jordan. Patients with hypoglycaemic events during the period of January 2007 to July 2017 were identified from the medical records of the Registry of the National Centre for Diabetes, Endocrinology and Genetics (NCDEG) with a diagnosis of hypoglycaemic event. Antidiabetic medications were extracted manually via dispensing data from the pharmacy records in the year prior to the event. Antidiabetic combination therapy was defined as the use of two or more antidiabetic medications at the same time. A secondary analysis was performed in patients who had a hypoglycaemic event confirmed by the measurement of blood glucose ≤ 70 mg/dL. Conditional logistic regression was used to analyse the data. We compared the use of antidiabetic combination therapy during the risk period (15 days that precede the event date) with a control period of the same length after a 30-day washout period. Sensitivity analyses were conducted using different exposure definition and different risk windows.

Results: 185 patients (79 male and 106 female) were identified during the study period and were included in the main analysis. The average

age was 59.5 (SD ± 10.3) years old. Compared with monotherapy, the odds ratio (OR) of hypoglycaemic events for patients with multiple antidiabetic therapy was 5.00 (95% CI 1.10-22.82). The OR was 6.00 (95% CI 0.72-49.84) for the secondary analysis in 97 patients. Double risk was found in patients with insulin and sulfonylurea-based combination therapy (OR, 10.00, [95% CI 1.28-78.12]) and no difference for the secondary analysis when compared with monotherapy. Sensitivity analyses confirmed the study findings.

Conclusions: This study shows that the use of multiple antidiabetic medications increases the risk of hypoglycaemic events. Doctors and patients need to be extra vigilant about hypoglycaemic events when patients are on multiple antidiabetic therapy.

992 | Sodium-glucose co-transporter-2 inhibitors and the risk of fractures in patients with type 2 diabetes

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Background: Sodium-glucose co-transporter type 2 (SGLT-2) inhibitors have been associated with an increased risk of fractures of the upper or lower limbs (FULL) in patients with type 2 diabetes (T2DM).

Objectives: To compare the risk of FULL in users of SGLT-2-inhibitors and other antidiabetic drugs in Germany.

Methods: We used the InGef (former HRI) database to conduct a cohort study with nested case-control analysis in new users of non-insulin antidiabetic drugs between 12 November 2011 and 31 December 2016. FULL cases were selected based on ambulatory diagnoses in combination with specific diagnostic claims or based on primary hospital discharge diagnoses. For each case, up to 40 controls were randomly selected using risk-set sampling. We applied conditional logistic regression to estimate confounder adjusted odds ratios (OR) with 95% confidence intervals (CI) of FULL comparing current use of metformin + SGLT-2 inhibitor or metformin + one drug from another antidiabetic drug class to metformin+dipeptidyl-peptidase-4 (DPP-4) inhibitor as reference. In subgroup analyses, we tested for effect modification by age group (<75 vs 75+ years) and number of present risk factors for FULL (≤ 3 vs 4+).

Results: The cohort comprised 210 042 new users of non-insulin antidiabetic drugs with a mean age of 63.9 years (SD 12.8) and 42% females. The crude incidence rate of FULL was 9.5 FULLs per 1000 person-years. For the nested case-control analysis, 5194 FULL cases were matched to 204 676 controls. Overall, no increased risk of FULL was observed comparing metformin + SGLT-2 inhibitor (OR: 1.10; 95%-CI: 0.74-1.64) to metformin + DPP-4 inhibitor. Similarly, no increased risk was observed for metformin + drugs from other antidiabetic drug classes compared to metformin + DPP-4 inhibitor.

No significant effect modification was observed by age group and number of present risk factors for FULL, although risk estimates were numerically elevated for older age and 4+ risk factors.

Conclusions: Our study suggests that SGLT-2 inhibitors are generally not associated with an increased risk of FULL. Further studies with sufficient sample size are required to investigate the risk of FULL in older patients and those with pre-existing risk factors for fractures.

993 | Proton pump inhibitor (PPI) prescriptions and breast cancer recurrence: A Danish Nationwide Prospective Cohort Study

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Background: PPIs are indicated for acid-peptic disorders. PPIs inhibit the growth of breast cancer cell lines and inhibit V-ATPase, which is sometimes overexpressed in breast cancer cells. This may mediate chemotherapy resistance.

Objectives: To examine the association of PPI prescription use during chemotherapy, and throughout follow-up, with the risk of breast cancer recurrence.

Methods: We included all Danish women diagnosed with non-metastatic breast cancer registered in the Danish Breast Cancer Group (DBCG) 1996-2008. We ascertained information on PPIs and potentially confounding drugs from the National Prescription Registry. Follow-up began on the date of diagnosis in the overall analysis, or at 6 months after diagnosis (see below), and continued to the first of breast cancer recurrence, death or emigration, 10 years, or January 1, 2013. We evaluated PPI use during the first 6 months after diagnosis (1 or more prescriptions from diagnosis to 6 months after diagnosis), to approximate PPI use during chemotherapy; and overall PPI use (1 or more prescriptions) as a time-varying exposure lagged by 1 year. We used Cox regression analyses to calculate hazard ratios (HRs) and associated 95% confidence intervals (95%CI) of recurrence adjusted for potential confounders.

Results: Among 34 189 patients, (233 129 total person-years), 7740 women had 1 or more PPI prescription after diagnosis; 5320 patients developed recurrent disease. PPI use during the first 6 months after diagnosis was associated with a decreased risk of recurrence among patients who received chemotherapy (HR_{adjusted} = 0.71; 95% CI = 0.54, 0.92), but not among patients not receiving chemotherapy (HR_{adjusted} = 1.00; 95% CI = 0.84, 1.18). Overall PPI use was not associated with recurrence (HR_{adjusted} = 1.05; 95% CI = 0.92, 1.20).

Conclusions: Our findings to date suggest that PPI use concurrent with chemotherapy, but not throughout follow-up, is associated with a reduced risk of breast cancer recurrence.

994 | Metformin use and risk of dementia: A meta-analysis of observational studies

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Background: Diabetes and dementia typically affect the older age population and are the common co-morbidities. Metformin is the first line drug to treat type-2 diabetes; however, the association between metformin use and risk of dementia is unclear.

Objectives: The current meta-analysis is aimed to assess the risk of developing dementia among metformin users.

Methods: This meta-analysis was conducted according to PRISMA guidelines. An electronic literature search was carried out in PubMed and Cochrane central using Mesh term related to "dementia" and "metformin." Search period was from inception to January 2018. We included studies clearly reporting the use of metformin in the patients who were not having dementia at the baseline of the study. Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies. Pooled risk of developing dementia in metformin users was the primary outcome. Subgroup analyses were also performed based on dementia sub-types. Statistical analyses were performed using Review Manager (RevMan v 5.3).

Results: A total of six articles qualified for inclusion in the meta-analysis, comprising 758 822 patients of which 95 968 were on metformin. Majority of the included studies were of high quality on NOS. Study found no significant effect of metformin on the risk of developing dementia with an adjusted pooled risk ratio (RR) of 1.04 ([95% CI: 0.88-1.23], $p = 0.61$) and unadjusted RR of 1.05 ([95% CI: 0.51-2.14], $p = 0.09$). Subgroup analysis based on dementia sub-types (Alzheimers and vascular dementia) also reflected the statistically non-significant effect on metformin user for the incidence of dementia with pooled risk ratio of 1.14 ([95% CI: 0.64-2.05], $p = 0.66$) and 1.41 ([95% CI: 0.61-3.29], $p = 0.41$).

Conclusions: The results indicate that metformin does not increase the risk of developing dementia. However, controlled studies with large sample size would further help to confirm the conclusions and provide robust information for clinical strategies.

995 | The rate of hypoglycaemic events in individuals with type 1 diabetes; systematic review and meta-analysis of observational studies

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Background: Hypoglycaemia is the most frequent complication in individuals with type 1 diabetes using insulin therapy. Achieving an optimal glycaemic control is a challenge, and hypoglycaemia is considered as a barrier in diabetes mellitus management.

Objectives: To review studies that estimate hypoglycaemic events rate in individuals with type 1 diabetes.

Methods: The PubMed, Embase, and Cochrane databases were used to search for observational studies published up to July 2017. Observational studies of the incidence of hypoglycaemia in type 1 diabetes mellitus were included. The primary outcome of this review was the rate of hypoglycaemic events in individuals with type 1 diabetes. The events rate is expressed as hypoglycaemic events per 100 patient-years. Random effect meta-analysis was conducted to calculate the pooled rate of hypoglycaemia using STATA software.

Results: A total of 31 288 citations were identified of which 29 studies with 137 874 patients were included in the meta-analysis. The pooled estimate of the rate of hypoglycaemic events was 149.19 events per 100 person-years (95% CI, 145.53-152.85). The pooled events estimate of hypoglycaemia for self-reported, and database were 83.47 events per 100 patient-year (95% CI, 51.52-115.41), and 96.75 events per 100 person-years (95% CI, 94.66-98.84), respectively.

Conclusions: Insulin-induced hypoglycaemic events were very common in type I diabetic individuals. Further studies are warranted to investigate the risk factors at the patient level.

996 | Rivaroxaban and severe cutaneous adverse reaction using case-crossover analysis

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Background: Rivaroxaban was one of the recently developed oral anticoagulants (OACs) replacing warfarin. In 2017, regulatory agencies announced the possibility of Stevens-Johnson syndrome by rivaroxaban.

Objectives: To evaluate the association between rivaroxaban and severe cutaneous adverse reaction (SCAR)

Methods: We used the Health Insurance Review and Assessment (HIRA) Service database between January 2011 and April 2017. HIRA database contained medical information of entire Korean population. Among the patients prescribed OACs, those who were 20 years old or more and diagnosed with SCAR (international classification of diseases-10: L511-3) during the hospitalization were included. For the case-crossover analysis, case period was defined as 8 weeks before SCAR occurred, and the same four periods were set as control periods in past 180-day intervals. The odds ratio (OR) was calculated by conditional logistic regression and adjusted by carbamazepine, allopurinol, phenobarbital, lamotrigine, phenytoin, and oxicam-nonsteroidal anti-inflammatory drugs.

Results: A total of 632 814 patients prescribed OACs, during the study period. Among them, 68 patients were diagnosed with SCAR.

In 6 of 68 patients, rivaroxaban was prescribed in the case period. Crude and adjusted OR was 4.11 (1.09-15.47) and 1.30 (0.16-10.41), respectively. The results shown by modifying the interval to 120 and 240 days had no difference with the main results. During case period, three out of six patients received allopurinol and other two received lamotrigine.

Conclusions: The association between rivaroxaban and SCAR was not statistically significant. However, further study was needed because of the lack of statistical power due to the limit of the number of participants.

997 | Sequential pattern mining to predict prescribed medications following hospitalisation for heart failure

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Background: Sequential pattern mining is a novel technique that can be employed to identify temporal relationships between prescribed medications and event of clinical interest.

Objectives: The aim of this case-crossover study was to apply a CSPADE algorithm to determine frequent guideline-line recommended heart failure pharmacological treatments prescribed after a first-time event of heart failure-related hospitalisation.

Methods: A nationwide representative sample of New Zealanders aged 65 years and older was sourced from the pharmaceutical collections and hospital discharge information. Prescription records (2005-2016) of drugs of interest were sourced from the New Zealand (NZ) pharmaceutical collections. Medication exposure was classified at individual drug level belonging to medication classes including angiotensin converting enzyme inhibitors, beta-blockers, loop diuretics, and digoxin as recommended by NZ heart failure guidelines. The first-time coded diagnosis of heart failure between 01/01/2005 and 31/12/2016 was extracted from the National Minimum Dataset. The CSPADE algorithm was applied to the case-period drug initiation data to find all frequent guideline-line recommended heart failure drug sequences with a prevalence greater than 1.0%. We computed a matched odd ratio (MOR) by using the control-period drug-initiation data as a reference.

Results: We identified a total of 32 625 individuals (mean age 79.1 years) from 2005 to 2016 with incident heart failure related hospitalisation. Sequential pattern mining revealed carvedilol (MOR = 3.36 95% CI 3.05-3.71) was frequently prescribed for the treatment of heart failure, and for a 2-drug mined sequence spironolactone followed by digoxin (MOR = 5.19, 95% CI 3.76-7.83) was frequently prescribed. The addition of furosemide to spironolactone occurred less frequently (MOR = 1.78, 95% CI 1.57-2.03).

Conclusions: Sequential pattern mining is a novel method to ascertain if prescribers are adhering to guidelines. This novel methodology can also be extended to real-world populations to ascertain drug patterns associated with adverse drug events.

998 | Dynamics of the QTc-interval during use of intravenous ciprofloxacin in ICU patients

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Background: Prolongation of the QT interval is an adverse effect associated with the use of fluoroquinolones. It is unknown whether or not QTc-prolongation is more pronounced at Cmax. In addition, intravenous administration in critically ill patients might increase the QTc-prolonging effect.

Objectives: To assess the dynamics of the QTc-interval over a 24-hour time interval during intravenous ciprofloxacin in ICU patients.

Methods: An observational study was performed in ICU patients (≥ 18 years) admitted to the Erasmus University Medical Centre receiving ciprofloxacin intravenously. Continuous ECG data were collected 2 hours before and 24 hours after the first administration. QT-analyses were performed using the high-end holter software SynescopeTM. Intraindividual changes were analysed using the paired Student's *t* test, and the course of the QTc-interval was compared with a control group without QTc-prolonging drugs using the independent Student's *t* test.

Results: A total of 30 patients ($n = 15$ index, $n = 15$ control) were included for analysis. The mean QTc-interval during administration (405.7 ± 21.6 ms) did not significantly differ from baseline (400.4 ± 29.7 ms; $p = 0.075$). No peak QTc-time was found to be related to ciprofloxacin administration. There was no significant difference between the mean QTc-interval of the ciprofloxacin group (403.7 ± 28.9) and the control group (399.2 ± 21.6 ms; $p = 0.419$).

Conclusions: Intravenous ciprofloxacin does not have a significant effect on the QTc-interval over a 24-hour time interval in ICU patients.

999 | Incidence of major and clinically relevant non-major (CRNM) bleeding in patients prescribed rivaroxaban in secondary care: Results from the Rivaroxaban Observational Safety Evaluation (ROSE) study

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Background: The ROSE Specialist Cohort Event Monitoring (SCSEM) study was conducted to monitor the safety and use of rivaroxaban for Stroke Prevention in patients (pts) with non-valvular AF (SPAF) and the prevention and/or treatment of Deep Vein Thrombosis and/or Pulmonary Embolism (DVT/PE). Bleeding risk has been previously estimated in various settings; this study aimed to estimate risk in secondary (2°) care real-world pts ≤ 12 weeks (wks).

Objectives: To estimate the incidence of major and CRNM bleeding in pts prescribed rivaroxaban for SPAF and DVT/PE indications in 2^o care in England and Wales.

Methods: Pts identified through speciality groups (2013-2016), supported by UK Clinical Research Networks. Risk factors for bleeding (HAS-BLED) and bleeding outcomes were collected via detailed questionnaires completed by hospital specialists at baseline and ≥ 12 wks. Summary descriptive statistics and 12-wk incidence estimates were calculated.

Results: Cohort consisted of 2542 pts: 965 pts with AF (38.0% of cohort; median age 76 years (yrs) [IQR 69, 83], 517 [53.6%] male), median HAS-BLED score 2 (IQR 1-3) (moderate risk of major bleeding); 1532 pts with DVT/PE (60.3% of cohort; median age 63 yrs [IQR 48, 73], 836 [54.6%] male), median HAS-BLED score 1 (IQR 0-2) (low risk of major bleeding). AF group: Rate Major + CRNM bleeding 28.2 per 100 pt yrs (95% CI 21.0, 37.1; n = 51). Rate Major Bleed (MB) 5.5 (95% CI 2.6-10.1; n = 10), CRNM bleeding 22.7 (95% CI 16.3-30.8; n = 41). MB risk in pre-specified sites: gastrointestinal (GI) (0.2%; n = 2), urogenital (UG) (0.2%; n = 2), intracranial (IC) (0.2%; n = 2), and all other critical organ (excluding IC) (0.1%; n = 1). DVT/PE group: Rate Major + CRNM bleeding 36.2 (95% CI 29.4, 44.1; n = 98). Rate MB 8.3 (95% CI 5.3, 12.5; n = 23), CRNM bleeding 27.6 (95% CI 21.7, 34.6; n = 75). MB risk in pre-specified sites: GI (0.7%; n = 11), UG (0.3%; n = 5), IC (0.1%; n = 1) and all other critical organ (excluding IC) (0.0%; n = 0).

Conclusions: The incidence of major bleeding was low, and no new safety concerns were raised. Unique aspects of this study design enabled collection of highly detailed information from cardiologists, facilitating accurate calculation of risk scores and the application of clinical trial outcome definitions, in a real-world setting. Differences in methodology between this and other study designs prevents meaningful comparison.

1000 | Outcomes and predictors of low anticoagulation control in new users of warfarin

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Background: Over- and under-coagulation with warfarin is associated with hemorrhagic and thromboembolic events, respectively. Genetic and clinical factors may affect the anticoagulation control, and the causes of this variability remain to be clarified.

Objectives: To assess the level of anticoagulation control and the predictors of low anticoagulation control.

Methods: The Quebec Warfarin Cohort (QWC) is a prospective study, systematically investigating patient-level factors linked with the safety and efficacy of warfarin. The QWC has recruited 1059 new

warfarin users, with prospective follow-up using telephone questionnaires every 3 months for 1 year, and using health care administrative databases (RAMQ and Med-Echo) for 1 year prior to cohort entry. Genetic material was collected, and genotyping of CYP2C9 and VKORC1 genes was conducted. Measured outcomes included the percentage of time patients spent within the therapeutic INR range (TTR), warfarin dose, bleeding, and thromboembolic events. We report the baseline characteristics, outcomes after 1-year of follow-up, and predictors of low anticoagulation control (TTR <60%). We used a logistic regression to assess predictors of low anticoagulation control.

Results: Participants had a mean age of 71 years and 62% were men. The most common indication for warfarin was atrial fibrillation. Mean time in the therapeutic range (TTR) was 56% (± 25) in the 3-month following warfarin initiation, and 70% (± 21) between 3- to 12-month interval where 71% of them had TTR $\geq 60\%$. At the 3-month time point, the mean daily warfarin dose was 4.7 mg (± 2.2). During follow-up, the rate of stroke or systemic embolism was 1.8 events per 100 person-years, 3.3 events per 100 person-years for major bleeding events, and minor bleeding 18.9 events per 100 person-years. Significant predictors of low anticoagulation control were chronic kidney disease, prior major bleeding, dyslipidemia, high CHA₂DS₂-VASc score, congestive heart failure, and coronary artery disease, where odd ratios ranged from 1.4 to 2.5.

Conclusions: The QWC represents a good research opportunity to investigate clinical and genetic factors in a warfarin anticoagulated population. Overall mean TTR was at 56% during follow-up, and several co-morbidities seem to be linked with low anticoagulation control.

1001 | Respiratory effect of angiotensin-converting enzyme inhibitors in people with asthma: A nested case control study

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Background: Angiotensin converting enzyme (ACE) inhibitors are widely prescribed treatments for high blood pressure, heart failure, and chronic kidney disease, conditions which commonly affect people with asthma. However, ACE inhibitors can increase levels of chemicals in the body called bradykinin which may cause airways to contract in people with active asthma.

Objectives: To evaluate the association between ACE inhibitor exposure and exacerbation of asthma

Methods: Data from The UK Clinical Practice Research Datalink (CPRD) was used to identify a large UK cohort of adults patients with active asthma prescribed ACE inhibitors and angiotensin-II receptor antagonists. Cohort eligibility criteria including having been registered with a general practice for at least 1 year, having been prescribed an asthma medication, having received a diagnostic code for asthma in their electronic medical record, present between 1 January 1998 to 30 June 2014. Nested case control studies were

conducted evaluating (1) risk of severe asthma exacerbation (defined as hospitalisation or death from asthma) and (2) risk of moderate asthma exacerbation (defined as rescue oral steroid courses in primary care) with current ACE inhibitor and angiotensin-II receptor antagonist exposure using conditional logistic regression to calculate incidence rate ratios (IRR).

Results: For severe asthma exacerbations, 1025 cases were matched to 10 250 controls, and for moderate asthma exacerbations, 15 940 cases were matched to 63 719 controls. Acute exposure to ACE inhibitors and ARBs was not significantly associated with exacerbation of asthma. In contrast, chronic ACE inhibitor exposure was associated with a significantly reduced relative incidence of both moderate and severe asthma exacerbations (IRR 0.88, 9% CI 0.83-0.93 and IRR 0.57, 95% CI 0.51-0.64) compared with no exposure. Chronic ARB exposure was also associated with a significantly reduced relative incidence of moderate and severe asthma exacerbations (IRR 0.91, 9% CI 0.85-0.94 and IRR 0.48, 95% CI 0.41-0.56) compared with no exposure.

Conclusions: In people with active asthma and chronic comorbid conditions managed with ACE inhibitor and ARB therapy, chronic exposure to ACE inhibitors and ARB therapy may reduce the relative incidence of asthma exacerbations.

1002 | Psoriasis during angiotensin conversion enzyme inhibitor exposure: A case/non-case study using the French Pharmacovigilance Database

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Background: Angiotensin conversion enzyme inhibitors (ACEIs) can induce or aggravate psoriasis. The Summary of Product Characteristics (SmPC) of almost ACEIs mentions psoriasis. The literature data are sparse and often contradictory.

Objectives: To assess the association between psoriasis and ACEI exposure.

Methods: We assessed the association between psoriasis and ACEI exposure using a case/non-case approach which is a validated method for safety signal detection. Cases are reports of "psoriatic conditions" (High Level Term, MedDRA version 19.0) registered in the French Pharmacovigilance Database (FPVD) from 1985 to 31 December 2017. Non-cases are all other adverse drug reactions (ADRs reported in the FPVD during the same period. This method allows comparison of ACEI exposure (benazepril, captopril, enalapril, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, and trandolapril) among cases and non-cases by calculation of the Reporting Odds Ratio (ROR) and its 95% confidence interval (95%CI).

Results: During the study period, 7 115 689 spontaneous reports of ADRs were registered in the FPVD. Ninety-seven cases were psoriatic manifestations with ACEIs. The average age was 68.10 +/- 12.55 years (range 27 to 89), the male/female sex-ratio was 2.73. Thirty-eight percent of cases were considered serious. Time to onset

(when given) was less than 1 year. Outcome was favorable after ACEI discontinuation in 73% of cases. The ROR for psoriasis with this therapeutic class was 2.61 (2.13-3.21). The most suspected ACEIs were ramipril (n = 22, ROR = 2.29, 95% CI = 1.50, 3.49), captopril (n = 20, ROR = 3.00, 95% CI = 1.93, 4.66), and perindopril (n = 15, ROR = 2.02, 95% CI = 1.22, 3.37). Trandolapril was the ACEI with the highest ROR (n = 8, ROR = 6.81, 95% CI = 3.38, 13.71).

Conclusions: Our study shows statistically significant RORs for almost ACEIs, which constitutes a potential safety signal. Ramipril, captopril, and perindopril accounted for 60% of all cases reported, and trandolapril had the highest ROR value. The SmPC of ACEIs should be harmonized, and increased awareness among health care professionals is needed.

1003 | Characteristics of patients initiated on a reduced dose of rivaroxaban for atrial fibrillation (AF)—Results from the ROSE (Rivaroxaban Observational Safety Evaluation) study

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Background: Rivaroxaban is used to treat a range of conditions, including prevention of stroke and systemic embolism in patients with AF. This indication requires a fixed once-daily (od) dose (20 mg) with dosage reduction to 15 mg once daily only recommended in patients (pts) with renal impairment (creatinine clearance 15-49 ml/min). However, other clinical factors might be considered by the prescriber when choosing an initial dose.

Objectives: To describe the clinical characteristics of pts prescribed an initial dose of (≥ 20 mg and < 20 mg daily) for treatment of AF in secondary care.

Methods: The ROSE study was a specialist cohort event monitoring study of pts prescribed rivaroxaban. Specialists provided information from medical records via questionnaires at baseline and ≥ 12 weeks. Information on the prescribed initial dose and baseline characteristics including risk factors for bleeding (HAS-BLED criteria) was collected. For pts prescribed a reduced initial dose (< 20 mg daily), we assessed clinical characteristics vs. pts prescribed ≥ 20 mg daily.

Results: The cohort consisted of 965 pts with AF; of whom (18.3%, n = 177), were prescribed an initial dose of < 20 mg daily (15 mg od [n = 173]; 10 mg od [n = 3]; 4 mg od [n = 1]). The majority were female (57.6%, median age 84 yrs) vs pts prescribed ≥ 20 mg daily (20 mg od [n = 750]; 30 mg od [n = 16]), where the majority were male (56.4%, median age 75 yrs). 36/177 (20.3%) pts had a history of CKD 3-4 or 5. For 22 patients, the start dose was unknown. Frequency of HAS-BLED criteria in pts prescribed < 20 mg daily vs ≥ 20 mg daily was Hypertension (37.3% vs 38.5%), Abnormal renal function (Chronic dialysis, renal transplant, serum creatinine ≥ 2.3 mg/dL or 200 μ mol/L)

(3.4% vs 1.2%), Abnormal liver function (0.6% vs 1.0%), History of Stroke (31.1% vs 30.4%), History of Bleeding/predisposition (18.6% vs 16.3%), Labile INR (N/A), Age ≥ 65 yrs (96.1% vs 81.2%), Drug therapy (52.0% vs 51.4%), Alcohol (0% vs 4.8%).

Conclusions: In pts prescribed a reduced total daily dose of rivaroxaban <20 mg od, there were a higher proportion of females and those aged ≥ 65 yrs. Patients prescribed this lower dose were also more likely to have abnormal renal function, defined as per HAS-BLED, than those patients prescribed ≥ 20 mg daily. Although the label recommends dose reduction in AF pts with renal impairment, other factors seem to impact the choice of the initial dose in the clinical setting.

1004 | Assessment of initiation dose in patients prescribed rivaroxaban for stroke prevention in non-valvular AF (SPAF) and chronic kidney disease—Results from the ROSE (Rivaroxaban Observational Safety Evaluation) study

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Background: Rivaroxaban is used to treat patients with non-valvular AF for the prevention of stroke and systemic embolism. This requires a fixed daily dose (20 mg) with dosage reduction only recommended in patients with a reduced creatinine clearance (15–49 ml/min), a range encompassed within chronic kidney disease (CKD) stage 3–4 (eGFR 15–59) although CKD 3a (eGFR 45–59) is largely outside this range. Rivaroxaban is not recommended in patients with severe renal impairment (creatinine clearance <15 ml/min).

Objectives: To assess starting dose amongst patients with chronic kidney disease stage 3–4 or 5.

Methods: The ROSE study was a specialist cohort event monitoring study of patients prescribed rivaroxaban. Specialists provided information via detailed questionnaires at baseline (and ≥ 12 weeks). Baseline characteristics included starting dose and presence of either CKD stage 3–4 (eGFR 15–59) or CKD stage 5 (eGFR < 15). Starting dose was examined amongst patients with CKD stage 3–4 and 5 to assess how many patients had a reduced starting dose of less than 20 mg od.

Results: The cohort consisted of 965 patients with AF: 75 patients with history of either stage 3–4 CKD ($n = 73$, 7.6%) or stage 5 CKD ($n = 2$, 0.2%). Of the patients with CKD stage 3–4, 36 (49.3 %) were started on <20 mg daily (15 mg od [$n = 35$]; 10 mg od [$n = 1$]). 35 patients (48.0 %) were started on ≥ 20 mg (20 mg od [$n = 34$]; 30 mg od [$n = 1$]). Starting dose was missing for two patients (2.7%). Neither patient with CKD stage 5 had a dose reduction.

Conclusions: Our results suggest that amongst patients with CKD stage 3–4, approximately half were started on the recommended reduced dose of <20 mg od. Not all patients with CKD stage 3–4 would be recommended a dose reduction as per the product label. A

UK audit suggests that approximately 20% of patients in the UK with CKD 3 are 3b rather than 3a although the frequency may be higher in a hospital cohort.

1005 | Serious hypoglycemia and use of warfarin in combination with sulfonylureas or metformin

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Background: Prior research suggests that warfarin, when given concomitantly with some sulfonylureas, may increase the risk of serious hypoglycemia.

Objectives: To measure the association between warfarin use and serious hypoglycemia in users of either sulfonylureas (as object drugs) or metformin (as a negative control object drug).

Methods: Design - Self-controlled case series. **Setting** - Five large US Medicaid programs constituting ~40% of enrollees nationwide, with Medicare claims for dual enrollees, from 1999 to 2011. We included adults who experienced serious hypoglycemia while receiving glimepiride, glipizide, glyburide, or metformin. **Exposure of interest** - Active prescription for warfarin during a period covered by a prescription for glimepiride, glipizide, glyburide, or metformin. Exposed time was categorized into pre-specified risk windows based on time since the beginning of concomitancy. **Outcome measure** - Serious hypoglycemia, ascertained by the ICD-9-CM discharge diagnosis codes (inpatient claims: principal position; emergency department claims: any position) 251.0, 251.1, 251.2, or 280.8X unless accompanied by one of the exclusionary diagnosis codes (positive predictive value ~78–89%). **Statistical analysis** - We calculated rate ratios (RRs) for warfarin-exposed time vs unexposed time using conditional Poisson regression, controlling for time-varying covariates, including drugs that can cause hypoglycemia or hyperglycemia, acute infection, etc.

Results: Across all risk windows combined, warfarin was associated with a statistically elevated rate of serious hypoglycemia when given concomitantly with glimepiride (RR: 1.47; 95% confidence interval [CI]: 1.07, 2.02) and metformin (RR: 1.73; 95% CI: 1.38, 2.16). In the late risk window (>120 days), the RR for warfarin was elevated with concomitant glipizide (RR: 1.72; 95% CI: 1.29, 2.29), glyburide (RR: 1.57; 95% CI: 1.15, 2.15), and metformin (RR: 2.26; 95% CI: 1.67, 3.05), and nearly statistically elevated with concomitant glimepiride (RR: 1.56; 95% CI: 0.97, 2.50).

Conclusions: These results are consistent with a previously hypothesized hypoglycemic effect of warfarin in type-2 diabetes patients through inhibition of the carboxylation of osteocalcin. Physicians and patients may need to be vigilant about the potential elevated risk of serious hypoglycemia associated with warfarin use during sulfonylurea or metformin therapy, especially with prolonged concomitancy.

1006 | Comparative safety of co-prescribed calcium channel blockers and oral anticoagulants for adverse bleeding events in atrial fibrillation

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Background: Direct oral anticoagulants (DOACs) have fewer drug interactions than VKAs. However, potential interactions with commonly co-prescribed medications are a safety concern. Verapamil (V) and diltiazem (D) are inhibitors of P-glycoprotein and diltiazem has CYP3A4 inhibitory activity, interactions which may increase bleeding risk.

Objectives: To evaluate the risk of bleeding with co-prescribed anticoagulants and V/D using an active comparator design.

Methods: This retrospective cohort study utilized claims data from 2010 to 2015. New users of anticoagulants with atrial fibrillation were identified. V and D use was assessed in the 6 months prior to this index date and required minimum 90 days cumulative exposure. Amlodipine (A) was chosen as the active comparator as a similar medication with no interaction profile. Due to small sample size and expected event rates, the V and D groups were combined. Inverse probability of treatment weights (IPTW) were generated to balance the V/D and A groups on measured baseline characteristics stratified by OAC treatment. A proportional hazards model assessed the risk of major, moderate, and overall bleeding over a 1-year follow-up.

Results: A total of 15,623 OAC users with V/D or A co-prescribed including 8,469 warfarin, 2,675 dabigatran, 2,935 rivaroxaban, and 1,545 apixaban users. Primary results showed no increased risk of overall bleeding, moderate, or major bleeding for V/D versus A users for any anticoagulant. Only dabigatran+V/D showed an increased risk (HR=1.45 [1.01-2.12]) for minor gastrointestinal bleeding compared to dabigatran+A users. Sensitivity analyses showed no variation in results.

Conclusions: In this large study, the hypothetical drug interaction between DOACs and V/D did not show evidence of an increased risk of bleeding when compared to an active comparator group.

1007 | Benefit-risk profile of dabigatran 110 mg versus vitamin-K antagonists in patients with non-valvular atrial fibrillation: A cohort study in the French Nationwide Claims Database

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Background: The RE-LY trial compared dabigatran 150 mg or 110 mg with vitamin-K antagonists (VKA) for stroke prevention in patients with non-valvular atrial fibrillation (NVAf); dabigatran 110 mg was associated with similar rates of stroke and systemic embolism, but lower rates of major bleeding compared with VKA.

Objectives: To test the reproducibility of these findings in real life in countrywide French claims data.

Methods: Cohorts of new users of dabigatran 110 mg or VKA for NVAf in 2013 were identified and followed-up for one year in the SNDS 66 million persons nationwide French claims database. Dabigatran 110 mg and VKA patients were 1:1 matched on gender, age, date of the first drug dispensing, and high-dimensional propensity scores (hdPS) including CHA₂DS₂-VAsC and HAS-BLED risk factors. Hazard ratios (HR) [95% confidence interval] were estimated during first prescribed anticoagulant exposure, using Cox proportional hazards risk or Fine and Gray models.

Results: Of 103 101 new anticoagulant users for NVAf in 2013, 27 060 used dabigatran, 15 532 of whom used dabigatran 110 mg (57%), 44 653 with VKA; 14 442 were matched per arm. Mean age was 79 years, 49% male, 91% with CHA₂DS₂-VAsC score equal to or below 2 and 8% with HAS-BLED score above 3. One-year cumulative incidence of clinically relevant bleedings was respectively 2.9% and 4.7% for matched dabigatran 110 mg and VKA patients (HR: 0.62 [95% CI: 0.54-0.72]), 1.6% and 2.3% for arterial thrombotic events (0.69 [0.56-0.84]), 1.5% and 1.6% for acute coronary syndromes (0.93 [0.74-1.15]), 6.2% and 7.6% for death (0.84 [0.76-0.94]), 11.0% and 14.3% for the composite criterion of all events above (0.77 [0.72-0.84]). Results were similar for all patients with hdPS adjusted analyses.

Conclusions: In this nationwide real life study, dabigatran 110 mg was associated with lower arterial thrombotic event rates and significantly fewer clinically relevant bleeding or death. Overall, there were 23% fewer major outcomes with dabigatran 110 mg than with VKA, improving the clinical benefits found in the RE-LY trial.

1008 | Benefit-risk profile of dabigatran 150 mg versus vitamin-K antagonists in patients with non-valvular atrial fibrillation: Results from a matched cohort study in the French Nationwide Claims Database

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Background: The RE-LY trial compared dabigatran 150 mg or 110 mg to vitamin-K antagonists (VKA) for stroke prevention in patients with non-valvular atrial fibrillation (NVAf); dabigatran 150 mg was associated with lower rates of stroke and systemic embolism, but similar rates of major bleeding compared to VKA.

Objectives: To test the reproducibility of these findings in real life in countrywide French claims data.

Methods: Cohorts of new users of dabigatran 150 mg or VKA for NVAf in 2013 were identified and followed-up for one year in the SNDS 66 million persons nationwide French claims database. Dabigatran and VKA patients were 1:1 matched on gender, age, date of the first drug dispensing, and high-dimensional propensity scores (hdPS) including CHA₂DS₂-VASc and HAS-BLED risk factors. Hazard ratios (HR) [95% confidence interval] were estimated during first prescribed anticoagulant exposure, using Cox proportional hazards risk or Fine and Gray models.

Results: Of 103 101 new anticoagulant users for NVAf in 2013, 27 060 used dabigatran of whom 10 847 dabigatran 150 mg (40%); 44 653 used VKA; 8389 dabigatran 150 mg and VKA users were matched per arm. Mean age was 67 years, 67% male, about 65% with CHA₂DS₂-VASc score equal to or above 2; fewer than 5% had HAS-BLED scores above 3. One-year cumulative incidences of arterial thrombotic events with dabigatran 150 mg or VKA were respectively 1.3% and 1.7% (HR 0.76 [0.56-1.04]), 0.9% and 1.6% for acute coronary syndromes (0.58 [0.42-0.81]). The event rates for clinically relevant bleedings were respectively 1.4% and 3.4% (HR: 0.42 [95%CI: 0.33-0.54]), for death 1.4% and 3.1% (0.46 [0.35-0.59]), and 4.7% and 8.9% for the composite criterion of all events above (0.52 [0.45-0.60]). Results were similar with hdPS adjusted analyses of all patients.

Conclusions: In this nationwide real life study, the results of the RE-LY trial were partially reproduced, in that dabigatran was associated with slightly lower arterial thrombotic event rates, but significantly fewer clinically relevant bleeding or death. Overall there were 48% fewer major outcomes with dabigatran 150 mg than with VKA, confirming the overall clinical benefit found in the RE-LY trial.

1009 | Public health surveillance reveals an increase in health care utilization for generic vs brand-name warfarin users

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Background: Even with many direct oral anticoagulant options nowadays, brand-name or generic warfarin is still widely used to prevent atherothrombotic events in cardiology. Federal standards regulate bioequivalence of generic vs brand-name drugs through comparative bioavailability studies but do not regulate clinical equivalence or tolerability in a "real-life" setting.

Objectives: Through our provincial public health surveillance system, we sought to evaluate the impact of the generic warfarin commercialization on health care utilization: emergency room (ER) consultations or hospitalizations.

Methods: We performed an interrupted time series analysis using the Quebec Integrated Chronic Disease Surveillance System, a surveillance system of the second populous province in Canada (~8.3 million in 2016). Rates of health care utilization for warfarin users (n = 280 158) aged ≥66 years were calculated for 6-month periods, 5 years before up to 15 years after warfarin commercialization (from January 1996 to January 2016). Periods before and after generic warfarin commercialization were compared by negative binomial segmented regression models for all users with a specific variable for generic or brand-name users. Sensitivity analyses were also conducted.

Results: Generic warfarin analogs (n = 5) were commercialized beginning January 2001. There was an approximated mean rate of 1134 ER or hospitalizations for 1000 brand-name and generic users per 6-month period, similar before and after generics commercialization. After generics commercialization, there was an immediate increase in rates of health care utilization for generic (9.9%) vs brand-name users (0%), a statistically significant difference (9.9% [95% confidence interval: 4.4% to 15.5%], p = 0.0001). Rates of health care utilization remained higher for generic vs brand-name users until 15 years after generics commercialization, even though respective trends were parallel (difference: 0% [0% to 0.5%], p = 0.67).

Conclusions: Among generic warfarin users, we observed increased rates of health care utilization 6 months after generics commercialization. Risk and survival analysis studies controlling for potential confounding are required to better characterize generic substitution as stricter licensing process may be required.

1010 | Non-bleeding adverse events associated with direct oral anticoagulants: A sequence symmetry analysis using the French Healthcare Databases between 2013 and 2015

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Background: Use of direct oral anticoagulants (DOACs) has increased dramatically over the last 5 years. Continued monitoring of their safety profile is needed. However, both clinical trials and observational studies have mainly focused on bleeding adverse events to date.

Objectives: To assess non-bleeding adverse events associated with the use of DOACs by sequence symmetry analysis (SSA).

Methods: SSA was performed using nationwide data from the French National Healthcare databases (*Régime Général*, 50 million beneficiaries) to assess a cohort of 386 081 DOAC new users for the first occurrence of four types of non-bleeding outcomes: renal, hepatic, skin outcomes were identified by using hospitalization discharge diagnoses and gastrointestinal outcomes by using

medication reimbursement. Asymmetry in the distribution of each investigated outcome occurring before and after initiation of DOAC therapy was used to test the association between DOAC therapy and these outcomes. SSA inherently controls for all time-constant confounders and adjusted sequence ratios (aSR) were computed after correcting for temporal trends. Glaucoma and bleeding as well as depressive disorders were used as negative and positive control outcomes, respectively. Analyses were replicated on a cohort of 310 195 vitamin K antagonist (VKA) new users.

Results: This study demonstrated the expected positive association between either DOAC or VKA therapy and hospitalized bleeding as well as initiation of antidepressant therapy, while no association was observed between neither DOAC nor VKA therapy and initiation of antiglaucoma medications. For DOAC therapy, signals were associations with hepatic outcomes, including acute liver injury (for the 3-month time window $aSR_3 = 2.71$ [95% confidence interval, 1.79-4.52]) and gastrointestinal outcomes, including initiation of drugs for constipation and antiemetic drugs ($aSR_3 = 1.31$ [1.27-1.36] and 1.17 [1.12-1.22], respectively). No association was observed between VKA initiation and hepatic or gastrointestinal outcomes except for drugs for constipation ($aSR_3 = 1.15$ [1.11-1.18]).

Conclusions: Results of this nationwide study suggest that DOAC therapy is associated with severe liver injury and with gastrointestinal disorders requiring initiation of drugs for constipation or antiemetic drugs. Pending further studies, DOAC patients should be carefully monitored regarding these potential adverse events.

1011 | Calcium channel blockers and the risk for lung cancer: A population-based nested case-control study

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Background: Calcium channels are involved in the regulation of processes governing cell proliferation and apoptosis. It has been suggested that calcium channel blockers (CCBs) may increase the risk of lung cancer; however, current evidence is conflicting and limited.

Objectives: To investigate the associations between CCBs use and lung cancer.

Methods: We conducted a population-based nested case-control study utilizing the Clalit Health Services database. We formed a cohort of patients prescribed their first antihypertensive agent between January 1, 2000, and December 31, 2014. Cases were patients newly diagnosed with lung cancer during follow-up. Ten controls were matched by age, sex, calendar year of cohort entry, and duration of follow-up to each case. Multivariate conditional logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals

(CIs) of lung cancer associated with ever use of CCBs, when compared with use of other antihypertensive drugs. A secondary analysis was conducted to assess whether the association varies with cumulative duration of use.

Results: During a median follow-up of 6.2 years, we identified 4174 cases of lung cancer that were matched with 41 740 controls. Ever use of CCBs was associated with an increased risk of lung cancer (adjusted OR 1.13; 95% CI 1.06-1.21), when compared with use of other antihypertensive drugs. In the secondary analysis, a duration-response relation was observed, with the ORs gradually increasing with longer cumulative duration of CCB use (<5 years, OR 1.12, 95% CI 1.04-1.20; 5-10 years, OR 1.22, 95% CI 1.07-1.40; >10 years, OR 1.33, 95% CI 0.90-1.96; p -trend < 0.001).

Conclusions: The results of this large population-based study indicate that the use of CCBs is associated with a modest but significant increase in the risk of lung cancer. This association appeared to increase with longer durations of use.

1012 | Pre-diagnostic use of low-dose aspirin and risk of incident metastasis and mortality in patients with colorectal cancer

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Background: Previous studies have shown that the use of low-dose aspirin is associated with lower colorectal cancer incidence. To date, however, questions remain as to whether the use of low-dose aspirin before the diagnosis of colorectal cancer is associated with improved prognosis and lower mortality.

Objectives: To determine whether the use of low-dose aspirin before a diagnosis of colorectal cancer is associated with a decreased risk of colorectal cancer metastasis and all-cause mortality.

Methods: We conducted a population-based cohort study using the Health Search Database, a large Italian primary care database. We identified a cohort of 7478 patients newly diagnosed with non-metastatic colorectal cancer between January 1, 2000, and December 31, 2013. Cohort entry was set to the date of the colorectal cancer diagnosis, and pre-diagnostic use of aspirin was defined by the presence of at least one low-dose aspirin prescription at any time before cohort entry. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for incident metastasis and all-cause mortality associated with pre-diagnostic use of low-dose aspirin, when compared with non-use. In a secondary analysis, we assessed whether the association varied with cumulative duration of use.

Results: There were 314 incident metastatic events and 2189 deaths during a mean follow-up time of 4.4 and 4.7 years, respectively. Pre-

diagnostic use of low-dose aspirin was not associated with an overall decreased risk of incident metastasis (HR 0.88, 95% CI 0.63-1.22) or all-cause mortality (HR 1.09, 95% CI 0.96-1.22). In the secondary analysis, long-term cumulative use of low-dose aspirin (4 years or more) was associated with a decreased risk of incident metastasis (HR 0.35, 95% CI 0.13-0.99), whereas shorter durations were not (1 year or less: HR 0.82, 95% CI 0.54-1.25; 1.1-2 years: HR 1.21, 95% CI 0.70-2.09; 2.1-3 years: HR 1.09, 95% CI 0.54-2.22; 3.1-4 years: HR 1.07, 95% CI 0.46-2.50). No association was found between cumulative duration of use and all-cause mortality.

Conclusions: In this population-based study, pre-diagnostic use of low-dose aspirin was not associated with an overall decreased risk of incident metastasis or all-cause mortality. Long-term pre-diagnostic use of low-dose aspirin was associated with a decreased risk of incident metastasis but not all-cause mortality.

1013 | Angiotensin converting enzyme inhibitors and the risk of lung cancer

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Background: The potential effect of angiotensin-converting enzyme inhibitors (ACEIs) on lung cancer incidence has been subject to much debate, with the few observational studies on the topic reporting inconsistent findings.

Objectives: To determine whether the use of ACEIs, when compared with use of angiotensin receptor blockers, is associated with an increased risk of lung cancer.

Methods: A population-based cohort study was conducted utilizing the UK Clinical Practice Research Datalink. A cohort of 992 061 patients newly treated with antihypertensive drugs between January 1, 1995, and December 31, 2015, was identified and followed until December 31, 2016. Time-varying use of ACEIs was compared with use of angiotensin receptor blockers (ARBs), with exposures lagged by 1 year for latency purposes. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of incident lung cancer associated with use of ACEIs compared with use of ARBs. Secondary analyses were performed to assess whether risk varies by cumulative duration of use and time since initiation.

Results: The cohort was followed for a mean of 6.4 years (standard deviation 4.7), generating 7952 incident lung cancer events (crude incidence 1.3 [95% CI 1.2-1.3] per 1000 person-years). Overall, compared with use of ARBs, use of ACEIs was associated with an increased risk of lung cancer (incidence 1.6 vs 1.2 per 1000 person-years; HR: 1.13, 95% CI: 1.0001-1.29). HRs gradually increased with longer durations of use, with an association evident after 5 years of

use and peaking after more than 10 years of use (HR 1.31, 95% CI: 1.08-1.58). Similar findings were observed with time since initiation.

Conclusions: In this population-based cohort study, the use of ACEIs was associated with an increased risk of lung cancer. The association was particularly elevated among those using ACEIs for over 5 years.

1014 | Gender differences in efficacy and safety of direct oral anticoagulants in atrial fibrillation: systematic review and network meta-analysis

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Background: Studies indicate that women with atrial fibrillation (AF) are less likely to be prescribed anticoagulants despite the higher risk of stroke in women as compared with men

Objectives: To evaluate whether there is a sex difference in the safety and efficacy of direct oral anticoagulants (DOACs). We secondarily examined sex differences by specific DOACs

Methods: MEDLINE, EMBASE, Cochrane, and ClinicalTrials.gov were searched to identify randomized clinical trials of DOACs reporting outcomes of stroke and major bleeding in women and men with AF. Five trials met inclusion criteria through March 2017. Meta-analysis and network meta-analysis were performed using RevMan version 5.3 and the statistical package "netmeta" in R. Fixed effects model were used for low heterogeneity and a random effect for moderate or high heterogeneity

Results: The meta-analysis included 66 389 patients, 37.8% were women. Women treated with DOACs were at higher risk of stroke and systemic embolism compared with men treated with DOACs (relative risk, RR, 1.18; 95% CI, 1.05-1.34; $I^2 = 10\%$) but there was a significantly lower risk of major bleeding in women compared with men (RR, 0.85; 95% CI, 0.78-0.94; $I^2 = 0\%$). Network meta-analysis in women suggested a lower rate of major bleeding in women taking apixaban compared to dabigatran 150 mg (OR, 0.62; 95% CI, 0.44-0.88) and rivaroxaban (OR, 0.57; 95% CI, 0.40-0.81) and with edoxaban compared with rivaroxaban (OR, 0.68; 95% CI, 0.49-0.95). In men, there was a lower rate of major bleeding in men treated with apixaban compared with rivaroxaban (OR, 0.73; 95% CI, 0.57-0.95). As compared with warfarin, DOACs were associated with a decreased risk of stroke and systemic embolism in both women and men (RR, 0.79; 95% CI, 0.69-0.91; $I^2 = 12\%$, RR, 0.83; 95% CI, 0.74-0.93; $I^2 = 0\%$, respectively) and decreased risk of major bleeding compared with warfarin in both women and men (RR, 0.80; 95% CI, 0.66-0.97; $I^2 = 67\%$, RR, 0.88; 95% CI, 0.79-0.97; $I^2 = 43\%$).

Conclusions: The lower risk of bleeding seen in women treated with DOACs suggests that under-treatment of women cannot be justified. Further investigation of DOACs including differences between the DOACs in specific populations is warranted.

1015 | Automatically identifying prescribing cascades in clinical notes using natural language processing

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Background: Prescribing cascade, a phenomenon wherein a drug causes a side effect that leads to the prescription of a second drug(s) to treat the side effect, is well documented in medical practice. Presently, however, automatic methods that detect prescribing cascades in real time and alert health care providers to ensuing cascades are lacking.

Objectives: To examine whether natural language processing (NLP) of clinical notes can identify a common prescribing cascade (amlodipine causing pedal edema that leads to furosemide prescribing) in patients.

Methods: We used an NLP system that extracts names of drugs and clinical events (a named entity recognizer), and the relations in between them (a relational tagger) from clinical notes. Using this NLP output, we created a composite NLP-based algorithm to identify patients in whom amlodipine caused pedal edema and pedal edema lead to the use of furosemide. As a comparator, we used a claims data-based algorithm to identify potential cascade cases from administrative data (pharmacy codes for amlodipine followed by disease codes for edema followed by pharmacy codes for furosemide). Our database on which both algorithms were applied consisted of a set of 2.7 million clinical notes from 372 540 patients registered into the UMass Medical School electronic health record (EHR) system between 2013 and 2015. The notes on which the NLP algorithm was applied were generated from both in and outpatient encounters, irrespective of clinical specialty, included progress reports, discharge summaries, history and physical examination notes, procedure notes, and investigation notes. Also available were the pharmacy and diagnostic codes generated from the medical encounter claims. Using expert review as the gold standard, we compared the positive predictive value (PPV) of the NLP-based algorithm with the claims data-based algorithm for identifying prescribing cascades.

Results: The NLP algorithm retrieved 47 patients with a PPV of 84.1% (CI: 73.3%-94.9%). The claims data-based algorithm retrieved 43 patients with a PPV of 33.3% (CI: 15.5%-51.5%).

Conclusions: NLP of clinical notes provides an innovative and accurate method for identifying prescribing cascades in populations of patients at risk. NLP may also provide a useful tool to identifying these drug-related risks in the context of clinical care of patients in nearly real time.

1016 | Use of spontaneous reporting systems to detect host-medication interaction in drug-induced adverse events

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Background: Medical treatment should be tailored to an individual's characteristics to optimize treatment benefits. Spontaneous reporting systems have been used to detect the signs of highly disproportionate reporting rates of specific drug-adverse event combinations.

Objectives: We examined whether case-only analyses from spontaneous reporting systems can detect host-medication interaction in oral anti-diabetic drug-induced myocardial infarction.

Methods: The interaction between sex and the use of oral anti-diabetic drugs was mined among patients with myocardial infarction in the US Food and Drug Administration Adverse Event Reporting System (FAERS) from 2004 to 2014, including 55 718 males and 42 428 females. Odds ratio (OR) of multiplicative interaction was used to estimate the sex-drug interaction. The detected signs of these interactions were then validated by a nested case-control study utilizing a health care record database, Taiwan's National Health Insurance Research Database (NHIRD), from 2001 to 2014, including 33 079 cases and 165 395 controls, with conditional logistic regression analyses.

Results: In FAERS, a higher proportion of male patients than female patients used metformin (10.32% in males vs 7.82% in females) and sulfonylureas (4.75% in males vs 3.43% in females; after adjusting for patients' pharmacy-based chronic disease score, males had a higher risk of metformin-induced (OR = 1.07; 95% CI 1.02-1.13) and sulfonylureas-induced (OR = 1.21, 95% CI 1.13-1.30) myocardial infarction than females. Detected signs of interaction were validated in NHIRD (OR for metformin = 1.16, 95% CI 1.08-1.24; OR for sulfonylureas = 1.16, 95% CI 1.07-1.24).

Conclusions: Males have a higher risk of metformin- and sulfonylureas-induced myocardial infarction than females, which suggests the sex-drug interaction is a key issue in diabetes treatment plan. This case-only approach using information from spontaneous reporting systems may be a potential tool for screening host-medication interactions that cause adverse events.

1017 | Statin use and the risk of intracerebral hemorrhage: A population-based cohort study using Korean National Health Insurance claims database

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Background: Statins, lipid-lowering agents, are widely used for the primary and secondary prevention of cardiac and cerebrovascular diseases. Several large randomized trials suggested that statin use might increase the risk of intracerebral hemorrhage (ICH). However, the association between statin therapy and the occurrence of ICH is unclear. It is necessary to assess the impact of statin use on the risk of ICH.

Objectives: To determine the association between statin use and the risk of ICH.

Methods: We studied a retrospective cohort study using the Korean National Health Insurance Service-National Sample Cohort (NHIS-

NSC) database consisted of 1 million beneficiaries (2.2% of the total eligible Korean population). The patients over 20 years old with hyperlipidemia were extracted from the NHIS-NSC database in year 2002 to 2013. Of those, we compared the statin users with non-users using propensity-score matching (PSM) by 1:1 ratio to reduce the bias of confounding factors. During the follow-up period, the primary outcome was the risk of ICH. The secondary outcome was the 30-day mortality after ICH incidence, cardiac mortality, and incidence of ischemic stroke. The cox proportional hazard model was performed to evaluate the ICH risk of statin use. Subgroup analyses were performed for the primary outcome according to the risk factors related to ICH.

Results: After PSM, 56 078 patients were included out of total 275 512 adults with hyperlipidemia. During the mean follow-up period of 4.7 years, ICH occurred in 228 patients. Statin use had no significant association in increasing the risk of ICH (adjusted HR [aHR], 0.84; 95% CI, 0.64-1.08; $p = 0.18$). Among patients with type 2 diabetes, the risk of ICH was lower in statin users than non-users (aHR, 0.63; 95% CI, 0.41-0.97; $p = 0.03$). Statin therapy was significantly associated with reduced the cardiac mortality and incidence of ischemic stroke (aHR, 0.49; 95% CI, 0.43-0.56; $p \leq .0001$ and aHR, 0.88; 95% CI, 0.82-0.95; $p = 0.001$, respectively). However, there were no significant differences in the 30-day mortality after ICH incidence between statin and non-users (incidence, 26.0% and 22.6%; $p = 0.55$).

Conclusions: In comparison of statin users with non-users, statin therapy was not associated with the risk of ICH with improvements of the ischemic cardiac and cerebrovascular outcomes.

1018 | Statins and new-onset diabetes

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Background: Clinical trials evaluating statins have shown an increased risk of developing diabetes with these drugs, but dose-effect relationship remains poorly studied.

Objectives: To evaluate the association between new-onset diabetes and use of statins.

Methods: This nested case-control study was performed using data of the random representative sample of the French health care system database for the 2005-2015 period. The outcome of interest was the occurrence of new-onset diabetes identified from diagnosis data or reimbursement data for anti-diabetic drugs. The date of the first outcome identified constituted the index date; a 6-month lag-time period was considered before index date that was censored for the assessment of exposure and other studied variables. Patients aged 45 years and over with an outcome of interest between 2012 and 2015 (cases) and up to 10 case-matched controls on age, sex, numbers of different drugs dispensed and medical consultations, and use of

glucocorticoids, were included in the study. The associations between use of statins and occurrence of new-onset diabetes were evaluated by odds ratios (OR) obtained by conditional logistic regression adjusted on high dimensional disease risk score.

Results: This study included 5541 cases of new-onset diabetes matched to 54 086 controls. Median duration of follow-up period before index date was 8.8 years. Analyses have shown that risk of new-onset diabetes was increased for new users of statins (statin treatment initiating in the 6-month period preceding the lag-time period; OR 1.31; 95% confidence interval 95% CI 1.01-1.71), and for patients exposed to high cumulative dose of statins (≥ 5 years of cumulative exposure to statins; OR 1.12; 95% CI 1.01-1.25).

Conclusions: The results of this study confirmed the increased risk of developing diabetes with the use of statins, both more important at the beginning of treatment and after prolonged use of these drugs.

1019 | Concurrent use of DOACs and pharmacodynamic interacting drugs is associated with an increased risk of major bleeding compared with patients using DOACs alone: Nested case-control study in UK CPRD

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Background: Although many studies on bleeding risk associated with use of direct oral anticoagulants (DOACs) are conducted, the effect of concurrent use of potentially interacting drugs on this risk is not well studied.

Objectives: To evaluate the association between concurrent use of DOACs with concurrent use of potential pharmacokinetic or pharmacodynamic interacting drugs on major bleeding.

Methods: We used data from the UK Clinical Practice Research Datalink (period 2008-2015) to conduct a nested case-control study in a cohort of new users of DOACs (dabigatran, apixaban, and rivaroxaban). Cases were patients who were hospitalized with a primary discharge diagnosis of major bleeding while taking DOACs. Up to four controls were matched to each case on age, sex, and index date. Controls also had to be a current user of a DOAC on the index date. Conditional logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to estimate the risk of major bleeding associated with concurrent use (30 days prior to the index date) of potential pharmacokinetic or pharmacodynamic interacting drugs. The analysis was adjusted for well-known risk factors for bleeding

Results: We identified 393 cases from 29 120 new users of DOACs and 1494 controls. Most subjects were current users of rivaroxaban (58.8%). The concurrent use of DOACs and pharmacokinetic interacting drugs did not increase the risk of major bleeding vs use

of DOACs alone (45.0% vs 51.2%, adjusted OR 0.90; 95% CI 0.60-1.36). However, concurrent use of pharmacodynamic interacting drugs was associated with an increased risk of major bleeding (21.6% vs 13.5%, adjusted OR, 1.91; 95% CI, 1.39-2.62). This effect was mainly driven by selective serotonin reuptake inhibitors (SSRIs, adjusted OR, 1.73; 95% CI, 1.12-2.65) and antiplatelet drugs (adjusted OR, 1.90; 95% CI, 1.23-2.93), respectively.

Conclusions: Among patients taking a DOAC, concurrent use of an SSRIs or antiplatelet drug was associated with increased risk of major bleeding compared with DOAC use without these drugs.

1020 | Abstract Withdrawn

1021 | The impact of antihypertensive drugs on serum potassium and sodium levels in patients electively admitted to a tertiary hospital

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Background: Abnormal serum potassium and sodium levels may lead to serious cardiovascular and neurological conditions.

Objectives: To investigate the association between the use of different antihypertensives and the risk of developing disturbances in potassium and sodium serum levels.

Methods: A cross-sectional study was conducted in antihypertensive users, electively admitted to the University Medical Center Utrecht between January 2013 and September 2016. Data on patient characteristics, antihypertensives, and electrolyte levels were extracted from the Utrecht Patient Oriented Database. The association between the use of different antihypertensives and the electrolyte level was studied using linear and logistic regression.

Results: A total of 6369 elective admissions were included in this study. The most frequent electrolyte disorder was hyponatremia (29.5%), followed by hypokalemia (20.5%). Hyperkalemia (3.4%) and especially hypernatremia (0.1%) were less common. In comparison with the use of monotherapy of beta-blockers, use of monotherapy of calcium antagonists (adj. OR 3.08; 95% CI 2.13, 4.46), thiazide or thiazide-like (adj. OR 2.08; 95% CI 1.14, 3.82) and loop diuretics (adj. OR 1.92; 95% CI 1.13, 3.28) was significantly associated with higher odds of hypokalemia. Most combinations of antihypertensives with thiazide or thiazide-like or loop diuretics were significantly associated with lower potassium serum levels compared with monotherapy of beta-blockers. None of the antihypertensive therapies were significantly associated with hyperkalemia. Monotherapy of potassium sparing diuretics (adj. OR 2.72; 95% CI 1.11, 6.66) and angiotensin receptor blockers (adj. OR 1.63; 95% CI 1.01, 2.63), and some of the

combinations with a thiazide or thiazide-like or loop diuretic were significantly associated with higher odds of hyponatremia.

Conclusions: Monitoring of serum potassium and sodium levels should be encouraged in patients with antihypertensive drugs especially antihypertensives inducing hyponatremia or hypokalemia to avoid possible severe consequences of abnormal serum potassium and sodium levels.

1022 | The impact of sex on the associations between ace inhibitors and cough and angioedema: A systematic review and meta-analysis

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Background: Cough and angioedema are well-known adverse effects of angiotensin-converting enzyme (ACE) inhibitors. Some observational studies in patients using ACE inhibitors have observed that women have a higher incidence of cough and angioedema than men.

Objectives: To evaluate based on randomized controlled trials (RCTs), whether the risks of developing cough and angioedema with ACE inhibitors are modified by sex.

Methods: We searched PubMed and Cochrane databases for all years to August 2016. We included RCTs that contain information about the incidence of cough and angioedema in users of ACE inhibitors and controls (active/placebo) in men and women. We performed meta-analyses using the random effects model. Pooled risk ratios (RRs) for cough and angioedema associated with ACE inhibitors in women and men were estimated and tested for interaction.

Results: We included four RCTs in our analysis (three studies for cough and two studies for angioedema). We found that there was no difference in the RR to develop cough or angioedema for ACE inhibitors versus controls between women and men. For cough in women, the RR was 3.70; 95% CI (2.55-5.35) and for men, 2.61; 95% CI (1.30-5.27) (*P* value for interaction 0.39). For angioedema, these RRs were 5.56; 95% CI (2.45-12.62) and 6.35; 95% CI (1.81-22.36), respectively (*P*-value for interaction 0.86).

Conclusions: Our meta-analyses show that the risks of developing cough and angioedema associated with ACE inhibitors are not modified by sex. However, these findings should be interpreted cautiously due to limited number of studies involved.

1023 | Risk of mouth ulcer associated with the use of nicorandil in Korea

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Background: Nicorandil is one of the most common medication for angina pectoris symptoms. Recently, there are safety concerns surrounding nicorandil; however, there is limited data on the potential adverse drug events in patients with angina pectoris in Korea.

Objectives: To determine the relationship between use of nicorandil and mouth ulceration.

Methods: We performed a retrospective cohort study using the Korean National Health Insurance claims data from 2013 to 2016. Angina pectoris patients initiating treatment with either nicorandil or other angina pectoris treatment medications (ie, calcium channel blockers, nitrates, molsidomine, and trimetazidine), but not both, were included. Propensity score (PS) adjustment and matching of Cox proportional hazards regression models quantified the risk of nicorandil compared with other angina pectoris medication therapy on time to mouth ulceration. We performed sensitivity analyses by each other angina pectoris treatment medication.

Results: We identified 14 022 nicorandil and 139 467 other angina pectoris treatment medication patients. Balance in baseline characteristics between the treatment groups was achieved within propensity score quintiles and between propensity matched pairs (14 019 pairs). Compared with the other angina pectoris medication group, the nicorandil group had a significantly higher mouth ulceration (crude hazard ratio [HR] 1.31, 95% confidence interval [CI] 1.09-1.58; PS adjusted HR 1.35, 95% CI 1.12-1.63; PS matched HR 1.41, 95% CI 1.07-1.85). Subgroup analyses found that the increased risk of mouth ulceration associated with use of nicorandil compared with calcium channel blockers or nitrates, while no significant differences were observed between the nicorandil and molsidomine or trimetazidine groups.

Conclusions: Use of nicorandil was found to be associated with an increased risk for mouth ulceration. In spite of the known benefits of nicorandil, persons who may already be at higher risk of experiencing ulceration may be more careful to use nicorandil.

stroke) in adult psoriasis patients treated with biologic therapies or methotrexate (MTX)

Methods: A prospective cohort study was conducted using the BADBIR dataset from 09/2007 to 10/2016. Data were collected from 153 dermatology centres in the United Kingdom and Ireland. The primary outcomes were major CVEs occurring: (1) during therapy; or (2) plus 90 days follow from the last dose of therapy. Crude incidence rates (IRs) of major CVEs (per 1000 person-years, 95% confidence intervals [CIs]) were calculated in previously biologic naïve psoriasis patients aged 18 years or over treated with ustekinumab (UST), tumour necrosis factor- α inhibitors (TNFi; etanercept [ETN] or adalimumab [ADA]), ETN, ADA, or MTX. Propensity score Cox proportional hazard regression models were used to estimate hazard ratios with 95% CIs. The primary analysis compared UST against TNFi exposure, while UST, ETN, or MTX were compared with ADA in secondary analyses.

Results: The number of patients included in UST, TNFi, ETN, ADA, and MTX cohorts were 951, 4517, 1313, 3204, and 2189, respectively. The IRs (95% CI) per 1000 person-years during therapy were UST 3.61 (1.72-7.58), TNFi 2.46 (1.65-3.67), ETN 1.72 (0.72 - 4.13), ADA 2.77 (1.77-4.35), and MTX 1.92 (0.91-4.02) and up to 90 days after the last dose were UST 3.23 (1.54-6.77), TNFi 2.67 (1.86-3.84), ETN 1.86 (0.84-4.14), ADA 3.01 (2.00-4.53), and MTX 2.15 (1.12-4.13). No statistically significant differences in the risk of the primary outcomes were found during therapy (adjusted HR [95% CI] for UST versus TNFi: 1.17 [0.49-2.27]; UST versus ADA: 1.06 [0.39-2.89]; ETN versus ADA: 0.94 [0.3-2.88]; MTX versus ADA: 1.12 [0.3-4.17]) or up to 90 days after the last dose (adjusted HR for UST versus TNFi: 0.98 [0.43-2.25]; UST versus ADA: 0.87 [0.33-2.3]; ETN versus ADA: 0.82 [0.28-2.36]; MTX versus ADA: 1.06 [0.34-3.28]).

Conclusions: The IRs for CVEs for biologic therapies and MTX were similar, and there was no difference in the risk between these therapies.

1024 | Risk of major cardiovascular events in adult patients with psoriasis treated with biologic therapies or methotrexate: Cohort study in the British Association of Dermatologists Biologic Interventions Register (BADBIR)

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Background: The relationship between biologic therapies and major cardiovascular events (CVEs) in adult patients with psoriasis is uncertain.

Objectives: To examine the incidence rates and the risk of major CVEs (acute coronary syndrome, unstable angina, myocardial infarction, or

1025 | Comparison of smoking cessation pharmacotherapy safety during a government-sponsored reimbursement program: A population-based retrospective cohort study

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Background: Clinical trial safety assessments of smoking cessation pharmacotherapies have been underpowered and provided inconsistent findings, resulting in cardiovascular and neuropsychiatric safety warnings for varenicline and bupropion. Recently, the Canadian province of British Columbia implemented a reimbursement program providing 100% financial coverage for pharmacotherapies to aid smoking cessation.

Objectives: To investigate the risk of mortality, comparing nicotine replacement therapies (NRTs) with varenicline and bupropion, in a

population-based natural experiment. Secondary outcomes included hospitalization for cardiovascular events, and for neuropsychiatric events.

Methods: Using linked administrative databases, we conducted a retrospective cohort study of adults treated with varenicline, bupropion, or nicotine replacement therapy (NRT) for smoking cessation, from the start of the reimbursement program (Sept 30, 2011) until March 2014. Safety endpoints were assessed using logistic regression with a 12-month fixed follow-up period and high-dimensional propensity score adjustment. Sensitivity analyses included a 6-month follow-up and a Cox proportional hazards regression analysis. The primary outcome was all-cause mortality.

Results: The study included 147 610 patients who started on varenicline (49 030), bupropion (7362), or NRTs (91 218). Study cohorts were balanced on age and sex at baseline, although NRT users had a higher proportion of depression and cardiovascular disease. NRTs compared with varenicline were associated with a higher risk of mortality (Risk Ratio [RR] = 1.25, 95% CI [1.11-1.42]), cardiovascular events (RR = 1.09, 95% CI [0.99-1.20]), and neuropsychiatric events (RR = 1.25, 95% CI [1.11-1.41]), although the confidence interval for the increase in cardiovascular risk includes 1. NRTs compared with bupropion were associated with increased but non-significant risk ratios for mortality (RR = 1.18, 95% CI [0.92-1.52]), cardiovascular events (RR = 1.17, 95% CI [0.96-1.43]), and neuropsychiatric events (RR = 1.27, 95% CI [0.90-1.79]). Results were similar in all sensitivity analysis.

Conclusions: From a safety standpoint, these data suggest there is no reason to favor NRT therapy over varenicline or bupropion to aid smoking cessation.

1026 | Short-term HDL cholesterol (HDL-C) decrease and incidence of cardiovascular (CV) events

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Background: Several studies have demonstrated an inverse association between prolonged increases in HDL-C and CV risk. However, the literature describing the effect of short term decreases in HDL-C on CV risk is limited.

Objectives: To estimate the risk of CV events in subjects experiencing a decrease in HDL-C after initiating statin therapy for primary and secondary CV prevention while on short term treatment, compared with those with constant HDL-C levels.

Methods: As some statins users experience HDL-C decreases upon initiation, we conducted a retrospective cohort study comprised of subjects who initiated a treatment with statins and discontinued it within 9 months, using CPRD linked to hospital (HES) and mortality data. HDL-C measurements were assessed within 9 months before

and after statin initiation and subjects were followed for up to 5 years after statin discontinuation for CV events, comparing those with a decrease in HDL-C (>8%) to those with constant HDL-C (±8%). The cut-point was derived from the distribution of HDL-C change after statin initiation. Major adverse cardiac events (MACE) primary composite endpoint was defined as CV death, myocardial infarction, revascularization, and hospitalized ischemic stroke. We estimated crude, multivariable adjusted, and propensity score adjusted 5-year risk differences and hazard ratios, comparing Decrease and Constant HDL-C groups.

Results: From 17 543 subjects, 6454 were in the Decrease group and 11 089 in the Constant group. After adjustment for competing risks and confounding factors the 5-year cumulative risk difference for MACE events was 1.23% (95% CI: 0.28%, 2.18%). Differences in risk were small in magnitude and were not statistically significant until the 5th year of the follow-up. In line with this, the hazard ratio across groups for the composite MACE endpoint was higher in the Decrease compared with the Constant group, 1.20 (95% CI: 1.04, 1.39). The elevated risk in this group was mainly driven by an increased risk in ischemic stroke (1.44 95% CI: 1.08, 1.90) and CV death (1.23 95% CI: 0.93, 1.63).

Conclusions: In our study, we found that patients with a short-term decrease in HDL-C levels after statin initiation had a moderately increased risk of developing CV events compared with those with constant HDL-C levels; however, the magnitude of the difference observed between groups was small and not statistically significant until the 5th year of the follow-up. This study was sponsored by GSK.

1027 | Intraparenchymal hemorrhage following novel oral anticoagulant (NOAC) Or vitamin K antagonist (VKA) therapy: A systematic review and meta-analysis of clinical outcomes

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Background: Novel oral anticoagulants (NOACs) are increasingly used as an alternative to vitamin-K antagonists (VKA) for anticoagulation

and have shown lower rates of intracranial hemorrhage. There are conflicting results from the literature on the outcomes of intraparenchymal hemorrhages (IPH) associated with NOACs, and clinical concern regarding limited standardized reversal strategies.

Objectives: The aim of this systematic review and meta-analysis was to compare mortality, hematoma volume, and risk of hematoma expansion in patients who developed an IPH when exposed to NOACs in comparison with VKA.

Methods: This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Studies were selected that reported on mortality, hematoma expansion, and hematoma volume in NOAC-associated IPH. Pooled risk ratios (RR) were calculated for mortality and hematoma expansion and for hematoma volume (ml), a pooled mean difference (MD) was calculated using random-effects (RE) and fixed-effects (FE) models. Publication bias was assessed by visual inspection of funnel plot asymmetry and using Begg's and Egger's tests.

Results: Fifteen (15) unique studies reporting on 2281 patients were included in the systematic review of which 9 studies comparing NOAC-related IPH to VKA-related IPH and were pooled quantitatively. NOAC-related IPH was not associated with increased mortality (RE and FE: RR: 1.03; 95% CI: 0.89-1.22, I-square = 0%, *p*-heterogeneity = 0.29) or hematoma expansion (RE and FE: RR: 0.91; 95% CI: 0.74-1.12, I-square = 0%, *p*-heterogeneity = 0.19) compared with VKA-related IPH. The hematoma volume of NOAC-related IPH was smaller than VKA-related IPH (RE: MD: -9.31 ml; 95% CI: -16.35-2.28, FE: MD: -7.06 ml, 95% CI: -10.27 to -3.85), but with considerable heterogeneity that could not be alleviated (I-square = 75.0%, *p*-heterogeneity < 0.01). No significant publication bias was detected from Begg's and Egger's tests (*p* > 0.5).

Conclusions: NOAC-related IPH was not associated with increased mortality or hematoma expansion compared with VKA-related IPH and may be associated with a smaller hematoma volume.

1028 | Aromatase inhibitors and risk of myocardial infarction in post-menopausal women with breast cancer

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Background: Aromatase inhibitors (AIs) are increasingly used in treatment of hormone-receptor positive breast cancer in post-menopausal women. Data from large randomized controlled trials indicate that AIs, in comparison with tamoxifen, may be associated with increased risk of cardiovascular outcomes in post-menopausal women with breast cancer. To date, however, few population-based studies have been conducted to assess this possible association in the real-world setting.

Objectives: The objective of this study was to determine whether the use of AIs, when compared tamoxifen, is associated with an increased

risk of myocardial infarction (MI) in post-menopausal women with breast cancer.

Methods: We used the UK Clinical Practice Research Datalink linked with Hospital Episodes Statistics repository and Office for National Statistics to assemble a cohort of patients with newly-diagnosed non-metastatic breast cancer between April 1, 1988, and September 30, 2015. From this cohort, we identified patients newly-treated with AIs and tamoxifen. An as-treated exposure definition was used whereby patients were followed until a first MI during follow-up, discontinuation or switch, death from any cause, end of registration with the general practice, or end of the study period (September 30, 2016). Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of MI associated with use of AIs compared with tamoxifen. Secondary analyses were conducted by individual AI drug molecule and continuous duration of use. The models were adjusted for age, year of cohort entry, smoking, body mass index, alcohol-related disorders, and cardiovascular risk factors.

Results: A total of 14 740 and 13 553 patients were newly treated with AIs and tamoxifen, respectively. These patients were followed for a mean (standard deviation) of 3.3 (2.9) and 4.3 (4.1) years, respectively. Overall, the use of AIs was not associated with an increased risk of MI, when compared with tamoxifen (crude incidence rates: 5.1 vs 2.3 per 1000 person-years, respectively; adjusted HR: 0.96, 95% CI: 0.68-1.35). Similarly, the association did not vary according to AI drug molecule or duration of continuous use.

Conclusions: In this population-based study of post-menopausal women with breast cancer, the use of AIs was not associated with an increased risk of MI, when compared with tamoxifen.

1029 | Cardiovascular comorbidities and risk factors in accordance with pharmacogenetics in rheumatoid arthritis patients treatment with methotrexate—Preliminary data

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Background: Patients with rheumatoid arthritis (RA) have a higher occurrence of cardiovascular risk factors and cardiovascular diseases (CVD) account for about 50% often than in the general population. Despite modern approaches in RA therapy, methotrexate (MTX) is still considered as an anchor drug. Due to its anti-inflammatory activity, MTX has the beneficial effect on the risk of CVD development.

Objectives: The aim of our study is to determine whether folate pathway related single nucleotide polymorphisms (rs2298383, rs3761422, rs2267076, rs2236624, rs17602729, rs2372536, rs1127354, rs2236225, rs1801131, rs1801133, and rs4149056) might be predictive of increased cardiovascular comorbidities in RA patients treated with MTX.

Methods: Data from patients were collected in the University Hospital in Hradec Kralove from the 1st of September 2016 to the 31st of May 2017. Personal and drug anamnesis were obtained from medical documentation. Collection of data, which could tell us about CVD and cardiovascular risk factors such as blood pressure, height, weight, BMI, waist circumference, glycated haemoglobin, patients comorbidities, metabolic syndrome, and EKG as well as patients basic description was realized by completing specific questionnaires. Blood and urine samples for biochemical and haematological analysis were also gathered during patients visit.

Results: 120 genotyped patients with RA were enrolled (35 men and 85 women). All of whom fulfilled the 1987 RA criteria of the American College of Rheumatology, each patient with the history of MTX treatment. Genotyping was performed by quantitative PCR with allelic discrimination using commercial TaqMan (allele-specific) assays (Life Technologies, USA). In total, 24 CVD and 222 cardiovascular risk factors were found. The average age of the sample was 60.6 ± 11.8 . Δ DAS reflecting the change in RA disease activity was 2.07. Altogether, patients used 824 drugs. It means 7.8 drugs for each patient on average.

Conclusions: Treatment with MTX is connected with many adverse reactions, which could lead to serious side effects. On the other hand, in some patients, the usual dose of MTX is without therapeutic effect. We suppose that these situations might be caused by different genetic predisposition in the genes of the folate pathway. If we find a correlation between higher prevalence of CVD and those SNPs, it would help us to individualize dosing depending on patient's genotype. *Funded by SVV 260 417.*

1030 | Adverse events with recombinant G-CSF for neutropenia in cancer

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Background: Treatment of chemotherapy-induced neutopenia includes administration of recombinant granulocyte colony stimulating factor (rG-CSF).

Objectives: This study examined patient characteristics and adverse events for rG-CSF, including recently approved biosimilar products, in cancer patients.

Methods: Cancer patients newly initiating rG-CSF treatment between 7/1/2015 and 11/30/2016 were identified in the MarketScan Database. The first administration of filgrastim (FIL), tbo-filgrastim (TBO), or filgrastim-sdnz (SNDZ) served as the index date. Patients were continuously enrolled for >60 days prior and >30 days following the index date. Patient characteristics were evaluated during the baseline period, and adverse events (AE) were examined during the 30-day follow-up; FIL was the reference group.

Results: A total of 5470 patients (FIL: N = 4155, TBO N = 771, SNDZ N = 544) qualified for the study. Over 4% of FIL use was among pediatric patients compared with $<1\%$ for SNDZ and TBO ($p < 0.01$); use among elderly patients was similar across the 3 drug groups. FIL

patients were more likely to be male (45%) compared with TBO (40%) and SNDZ (36%) patients ($p < 0.01$); they were also more likely to be diagnosed with leukemia and less likely to be diagnosed with breast, gastrointestinal, lymphoma, and respiratory cancers compared with TBO and SNDZ ($p < 0.01$). There were no significant differences across groups for the majority of AEs (pyrexia, rash, nausea, vomiting, headache, epistaxis, diarrhea, arthralgia, leukocytosis, spleen rupture, acute respiratory syndrome, and capillary leak syndrome). TBO patients were more likely than FIL patients to experience cough (5.4% vs 3.4%), dizziness (3.0% vs 1.3%), dyspnea (9.5% vs 7.2%), fatigue (10.2% vs 7.1%), and thrombocytopenia (15.6% vs 12.7%) over the follow-up period ($p < 0.05$). SNDZ patients evidenced significantly lower rates of arthralgia (0.9% vs 3.4%), anemia (18.6% vs 24.8%), fatigue (4.2% vs 7.1%), and thrombocytopenia (7.9% vs 12.7%), but increased rates of dizziness (3.1% vs 1.3%), compared with FIL patients ($p < 0.05$).

Conclusions: Differences were noted in baseline demographic and clinical characteristics of the populations receiving the rG-CSFs which may be due to the differences in labeled indications such as cancer type or age, reimbursement policies, or provider preferences. Overall, safety profiles were similar with only slight differences in AE rates potentially due to underlying differences baseline characteristics of the populations.

1031 | Abstract Withdrawn

1032 | Use of systemic immunomodulating medications in children with atopic dermatitis

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Background: Atopic dermatitis (AD) is a chronic inflammatory skin condition with a prevalence of 18 million adults (7.2%), and 9.6 million (13%) children under the age of 18 in the United States, 3.2 million of those suffer severe AD. With a multitude of options and guidelines on topical treatment escalation, very little is known about the off-label use and comparative safety of systemic immunomodulating medications for the treatment of severe AD.

Objectives: This study seeks to understand patterns of off-label use of systemic immunomodulating medication in patients with severe AD and to determine how safe the use of such medication is in routine care settings

Methods: We used longitudinal claims data from commercially insured patients in the United States between 2003 and 2016 to identify children aged 18 or younger with a diagnosis of AD associated with an outpatient or inpatient encounter. A 180-day enrollment period was required before the first diagnosis of AD. Among those diagnosed, we computed the risk of initiating immunomodulating medications during the following

6 months. All analyses were conducted using the Aetion Evidence Platform.

Results: Among 1.6 million children <18 years with a diagnosis of AD, most were infants (0-1 years: 17.6%), babies (1-2 years: 12.2%), and young children (2-4 years: 15.4). 5.1% were in age group 16-18 years. Among younger children 50% of patients were female, after the age of 14 about 60% were female. Before the diagnosis of AD, the use of calcineurin inhibitor and biologic DMARDs was almost null. During the 6 months following a diagnosis of AD, in patients 2-4 years old, 35 per 1000 used topical calcineurin inhibitors pimecrolimus and 21 per 1000 tacrolimus. The incidence of biologic DMARDs during 6 months was 0.1 per 1000 patients and non-biologic DMARDs was 0.5 per 1000. In patients 14-16 years old, 32 per 1000 used calcineurin inhibitors pimecrolimus and 23 per 1000 tacrolimus. The incidence of biologic DMARDs during 6 months was 2.4 per 1000 patients and non-biologic DMARDs was 2.0 per 1000. In patients 16-18 the incidence of biologic DMARDs during 6 months was 2.6 per 1000 patients and non-biologic DMARDs was 2.2 per 1000.

Conclusions: In a commercially insured group of children <18 yo diagnosed with atopic dermatitis, the use of topical calcineurin inhibitors was meaningful. The use of systemic biologic immunomodulating agents was infrequent but steadily increasing with age.

1033 | Persistence on tofacitinib therapy in rheumatoid arthritis

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Background: The janus kinase inhibitor, tofacitinib, provides a convenient, orally administered alternative to existing biological disease-modifying antirheumatic drugs (bDMARDs) used for rheumatoid arthritis. Treatment persistence in real-world new users has not been established.

Objectives: To compare persistence, a proxy measure for effectiveness, between tofacitinib and bDMARDs in rheumatoid arthritis.

Methods: New-user cohort study (n = 19 734) from the Truven Health Marketscan research datasets. Users of tofacitinib, adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, and tocilizumab were identified from pharmacy and medical claims between November 2012 and December 2015. Patients with rheumatoid arthritis were followed until December 2016 or gaps in medical plan enrollment. Persistence was measured until discontinuation, based on a medication-free gap of 90 days, or switching. Comparisons were conducted using Kaplan-Meier methods and Cox regression. We included prior compliance to chronic medication in the regression model to reduce channeling bias from patient compliance. In sensitivity analyses, medication-free gaps of 60 and 180 days were also assessed. Persistence was assessed in switchers (n = 11 577) who were exposed to a different medication in the previous year.

Results: The mean age of new users was 53 years (SD 12), 80% were females. Median persistence of new users of tofacitinib (n = 1034) was 294 days (95% confidence interval [CI] 264-329). Tofacitinib new users had shorter persistence compared with most bDMARDs, with overall hazard ratio of 1.18 (1.08-1.29). The highest frequency of patients with good compliance (50.3%) was among tofacitinib users; hence, channeling based on compliance was excluded. Hazard ratios were affected by the length of medication-free gap: Longer gap was associated with decrease in magnitude. Switchers to tofacitinib had longer persistence (hazard ratio 0.89, 95% CI 0.82-0.96) compared with switchers to bDMARDs.

Conclusions: In rheumatoid arthritis, tofacitinib was associated with shorter persistence in new users, and longer persistence in switchers, compared with use of bDMARDs. We found channeling due to compliance as a possible cause of this effect to be unlikely. Persistence is a proxy to effectiveness; hence, tofacitinib may not be a good alternative to bDMARDs in new users but may be preferable in switchers. Further research is warranted to understand patterns of persistence for tofacitinib in spite of its ease of administration.

1034 | Incidence rate of serious infections in patients receiving biologic anti-inflammatory agents for treatment of rheumatologic, dermatologic, and gastrointestinal conditions

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Background: Select biologic agents have been associated with increased risk of developing serious infection among patients with rheumatoid arthritis (RA) and other inflammatory conditions.

Objectives: The study aims to (1) conduct a descriptive analysis of patients with autoimmune diseases treated with biologics and (2) inform recommended approaches to comparative safety and effectiveness of biologics based on availability of key data elements in the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) Distributed Research Network (DRN).

Methods: This retrospective cohort study was conducted among patients enrolled in an insurance plan that contributed data to the BBCIC DRN between 1 Jan 2006 to 30 Sep 2015. Eligible patients were required to (1) have newly initiated a disease modifying non-biologic, a TNF biologic, or a non-TNF biologic agent; (2) have a prior diagnosis of RA, psoriasis, or inflammatory bowel diseases (IBD), (3) be at least 18 years old, and (4) have at least 365 days of continuous medical and pharmacy coverage (baseline) prior to treatment initiation (index date). Follow-up started on index date and ended at the earliest of the occurrence of the outcome, treatment discontinuation or

switching, death, disenrollment, or end of study period. Serious infection was defined as an emergency room visit or hospitalization with a diagnosis code for infection. Descriptive statistics of patient characteristics ascertained during baseline and unadjusted incidence rates of serious infection during follow-up were calculated, stratified by condition and treatment.

Results: The study identified 111 611 eligible patients with RA (75% female), 61 959 with psoriasis (52% female), and 30 628 with IBD (51% female). Anti-TNF biologics were the most commonly initiated medications, accounting for 98% of IBD, 89% of psoriasis, and 79% of RA patients. The overall estimated incidence rate of serious infection was 9.8 (95% CI 9.5-1.0) cases per 100 person years in RA, 7.1 (6.8-7.5) in psoriasis, and 14.2 (13.6-14.8) in IBD patients. When stratified by treatment type, serious infection rates were lowest for patients initiating TNF agents for both RA and psoriasis and for non-biologic agents for IBD. When stratified by year, there was no appreciable change over time.

Conclusions: This large-scale descriptive analysis provides initial evidence that the BBCIC DRN can produce event rates similar to those from earlier pivotal studies.

1035 | The longitudinal population-based PHARMO-IBD cohort: Insights Into treatment effects and disease course

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Background: The use of biological agents in the treatment of inflammatory bowel disease (IBD) has resulted in a growing interest in their long-term effectiveness, adverse effects, and cost burden.

Objectives: To create a dynamic prospective cohort of patients suffering from IBD with detailed information on evolving healthcare consumption, including the use of biological agents.

Methods: Patients with a diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) as recorded by a general practitioner (GP) between 2007 and 2016 were selected from the GP Database of the PHARMO Database Network, resulting in the PHARMO-IBD cohort. All these patients have information available on diagnoses and symptoms, laboratory test results, referrals to specialists and drug prescriptions as recorded by their GP. For a subset of patients, information from the In-patient Pharmacy Database of the PHARMO Database Network is available, which includes drug dispensings from the hospital pharmacy, given during a hospitalization or day care admission. In this subset, treatment with infliximab after CD or UC diagnosis was determined.

Results: A total of 9404 patients diagnosed with CD or UC were included in the PHARMO-IBD cohort, of whom 45% was diagnosed with CD and 55% with UC. The majority of patients with CD was female (61%) and mean ($\pm$ SD) age was 41 ($\pm$ 18) years. Among patients with UC, 51% was female and mean ($\pm$ SD) age was 48 ($\pm$ 19) years. In

the subset of patients, 26% of CD patients were treated with infliximab after diagnosis, of whom 75% with the originator infliximab. A quarter of infliximab users switched to a biosimilar. The percentage of patients with UC receiving infliximab was lower (6%).

Conclusions: The PHARMO-IBD cohort, which will be updated regularly, enables studying patient-centric trends and epidemiological assessments of drug effectiveness and safety in routine daily practice. In addition, as PHARMO is expanding the In-patient Pharmacy Database in order to increase the number of patients with information available on biological agents, patient level prediction modelling will be possible.

1036 | Evaluation of health direct costs associated with the use of biosimilar and originator erythropoiesis stimulating agents (ESAs): An Italian, multi-regional, population-based study

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Background: Chronic kidney disease (CKD) is a growing public health issue worldwide. The highest direct costs were observed for dialysis patient (yearly costs for peritoneal dialysis: €30,000; haemodialysis: €44,000). Erythropoiesis stimulating agents (ESAs) have a relevant economic burden in CKD and biosimilars guarantee 25-30% saving of ESA purchase costs in CKD patients.

Objectives: To explore the direct costs of CKD patients treated with ESAs in five large Italian areas.

Methods: A multicentre, cohort study was conducted in the context of the "Assessment of Short and Long Term Risk-Benefit Profile of Biologics through Healthcare Database Network in Italy" project, funded by the Italian Ministry of Health. It was conducted using healthcare databases of Tuscany, Umbria Regions and Caserta, Treviso, Palermo Local Health Units (LHUs), covering a total population of around 8 million persons during the years 2009-2014. We identified incident CKD ESA users (washout >1year) treated for at least 1 year. Yearly mean direct costs (ie, ESA drugs, concomitant drugs, hospitalizations, diagnostic tests, and dialysis) per patient were stratified by ESA type and CKD stage. Assuming a 50% of biosimilar uptake, the yearly mean cost-saving was calculated. We identified inappropriate ESA users considering the haemoglobin value (measured within the month prior

to the ESA dispensing) out of the recommended ranges and we estimated yearly costs per patient related to ESA inappropriate dispensing

Results: During the study years, 7810 incident CKD ESA users were identified. Of these, 2921 users reported information on CKD stage (I-III stage: 40%; IV-V stage: 27%; dialysis: 33%). The ESA-related yearly mean cost represented 17% (€1,551) of total yearly costs in I-III stage, decreasing to 13% (€1,493) in IV-V stage and to 6% (€2,045) in dialysis. Assuming a 50% of biosimilar uptake in CKD, the annual mean cost-savings would amount from €65,730 (I-III CKD stage) to €118,769 (dialysis). However, 9% of first ESA dispensing was inappropriate (yearly mean ESA cost: €1,341) increasing to 41% of all the following dispensing concerning ESA maintenance treatment (yearly mean ESA cost: € 1,810) during the first year of treatment

Conclusions: The management of CKD patients requires high costs. Appropriate ESA use and of other therapeutic interventions to slow down the renal impairment are essential for minimizing clinical and economic burden of CKD population

1037 | Exposure- and dose-response analyses in dose selection and labeling of FDA-approved biologics

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Background: Biological drug products represent an increasingly important part of the pharmaceutical market. Despite this, little is known regarding how sponsors determine the dose to be studied in registrational trials or to be proposed in labeling for biologics.

Objectives: To examine how exposure-response and dose-response analyses were used to determine dosing in pivotal trials or the labeling for FDA-approved biologics.

Methods: Retrospective review of publicly available biologics license applications (BLAs) approved by the FDA's Center for Drug Evaluation and Research (CDER) between 2006 and 2016. Products of interest included monoclonal antibodies, proteins for therapeutic use, non-vaccine and non-allergenic immunomodulators, growth factors and cytokines. We excluded products regulated by the FDA's Center for Biologics Evaluation and Research (CBER) such as cellular products, gene therapy products, vaccines, allergenic extracts, and plasma-derived products. We extracted relevant characteristics of each biologic from its review package by FDA. We used descriptive statistics to characterize the rationale for the selected dose(s) in registration trials, with a particular focus on the role of exposure-response/dose-response analyses. We also examined how exposure-response/dose-response analyses were used to support the labeling dose and the basis for postmarketing requirements or commitments related to dose optimization.

Results: A total of 79 BLAs were examined, of which 59 contained information about the rationale for dose selection in registrational trials. Dose selection in registrational trials was more often attributed to clinical efficacy (73% of applications) than clinical safety (42%) or maximum tolerated dose (12%). The dosing of products whose dose was apparently selected based on clinical efficacy was often (72%) determined by the dose-response relationship, more so than exposure-response or PK/PD (14%). In support of doses that were described in labeling, exposure-response analyses for efficacy were performed more commonly (53%) than dose-response analyses (21%). This trend was apparent after 2012.

Conclusions: This is the first study to summarize the justification of dose selection and the labeled dose of biologics approved by the FDA. Dose-response analyses have been often used as the rationale for dose selection of registrational studies, while exposure-response analyses are becoming more prevalent in support of the dosing guidelines in labeling.

1038 | Characteristics of golimumab initiators in routine care

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Background: Golimumab (Simponi®) is a monoclonal antibody against tumor necrosis factor alpha (TNF) that is efficacious in treating arthritic disease (rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis) among other diseases.

Objectives: We sought to describe users of golimumab and contrast them with users of other arthritis therapies in settings of routine care in the United States.

Methods: This study was sourced from the Optum research database, reflecting reimbursement claims for health care provided to patients in health plans affiliated with Optum. A prospective cohort study of golimumab initiators along with initiators of other anti-TNF medications and non-biologic therapies was conducted. Patients initiating one of the study medications with a baseline diagnosis of arthritic disease were accrued between April 2009 and May 2015. Baseline characteristics of the cohorts are described.

Results: A total of 1588 golimumab initiators with one of the rheumatic conditions listed above were identified along with 357 initiators without a diagnosis of any of the three rheumatic conditions. Cohorts of 14 648 other anti-TNF biologic initiators and 52 679 non-biologic initiators were also identified. The average age of golimumab initiators (48.1 years) and other anti-TNF initiators (46.5 years) was similar on cohort entry and contrasts somewhat with non-biologic initiators (51.6 years). In the 6 months prior to initiation, 43.5% of golimumab initiators were previously treated with an anti-TNF drug compared with 17.5% who received such treatment among the other anti-TNF initiator cohort and 30.1% of the non-biologic cohort. Three or more rheumatologist visits were present among 79.0% of the golimumab initiators compared with

64.9% of the other anti-TNF initiators and 80.5% of the non-biologic initiators. There were 91.7% of initiators in the golimumab cohort who had 2 or more different prior treatments for rheumatoid arthritis versus 80.2% of the other anti-TNF cohort, and 85.6% of the non-biologic cohort.

Conclusions: Golimumab initiators have more extensive health care utilization than other anti-TNF initiators, indicating that golimumab is used for treatment of patients with more advanced or refractory disease. Comparative effectiveness or safety studies conducted in real-world data settings would need to account for such differential prescribing in order to address the potential issue of confounding by indication for whatever outcomes are being studied.

1039 | Characteristics of ustekinumab initiators in routine care

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Background: Ustekinumab (Stelara®) is a monoclonal antibody against interleukin-12/23 that is efficacious in treating psoriasis and other diseases. First available in the United States in 2009, ustekinumab is labeled for the treatment of adult patients with moderate-to-severe psoriasis who are candidates for phototherapy or systemic therapy.

Objectives: We sought to describe users of ustekinumab and compare them with users of other psoriasis therapies in the setting of routine care in the United States.

Methods: This study was sourced from the Optum research database, reflecting reimbursement claims for healthcare provided to patients in health plans affiliated with Optum. A prospective cohort study of ustekinumab initiators along with initiators of tumor necrosis factor (TNF) inhibitors and non-biologic therapies was conducted. Patients initiating one of the study medications with a baseline diagnosis of psoriasis were accrued between September 2009 and December 2014. Baseline characteristics of the cohorts are described.

Results: A total of 2040 ustekinumab initiators were identified along with 7589 anti-TNF biologic initiators and 11 492 non-biologic initiators. The average age of the ustekinumab initiators (44.7 years) and the anti-TNF initiators (44.4 years) was almost the same at treatment initiation and contrasts somewhat with the age of non-biologic initiators (46.3 years). In the 6 months prior to starting treatment, 33.9% of ustekinumab initiators were treated with an anti-TNF drug compared with 15.4% of patients in the anti-TNF initiator cohort and 8.6% of patients in the non-biologic cohort. Moreover, 21% had 3 or more dermatologist visits compared with 13.9% of anti-TNF initiator initiators and 14.5% of the non-biologic initiators. Among ustekinumab initiators, 40.6% had 2 or more different prior treatments for psoriasis versus 24.7% of anti-TNF initiators, and 12.5% of non-biologic initiators.

Conclusions: Ustekinumab initiators have more extensive healthcare utilization than anti-TNF initiators, indicating that ustekinumab is more often used for treatment of patients with advanced or refractory disease. Comparative effectiveness or safety studies conducted in

real-world data settings would need to account for such differential prescribing in order to address potential confounding by indication for outcomes being studied.

1040 | Use, safety, and effectiveness of targeted therapies in colorectal cancer according to age and frailty

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Background: Metastatic colorectal cancer (mCRC) is increasingly treated with targeted therapies whose real-life evaluation is insufficient, especially in elderly and frail patients.

Objectives: We aimed to describe use, safety, and effectiveness of targeted therapies in first-line mCRC treatment according to age and frailty.

Methods: Two cohorts of patients initiating bevacizumab or cetuximab (KRAS wild-type) in first-line mCRC treatment were pooled. An ad hoc frailty criterion was built using factors associated with death or grade 3/4 adverse events in Cox multivariate analysis. Use, safety, 2-year overall, and progression-free survival (OS and PFS) were compared between younger and elderly (<75 vs ≥75 years) and not frail and frail patients, according to the ad hoc frailty criterion.

Results: Eight hundred patients (51.4% bevacizumab) were included: 62.3% male, 15.8% ≥75 years, 14.8% Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) ≥2. At 2 years, 399 patients (49.9%) had at least one grade 3/4 adverse event and 186 (23.3%) had died. In multivariate analysis, ECOG-PS ≥1, >1 metastatic site and abnormal transaminases were associated with death or grade 3/4 adverse event and included in the frailty criterion. Frail patients (12.5%) were not older than not frail patients (median age 64 vs 65 years, $p = 0.64$). Cardiac and renal disorders were more frequent in elderly patients (60.3% vs 42.3%, $p < 10^{-3}$ and 10.3% vs 4.7%, $p = 10^{-3}$ respectively); yet, not in frail patients. Denutrition was more frequent in elderly and frail patients (13.5% vs 6.7%, $p = 0.007$ and 13.0% vs 7.0%, $p = 0.04$, respectively). Elderly patients were more often treated with 5-fluorouracil alone (6.4% vs 0.5%, $p < 10^{-3}$), without difference between frailty groups. Discontinuation of first-line therapy was more frequent in frail than in not frail patients (94.0% vs 82.7%, $p = 0.005$), without difference between age groups. Grade 3/4 adverse events were not different across age and frailty groups. Median OS (months [95% CI]) was similar between elderly and

younger patients (22.8 [18.2;-] vs 24.0 [23.2;-], $p = 0.37$) but shorter in frail patients than in not frail patients (14.9 [11.6; 20.6] vs not reached, $p < 10^{-3}$). The same was observed for PFS.

Conclusions: Unlike frailty, age have an influence on treatment choice but not on survival. This large cohort confirms that elderly mCRC patients could benefit from targeted therapies as younger, but their use remains questionable in frail patients independently of age.

1041 | Real-life treatment and survival in metastatic colorectal cancer elderly patients: A population-based study

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Background: Metastatic colorectal cancer (mCRC) is increasingly treated by targeted therapies but little is known about real-life mCRC treatment in elderly patients.

Objectives: This study aimed to describe the current real-life first-line treatment modalities in elderly mCRC patients, identify factors associated with each modality, and describe survival according to treatment modalities.

Methods: A cohort of mCRC patients aged ≥ 65 years at diagnosis (baseline) was identified using a French national health care insurance system claims database (*Echantillon Généraliste de Bénéficiaires*, EGB), between 2009 and 2013. Treatment modalities were (i) treatment with ≥ 1 anticancer medication vs best supportive care (BSC) and (ii) among treated patients, treatment with targeted therapy vs conventional chemotherapy alone. Patients were followed until death or end of 2016. Multivariate logistic regression modelling was used to identify factors associated with (i) treatment by ≥ 1 anticancer medication and (ii) treatment by targeted therapy. 3-year overall survival (OS) was estimated in all treatment groups using the Kaplan-Meier method adjusted on factors previously identified by logistic regression (corrected prognostic group method).

Results: 503 patients were included: median age 78 years, 54% male. Of these, 271 (54%) were treated with ≥ 1 anticancer medication. Among treated patients, 131 (48%) received targeted therapy. In multivariate analysis, age ≥ 75 years, renal failure, denutrition, >3 concomitant non-anticancer medications, antidiabetic agents, and medical home visits were associated with a lower likelihood of treatment with anticancer medications. Among treated patients, age ≥ 75 years, previous history of cancer, lymph node metastases, and single metastatic site were associated with a lower likelihood of treatment with targeted therapy.

After adjustment, the 3-year OS probability was significantly higher in treated patients in comparison with BSC patients but there was no difference among patients treated by targeted therapy in comparison to those treated with conventional chemotherapy alone.

Conclusions: Older age remains a central criterion to decide the prescribing and choice of anticancer medications in elderly patients with mCRC while their effectiveness is confirmed in this population. Real benefit of targeted therapies vs conventional chemotherapy alone needs to be confirmed in this population.

1042 | Use of biological anti-inflammatory drugs in dermatology, gastroenterology, and rheumatology in the Capital Region of Denmark

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Background: During the last 20 years, several drugs with a new mechanism of action have been introduced in the treatment of the chronic inflammatory diseases: rheumatoid arthritis, inflammatory bowel disease, and psoriasis. There is however limited knowledge on their prescription patterns and changes in connection with introduction of new drugs.

Objectives: The aim was to describe user characteristics and utilization patterns of biological anti-inflammatory drugs for the three most common chronic inflammatory diseases.

Methods: A retrospective cohort study was conducted using the in-hospital drug-use database for the Capital Region of Denmark, which includes all drug prescriptions and drug administrations. All biological anti-inflammatory drugs in the region are dispensed in out-patient clinics and are covered in the database. The study period was 1 January 2012 until 15 May 2016. Drugs included in Danish treatment guidelines during the period were included: abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, secukinumab, tocilizumab, ustekinumab, and vedolizumab. R version 3.3.3 was used for descriptive statistics including chi-squared test with Yates' continuity correction. The Danish Patient Safety Authority and the Danish Data Protection Agency have approved the study (3-3013-1884/1/and BFH-2016-058-04906).

Results: In total, 7463 patients were prescribed at least one of the drugs. Of these, 4190 (56.1%) were women. Median age at time of first prescription was 48.0 years (interquartile range 31.3-62.6 years), with no difference between sexes or change over the study period. During the study period, 862 (20.6%) women and 423 (12.9%) men, p value < 0.001 , were prescribed more than one of the study drugs. Infliximab was the most prescribed anti-inflammatory drug, given to 3087 (41.3%) patients. Both in the first and second half of the study

period, infliximab was the most prescribed anti-inflammatory drug to new patients, given to, respectively, 25.9% and 29.4% of the patients.

Conclusions: We found that there was no age-difference at the time of first prescription of biological anti-inflammatory drugs between sexes. Women were more likely to be treated with more than one biological anti-inflammatory drug. Infliximab was the most prescribed anti-inflammatory drug. Furthermore, infliximab was in both halves of the study period the main anti-inflammatory drug prescribed to new patients.

1043 | Clinical development of biologics approved by the US Food and Drug Administration, 2003-2016

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Background: Biological therapies are increasingly common in the United States, and their development programs often deviate significantly from the classic paradigm. Little is known regarding trends in regulatory strategy, resources, and outcomes of these products.

Objectives: To characterize the development programs and factors associated with first cycle approval for biologics approved by the US Food and Drug Administration's Center for Drug Evaluation and Research (FDA CDER).

Methods: We conducted a retrospective review of publicly available approval packages including clinical pharmacology/biopharmaceutics reviews, medical reviews, summary reviews, and approval letters for biologics approved by FDA CDER between 2003 and 2016. Outcomes and measures of interest were regulatory strategy (eg, use of expedited programs), resources required (eg, numbers of study patients and trials in efficacy program), and review outcomes (eg, first cycle approvals). Two reviewers extracted information about each drug and disagreements were independently adjudicated. Analysis focused on the prevalence and determinants of first cycle approval, since this is the single most important determination of regulatory success.

Results: We assessed 81 development programs for 75 unique therapies. Most programs (67%) made use of at least one Expedited Program designation and about half (49%) were designated as orphan products. The clinical pharmacology programs were highly variable and one in four (25%) did not include an ascending dose study, where the tolerability of the therapeutic is typically determined before pivotal trials. Most BLAs were approved (62 [77%]) on the first review cycle, a period that by law is 6 months for applications with priority designation and 12 months for standard reviews. Over time, an increasing number of programs have been approved during the first review cycle or based on zero or one pivotal trial.

Conclusions: Current biologics programs reflect a contraction of the classic phases of drug development. Considerable regulatory flexibility, with fewer clinical pharmacology studies, registrational trials, and

patients, coincides with a growing proportion of biologics approved on an annual basis. The safety and effectiveness of these newly approved therapeutics should be closely monitored after approval to determine if this paradigm is adequate.

1044 | Treatment patterns and sequencing in patients with inflammatory bowel disease

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Background: Little is known about real-world treatment sequencing of biologic therapy in patients with ulcerative colitis (UC) or Crohn's disease (CD).

Objectives: To characterise treatment patterns and sequences for patients with UC or CD newly initiating biologics.

Methods: This was a retrospective cohort study using Truven Health Analytics® MarketScan® health insurance databases (GSK funded). Claims data were analysed for patients (≥ 18 years old) with UC (ICD-9 556.xxx) or CD (ICD-9 555.xxx) who initiated biologics 1 January 2009-31 December 2013. Treatment sequences were described during a 2-year follow-up period. Any period greater than the allowable gap (60-120 days, depending on biologic type) was defined as discontinuation.

Results: In the UC (n = 2403) and CD (n = 4677) cohorts, 71% and 79%, respectively, initiated biologics as monotherapy; the most common treatments were infliximab or adalimumab. Approximately one-third of patients with UC and CD continued with their first-line biologic over the 2-year follow-up. Second-line therapy was required in 69% of patients with UC and 70% of patients with CD; these patients most commonly received a different biologic monotherapy (25% for UC, 39% for CD). In patients who only received one line of therapy, the median duration of therapy was 427 days for patients with UC and 444 days for patients with CD. In both cohorts, the median duration was longest for the first-line therapy and decreased with subsequent lines of therapy. A proportion of patients with UC (22%) and CD (33%) were consecutively treated with biologics, with some patients receiving up to 5 lines of therapy during the 2-year follow-up. In the UC cohort, the most common first-line biologic was infliximab (70%). Of patients starting on infliximab, the largest proportion (44%) received no additional lines of therapy and a minority (16%) received a biologic as second-line therapy. In the CD cohort, the highest proportion of patients (51%) received adalimumab as first-line therapy. No additional lines of therapy were received in 44% of patients, and a small percentage of patients (25%) received a biologic as second-line therapy.

Conclusions: While current biologic treatments seem effective in a proportion of patients with UC or CD, others require multiple lines of therapy, potentially indicating suboptimal efficacy, adverse reactions or development of treatment resistance. Future analyses on how biologics with novel modes of action impact biologic cycling in treatment-refractory patients may provide useful insights.

1045 | Incidence and treatment characteristics of urinary tract infections—On-line survey

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Background: Urinary tract infection (UTI) is the third most common infection encountered in ambulatory care. UTI infections have mostly bacterial etiology that requires antibiotic treatment. Beside antibacterial prescription, use of non-steroidal anti-inflammatory drugs (NSAIDs) and antispasmodics also have significant role in the therapy of UTI.

Objectives: The aim of the present study was to assess the frequency and the ambulatory care management of UTI in Hungarian adults. The knowledge of patients on UTI prophylaxis was also evaluated.

Methods: An online questionnaire was developed and pilot-tested by the multidisciplinary team. The questionnaire consisted of six domains: (1) demography, (2) presence of risk factor and UTI in the previous 1 year, (3) symptoms, (4-5) diagnostic test performed and therapy prescribed by GP or urologist, and (6) knowledge on UTI prophylaxis. The questionnaire was distributed by social networking sites. Odds ratio was calculated for UTI risk factors.

Results: The questionnaire (QA) was offered to 38 community groups, of which 8 started distribution of the QA. A total of 376 questionnaires were filled in. Mostly women (89%) completed the questionnaire, and responses were received from all Hungarian regions. During the preceding 1 year, 46% of respondents experienced UTI symptoms. The most relevant identified risk factor was childhood UTI, with an odds ratio of 2.42 (CI 95%: 1.46-3.98). Only every second patient visited the GP, while 17 % of patients seek advice from urologist. The GP prescribed antibiotics for 85% of patient, while urologist ordered antibiotic therapy for 82.8 % of patients with UTI symptoms. Analgesics, NSAIDs were recommended only in 12% of cases by GPs, while by 24.1 % by urologists. Antispasmodics were recommended for 15 patients with UTI symptoms. In total, 74 patients (19.7 %) gave correct answers to all basic statements on UTI prophylaxis.

Conclusions: The prevalence of UTI was high. Adjunctive therapy for UTI (antispasmodics, analgesics) was underused. The knowledge of respondents on UTI prophylaxis was incomplete. All these suggest that management of UTI should be improved in Hungary.

1046 | Development and validation of a prediction model for poor outcome of tuberculosis treatment: A nationwide, register-based retrospective cohort study from the Netherlands

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Background: Though multi-drug resistant tuberculosis (MDR-TB) is still relatively controlled in the Netherlands, more efficiency is needed to target those patients most at risk.

Objectives: The main objective of the study is to develop and validate a multivariable prediction rule for poor outcome among adult patients with a first diagnosis made in the Netherlands of drug-susceptible tuberculosis (DS-TB).

Methods: A retrospective cohort study was performed using data from the National Tuberculosis Registry (NTR) covering 1993-2015. Adult DS-TB confirmed as the first episode of TB and infected by *M. tuberculosis* pathogen were eligible for inclusion. Poor outcome was defined as death, defaulted, or failed treatment during follow-up. Potential predictors were defined based on a previous systematic review from several perspectives, ie, patient characteristics, diagnostic characteristics such as signs and symptoms, comorbidities, setting, TB disease, and treatment.

Results: Preliminary analysis, showed that in the 2005-2015 derivation cohort, an age over 85 years (OR: 3.46; 95% CI: 1.71-7.00), meningeal and central nervous system TB (5.19; 2.49-10.82), miliary TB (2.61; 1.32-5.18), drug addiction (2.16; 1.06-4.38), being prisoner (3.68; 1.86-7.28), malignancy (2.23; 1.14-4.39), hospitalization at entry (1.46; 1.063-2.01) were potential predictors for poor outcome among 4840 patients. Reliability of the final regression model was good (Hosmer-Lemeshow goodness-of-fit test *p* value 0.98), and the discriminative value was moderate (area under the receiver-operating curve 0.67; 95% CI 0.63-0.71).

Conclusions: Our preliminary result demonstrated that a potential clinical prediction model can be developed for poor outcome of TB. Internal and external validations will be a further step to achieve a robust prediction model.

1047 | Estimating the prevalence of HIV among liver transplant candidates in the United States

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Background: Despite the high burden of liver disease among HIV-infected (HIV+) individuals, the prevalence of HIV among candidates on the US liver transplant waitlist is unknown.

Objectives: To estimate the prevalence of HIV among US liver transplant candidates and to describe the temporal, geographic, and demographic characteristics of HIV+ candidates on the liver transplant waitlist.

Methods: Our retrospective cohort study (2001-2012) linked data from a national transplant registry (the Scientific Registry of Transplant Recipients [SRTR]) to pharmacy claims from a national health care technology and analytics company (QuintilesIMS). Patients were linked by the SRTR using social security number then released with encrypted identifiers. We identified HIV+ candidates by fills of prescription medications exclusive to HIV treatment. After exploring potential mechanism(s) of missingness, we estimated the prevalence of HIV on the US liver transplant waitlist using multiple imputation by chained equations (MICE). We then compared the characteristics of HIV+ (vs HIV-) candidates using rank-sum and chi-squared tests and examined the temporal and geographic distributions of HIV+ candidates.

Results: In the study period, the linkage captured 87.1% ($n = 76\,783$) of the US liver transplant waitlist and identified 606 HIV+ candidates. By MICE, the HIV prevalence on the liver transplant waitlist was 0.88% (95% CI: 0.81%-0.94%). HIV+ candidates were more often young (median [IQR]: 50 [45-55] vs 54 [49-60]), black (19.1 vs 8.1%), and male (82.3 vs 64.6%), with public insurance (47.7 vs 37.1%), and liver disease due to hepatitis C virus (51.5 vs. 31.4%) and were less likely to be obese (18.5 vs 40.0%) than HIV- candidates ($p < 0.001$ for all). Based on model for end stage liver disease scores, there was no difference in disease severity by HIV-status at the time of waitlist entry (median [IQR]: 15 [12-22] vs 16 [12-22]; $p = 0.2$). The number of HIV+ candidates listed each year increased over time (from 29 in 2002 to 70 in 2011), and the prevalence of HIV ranged from 0%-2.5% across organ donation service areas.

Conclusions: We used a novel data linkage to identify a unique and previously unstudied population of HIV+ liver transplant candidates on the US waitlist. We found that the burden of HIV on the liver transplant waitlist was twice as high as the prevalence of HIV in the US population. Identifying these candidates is the first, critical step toward understanding the impact of HIV on survival and access to liver transplantation.

1048 | Developing and validating the Personal Risk of Oncogenic Human Papillomavirus (PRO-HPV) infection score in US Women

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Background: Determining risk scores for genital high-risk human papillomavirus infection in women will allow the development of more efficient cervical cancer screening strategies.

Objectives: To develop and validate point scores to predict the likelihood of any genital high-risk human papillomavirus infection in women.

Methods: We used data from the 2005-2014 US National Health and Nutrition Examination Survey (7337 women aged 25-59 years; 6300

women aged 30-59 years). Predictors were reproductive health practices, risk behaviors, and demographic variables. The outcome was a positive result for any of the 21 genital high-risk human papillomavirus genotypes. The 2005-2012 cohorts were used as training and testing sets to develop scores that best classified women into three risk groups: low risk (<20%), average risk (20-30%), and high risk (>30%). We selected final predictors based on the Akaike information criterion. The 2013-2014 cohort was used to validate the final scores.

Results: From the training and testing sets, two point scores (six self-reported variables for each score) were created to predict any high-risk human papillomavirus risks for the two age groups. In the validation set, the observed high-risk human papillomavirus prevalence in each risk group fit well into the predicted ranges. The scores had fair discrimination (c-statistics: 0.67 to 0.68) and good calibration between the predicted and observed rates of high-risk human papillomavirus infection.

Conclusions: The Personal Risk of Oncogenic Human Papillomavirus (PRO-HPV25 and PRO-HPV30 for women aged 25-59 and aged 30-59 years) scores could help to stratify the risk of genital high-risk human papillomavirus infection, which could be used to personalize cervical cancer screening recommendations.

1049 | The economic burden of human immunodeficiency virus in the United States

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Background: HIV prevalence in the United States is still high despite the effort to reduce incidence and control transmission. According to the CDC, in 2015, an estimated 1.1 million people were diagnosed with HIV and about 162 500 were undiagnosed. Although the annual incidence rate for HIV declined by 10%, the estimated number of new cases are still high—37 600. With these high incidence and prevalence rate, the associated economic burden is expected to be worrisome.

Objectives: We aim to explore the economic burden of HIV management in the United States.

Methods: This study utilized a pooled cross-sectional study design using a nationally representative data—2006, 2007, 2008, 2009, 2010, 2011, and 2012 Medicare Current Beneficiary Survey (MCBS) data. This study analyzed economic burden of HIV management using generalized linear model.

Results: A weighted population of 103 860 000 eligible participants were identified of which 0.17% (wt. = 178 010) were diagnosed of HIV. Majority of the participants are aged between 65 and 74 (wt. = 63 281 685) and 77.51% (wt. n = 80 499 767) are non-Hispanic whites. Result shows that demographic features of participants who have HIV and those who do not, varies significantly. Mean annual cost of HIV management is 22 690 per patient.

After adjusting for other variables in the model, we found that participants with HIV pays 10 287.89 dollars more on medical care compared with participants who do not. Prescription (1.03 [95% CI: 5555.292, 15020.51]). We plan to further explore the economic burden of HIV on prescription cost, inpatient care, and outpatient care.

Conclusions: Our preliminary result shows that HIV infection constitute a significant economic burden in the United States.

1050 | Incidence of pediatric acute bacterial skin and skin structure infection (ABSSSI) from 2005 to 2015

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Background: Overall, rates of ABSSSI increased with the emergence of community-acquired staphylococcal skin infections. However, the incidence of pediatric ABSSSI is poorly understood.

Objectives: To estimate the annual age-specific incidence of ABSSSI in children less than 18.

Methods: All physician office, emergency department, and hospital encounters occurring between 2005-01-01 and 2015-12-31 with an ABSSSI diagnosis were identified in Truven, a US-based electronic insurance claims database. An ABSSSI diagnosis was defined as having an ICD-9 code for cellulitis, abscess, post-operative infection, carbuncle, post-trauma wound infection, erysipelas, or orbital cellulitis. ICD-9 codes were mapped to ICD-10 codes using the general equivalence mappings (GEMS) tool. The analysis was limited to first ABSSSI per year. The denominator included total number of children enrolled, with no minimum enrollment required. Unadjusted annual age-stratified incidence rates were summarized into 3 age groups (0-1, 2-11, and 12-17). Cases were classified as ambulatory or inpatient depending on where the index claim occurred.

Results: There were 2 144 959 ABSSSI episodes identified. The incidence per 1000 patients of ABSSSI increased from 2005 (15.2) through 2007 (19.9) and then remained relatively stable through 2015 (20.3). The initial analysis suggested decreasing overall incidence of ABSSSI for all age groups from 2014 to 2015 (from 19.2 to 15.2 per 1000 patients). However, after removal of patients post introduction of ICD-10 codes and application of a weighting factor, this observed decrease was corrected. The majority of ABSSSI cases were diagnosed in the ambulatory setting for all age groups (93-97%) and thus are similar to the overall incidence, with the highest incidence in the 12 or older group. The incidence was significantly lower in the inpatient setting, with the highest incidence in the less than 2 age group (1.31 per 1000 patients).

Conclusions: The overall incidence of ABSSSI remained relatively stable from 2007 to 2015. The majority of ABSSSI cases were diagnosed in the ambulatory setting, and the highest incidence in the inpatient setting was in the less than 2 age group. As part of this

study, complementary work is ongoing to describe in more detail the limitations of the GEMS mapping tool.

1051 | Incidence of herpes zoster among rheumatoid arthritis patients in Japan from 2013 to 2016: The results using JDM-PV web tool

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Background: Despite accumulating literature for rheumatoid arthritis (RA) area in Japan, epidemiological studies evaluated RA prevalence are quite sparse and evidence on incidence of herpes zoster among RA patients are still limited.

Objectives: The present study aimed to evaluate RA prevalence and incidence of herpes zoster among patients with RA using a large-scale claims database in Japan.

Methods: Insured patients aged 18 to 74 years from January 2013 to December 2016 were analyzed using a JDM-PV web tool that can access database through internet managed by Japan Medical Data Center (JMDC) Co Ltd, Japan. We described annual number of RA patients and examined its prevalence stratified by gender and age categories. Thereafter, we showed crude incidence rates of herpes zoster in the following four groups: the overall JMDC population; patients with any prescriptions of systemic corticosteroid, non-steroidal anti-inflammatory drugs (NSAIDs); and all anti-RA drugs including methotrexate (MTX); and biological disease-modifying anti-rheumatic drugs (bDMARDs); MTX prescribed patients or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs); bDMARDs prescribed patients. Patients who had a prescription even once for baseline periods (2013 to 2015) were included in spite of new drug users or not.

Results: We observed roughly 11 000 RA patients each year, and the ratio between men and women was 1 to 2.3. The estimated prevalence of rheumatoid arthritis was stable between 2013 and 2016 (0.55-0.58%), and those among women were around 2.8-fold higher than those among men in 2016 (men 0.31%, women 0.91%). RA prevalence also increased with age group (40-49, 70-74 aged group; 0.20, 2.36%). Incidence rates of herpes zoster defined by ICD-10 code + anti-herpes virus drugs were 0.66 per 100 person-years in the overall JMDC population and those among women were higher than those among men. Among RA patients, similar incidence rates (per 100 person-years) of herpes zoster were found for any anti-RA drugs (2.08), MTX (1.77), and bDMARDs (2.11).

Conclusions: Although careful consideration is required with its interpretation due to the limitation of JDM-PV web tool which can provide simple definitions by combination of ICD-10 and prescription codes, our findings suggest that incidence rates of herpes zoster among RA patients are more than twofold higher than those among the overall JMDC population. Further studies should examine the incidence rates of herpes zoster by detailed definitions.

1052 | Barriers and facilitators to initiating and completing direct-acting antiviral therapy for chronic hepatitis C infection

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Background: Approximately 3.9 million Americans are infected with chronic hepatitis C virus (HCV) infection, a major cause of cirrhosis, end-stage liver disease, and hepatocellular carcinoma. While new direct-acting antiviral (DAA) medications have high (>90%) rates of cure, fewer than 10% are prescribed this therapy in the United States. Patients' perceptions about the barriers and facilitators to initiating DAA treatment remain unknown.

Objectives: To explore perceptions of barriers and facilitators to DAA treatment among patients with chronic HCV and to ascertain whether there are differences by HIV status.

Methods: We conducted a qualitative observational study, utilizing two focus groups of 14 patients in care for chronic HCV infection (nine coinfecting with HIV) and open-ended, semi-structured interviews among 23 patients with HCV (15 coinfecting with HIV). Interviews were audio-recorded, de-identified, and entered into NVivo 11.0. We analyzed data using a modified grounded theory approach, combining inductively and deductively derived codes, to investigate domains related to facilitators and barriers to HCV care, including testing, treatment, and cure; physician-patient interactions; and interactions with non-health care individuals. We summarized our findings within domains and investigated patterns that emerged.

Results: HIV+ and HIV- individuals described barriers to care, including a lack of public discussion/education about HCV and fear associated with uncertainties of their long-term HCV-related health. Facilitators to care included high cure rate as a motivation to adhere to treatment and a belief in the value of treatment given the high costs of antiviral regimens. HCV monoinfected patients experienced barriers of insurer denial of DAA treatment. Persons with HIV/HCV described how the additional diagnosis of HCV complicated their experience with HIV, at diagnosis and during treatment. Facilitators to HCV treatment among HIV/HCV included more experience with medication routines and established process support, derived from their experiences with antiretroviral therapy for HIV.

Conclusions: Irrespective of HIV status, the lack of public education about HCV is a barrier to care. HCV monoinfected patients faced barriers to treatment due to insurer denial of antiviral therapy, while treatment among HIV/HCV patients was facilitated by support networks and established medical routines.

1053 | Associations between use of anti-infective medications and genital human papillomavirus infections in the US population

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Background: Anti-infective medications are commonly used, but knowledge about the association between their use and infections of genital human papillomavirus (HPV) is still limited.

Objectives: To investigate associations between anti-infective medications and genital HPV infections in the US population.

Methods: We conducted a cross-sectional study using the 2005-2014 National Health and Nutrition Examination Survey. The outcomes examined included any type or any high risk type of genital HPV infected, number of total genital HPV types infected, and number of total high risk genital HPV types infected. Key independent variables included any antibiotics, antiviral, or other anti-infective used regardless of duration last month, any antibiotics used for ≥ 3 , 7, or 14 days, and any antiviral used for ≥ 4 weeks, 12 weeks, or 1 year. Multivariable logistic regression and multivariable negative binomial regression were performed for binary and count outcomes, respectively. Covariates adjusted for included age, race, smoking, number of sexual partners in the past year, HPV vaccination status, history of sexual transmitted infections, and with or without including HIV status.

Results: A total of 10 508 participants were included in this analysis. There were no statistically significant associations between antibiotic used and genital HPV outcomes (all $p > 0.05$). Antivirals were significantly associated with an increased risk of genital HPV infection. The adjusted odds ratios of any antiviral used for ≥ 4 weeks with any HPV type and any high-risk HPV type were 3.44 (95% CI 1.57-7.56, $p = 0.003$) and 2.49 (95%CI 1.27-4.88, $p = 0.009$). There were no significant associations between antiviral used and number of total types or number of total high risk types (eg, relative risk ratio between any antiviral used for ≥ 4 weeks and number of total genital HPV types was 1.32 [95% CI 0.93-1.87, $p = 0.113$]). Other anti-infective medications were only significantly associated with any type of genital HPV (aOR = 1.72, 95% CI 1.00-2.94, $p = 0.049$).

Conclusions: There may be an association between antiviral use and genital HPV infection. Further research is needed to confirm this association.

1054 | Osteoporosis-related fracture events

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Background: Osteoporosis-related fractures represent a public health problem and unmet need. Even patients hospitalized for fracture remain subsequently untreated. Current data describing diagnosis and treatment are central to highlighting the treatment gap and helping health care providers, payers, and policymakers provide access to appropriate therapies.

Objectives: To examine baseline characterization of US patients with a fragility fracture.

Methods: The current study included commercial and Medicare Advantage health plan members who had evidence of a qualifying fragility fracture between 2007 and June 2017 (identification period).

Fractures were considered qualifying if they were either identified during an inpatient stay or were accompanied by a repair procedure code. Patients ≥ 50 years of age with evidence of a qualifying fracture and continuous enrollment with medical and pharmacy benefits for 12 months pre-index event (baseline) and at least 1 month after index (follow-up) were included. Patients with Paget's disease or malignancy (except for non-melanoma skin cancer) at baseline or within 30 days of follow-up were excluded. Patients were classified into four cohorts based on the observed diagnoses and/or treatment of osteoporosis at baseline. Diagnoses of osteoporosis could be in any position on the medical claim. *P* value was calculated using the Cochran-Armitage trend test.

Results: Of 1 841 263 patients with fractures in the identification period, 302 772 met the eligibility criteria. 67% ($n = 201\ 693$) were ≥ 65 and 72% ($n = 216\ 680$) were female. 71% ($n = 214\ 788$) were commercial enrollees. The most commonly observed fracture sites were spine ($n = 66\ 172$; 22%), radius or ulna ($n = 58\ 999$; 19%), and hip ($n = 41\ 512$; 14%). Of all patients with a qualifying fracture, approximately 80% ($n = 240\ 412$) were neither diagnosed nor treated for osteoporosis at baseline. 9% ($n = 27\ 992$) were diagnosed but not treated, 5% ($n = 14\ 045$) were treated but not diagnosed, and 7% ($n = 20\ 323$) were diagnosed and treated. The proportion of patients diagnosed with or treated for osteoporosis decreased steadily over time (25% in 2007, 18% in 2017, $p < 0.001$).

Conclusions: The current study findings confirm a consistent high level of under diagnosis and under treatment. Further documentation of cost of illness following an osteoporosis-related fracture including identification of high cost drivers who may benefit from earlier targeted therapies will be of value.

1055 | Determination of incidence of hepatitis B virus reactivation during immunosuppressive therapies for rheumatoid arthritis using a validated administrative data

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Background: Reactivation of hepatitis B virus (HBV) is a well-recognized complication in patients with previously-resolved HBV (prHBV) infection, defined as serum anti-HBs and/or anti-HBc antibody positivity despite a negative serum HBsAg status, who are undergoing immunosuppressive drugs (ISDs). However, the incidence of HBV reactivation due to ISDs for rheumatoid arthritis (RA) among patients with prHBV infection is still unclear.

Objectives: The purpose of this study was to use administrative data base to determine the incidence of HBV reactivation due to ISDs for RA in Japan. We also evaluated the positive predictive value (PPV) of

an algorithm to detect prHBV infection from administrative data through comparison with chart abstraction.

Methods: A retrospective cohort study was conducted. Data of adult patients who had been diagnosed with RA, underwent periodic HBV-DNA testing or received NAs (entecavir and/or tenofovir) between April 2011 and March 2015 were extracted from the Medical Information Analysis (MIA) databank managed by the National Hospital Organization Headquarters. We hypothesized that subjects who underwent periodic HBV-DNA testing while receiving ISDs therapies have prHBV infection. To identify patients who had prHBV infection and reactivation, physicians and a pharmacist conducted chart abstractions in three NHO hospitals. The PPV for identifying suspected prHBV infection was calculated, considering the chart abstraction as the reference standard. Finally, incidence rate of reactivation was determined.

Results: During the study period, 211 patients from three hospitals were extracted from the MIA data bank, and 175 patients were identified as having prHBV infection. The PPV was 83%. Among them, five patients had HBV reactivation. Incidence rate of HBV reactivation was 1.1/100 person-years.

Conclusions: The PPV for identifying suspected prHBV infection in RA patients receiving ISD was 83%. Administrative data-based incidence rate of HBV reactivation might be lower than actual rate, because of the result. Administrative data can be used to estimate a population-based incidence of disease if detection algorithm is improved.

1056 | Association of body mass index with osteoarthritis prevalence and prescription analgesic utilization in overweight or obese patients with osteoarthritis

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Background: Body mass index (BMI) is an important modifiable risk factor for the development and progression of osteoarthritis (OA).

Objectives: To evaluate the association of BMI with (a) OA prevalence and (b) utilization of OA-related medications in young and middle-aged adults.

Methods: De-identified health insurance claims and linked electronic health record (EHR) data were obtained for a US cohort of patients aged 18-64 years with a measured BMI ≥ 25 kg/m² recorded in the EHR in 2014. BMI classifications were overweight (BMI 25-29 kg/m²) and obese class I, II, and III (BMI 30-34, 35-39, and ≥ 40 kg/m², respectively). The prevalence of OA and OA-related medication use (defined as ≥ 2 outpatient prescription fills) was assessed with medical and pharmacy claims data from a 1-year evaluation period spanning the 6 months before and after the earliest BMI measure from 2014. The association

between BMI and study outcomes—adjusted for age, sex, and region—was quantified with logistic regression.

Results: 160 691 patients (median age 48 yr; 50% female) were eligible for inclusion; 15 451 (9.6%) had an OA diagnosis. The adjusted prevalence of OA increased monotonically with increasing BMI ($p < 0.001$), from 7.4% in overweight patients to 15.9% in class III obese patients. Among the 15 451 patients with OA, higher BMI was associated with significantly greater adjusted utilization rates of the following OA-related medications ($p < 0.001$ for all): prescription opioids, NSAIDs, intra-articular injections, antidepressants, and anticonvulsants such as gabapentin. Adjusted utilization rates for overweight and class III obese patients were 36.6% and 46.1% for prescription opioids, 25.6% and 34.2% for NSAIDs, 30.8% and 41.0% for intra-articular injections, 24.4% and 30.9% for antidepressants, and 12.0% and 17.8% for anticonvulsants, respectively. BMI was not significantly associated with the use of muscle relaxants or anxiolytics/sedatives among OA patients.

Conclusions: In this large population-based study of young and middle-aged adults, higher BMI was associated with increased OA prevalence. Among patients with OA, higher BMI was associated with greater use of opioids, other prescription analgesics, and intra-articular injections. Weight management may serve as an effective primary and secondary prevention strategy for reducing the disease burden associated with OA and delaying the need for medical management of OA-related pain.

1057 | Secular trends in major osteoporotic fractures among 50+ adults in Denmark between 1995 and 2010

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Background: Literature shows a mostly decreasing trend in osteoporotic fractures in Western and Nordic countries and an increasing trend in Asia. In the case of Denmark, apart from a few studies that estimated the incidence rates (IRs) of osteoporotic or forearm fractures for a single year, or reported the trend in hip fracture, there are no studies to date that evaluate the trend in all major osteoporotic (MOP) fractures sites over a longer time period.

Objectives: To investigate the IRs of MOP fractures among adults aged 50 years or older in the full country of Denmark over the period 1995–2010.

Methods: A series of cross-sectional analyses was done using the Danish National Health Service Register ($n = 5.5$ million). Participants were aged 50+ in Denmark with a MOP fracture between 1995 and 2010. Age- and gender-specific IRs of MOP fractures per 10 000 person years (PYs) were estimated. IRs of MOP fractures were broken down to individual sites, ie, of the hip, vertebrae, humerus, or forearm (radius/ulna). Also, women-to-men IR ratios were calculated for MOP fractures.

Results: A general decline was observed in IRs of MOP fractures for the whole population (from 169.8 per 10 000 PYs in 1995, to 148.0

in 2010), which was more pronounced among women. 31% decline was observed in hip fracture rates among women (from 87.2 to 59.9 per 10 000 PYs) and 19% decline among men (from 36.5 to 29.6 per 10 000 PYs). The trend in clinical vertebral fracture was slightly decreasing for women and increasing for men. The women-to-men rate ratio of MOP fractures decreased significantly from 2.93 to 2.72 during study period.

Conclusions: We observed declining trends in MOP fractures and hip fracture for both sexes. Also, a lower rate of decrease of hip fracture and an increasing trend in vertebral fracture was noticed among men. Considering our observations and the major economic burden which is accompanying this devastating disease, more attention should be paid to MOP fractures, especially in men.

1058 | Increasing risk of post-surgery infections among hip fracture patients: A nationwide study 2005–2016

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Background: Post-surgery infections are associated with excess mortality among hip fracture patients. Changes in hospital care, including orthogeriatrics, could have had an impact on this, but data on recent trends in the risk of infections are lacking.

Objectives: We aimed to examine trends in the risk of infections in the month following hip fracture surgery, including hospital-treated infections, as well as community-based ones, in Denmark from 2005 to 2016.

Methods: We conducted a population-based cohort study based on individual-level record linkage of data from Danish nationwide registries. To evaluate the risk of infections, we identified any first time hospital diagnosis (admission or outpatient record) of infection, or community infection identified by first time antibiotic prescription/s, after hip surgery date. In addition, we examined specific infections, such as pneumonia hospitalization. We calculated biennial incidence rates (IR) per 1000 person-years (PY) with 95% confidence interval (95% CI), and, based on pseudo values methods, adjusted risk ratios (RRs) with 95% CI per calendar period, using the period 2005–2006 as a reference. RRs were adjusted by age, sex, and comorbidity (Charlson Comorbidity index [CCI]). All analyses were calculated 30 days after surgery.

Results: A total of 74 771 patients aged 65 years or older, with first time hip fracture surgery, were included. Risk of post-operative infections increased in the study period: IR of 30-day hospital-treated infections increased from 4.12 (95% CI: 3.91–4.35) in 2005–2006 to 5.57 (95% CI: 5.30–5.85) in 2015–2016 (adjusted RR 1.32 [95% CI: 1.23–1.41]), irrespective of patient's age, sex, and comorbidity. IR of hospital-treated pneumonia increased from 1.34 (95% CI: 1.22–1.47)

in 2005-2006 to 2.42 (95 % CI: 2.25-2.60) in 2015-2016 (adjusted RR: 1.69 [95% CI: 1.49-1.91]). Finally, 30 days IRs of community-based infection increased from 6.78 (95 % CI: 6.50-7.07) in 2005-2006 to 11.28 (95 % CI: 10.89-11.6) in 2015-2016 (adjusted RR 1.56 [95 % CI: 1.49-1.64]).

Conclusions: We found an increased risk of infection following hip fracture surgery during the 12-year study period. Given the high mortality following infections in the elderly, further research is needed to identify patients at increased risk to target preventive treatment and potentially reduce complications and mortality in hip fracture patients.

1059 | Long-term risperidone exposure does not increase the risk of osteoporosis-related fractures

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Background: Antipsychotic agents can increase circulating serum prolactin levels, which may lead to bone loss, osteoporosis, and increased fracture risk.

Objectives: We investigated whether risperidone, an atypical antipsychotic, was associated with an increased fracture risk by estimating the incidence of hip/femur and non-hip/femur fractures in users of risperidone (RIS), other atypical (OA) antipsychotics, and conventional (TYP) antipsychotics.

Methods: This population-based retrospective cohort study used claims data from the Taiwan National Healthcare Insurance database. All patients aged at least 18 years who initiated treatment with risperidone or any other antipsychotic between 1998 and 2012 were included. Incident hip/femur fractures and non-hip/femur fractures after 6 months of drug exposure were identified using ICD-9 codes from inpatient records. Exclusion criteria were a record of prior fracture or bone surgery at the same site, bone metastases, or fractures due to accident. Cox proportional hazards models estimated hazard ratios and 95% CIs after adjusting (aHR) for potential confounders (age, gender, comorbidities, and concurrent medication) for associations between antipsychotic use and osteoporosis related fractures.

Results: There were 340 939 patients included in the analysis; 148 699 individuals in the RIS exposure group, 258 957 in the OA group, and 341 073 in the TYP group. The mean age of patients in each group ranged from 50.3 to 54.85 years, and 47.6% to 52.6% of patients in each group were male. There were 2832 hip/femur fractures and 2693 non-hip/femur bone fracture (vertebra, clavicle, humerus, radius/ulna, wrist, pelvis, and tibia/fibula) identified during the follow-up period. Incidence rates of hip/femur fracture were 636.8/

100 000 person-years (py) (RIS group), 885.7/100 000 py (OA group), and 519.4/100 000 py (TYP group). The aHR of hip/femur fracture was 0.92 (95% CI 0.84-1.01) comparing the OA with RIS group, and 0.996 (95%CI 0.89-1.11) comparing the TYP group with RIS. The aHR of non-hip/femur fracture was 1.08 (95% CI 0.98-1.20) for the OA group versus RIS group and 1.10 (95% CI 0.99-1.22) for TYP versus RIS groups.

Conclusions: There was no statistically significant increase in the risk of bone fracture associated with long-term risperidone use.

1060 | A retrospective study to assess the risk of falls due to prescribed drugs in inpatients

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Background: Falls and related injuries are important issues for patient safety in many hospitals and nursing care facilities. Although many reports examining the relationship between accidents and drugs with a sedative effect have been reported, the correlation between the risk of falls and total prescribed drugs but not only sedative drugs is insufficient.

Objectives: The aim of this study was to clarify the association between the risk of falling and prescribed drugs.

Methods: We performed a cohort study using patients admitted to Gunma University Hospital from 2013 to 2014. All reports of falling accidents from ward medical staff were investigated. A logistic regression analysis was used to identify the independent risk factors of falling.

Results: A total of 22 108 patients were enrolled in this study and 778 (3.5%) resulted in falls. Multivariate analysis revealed the following factors as independent high-risk factors of falling: 70 years of age or older (odds ratio [OR]: 2.30, 95% CI: 1.96-2.70), use of hypnotics (OR: 1.38, 95% CI: 1.18-1.63), antipsychotics (OR: 2.38, 95% CI: 2.38-3.50), antiepileptics (OR: 1.83, 95% CI: 1.37-2.44), analgesics (OR: 1.32, 95% CI: 1.11-1.57), antihypertensives (OR: 1.57, 95% CI: 1.32-1.87), antidiabetics (OR: 1.44, 95% CI: 1.19-1.73), anticoagulant and antiplatelet drugs (OR: 1.43, 95% CI: 1.18-1.73), anticancer drugs (OR: 1.81, 95% CI: 1.33-2.47), laxatives (OR: 1.76, 95% CI: 1.48-2.08), antimicrobial drugs (OR: 1.37, 95% CI: 1.17-1.62), and steroids (OR: 1.59, 95% CI: 1.30-1.95).

Conclusions: In our study, antipsychotics showed highest risk of falls, and drugs without sedative effects such as antihypertensives also showed a certain risk of falls. Although more detail studies were needed to clarify the risk drugs for falls because we did not assess the impact of disease requiring those drugs on risk of falls, we believe

that studies of the risk of drugs for falls contribute to prevent the falling accidents and improve ADL of patients.

1061 | Defining readmissions in a claims database among patients receiving open reduction internal fixation for femur, tibia, or fibula

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Background: Open reduction internal fixation (ORIF) is a standard treatment for fractures of the femur, tibia, and fibula. In claims databases, readmissions rates, an indication of unsuccessful initial treatment, are calculated mainly based on all records in the inpatient files, some of which may not be true hospital readmissions but may represent admissions to rehabilitation or aftercare or transfer to a different facility.

Objectives: To evaluate the impact of different definitions for readmissions on readmission rates among patients who have undergone ORIF in claims databases, specifically type of care facility and days from first hospitalization discharge.

Methods: Patients who received ORIF in an inpatient setting (index) between January 1, 2010, and January 31, 2017, in Truven Commercial and Medicare databases were identified. Readmission rates within 90 days from discharge were evaluated using different definitions. Readmissions were calculated starting from the index day of discharge to 2 days after discharge. Readmission rates were also reported after accounting for records for rehabilitation, aftercare or transfer using discharge status, provider type and diagnosis-related group (DRG) codes. For patients with "transferred" as the discharge status for the index hospitalization, readmissions were calculated from 2 days after discharge to adjust for any records due to the transferred status.

Results: A total of 82 762 patients with ORIF for femur, tibia, or fibula were identified. The mean (SD) age of the cohort was 60.1 (23.1) years and most were females (62.3%). The readmission rate calculated from the same day as the discharge was 14.7%. After accounting for rehabilitation, aftercare, and transfer, the corrected readmission rate was 8.6%. For the index hospitalization, 41.6% patients had "transferred" as the discharge status. Readmission rates calculated 1 and 2 days after index discharge were 8.5% and 7.7%, respectively.

Conclusions: This study found that readmissions rates ranged from 14.7% to 8.6% if transfers and admissions to other facility types were accounted for and were halved if days since discharge increased from 0 to 2. Given the wide range based on definitions, health care researchers may need to clearly define the calculations for readmissions. Future research needs to compare different definitions for readmissions in other retrospective databases such as a hospital billing database.

1062 | Risk of cardiovascular events in type 2 diabetes patients initiating second-line therapy with glucose lowering drugs: A population-based analysis

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Background: Type 2 diabetes (T2D) patients are at high risk of cardiovascular events. Recent trials have described a protective cardiovascular effect of new diabetes drugs, including sodium-glucose cotransporter-2 inhibitors (SGLT-2), but whether these findings hold true in the general population remains uncertain.

Objectives: To compare the risk of cardiovascular events among patients initiating SGLT-2 or other second-line agents after metformin.

Methods: Using the MarketScan database (2011-2015), we created a cohort of new users of either sulfonylureas or a newer agent (SGLT-2, dipeptidyl peptidase-4 inhibitor - DPP-4, or glucagon-like peptide-1 - GLP-1) as second-line therapy, after metformin. Cohort entry was defined by date of the first prescription of the second-line agent. Time to first cardiovascular event after cohort entry (acute myocardial infarction - AMI, unstable angina, ischemic or hemorrhagic stroke) was compared using Cox regression models. Patients were censored at the time of death, loss of insurance coverage, discontinuation or switching initial therapy, or end of study period. Models were adjusted for baseline variables: age, sex, year of cohort entry, employment status, place of residence, and comorbidities.

Results: We studied 118 774 T2D individuals (mean age 56.0, 54% male); 2.1% of patients had an AMI and 5.5% had an ischemic or hemorrhagic stroke event prior to cohort entry. Most patients were sulfonylurea initiators (48.2%), 34.6% were on DPP-4, 11.0% on GLP-1, and 6.2% on SGLT-2. After an average of 2.8 years of follow-up, the rate of AMI events was 3.4 by 1000 person-years in sulfonylurea users, 2.7 in DPP-4, 2.5 in GLP-1, and 2.3 in SGLT-2. Compared with sulfonylureas users, the risk of cardiovascular events was lower in users of other drugs: 39% lower for SGLT-2 (adjusted hazard ratio, aHR = 0.61; 95% CI = 0.39-0.96), 22% for DPP-4 (aHR = 0.78; 95%CI = 0.69-0.90) and 36% lower for GLP-1 (aHR = 0.66; 95% CI = 0.48-0.89).

Conclusions: This real-world analysis of second-line agents suggests that compared with sulfonylureas, newer agents are associated with lower cardiovascular events. Our results are consistent with findings of recent trials although residual confounding including channeling may partially explain our findings.

1063 | The clinical and economic effects of switching US Medicare beneficiaries with type 2 diabetes from analog to human insulin

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Background: Prices for newer analog insulin products have been increasing in recent years. Lower-cost human insulin may be effective for many patients with type 2 diabetes.

Objectives: To evaluate the clinical and economic effects of a managed care organization's conversion program switching Medicare beneficiaries with type 2 diabetes mellitus from analog to human insulin.

Methods: A consecutive sample of 14 635 participants who filled insulin prescriptions between January 2014 and December 2016 was identified from a Medicare Advantage and prescription drug plan operating in 4 US states (CA, AZ, NV, and VA). Outcomes were mean hemoglobin A1c (%), rates of severe hypoglycemia or hyperglycemia events and risk of reaching the Part D coverage gap. Data were analyzed using interrupted time series and segmented regression with cut points at the beginning and end of 2015.

Results: 14 635 members (mean age = 72.5) filled 221 866 insulin prescriptions. Insulin conversion decreased the proportion of scripts filled by analog insulins from 90% to 30%. The baseline mean hemoglobin A1c was 8.46% and decreased at a rate of -0.02% per month during 2014. The beginning of the conversion program in 2015 was associated with a level change of +0.14% ($p < 0.01$) and a slope change of 0.02% ($p < 0.01$). The baseline rate of severe hypoglycemia was 4.21 per 1000 person-years (py) and increased at a rate of 0.36/1000 py during 2014. The baseline rate of severe hyperglycemia was 22.33/1000 py and increased at a rate of 0.30/1000 py. For both hypoglycemia and hyperglycemia, the level and slope changes in the 12-month intervention and post-intervention segments were not statistically significant. The intervention reduced the risk of reaching the coverage gap by 55% (HR 0.45, nominal 95% CI: 0.43-0.48, $p < 0.001$).

Conclusions: Switching Medicare beneficiaries with diabetes from analog to human insulin did not change the rates of hospitalization for hypoglycemia or hyperglycemia, slightly increased mean A1c, and reduced the risk of reaching the Part D coverage gap.

1064 | Association between sodium-glucose cotransporter-2 (SGLT-2) inhibitors and lower extremity amputation: A retrospective cohort study

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Background: Evidence from clinical trials suggests that canagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor for the treatment of type 2 diabetes, may be associated with lower extremity amputation.

Objectives: To quantify the association between oral type 2 diabetes medication use, foot and leg amputation, and other vascular outcomes, including peripheral arterial disease, critical limb ischemia, osteomyelitis, and ulcer.

Methods: We conducted a retrospective, new user design cohort study using Truven MarketScan Commercial Claims and Encounters data from September 2012 and September 2015. We focused on 2.0 million commercially insured individuals and used propensity score weighting to balance baseline differences among groups. Sensitivity analyses varied statistical models, assessed the effect of combining DPP-4 inhibitors and GLP-1 agonists as a single referent group, and adjusted for baseline use of older oral agents. Exposures of interest were new use of SGLT-2s alone, dipeptidyl peptidase-4 [DPP-4] inhibitors alone, glucagon-like peptide-1 [GLP-1] agonists alone, or other anti-diabetic agents (any combination of sulfonylurea, metformin, or thiazolidinediones). Outcomes and measures of interest were foot and leg amputation defined by validated ICD-9 and CPT codes.

Results: Of 2.0 million potentially eligible individuals, a total of 933 073 were included in the final analyses, including 38 692 (4.2%) new SGLT-2 inhibitor users, 101 408 (10.9%) new DPP-4 inhibitor users, and 37 932 (4.1%) new GLP-1 agonist users. After propensity score weighting and adjustment for demographics, severity of diabetes, comorbidities, and medications, there was a non-statistically significant increased risk of amputation associated with new use of SGLT-2 inhibitors compared with DPP-4 inhibitors (adjusted hazard ratio [aHR] 1.50, 95% confidence interval [CI] 0.85-2.67) and GLP-1 agonists (aHR 1.47, CI 0.64-3.36). SGLT-2 inhibitor use was associated with amputation compared with sulfonylureas, metformin, or thiazolidinediones (aHR 2.12, CI 1.19-3.78). These results persisted in sensitivity analyses.

Conclusions: SGLT-2 inhibitors may be associated with increased risk of amputation compared with some oral type 2 diabetes treatments. Further observational studies are needed with extended follow-up and larger sample sizes given the importance of the primary outcome of interest.

1065 | Rates of kidney function decline and urinary tract infection for sulfonylureas, DPP4is and SGLT2is: A new-user cohort study

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Background: Prescribing options for T2DM drug intensification have changed. At first stage intensification, as well as sulfonylureas (SUs), clinicians increasingly prescribe new drugs: dipeptidyl peptidase 4 inhibitors (DPP4is) and sodium glucose cotransporter 2 inhibitors (SGLT2is). Few studies have compared long-term outcomes for these drugs.

Objectives: We compared rates of kidney function decline and urinary tract infection (UTI) for recipients of SUs, DPP4is and SGLT2is after metformin monotherapy.

Methods: We used UK primary care data to identify adults that intensified treatment from metformin monotherapy to an SU, DPP4i or SGLT2i, 2014-2016. We excluded recipients of other drugs such as insulins as we found few prescriptions. We restricted to recipients of at least one further metformin prescription to confirm intensification rather than switching. The primary outcome was a 30% fall in estimated glomerular filtration rate (eGFR), or diagnosis of end-stage renal disease. We used creatinine test results to calculate eGFR. The secondary outcome was a diagnosis of UTI. We present the results of a cohort study, analysed using Cox regression. We will present a fully adjusted model and explore other outcomes such as cardiovascular disease, retinopathy, and mortality.

Results: We studied 6499 people: 3279 recipients of SUs, 2614 of DPP4is, and 606 of SGLT2is. Rates of kidney function decline were similar for each drug, with 10.0 (95% CI 7.9-12.6) events per 1000 person-years (py) in the SU cohort, compared with 8.6 (95% CI 6.4, 11.4) and 5.9 (95% CI 2.6-13.1) in the DPP4i and SGLT2i cohorts. After age and sex adjustment, compared with SUs, the hazard rate was 0.88 (95% CI 0.60-1.27) for DPP4is, and 0.89 (95% CI 0.38-2.08) for SGLT2is. UTI rates were comparable with 6.6 (95% CI: 5.4-8.2) events per 1000 py in the SU cohort: compared with 6.9 (95% CI: 5.4-8.8) and 8.1 (95% CI: 5.1-13.1) for DPP4is and SGLT2is. After age and sex adjustment, the DPP4i group had a HR of 1.01 (95% CI 0.73-1.41), and the SGLT2is was 1.20 (95% CI 0.70-2.03).

Conclusions: Our analysis shows people intensifying treatment with an SU experienced falls in kidney function and UTIs at similar rates to those on SGLT2is or DPP4is. Our previous work showed people starting SGLT2is had fewer comorbidities, so rates may differ in multivariate analyses. We plan to account for confounding factors and study more outcomes. This work will offer comparative outcome rates for commonly used T2DM drugs, to further understanding of relative benefits.

1066 | Evaluation of weight change and hypoglycemia as potential mediators in the association between insulin use and death

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Background: Among patients with type 2 diabetes on metformin therapy, adding insulin was shown to be associated with a higher risk of all-cause death compared with adding a sulfonylurea. Insulin has also been associated with a higher risk of hypoglycemia and weight gain compared to sulfonylurea.

Objectives: To evaluate whether weight change or hypoglycemia were important mediators in the causal pathway from insulin use to death.

Methods: We assembled a retrospective cohort of veterans who initiated diabetes treatment with metformin between 2001 and 2008 and

followed them through 2012 for intensification with a sulfonylurea or insulin. The mediators of interest, change in body mass index (BMI), and occurrence of hypoglycemia (hospitalization due to hypoglycemia or outpatient blood glucose measurement <60 mg/dL) were assessed during the first 12 months following intensification. Cohort patients were followed for the outcome of all-cause death after the 12-month period. To evaluate whether change in BMI or hypoglycemia mediated the association between insulin use (compared to sulfonylurea use) and time to death, we built propensity score weighted Cox proportional hazards models with and without the mediator to estimate the indirect effect and proportion mediated, and used bootstrapping to obtain 95% confidence intervals.

Results: Of 28 892 patients who intensified metformin monotherapy with a sulfonylurea or insulin and remained on the intensified therapy for 12 months, 27 239 (94.3%) added a sulfonylurea and 1653 added insulin. The median 12-month change in BMI (kg/m²) was 0.26 (inter-quartile range [IQR] -0.59, 1.05) and 0.36 (IQR -0.79, 1.59) among sulfonylurea and insulin users, respectively. Hypoglycemia occurred in 1.8% of sulfonylurea users and in 2.8% of insulin users. The propensity score-weighted hazard ratio for death comparing insulin users to sulfonylurea users was 1.14 (95% confidence interval [CI] 0.83, 1.59). When change in BMI was added to the model, the hazard ratio became 1.12 (95% CI 0.81, 1.54). The proportion of effect of insulin on death mediated through change in BMI was 0.15 (95% CI -0.56, 2.58). When hypoglycemia was added to the original model, the hazard ratio became 1.14 (95% CI 0.83, 1.57). The proportion of effect of insulin on death mediated through hypoglycemia was 0.001 (95% CI -0.72, 0.75).

Conclusions: We found no evidence that change in BMI or hypoglycemia was mediators in the association between insulin use and all-cause death.

1067 | Assessing interactions between metformin and exercise on HbA_{1c}, functional capacity, lipid profile, quality of life, and weight

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Background: Exercise is considered as first-line therapy for type 2 diabetes, but pharmacological agents are often required, with metformin as first-line oral antidiabetic. Although a combination of metformin-exercise is recommended, it remains unclear if their effects are independent, with studies suggesting that the benefits of metformin and exercise might not be additive.

Objectives: We aimed to evaluate the impact of metformin-exercise interaction on changes in HbA_{1c}, functional capacity, lipid profile, quality of life, and weight.

Methods: A retrospective cohort study using data from participants in a 12-week cardiovascular rehabilitation program between 2014 and 2016. Exposure to metformin was determined through recorded prescriptions, and average minutes of exercise per week were computed from exercise logs. The primary outcomes were changes in HbA_{1c} and functional capacity (6-minute walk test [6MWT]) over 12 weeks. Secondary outcomes were changes in lipid profile, quality of life, and weight. Directed acyclic graphs were used to identify potential confounders, accounted for with multiple linear regression.

Results: The cohort included 403 patients (mean age: 65 years) from 85 metformin users and 318 non-users. The average exercise minutes/week was 102.7 ± 48.7 among metformin users and 107.7 ± 58.1 among non-users. Although changes in HbA_{1c} were similar for both groups, the coefficient for metformin-exercise interaction indicated greater improvements in 6MWT among metformin users (0.383, 95% CI: 0.005, 0.762). There were no between group differences in any of the secondary outcomes.

Conclusions: In this study of real-world patients, the combination of metformin-exercise led to greater gains in functional capacity than exercise alone. Combining metformin and exercise did not appear to influence the effects of either treatment on other outcomes.

1068 | Differences between randomized clinical trial patients and real-world initiators of liraglutide

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Background: Drug effectiveness and safety may differ between randomized clinical trial participants and patients treated in routine clinical care.

Objectives: To examine whether real-world liraglutide initiators would have been eligible for inclusion in the phase III randomized clinical trials of liraglutide and describe their clinical characteristics and baseline therapy.

Methods: This was a population-based cross-sectional study using health care databases in Northern Denmark during 2009-2015. We identified 9251 patients who initiated therapy with liraglutide and assessed their eligibility for participation in the LEAD 1-5 trials that led to registration of liraglutide. Patients were further characterized according to baseline glucose-lowering drug (GLD) use at liraglutide initiation, age, sex, diabetes duration, and complications, HbA_{1c}, comorbidities, and renal and hepatic function.

Results: Liraglutide initiators mostly came from metformin + other non-insulin GLD use (34%), metformin + insulin use (21%), single

metformin use (20%), single insulin use (9%), or no previous GLD therapy (6%). Real-world liraglutide initiators frequently had comorbidities that would have caused non-eligibility for the LEAD 1-5 trials, including previous cardiovascular disease (29%) or other clinically significant comorbidities (11%). Further, 27% of patients had HbA_{1c} levels outside the typical trial inclusion values of 7%-10% or 7%-11%. Overall, 73% of all real-world liraglutide users would not have been eligible for participation in any of the LEAD 1-5 trials.

Conclusions: Seven out of 10 real-world initiators of liraglutide exhibited one or more clinical characteristics that would have led them to be excluded from the trials that led to registration of liraglutide.

1069 | Balance of unmeasured variables after propensity score matching in claims-based studies of anticoagulants: A validation study linking claims data to electronic health records

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Background: Claims databases are routinely used to study the effectiveness and safety of anticoagulants, but often do not contain data on important clinical characteristics such as disease severity and duration, renal function, and body mass index (BMI) which are routinely captured in electronic medical records (EMR).

Objectives: To assess potential residual confounding associated with unmeasured characteristics in claims, through a validation study based on EMR.

Methods: Within a US claims database, we identified adult patients with non-valvular atrial fibrillation (NVAf) initiating dabigatran or warfarin between October 2010 and December 2014. For a subset of patients, we obtained information on potential confounding variables from the EMR. Within this claims-EMR linked subset, we used 1:1 propensity score (PS) matching to balance 78 pre-defined claims-based characteristics, composed of medical comorbidities, medication use, and measures of health care use. We calculated absolute standardized differences (SD) to confirm the balance of claims-based covariates and to assess the balance of EMR-based covariates not included in the PS model, after PS matching.

Results: Within the claims-EMR linked population (N = 3696), we PS-matched 846 dabigatran and warfarin initiators (out of 1130 and 2566, respectively). All claims-based characteristics were balanced after PS-matching with SD < 0.10. Although EMR-based characteristics were not included in the PS model, mean BMI (SD = 0.01), mean eGFR (SD = 0.09), time since first recording (ie, duration) of atrial fibrillation (SD = 0.08), and prior stroke (SD = 0.00), for example, were well balanced across comparison groups. Moderate imbalances were observed for duration of diabetes (SD = 0.17) and duration of congestive heart failure (SD = 0.23). For most variables assessed, the balance

of EMR variables either improved or remained good after PS-matching. For some of the EMR variables such as smoking and blood pressure, the proportion of patients with missing values was high (>85%), thus limiting inferences on balance.

Conclusions: A new user cohort with matching based on a claims-based PS including proxies for disease duration and severity can achieve balance and mitigate confounding associated with characteristics unmeasured in claims. The minor residual imbalances observed for some variables can be accounted for using quantitative bias analysis.

1070 | Propensity scores balance individual covariates and also combinations of covariates (phenotypes)

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Background: Clinical epidemiology depends on equipoise, where patients with nearly identical characteristics are treated in different ways, to make comparisons across patients, and this phenotypic overlap is a way to address confounding. Propensity score (PS) matching achieves this aim by balancing covariates across compared groups.

Objectives: In an observational safety study of an adolescent male vaccine, PS matching was used to balance study subject characteristics across cohorts. We sought to evaluate the extent to which the PS that balanced individual baseline characteristics had the effect of identifying and balancing phenotypes across cohorts.

Methods: Within a health insurance claims database (Optum), vaccine recipients were PS matched to non-recipients between 2009 and 2016. Demographic characteristics, measures of health care utilization, enrollment characteristics, comorbidities, procedures, and medications were included in the PS. Separate PS models and matching was conducted by calendar year, and matched cohorts were pooled across years. Baseline variables were examined in the 12-months prior to (and including) the index date.

Results: Baseline characteristics were compared among the subset of 2991 vaccine recipients and 289 746 non-recipients in 2016 prior to PS matching. Vaccine recipients more frequently were in the age range of 11-17 (78% vs 28%) had a baseline visit with a diagnosis of contusions of lower limbs (80% vs. 40%), administration of another vaccine (45% vs, 9%), and encounters for general exams (83% vs 37%) than non-recipients. Together, these characteristics may represent a phenotype of "athlete-like" adolescent vaccine recipients who are generally healthy, and who are receiving health physicals for participation in school-related sports or injuries related to them, during which they receive the vaccine. Non-recipients were more likely to have a diagnosis of essential hypertension (8% vs 1%), have an ECG performed (10% vs 5%), and have dispensings of narcotic analgesics (10% vs 3%) in baseline compared with vaccine recipients. This latter phenotype may represent older subjects with "chronic health conditions" who have a low probability of receiving the study vaccine. After PS matching, the individual covariates were

well balanced and the phenotypes, even those not pre-specified, were also balanced.

Conclusions: Beyond its value in removing confounding by balancing covariates, the PS is also useful in identifying and balancing patient phenotypes.

1071 | Standard propensity score weighting did not result in balanced cohorts, now what?

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Background: Outcomes for drug A, a recently approved oral atypical antipsychotic (OAA) was compared with outcomes for 4 other OAAs (B, C, D, and E). Propensity score (PS) methods were used to balance the baseline characteristics of the cohorts. However, using standard methods, imbalance remained.

Objectives: Different PS weighting methods (inverse probability treatment weights [IPTWs] and standard mortality ratios [SMRs]) were applied, and their ability to achieve balance in baseline characteristics between drug A and each of the other 4 OAA cohorts was assessed.

Methods: Adults with ≥ 1 prescription fill for drug A ($n = 230$), B ($n = 2726$), C ($n = 984$), D ($n = 3056$), or E ($n = 1623$) and a bipolar I mixed disorder diagnosis from MarketScan® claims data were identified. PSs were derived using separate logistic regression models for cohort A and each other OAA, including pre-index demographic and clinical characteristics. The overlap in the distribution of PSs (area of common support [ACS]) were compared between cohort A and each OAA. IPTW [$1/PS$ A; $1/(1-PS)$ other OAA] and SMR weights [PS/PS A; $PS/(1-PS)$ other OAA] were applied. Un-weighted, IPTW, and SMR-weighted baseline characteristics were then compared between cohort A and the other OAA cohorts using standardized differences, chi-squares, and t tests.

Results: Un-weighted cohort A patients had greater pre-index bipolar I episode rates and psychiatric drug use than each of the other OAA cohorts. The ACS between cohort A and C was moderate and the ACS between cohort A and cohorts B, D, and E were very small. Comparing IPTW baseline characteristics, demographic imbalance increased between A and each other OAA cohorts. IPTW improved clinical characteristic balance for A versus C and E cohorts, but only slightly improved balance versus B and D cohorts. In addition some clinical characteristics balanced in the un-weighted comparisons were now imbalanced. Applying SMR weights, all baseline demographic and clinical characteristics were balanced. On applying IPTWs cohort A more resembled the other cohorts, whereas with SMR weights the other OAA cohorts more resembled cohort A.

Conclusions: SMR should be considered when the cohort of primary interest differs significantly from the broader underlying population to which it is being compared, the ACS is small, and IPTW leaves imbalance. This often occurs when there is a new entrant in an already

crowded market. Interpretational differences between IPTW and SMR-weighted analyses should be highlighted in any presentation of the findings.

1072 | Propensity score (ps) matched approaches to estimate the association between liraglutide use and thyroid cancer (TC)

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Background: Liraglutide users differ clinically from users of other anti-diabetic drugs (ADs). Comparisons of TC risk must account for these differences to reduce confounding.

Objectives: To estimate the association between liraglutide and risk of TC compared with other ADs, using a variety of PS matched approaches.

Methods: A new-user cohort study was performed using a large US health insurance database (Optum Research Database, 2010-2014). Eligible patients had observed dispensings for ADs, with no dispensing of that drug or drug class in the prior 6 months. A validated TC algorithm was used. Demographics, comorbidities, medication use, and health care utilization during the 6 months prior to cohort entry were candidates for the PS models. PS models were developed separately within blocks of calendar time, for 5 drugs/drug classes and 3 *all comparators* groups. The primary analysis, a 1:1 PS-matched intention-to-treat analysis, allowed patients to match into multiple comparator groups during the study period. Additional analyses included variable matching ratios (1 to up to 4) and restriction to first observed initiation for matching. Poisson regression models estimated the relative risks (RR). Generalized estimating equations were used to account for the paired nature of the matched data.

Results: For each PS matched approach, cohorts were well balanced; the size of the matched cohorts varied considerably due to patient characteristics and prevalence of the drugs on the market. Across a wide range of analyses, findings were generally consistent with no increased risk of TC among liraglutide initiators. For example, the primary analysis of *all comparators minus exenatide* found a RR of 1.7 (95% confidence interval [CI]: 1.0-2.8). When a variable matching ratio was used, the RR was 1.3 (95% CI: 0.8 - 2.2). When restricted to the first matched initiation, the RR was 1.4 (95% CI: 0.8-2.4).

Conclusions: Use of a variety of PS matching approaches provides additional confidence about the control of confounding and the inference that there is no elevated risk of TC associated with use of liraglutide.

1073 | Incremental utility of additional clinical information and propensity score methods in controlling for severe confounding by indication

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Background: Centers for Medicare and Medicaid Services reimburse carotid artery stenting (CAS) only when performed on patients at high surgical risk for carotid endarterectomy (CEA). A comparative effectiveness research (CER) study of CAS vs CEA would likely be susceptible to confounding by indication. Incremental utility of advanced analytic techniques such as high dimensional propensity score (hdPS) and additional clinical information are not well understood.

Objectives: To demonstrate how different PS based techniques perform with and without detailed clinical data in comparing CAS to CEA.

Methods: We included Medicare beneficiaries linked to Society for Vascular Surgery's Vascular Registry >65 years old who underwent CAS/CEA in 2005-2008. We compared various hazard ratios (HRs) for death while adjusting for confounding by combining various (1) PS models (investigator-specified [IS-PS] vs hdPS); (2) data sources (claims only, registry only, and claims + registry); and (3) PS adjustments, ie, matching vs quintile adjustment with or without trimming. HR of 1 was used as a benchmark based on a large clinical trial, CREST.

Results: The study included 1999 CAS and 3255 CEA patients (mean age: 76; 59% male; 93% white). CAS patients were more likely to be symptomatic and at high surgical risk, with a higher prevalence of severe heart failure, recurrent stenosis and past coronary events making them at higher risk for death (crude HR = 1.82 for CAS vs CEA). The AUC for PS models were 0.67 for claims only IS-PS, 0.77 for claims only hdPS, and 0.94-0.96 for registry only or registry + claims IS-PS/hdPS. HRs from hdPS quintile adjustment with trimming were 1.47 and 1.41 for claims-only IS-PS and hdPS, respectively, and for registry only IS-PS and hdPS 1.36 and 1.38, respectively. When both registry and claims were used, HR was 1.21 for IS-PS and 1.18 for hdPS. Estimates from PS matching and no trimming were similar to the above except for the registry + claims IS-PS which had slightly higher HRs (1.34-1.36).

Conclusions: In a cardiovascular CER study with severe confounding by indication, both claims and registry variables were necessary to control for the bias, although AUC for models from registry data with or without claims were very similar. Also, hd-PS generally outperformed IS-PS and provided the best estimate for registry + claims models. Researchers should seek for both advanced analytic techniques and additional clinical information to control for strong confounding by indication.

1074 | Cost-utility of screening for renal dysfunction to detect the onset and progression of chronic kidney disease among elderly patients treated with proton-pump inhibitors

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Background: Proton-pump inhibitors (PPIs) have been associated with chronic kidney disease (CKD), which is a concern given the high prevalence of PPI use in the United States. Screening for renal dysfunction has been shown to be cost-effective in populations at increased risk of CKD, but the cost-utility of renal screening in PPI users is unknown.

Objectives: To assess the cost-utility of routine creatinine screening vs usual care to minimize costs associated with incidence of CKD and subsequent progression to end-stage renal disease (ESRD).

Methods: A Markov model was used to evaluate the cost-utility, from a Medicare payer perspective, of routine screening vs usual care among a hypothetical population of ten million elderly (age ≥ 65) US individuals with no baseline CKD who are using PPIs. Transition probabilities between four health states (no disease, CKD, ESRD, and death) were derived from literature. Outcomes included the total expected number of deaths, total per-person costs of CKD and ESRD screening and treatment, and total per-person quality-adjusted life years (QALYs). Cost-utility was evaluated using incremental cost-utility ratios (ICURs) of cost per QALY gained, assuming an annual discount rate of 3%. In sensitivity analysis, we doubled the probabilities of CKD incidence and progression to reflect a population with established risk factors such as diabetes or hypertension. We also performed a threshold analysis to assess scenarios under which screening would no longer be cost-effective.

Results: Over a 20-year time horizon, routine screening was associated with fewer deaths (screening vs usual care; 5.09 vs 5.26 million), higher total per-person costs (\$206,099 vs \$204,021), and higher per-person QALYs (11.5 vs 11.4) compared with usual care. Screening was cost-effective (ICUR \$16,301/QALY gained) at a willingness-to-pay threshold of \$50,000/QALY gained. Cost-utility of screening improved in populations with doubled risk of CKD incidence and progression (ICUR \$7,433 per QALY gained). Screening was no longer cost-effective in populations with very low incidence of CKD (<0.1% per year).

Conclusions: Routine creatinine screening appears to be cost-effective in patients ≥ 65 years without CKD who are using a PPI, but cost and QALY gains are marginal. The cost-utility is improved in higher-risk populations with diabetes and/or hypertension, but screening may not be cost-effective in populations with very low incidence of CKD.

1075 | Health-related quality of life in type 2 diabetes mellitus (T2DM) patients starting with new glucose lowering drugs (GLD): An inception cohort study in Portugal

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Background: Portugal is one of the European countries with the highest uptake of the recently launched GLD. Although new GLD are being used in large numbers of patients, evidence supporting its use with respect to patients' perspective comparison on the outcomes in a daily practice setting is limited.

Objectives: To assess baseline and change after 26 weeks of treatment in health-related quality of life (HRQoL) among T2DM patients initiating one of the dipeptidyl peptidase 4 inhibitors (DPP-4), glucagon-like peptide-1 analogues (GLP-1), or sodium-glucose cotransporter inhibitors (SGLT2) drugs in daily practice.

Methods: A nationwide multicenter inception cohort study was implemented. Eligible population consisted of T2DM patients initiating one of the DPP-4, GLP-1, or SGLT-2. Participants were divided into (1) incident new users (INU) (patients who used for the first time one of the monitored drugs and had no current or prior experience with DPP-4, GLP-1, and SGLT2) and (2) prevalent new users (PNU) (patients who used in the past or at recruitment at least one drug of the monitored drug classes, but not the inception drug) subgroups. A structured questionnaire collected demographic and clinical data at cohort entry. HRQoL was assessed using the EuroQol EQ-5D that was administered at baseline and 26 weeks after the index date. Both EQ-5D index and VAS scores were computed. Changes from baseline to endpoint were analyzed. Multivariate logistic regression was used to explore factors that might be associated with a meaningful change in health status over the study period.

Results: 1303 eligible patients were recruited. At enrolment, the mean index and VAS scores were 0.68 and 67.00, respectively. Over the 26 weeks, a mean positive change in the index and VAS score was observed, the later was significant. No differences amongst INU and PNU subgroups were observed. Overall, patients with worse health conditions at baseline were more likely to experience larger meaningful improvements in HRQoL than those with better conditions.

Conclusions: Results retrieved from this study of T2DM patients starting with, or switching to new GLD, support those collected from clinical trials, suggesting that HRQoL were not adversely affected and in some patients, might be modestly improved.

1076 | Change of health-related quality of life tuberculosis patients after receiving treatment: A longitudinal study

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Background: Pulmonary tuberculosis (TB) remains a major public health challenge in Indonesia. However, little attention is paid to the impact of health-related quality of life (HRQL) among TB patients. We compared HRQL between persons diagnosed and treated for TB disease at the beginning and at the end of TB treatment.

Objectives: To evaluate improvement of symptoms, activity, disease impact, and quality of life each month from beginning of treatment until at the end of 6 months of treatment.

Methods: A longitudinal study design was used for this study in adult, pulmonary TB Active in Lung Hospital and Primary Health Centers in Yogyakarta, Indonesia. A survey was performed by face-to-face interview using validated St George Respiratory Questionnaire Short Form (SGRQ) which contained 50 items in 3 domains (symptoms, activities, and disease impact) specific to respiratory illness and originally developed to assess patients with airways disease. The QoL was measured using EQ5D3L. The questionnaires were completed at baseline and at 1, 2, 3, 4, 5, and 6 months of TB treatment.

Results: All 89 patients (mean age 39.24 ± 14.44 and 60% male) after 6 months of treatment there was a significant improvement in symptoms, activity disease impact and QoL with the biggest increase at the end of treatment. The total QoL was significantly increased from 0.38 ± 0.52 at the beginning of treatment into 0.58 ± 0.41 ; 0.58 ± 0.41 ; 0.67 ± 0.37 ; 0.76 ± 0.30 ; 0.80 ± 0.28 ; 0.82 ± 0.32 after first, second, third, fourth, fifth, and at the end of sixth months of treatment. Similarly with symptoms, limitation of activities, and disease impact scores were reduced significantly month by month indicating patients improvement compared at the baseline (symptoms score 50.37 ± 21.14 at baseline, 30.69 ± 21.47 ; 24.27 ± 20.68 ; 17.98 ± 17.10 ; 13.77 ± 14.07 ; 11.17 ± 14.27 respectively at 1–6 months; activity score 90.86 ± 45.16 at baseline, 61.70 ± 43.56 ; 50.44 ± 42.03 ; 39.87 ± 36.86 ; 36.18 ± 34.45 ; 31.50 ± 25.70 , respectively; disease impact 64.42 ± 33.64 at baseline, and 22.21 ± 16.28 at the end of 6 months of treatment).

Conclusions: Adherence of TB treatment improved health-related quality of life in tuberculosis patients in Indonesia

1077 | A systematic review of models used in quantitative benefit-risk assessment of rotavirus vaccination

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Background: Two vaccines are currently marketed worldwide to prevent the risk of rotavirus gastroenteritis (RVGE) in children below 5 years. As post-marketing safety studies have indicated a transient increased risk of intussusception (IS) after vaccination, several modelling of benefit-risk (BR) of rotavirus vaccination have been conducted in various settings.

Objectives: To provide a comprehensive overview of available quantitative models having assessed the BR balance of rotavirus vaccination and to compare their characteristics, modelling approaches and estimates both for benefits and risks.

Methods: Medline, Scopus, and ISI Web of Knowledge databases were systematically searched to identify articles in English language published between January 2006 and December 2017. The search strategy combined 2 key search strings related to the following concepts: BR and rotavirus vaccines.

Results: Of 386 potentially relevant publications, a total of 10 peer-reviewed articles, using quantitative BR models to assess the BR of rotavirus vaccination, were retained on the basis of pre-selected criteria. Four studies were performed in low-middle-income countries (LMICs). All the studies used a model with a force of infection assumed to be constant over time (static), did not consider indirect effect of vaccination (herd immunity), considered that individuals did not enter and exit the cohort during the study period (fixed cohort), and considered the population and not individual characteristics (aggregate). Most (6/10) of the models were probabilistic and presented sensitivity/scenario analyses (8/10). Depending on the models, for every vaccine-related IS hospitalisation and for one IS-associated death, 190 (Singapore) to 1265 (Brazil) RVGE-associated hospitalisations and 71 (USA) to 615 (158 LMICs) RVGE-associated deaths would be prevented, respectively, by vaccination.

Conclusions: This review showed a favourable BR balance of rotavirus vaccination in all considered settings. Some differences in terms of model characteristics and/or modelling approaches were noted across studies. Standardizing methods used to quantitatively assess BR of rotavirus vaccines would allow identifying parameters affecting the BR estimates, especially when comparing areas with different socio-economic levels.

1078 | Impact of rotavirus vaccination in Taiwan: An interrupted time-series analysis

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Background: Rotavirus is a common cause of acute gastroenteritis among young children and results in considerable health care

utilizations. Since 2006, monovalent and pentavalent live oral rotavirus vaccines have been licensed in Taiwan as a 2- or 3-dose schedule administered by 24 or 32 weeks of age. The rotavirus vaccines are available for private market use, but not recommended for inclusion in the National Immunization Program; vaccination coverage of at least one dose was only 53% by 2014.

Objectives: To evaluate the population-level incidence of rotavirus-associated gastroenteritis (RVGE) among children by age 7 years in Taiwan before and after vaccine introduction.

Methods: Patients with a first-ever ICD-9-CM diagnosis of RVGE (008.6x, 008.8, 558.9, and 787.91) in 30 days at ages 0-6 years were identified from the 2002-2014 National Health Insurance claims databases. Monthly incidence of RVGE visits and RVGE hospitalizations were estimated, stratifying by age group (<1, 1-3, and 4-6 years). An interrupted time-series analysis was performed to test for changes in the level and slope between the pre- (January 2002-August 2006) and postintroduction (September 2008-December 2014) segments using a segmented generalized linear model.

Results: There were 15 166 898 RVGE visits and 356 415 RVGE hospitalizations across ages 0-6 years during 2002-2014. The annual incidence of RVGE visits across all ages rose from 51 442 per 100 000 in 2002 to 96 337 per 100 000 in 2014 ($p < 0.001$). Among children aged <1 year, however, the mean annual incidence of RVGE was 77 099 visits and 3920 hospitalizations per 100 000 during 2002-2006, but has decreased from 70 150 visits and 3180 hospitalizations per 100 000 in 2008 to 56 382 visits and 1869 hospitalizations per 100 000 in 2014 ($p < 0.001$). Incidence of RVGE visits and RVGE hospitalization in this age group were 31% and 50% lower than expected after rotavirus vaccine introduction, respectively.

Conclusions: Although with suboptimal vaccination coverage, introduction of rotavirus vaccines into Taiwan has substantially decreased RVGE visits and RVGE hospitalizations among infants.

1079 | Unspecific ICD-10 hospital discharge diagnoses after HPV vaccination: A nationwide matched cohort and time series study

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Background: Since inclusion of HPV vaccination in pediatric care in the late 2000s, diffuse autonomic symptoms have emerged among vaccinated girls, which undermine public confidence in the vaccine.

Objectives: To examine the risk of unspecific ICD-10 discharge diagnoses in HPV-vaccinated vs unvaccinated girls made during hospital contacts (outpatient clinics, emergency departments, or inpatient admissions), including pain, malaise/fatigue, hypotension/syncope, and tachycardia. We also examined nationwide time trends in these diagnoses in Danish girls and boys.

Methods: Cohort outcome analysis and time series study based on the Danish Civil Registration System, National Patient Registry, Health Insurance Service Registry, Prescription Registry, and labour market databases. The study included all 184 597 HPV-vaccinated girls aged between 11 and 18 years in 2008-2014 in Denmark and 44 038 age-matched girls who did not receive HPV vaccine. All girls entered the study population at age 11. Exposure to the HPV vaccine was a time-varying variable. Incidence rates of discharge diagnoses were assessed, using Cox regression to adjust for comorbid conditions, prior healthcare contacts, ethnicity, and parental education, employment, income, and marital status.

Results: Between 2008 and 2012, more than 85% of 11-year-old girls received the HPV vaccine, usually before they turned 13 (94%). By 2014, only 28% of girls received this vaccine. Adjusted IRRs in HPV vaccine-exposed vs unexposed girls were increased, as follows: 1.08 (95% CI 1.03-1.14) for abdominal pain, 1.26 (1.08-1.46) for unspecific pain, 1.36 (1.21-1.54) for headache, 1.39 (1.26-1.53) for hypotension/syncope, 1.59 (1.24-2.04) for tachycardia, and 1.60 (1.25-2.04) for malaise/fatigue. The IRR for death was clearly decreased at 0.39 (0.23-0.65). IRRs for negative control outcomes (trauma, cancer, diabetes, pneumonia, asthma, and appendicitis) were close to 1.0. In time-trend analyses, we observed a steady increase in the above diagnoses in both girls and (largely HPV-unvaccinated) boys between 2002 and 2016, unrelated to HPV vaccination introduction in 2008.

Conclusions: We found increased rates of a number of unspecific diagnoses in HPV-vaccinated vs unvaccinated girls, but no increase on the population level after vaccine introduction. It is unclear if our results reflect causal vaccine effects, differences in care seeking, or lack of knowledge about diagnostic specificity, coding practice, and etiological window.

1080 | Adverse events following DT-IPV and MMR vaccines in 9-year-old children primed with whole-cell or a cellular pertussis-containing vaccines

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Background: In 2013, the Netherlands Pharmacovigilance Centre Lareb received an increased number of adverse events (AEs) concerning major local reactions after dT-IPV vaccination in 9-year-olds. This finding needed further study since extensive limb swelling (ELS) at the age of 9 has hardly been reported before 2013.

Objectives: To study whether there has been an increase in local reactions after the booster dose given at nine years of age in acellular pertussis primed children compared with children primed with whole cell pertussis vaccines.

Methods: We conducted a questionnaire study to compare the occurrence and severity of AEs after the dT-IPV vaccination, simultaneously given with their second MMR vaccination, in 9-year-old children who received aP- or wP-containing vaccines in infancy. 4318 Parents were asked to report in questionnaires local and systemic AEs that

developed in the week prior, and 1 and 3 weeks after vaccination. The percentage of infants experiencing AEs within one week after immunization and 95%CI were computed by type and severity of the AE. Logistic regression analysis was used to calculate odds ratios (ORs) for the relationship between local reactions and systemic AEs after vaccination at 9 years of age in wP- and aP-primed children.

Results: Response rates for the consecutive questionnaires were 14.3% (n = 617), 15.6% (n = 672), and 14.6% (n = 630), respectively. Local reactions at the dT-IPV injection site occurred in 80.8% of the children within 7 days after dT-IPV vaccination. Pain was the most reported symptom (77.4%). Lower risks of swelling of the arm (OR 0.76; 95% CI 0.59-0.99) and reduced use of the arm (OR 0.72; 95% CI 0.58-0.89) were found in aP-primed children compared to wP-primed children. This is mainly caused by decreased frequencies of mild reactions; moderate and pronounced local reactions and the frequencies of systemic events were not different between these groups.

Conclusions: In our reactogenicity study, we did not find an increase in major local reactions after the dT-IPV vaccination at 9 years of age in children primed in infancy with an aP-vaccine, in contrast to a signal observed in the Dutch spontaneous surveillance system for AEs. However, although the occurrence of ELS seems to be rare, the frequency of local reactions remained high. This study shows that monitoring the reactogenicity of vaccines after changes of the NIP and cooperation with Lareb for signal detection are useful tools for evaluation the vaccination program.

1081 | Serosurvey and its impact on national immunization strategy in the Czech Republic

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Background: Serological surveys have been carried out in the Czech Republic since 1960s and provide rationale for change of immunization policy and implementation of new strategies into practise.

Objectives: The main objectives are to determine the impact of age based immune rates and susceptibility rates and to address appropriate schedules and number of doses and timing for vaccine administration.

Methods: 100 collaborating general practitioners, 100 collaborating pediatricians, 3200 serum samples, age cohort 1-64 years, 32 age cohorts. Four infectious diseases have been tested (measles, mumps, pertussis, and hepatitis B). 30 districts of all the 14 regions were enrolled. Serosurvey has been provided since March 25, 2013, till May 3, 2013. Final report was prepared in April 2014.

Results: Prevalence of measles antibody among immunized age cohort (2-44 years) remains high with 86-93%. The most susceptible age cohort is 40-44 years and 35-39 years. Two dose schedule with high coverage should be kept. High coverage in mumps, however, lower levels of antibody in those immunized 5 and more years ago. Lower antibody persistence in pertussis (70% in the age of 5 years.)

Conclusions: Serological surveys monitor levels of antibodies against selected communicable diseases and provide basic information about the susceptibility and herd immunity of the population. The surveys are used for evaluating the overall effectiveness of vaccination programs and generate a major basis for important decisions about interventions and changes in immunization schedules.

1082 | Estimating incidence of adverse events following vaccination in observational databases when exposure information is unavailable: A contribution from the advance project

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Background: Epidemiological models of diseases and exposures synthesize estimates from disparate sources which may lack data on important parameters such as vaccine exposure. To model vaccination risks, estimates of the excess incidence of adverse events following immunization are needed.

Objectives: To compare methods for estimation of incidence rates (IRs) of adverse events following immunization when data on the exposure are unavailable in a certain data source (DS), but available in other DSs.

Methods: We estimated IRs of febrile seizures (FS), fever, and persistent crying (PC) in risk periods following acellular pertussis vaccination in general practice (GP) or record linkage DSs in Italy, Denmark, Spain, and the United Kingdom. Risk period IRs were derived by multiplying the baseline (non-risk) period IR for DS *i* by an incidence rate ratio (IRR) obtained from the meta-analysis of IRRs estimated using the self-controlled case series method in DSs other than *i*. We also derived risk period IRs using two further methods: (1) meta-analysis of risk period IRs from DSs other than *i* and (2) multiplication of the background IR for DS *i* (including risk and non-risk periods) during the recommended month of age at the dose by the meta-analyzed IRR from DSs other than *i*.

Results: For FS after dose 1, observed, meta-analyzed, from baseline and from background IRs (95% CI) were 4.07 (2.99, 5.42), 0.77 (0.21,

2.81), 1.21 (0.45, 3.26), 0.75 (0.27, 2.05) in a record linkage DS and 0.51 (0.11, 1.50), 1.54 (0.52, 4.61), 0.53 (0.19, 1.52), 0.40 (0.14, 1.21) in a GP DS. For fever, the corresponding IRs in the same DSs were 30.17 (27.09, 33.51), 90.19 (69.60, 130.18), 13.25 (9.54, 18.40), 17.37 (12.51, 24.15) and 90.28 (82.75, 98.31), 66.09 (29.39, 148.61), 34.34 (22.58, 52.24), and 43.15 (28.36, 65.67).

Conclusions: For well-captured events in a DS, such as FS in the record linkage DS, derivation of IRs using estimates from DSs lacking data on FS (GP DSs) produced a risk period IR inconsistent with that observed. In a GP DS, observed IRs for symptoms such as fever differed from IRs derived via multiplication by meta-IRR which included record linkage DSs. This shows the importance of studying database heterogeneity before parameter derivation. The similarity of derived IRs using baseline vs background IRs may negate the need to identify a non-risk period when the risk period is short. This study was for system testing and not to inform regulatory/clinical decisions on pertussis vaccination.

1083 | Characteristics of vaccination errors reported to the European adverse event database EudraVigilance

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Background: Among all post-marketing medication error reports submitted to EudraVigilance, vaccines are the most frequently reported medicinal product. This study aims to describe the characteristics of the medication error reports relating to vaccines.

Objectives: This study aims to describe the characteristics of the medication error reports relating to vaccines.

Methods: EudraVigilance is a spontaneous reporting database for adverse events. We extracted Individual Case Safety Reports (ICSRs) submitted to EudraVigilance between 1 January 2001 and 31 December 2016. Reports were included for analysis if (1) a vaccine was reported as interacting or suspect drug and (2) at least one medication error term was listed as an adverse reaction. ICSR were stratified by age and gender of the patient, by year of reporting, region of origin (EU/non-EU), reporter profession (Healthcare professional/non-healthcare professional), seriousness of outcome, ATC, and type of medication error.

Results: In total, 7097 ICSR were included in the study. We observed a yearly increase in the reporting of medication errors with vaccines. The majority of reports was classified as serious, but non-serious reports were increasingly reported since 2012. The mean age of patients was 24.1 years old. The most frequently reported vaccines were influenza vaccines (13.5%), bacterial and viral vaccines combined (12.3%), and hepatitis vaccines (11.8%). A total of 8167 medication error terms were reported. The most frequently reported terms were "Inappropriate schedule of drug administration" (27.2%), "Incorrect

route of drug administration" (12.5%), and "Drug administered to patient of inappropriate age" (10.0%). Both the medication error term as well as the vaccine reported were dependent on the age category of the patient. For infants and children, the medication error "Drug administered to inappropriate age" was reported more often than for all other age categories.

Conclusions: Vaccination errors are increasingly reported to EudraVigilance, with characteristics deviating from general medication errors. Based on our results, it is recommendable to analyse vaccination errors separately from other drugs, as well as develop specific measures to prevent errors in this medicinal group.

1084 | Pilot study to assess research capacity for malaria vaccine pharmacovigilance in Ghana and Kenya

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Background: The RTS,S vaccine for malaria prevention was prequalified for use in Kenya and Ghana. Identified and potential adverse events following immunization (AEFI) of interest for this vaccine include febrile convulsions and meningitis. Diagnosis and reporting of AEFI are necessary for vaccine safety surveillance.

Objectives: The goal of this pilot study was to assess the capacity and ability to conduct post-licensure vaccine benefit-risk monitoring of RTS,S in 2 districts in Ghana within the Navrongo Health Research Centre (NHRC) Health Demographic Surveillance Site (HDSS) and 3 districts in Kenya within the Kenya Medical Research Institute (KEMRI)/Centers for Disease Control and Prevention (CDC) HDSS. The objectives were to understand how information on population demographics, vaccine exposure, and potential AEFI of interest are identified, collected, and reported, to evaluate if the available data allows post-licensure vaccine benefit-risk monitoring, and to identify gaps and make recommendations for system improvement.

Methods: Key informant interviews were conducted with community health nurses, malaria health officers, clinicians, data collectors, and data analysts at health facilities at both HDSSs using open-ended questionnaires in January 2018.

Results: In the NHRC study area, 30 interviews were conducted at 21 health facilities. At KEMRI/CDC, 42 interviews were conducted at 13 health facilities. Health facilities in all districts surveyed record child immunization data in paper booklets kept by parents and in a master register maintained at the health facility. Validation of the health care practitioners' diagnoses of the potential outcomes of interest showed inconsistencies with the Brighton Collaboration case definitions and

within and between sites. AEFI, including data on vaccine administration and timing, is routinely submitted through designated forms to government agencies by health facilities in both Ghana and Kenya. Similarly, AEFI outcome data originating from routine health facilities enter the Health District Management specific databases for analysis. Further, linkage to vaccine administration and timing is done routinely in the NHRC study area but not routinely at KEMRI/CDC.

Conclusions: Vaccination administration and incident health outcomes are collected at all health facilities. Continued efforts are needed to assess and minimize potential reporting and registration inconsistencies to further improve the vaccine safety monitoring systems at the HDSSs.

1085 | Lessons learned on enhanced passive safety surveillance of influenza vaccines

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Background: Enhanced safety surveillance (ESS) of influenza vaccines aims to rapidly detect unexpected changes in reactogenicity before the peak influenza season, to allow early risk mitigation before exposure to the vaccine increases. Such surveillance is required on an annual basis per European Medicines Agency guidelines. Enhanced passive safety surveillance (EPSS) uses a strengthened routine pharmacovigilance (PV) system in combination with systematic exposure data collection. This novel method can be further fine-tuned in order to optimise EPSS.

Objectives: To provide an overview of current EPSS methods, associated challenges; and to offer potential strategies to optimise the operational conduct and scientific validity of EPSS.

Methods: EPSS is conducted in routine clinical care settings. It involves the systematic collection of real-time vaccine exposure data, along with an enhanced routine PV system whereby vaccinees are informed by trained healthcare professionals of the importance of reporting adverse reactions (ARs), particularly those occurring within 7 days post vaccination. Each vaccinee typically receives a vaccination card indicating the contact to report suspected ARs.

Results: The following are suggested strategies to mitigate potential challenges associated with conducting EPSS: (1) To ensure representation of all age groups, country selection should take into account national immunisation recommendations of the adult and paediatric target groups. Additionally, site selection should be based on estimated coverage rates per age group; (2) to expedite approval from Ethics Committees (which may not be familiar with EPSS), study plans should emphasise the passive nature of EPSS; (3) to minimise discrepancies between exposure and PV datasets, regular reconciliation between data sources should be conducted; (4) to enhance standard passive surveillance, consider use of customised vaccination cards that list ARs of interest, which may facilitate collection of less severe symptoms.

Conclusions: In contrast with routine PV systems, EPSS enables the capture of real-time exposure data along with facilitated AR reporting to improve the estimation of AR reporting rates. Continued experience and sharing lessons learned will further refine and optimise EPSS in future influenza seasons.

1086 | Knowledge and attitudes regarding cervical cancer and human papillomavirus vaccination in Czech secondary school students

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Background: Cervical cancer, the second most common type of cancer in women, is causally related to human papillomavirus (HPV). Since adolescents and young adults are target group for HPV vaccination, it is important to identify their knowledge and attitudes towards HPV and HVP vaccination.

Objectives: The study aimed to analyse the knowledge and attitudes regarding HPV, cervical cancer, and HPV vaccination in secondary school students in the Czech Republic.

Methods: The study was carried out in May 2017 at three secondary schools. A questionnaire comprised 15 items including questions on demographic characteristics, knowledge about cervical cancer and HPV, vaccination coverage, HPV perceived susceptibility and seriousness, and beliefs on HVP vaccination. Factor analysis and Cronbach's alpha were applied to test construct validity and reliability. Pearson's correlations and parametric and non-parametric tests were used to assess relationships among study variables.

Results: A total of 667 students participated (mean age: 16.8 y ± 1.18; 63% female). Among cervical cancer risk factors HPV infection was reported in 58.1% cases followed by promiscuity (14.5%), irregular gynaecological screening (6.8%), immunity disturbances (4.2%), having sexual intercourse at an early age (1.7%), 12.6% did not know. Only 37.8% had been vaccinated against HPV (female: 56.5%; male: 5.7%). The main reported reasons for not being vaccinated were concerns about vaccine safety, HPV vaccine cost, doubts on vaccine effectiveness, distrust of vaccines, the vaccine has not been offered. Knowledge score was significantly related to all three factors constituting item 14 - "HPV susceptibility" ($r = 0.176$; $p < 0.001$), "HPV preventability" ($r = 0.124$; $p < 0.05$) and "HPV seriousness" ($r = 0.113$; $p < 0.05$). According to the three factors constituting item 15 the knowledge score was significantly related to "vaccine perceived effectiveness" ($r = 0.209$; $p < 0.001$) and "vaccine perceived negative consequences" ($r = 0.265$; $p < 0.001$). Correlation with factor "vaccine safety" was not significant ($r = 0.002$; $p = 0.965$). In aggregate, higher knowledge corresponded with better acceptance of the HPV vaccine.

Conclusions: Knowledge and beliefs related to HPV, cervical cancer, and HPV vaccination appear to be important contributing factors in HPV vaccination even in this age group where the decision is often

made by parents. Making information widely available would help to make informed decisions and improve HPV vaccine acceptance.

1087 | Real-world data on the effect of doxycycline plus prednisone/prednisolone on COPD exacerbations compared with prednisone/prednisolone alone: A retrospective cohort study among COPD outpatients

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Background: Treatment of COPD exacerbations usually consists of systemic corticosteroids alone or in combination with antibiotics. Prednisone/prednisolone as a recommended oral corticosteroid has proven benefits including improvement of lung function and other COPD symptoms. However, the evidence about the effect of commonly used doxycycline on COPD exacerbation is not consistent and lacks supports from real-world data.

Objectives: To assess the effectiveness of a combination treatment of doxycycline plus prednisone/prednisolone compared with treating exacerbation with prednisone/prednisolone alone.

Methods: A retrospective cohort study was conducted based on the prescription database IADB.nl which belongs to University of Groningen. We focused on the first exacerbation treatment to exclude the influence of exacerbation history. The main outcome was treatment failure which was defined as a new prescription of prednisone/prednisolone or antibiotics between 15 and 30 days after the first exacerbation. A secondary outcome was the time to second exacerbation within 3 and 6 months

Results: In all, 8642 COPD patients were identified with a first exacerbation. Among these patients, 2989 (34.6%) were treated with combined treatment of doxycycline plus prednisone/prednisolone, while 5653 (65.4%) were given only prednisolone/prednisone. We did not find any difference for the treatment failure between combined treatment and prednisone/prednisolone alone therapy, the relative risk (RR) of treatment failure was 1.01 (95% CI: 0.89-1.14). After adjusting the medicines used for COPD, age, gender and related comorbidities, the adjusted RR was 0.96 (95% CI: 0.85, 1.09). The time to 2nd exacerbation within 3 and 6 months for combined and prednisone/prednisolone alone treatments were 44.0 vs 43.2 days ($p = 0.35$) and 123.4 vs 120.1 days ($p = 0.22$), respectively.

Conclusions: The combination treatment of doxycycline plus prednisolone/prednisone did not show more benefits on exacerbations compared with prednisone/prednisolone alone among COPD outpatients. However, potential remaining confounding by indication may exist in this study, and more qualified studies are still needed.

1088 | Emtricitabine/tenofovir (Truvada®) fixed-dose combination in pre-exposure prophylaxis of human immunodeficiency virus: An observational drug utilization study using the French national health insurance database

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Background: Emtricitabine/tenofovir disoproxil fumarate (Truvada®) has been approved in Europe since March 2017 to reduce the risk of sexually transmitted HIV-1 infection in adults who are at high risk of being infected (pre-exposure prophylaxis, PrEP) in combination with safer sex practices. In France, Truvada® benefited from a pre-market authorization in PrEP from January 2016 until its date of approval. Its appropriate use is expected to reduce HIV incidence in high risk populations.

Objectives: The study objectives were to evaluate the number of initiators of Truvada® in PrEP in France between January 1, 2016, and July 31, 2017, and to describe their main characteristics, according to the periods before and after approval of Truvada® in PrEP.

Methods: A longitudinal, retrospective observational study was conducted using the French national health insurance database (SNIIRAM), which covers almost the entire French population (65.3 million inhabitants). Individuals without HIV infection and with a first reimbursement for Truvada® in PrEP during the study period were included.

Results: A total of 5352 individuals (mean 282/month) initiated Truvada® in PrEP during the study period, with a steady but moderate increase across the study period (3536 initiators before approval, mean 253/month and 1816 initiators after approval, mean 363/month). Truvada® initiators were overwhelmingly men (97.5%) with a median age of 37 years (IQR 30-45) at initiation. 7.3% of Truvada® initiators benefited from a complementary universal health insurance (free access to healthcare for people with an annual income >50% of the poverty threshold). Truvada® initiators were mostly affiliated to health insurance plans of the regions having the highest HIV prevalence in metropolitan France: Ile-de-France (49%), Auvergne-Rhône-Alpes (10.5%), and Provence-Alpes-Côte d'Azur (9.9%). Most of the prescriptions (92.2%) were initiated at hospital, as recommended. Characteristics of Truvada® initiators did not markedly differ between the pre- and post-approval periods.

Conclusions: Number of Truvada® initiators has increased steadily but moderately in France since January 2016, reaching more than 5000 as of July 2017. Truvada® initiators were mostly males with high socio-economic level suggesting that PrEP initiators are mainly men who have sex with men among whom HIV incidence is particularly high in France.

1089 | Prescribing of oral fluoroquinolones in Canada for treatment of acute bacterial sinusitis: A retrospective cohort study

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Background: Systemic oral fluoroquinolones are among the most widely prescribed class of antibiotics and are associated with potential harmful side effects. Their use has been expanding to milder infections, such as acute bacterial sinusitis (ABS), with limited evidence of superiority to first-line antibiotics.

Objectives: To compare repeat primary care visits and subsequent antibiotic dispensations within 30 days after initial antibiotic dispensation for ABS treated with a fluoroquinolone versus other antibiotics (eg, amoxicillin, amoxicillin/clavulanate).

Methods: We conducted a retrospective population-based longitudinal study using administrative health data from 6 Canadian provinces (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan) between January 1, 2005, and the latest date of data available for each site. We identified ABS events and determined antibiotic exposure by the first antibiotic dispensation occurring within ± 5 days. High-dimensional propensity scores adjustments were used to ensure comparable treatment groups and minimize residual confounding. Adjusted odds ratios (aORs) and their 95% confidence intervals (CIs) were estimated separately for each of the outcomes of interest. Site-level results were pooled using meta-analytic methods.

Results: Among 923 380 patients, 1 464 533 new ABS events were identified. Over the study period, between 2% and 11% of ABS episodes treated with an antibiotic were prescribed a fluoroquinolone. Fluoroquinolones were not associated with better outcomes compared to other antibiotics. We observed a modest but statistically significant increase in repeat primary care visits (aOR = 1.23, 95% CI: 1.13-1.34) following fluoroquinolone use. No difference was found for subsequent antibiotic dispensations (aOR = 0.97, 95% CI: 0.92-1.02).

Conclusions: Fluoroquinolones are not commonly used in the first-line treatment of ABS in Canada. Compared with other antibiotics, fluoroquinolones were associated with a modest increase in repeat primary care visits but made no difference in the need for subsequent antibiotics within 30 days following the initial antibiotic dispensation for ABS.

1090 | Prescribing of oral fluoroquinolones in Canada for treatment of uncomplicated urinary tract infection: A retrospective cohort study

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Background: Systemic oral fluoroquinolones are among the most widely prescribed class of antibiotics and are associated with potential harmful side effects. Their use has been expanding to milder infections, such as uncomplicated urinary tract infections (uUTI), with limited evidence of superiority to first-line antibiotics.

Objectives: To compare repeat primary care visits, hospitalizations, and subsequent antibiotic dispensations within 30 days after initial antibiotic dispensation for uUTI treated with a fluoroquinolone versus other antibiotics (eg, nitrofurantoin, sulfamethoxazole/trimethoprim).

Methods: We conducted a retrospective population-based longitudinal study using administrative health data from 6 Canadian provinces (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan) between January 1, 2005, and the latest date of data available for each site. We identified uUTI events among women and determined antibiotic exposure by the first antibiotic dispensation occurring within ± 5 days. High-dimensional propensity scores adjustments were used to ensure comparable treatment groups and minimize residual confounding. Adjusted odds ratios (aORs) and their 95% confidence intervals (CIs) were estimated separately for each of the outcomes of interest. Site-level results were pooled using meta-analytic methods.

Results: Among 984 462 patients, 1 692 148 new uUTI events were identified. Over the study period, between 18% and 51% of uUTI episodes treated with an antibiotic were prescribed a fluoroquinolone. We observed a reduction in repeat primary care visits (aOR = 0.90, 95% CI: 0.87-0.92), hospitalizations (aOR = 0.87, 95% CI: 0.75-1.00), and subsequent antibiotic dispensations (aOR = 0.78, 95% CI: 0.76-0.81) for uUTI initially treated with a fluoroquinolone compared with other antibiotics. However, the absolute reductions with fluoroquinolones were modest (repeat primary care visits 1.60%, hospitalizations 0.09%, and subsequent antibiotic dispensations 3.84%).

Conclusions: Fluoroquinolones, primarily ciprofloxacin, are commonly used in the first line treatment of uUTI in Canada. Compared with other antibiotics, fluoroquinolones were associated with modest reductions in repeat primary care visits, hospitalizations, and subsequent antibiotic dispensations within 30 days following the initial antibiotic dispensation for uUTI.

1091 | Antibiotic prescription in Southern Italian outpatients: Real-world data analysis of prevalence, socioeconomic and sociodemographic variables and geographic variability

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Background: Antibiotics may be prescribed for the treatment of various diseases, but the most of population take them unnecessarily. Antibiotic overuse and misuse contributes not only to the development of resistance but also to treatment failure and increase in mortality.

Objectives: To analyze the geographic variation in systemic antibiotic prescription at a regional level and to explore the influence of socioeconomic and sociodemographic variables.

Methods: Retrospective analysis of reimbursement pharmacy records in the outpatient settings of Italy's Campania Region in 2016. Standardized antibiotic prescription rates were calculated at municipality and Local Health Unit (LHU) level. Antibiotic consumption was analyzed as DDD/1000 inhabitants per day.

Results: Average antibiotic prevalence rate was 46.8%. At LHU level, the age-adjusted prevalence rates ranged from 41.1% in Benevento to 51.0% in Naples2. Significant differences were found among municipalities: from 15.2% in Omignano (Sa-LHU) to 61.9% in Moschiano (Av-LHU). The geographic distribution also showed significant differences in terms of antibiotic consumption: from 6.7 DDD/1000 inhabitants/day in Omignano to 41.6 in San Marcelino (Ce-LHU). Logistic regression showed that both municipality type and average annual income level were the main determinants of antibiotic prescription. Urban municipalities were more than eight times as likely to have antibiotic high prevalence rates compared with rural municipalities (adjusted OR: 8.62 [95% CI: 4.06-18.30, $P < 0.001$]). Municipalities with low average annual income level were more than eight times as likely to have antibiotic high prevalence rates compared with high average annual income level municipalities (adjusted OR: 8.48 [95% CI: 3.45-20.81, $P < 0.001$]).

Conclusions: We provide a snapshot of Campania's antibiotic consumption, evidencing the impact of both socioeconomic and sociodemographic factors on the prevalence of antibiotic prescription. The observed intraregional variability underlines the lack of shared therapeutic protocols and the need of a careful monitoring. Our results can be useful for decision-makers to plan educational interventions, thus optimizing health resources and improving rational drug use.

1092 | Misuse among the most frequently prescribed antibiotics to outpatients in Mexico City

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Background: Misuse of antibiotics is a globally recognized problem that has not been studied using prescription data. There are several factors that may influence incorrect prescription of antibiotics, but none of them have been identified considering actual prescribed doses to outpatients in Mexico City.

Objectives: (i) To estimate the frequency of antibiotic prescription and the prescribed daily dose (PDD) to outpatients in Mexico City and (ii) to identify misuse in antibiotic prescription and the associated factors to misuse

Methods: A retrospective, cross-sectional drug utilization study was performed based on antibiotic prescriptions of outpatients from Mexico City. This is a non-large database study, and the calculated sample size was 1368 prescriptions, which were randomly selected using clusters sampling. Prescriptions were classified and analyzed according to the ATC/DDD system, those from physicians or dentists with at least one antibiotic and adult patients were included and illegible or those with incomplete posology were excluded. Misuse was defined as the discrepancy from the unit of the ratio between the PDD calculated as the average prescribed dose for each ATC class and the defined daily dose (DDD) reported by the World Health Organization ($PDD/DDD \neq 1$) and compared using a chi-square test for seven independent variables including drug, pharmacological group, dosage form, administration route, prescriber's gender and specialty and patient's gender.

Results: The main prescribed antibiotics to outpatients from Mexico City included 6 pharmacological groups: quinolones (27%), penicillins (24%), cephalosporins (19%), macrolides (10%), lincosamides (8%), and sulfonamides (4%). Among all ATC antibiotic classes, there was significant misuse for clindamycin (100%) and azithromycin (100%) followed by amoxicillin whether it is alone or in combination with clavulanic acid (96%), betalactamics and lincosamides were the groups with more discrepancies of dosing. All of independent variables except patient's sex showed to be associated with misuse ($p < 0.001$). Tablets and capsules, oral administration, a female prescriber, and being general practitioner or dentist are factors associated to misuse.

Conclusions: The most frequent prescribed drugs show to have the greater misuse rate, and the factors associated to it are solid dosage forms orally administered as well as female prescribers and non specialists. These findings are essential to optimize interventions towards antibiotics adverse effects.

1093 | Therapy completion of direct-acting antivirals for hepatitis C

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Background: Direct-acting antivirals (DAA) are well-tolerated and effective for hepatitis C virus (HCV) infection, but therapy completion

of first generation of DAAs is low. Real-world data on completion rates of second generation of DAAs is scarce.

Objectives: To assess therapy completion rates in patients with HCV infection receiving second generation of DAAs.

Methods: We analyzed a retrospective cohort of individuals covered by private plans/Medicare and Medicaid using MarketScan databases. We selected adult patients with a diagnosis of HCV newly prescribed second generation of DAAs simeprevir/sofosbuvir (SIM/SOF), ledipasvir/sofosbuvir (LDV/SOF), and ombitasvir/paritaprevir/ritonavir/dasabuvir (OPrD) in 2014 and 2015. Therapy completion was defined as achieving 12 weeks of treatment. For LDV/SOF, we also measured therapy completion at 8 weeks as indicated when HCV RNA level is lower than 6 million IU/mL. Logistic regression was performed to estimate the odds ratio (OR) for the outcome of therapy completion adjusted for demographics, comorbidities, past use of HCV drugs, and health care use.

Results: We identified 10 267 treated HCV patients; 76% with LDV/SOF, 17% with SIM/SOF, 7% with OPrD + ribavirin (RBV). The median age was 59 years (interquartile range 54-62), 62% were male, 10% used other HCV drugs, and 20% were covered by Medicaid. At baseline, compared with patients covered by private plans/Medicare, Medicaid patients had a higher frequency of cirrhosis (45 vs 29%), hepatic decompensation (19 vs 11%), anaemia (19 vs 13%), HIV co-infection (9 vs 3%), and history of drug or alcohol abuse (20 vs 5%). Among all patients, therapy completion rates (95% confidence interval, CI) were 84.8% (82.2-87.4) for OPrD + RBV, 80.2% (78.4-82.1) for SIM/SOF, and 77.0% (76.1-77.9) for LDV/SOF. In patients with baseline cirrhosis, the rate for LDV/SOF was 89.5% (88.3-90.8) and for OPrD+RBV was 83.7 (78.4-88.9). In patients with previous use of other HCV drugs, the rates were 92.1% (90.2-94.0) and 89.5 (79.7-99.2), respectively. The rate measured at 8 weeks was 95.2% (94.7-95.6) for LDV/SOF. Compared with SIM/SOF, OPrD + RBV (adjusted OR 1.66, 95%CI 1.27-2.19) had higher odds of therapy completion. Medicaid patients did not have different odds to achieve therapy completion (adjusted OR 0.92, 95% CI 0.81-1.05) compared with private plans/Medicare.

Conclusions: These real-world data demonstrate that the majority of patients on LDV/SOF and PrOD regimens completed therapy and some patients' factors may facilitate therapy completion.

1094 | Outpatient antimicrobial prescriptions to Japanese children

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Background: Antimicrobial resistance is among the greatest public health threats. In April 2016, a national action plan for antimicrobial resistance was released in Japan. This plan has eight parts. One of these is a reduction in the use of oral cephalosporins, quinolones, and macrolides per 1000 inhabitants in 2020 by 50% of the level of use in 2013. In Japan, oral antimicrobials accounted for 90% of total antimicrobial consumption; prescription rates were also higher among children. It is necessary to investigate the prescription patterns of antimicrobials for children.

Objectives: The objectives of this study were to describe the prescription patterns of oral antimicrobials for children in Japan and examine the possibility of oral antimicrobial reduction by promoting appropriate use for children in Japan.

Methods: This was a retrospective, descriptive, administrative claims database study. Data were obtained from an administrative claims database maintained by the Japan Medical Data Center Co, Ltd (Tokyo, Japan). Drug information is coded through the Anatomical Therapeutic Chemical system, and diagnoses are coded by the International Classification of Diseases, Tenth Revision. The dataset was extracted from the records between January 2013 and December 2015. We defined bacterial diagnoses, analyzed outpatient claims for oral antimicrobials prescribed, and identified diagnoses for which antimicrobials are not recommended (common cold, acute sinusitis, gastroenteritis, non-suppurative otitis media, and acute bronchitis). We then identified claims with any secondary bacterial or non-bacterial diagnoses.

Results: Third-generation cephalosporins were mostly prescribed for children, followed by macrolides, penicillin, and quinolones. Acute bronchitis was the most identified diagnosis for which antimicrobials were not recommended, accounting for third-generation cephalosporins (24%), macrolides (36%), penicillin (22%), and quinolones (11%).

Conclusions: Our results revealed that some antimicrobials for children were prescribed for diagnoses for which antimicrobials were not recommended. Third-generation cephalosporins and macrolides for treating acute bronchitis in children had the reduction possibility of overuse. Moreover, quinolones were prescribed appropriately for children. We need to carefully choose antimicrobials for non-bacterial diseases.

1095 | Linezolid use in pediatric patients

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Background: Linezolid is used to treat bacterial infections, including pneumonia, skin infections, and infections caused by resistant bacteria. Linezolid use in pediatric patients is not well described.

Objectives: To determine the distribution of children aged 0 to 11 years receiving oral linezolid prescriptions.

Methods: The analysis was conducted using Truven MarketScan, a large US insurance claims database, and Cerner Health Facts[®], a US-based electronic health record database. Using Truven, all outpatient oral linezolid prescriptions for children aged 0 to 11 were identified through 2016-12-31. Linezolid use was described by year and age, using the first prescription per person per year. Linezolid prescription rates by age were calculated, where the denominator was the total number of children enrolled in that age group. This analysis was repeated for inpatient oral linezolid prescriptions identified in Cerner.

Results: There were 2813 outpatient oral linezolid prescriptions. Overall, 1-year-olds accounted for the most prescriptions (14%), while the remaining age groups represented a relatively similar proportion of prescriptions (7-9%). There was some fluctuation in prescriptions over time; however, the number of prescriptions was similar across age

groups. Similarly, the rate of prescriptions was highest in 1-year-olds with relatively similar rates shown among the other age groups.

A total of 638 inpatient oral linezolid prescriptions were identified. The <1-year-old age group received the most linezolid prescriptions (24%) followed by 1-year-olds (16%). The percent of linezolid prescriptions was similar among the remaining groups. The age distribution among patients receiving linezolid changed over time. Overall, <1- and 1-year-olds accounted for the most linezolid prescriptions each year (30-70% depending on year, with a lower proportion identified in more recent years). Similar to outpatients, the rate analysis showed the highest prescription rate in 1-year-olds. A low rate in the <1-year-olds was identified, likely due to a large inpatient denominator that included admissions for healthy newborns.

Conclusions: In the outpatient setting, where the majority of oral linezolid prescriptions occur, the overall number of prescriptions is relatively similar within each pediatric age group with the most prescriptions identified in 1-year-olds. In the inpatient setting, the percent of linezolid prescriptions among each age group varies more widely and the majority of prescriptions occurred in the <1- and 1-year-olds age groups; however, the use has decreased over time.

1096 | Antimicrobial stewardship program: An adventure from erratic towards utopia

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Background: Inappropriate antibiotic use has led to emergence of human infections due to multi-drug resistant (MDR) bacteria. Developing nations such as India are fertile breeding grounds for these organisms.

Objectives: To study hospital antibiotic (Abx) prescribing practices and to evaluate the impact of an educational intervention, as part of antimicrobial stewardship program.

Methods: A) A prospective study was conducted to obtain baseline antibiotic usage data at 1800 bed university hospital in south India. B) Antibiotic use in Defined Daily Doses (DDD) were calculated retrospectively. C) Data on use of reserve Abx for >7 days was captured. D) Capacity building workshops were conducted for 97 physicians and 25 microbiologists to provide them with rational approaches to dealing with Abx and a questionnaire was drafted to assess knowledge pre and post session. E) Clinical pharmacist driven screening of antibiotic use is now performed in the intensive care unit. Finally, before-after data were analyzed to assess the impact of the interventions.

Results: Over a 2 months baseline period, microbiological evidence (ME) for Abx selection was absent in 70% of patients; where ME was present, 4% of patients were prescribed with resistant Abx, and only 17% of MSSA patients were prescribed, designated 1st line antibiotics. Among patients on reserve Abx for >7 days, 43% were in ICU and 53% had ME to guide prescribing decisions. Meropenem and vancomycin were the most abused, with use in 55% of patients

without ME: the average treatment duration was 10.6 and 10 days respectively. The workshop for physicians and microbiologists demonstrated a post-test knowledge median of 78.90 (IQR 61.20-92.55), significantly different from the pretest median 61.20 (IQR 48.60-77.85): $p=0.028$ and post-test median of 68.05 (IQR 57.50-89.40), significantly different from the pretest median 55.00 (IQR 42.10-66.60): $p=0.017$, respectively. Initially DDD/100 bed days of meropenem, linezolid, vancomycin and teicoplanin were 6.58, 1.27, 0.50 and 1.44 whereas post intervention, DDD/100 bed days were 1.45, 0.18, 0.14 and 0.48 respectively: 37% of patients on reserve Abx lack an ME but 55% were prescribed an inappropriate dose. Out of 47 therapy recommendations from the clinical pharmacist, 60% were adopted by the physician.

Conclusions: Our study findings underscore the need for developing customized antibiotic stewardship programs emphasizing education of healthcare professionals for wiser use of antibiotics in settings with a high burden of MDR organisms.

1097 | The trend of inpatient utilization of colistin in Taiwan from 2006 to 2013: A cross-sectional study

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Background: According to the Infectious Diseases Society of America guidelines, colistin is indicated for the emergence of multidrug resistant (MDR) bacteria since 2012, particularly in hospital-acquired pneumonia. Drug utilization studies provide insights into the current prescribing practices and may further facilitate the rational use of drugs.

Objectives: To assess the trend of inpatient consumption of colistin in Taiwan across 2006-2013.

Methods: We performed a cross-sectional study by using 1 million sampling dataset (Longitudinal Health Insurance Database, LHID2010) which derived from Taiwan's National Health Insurance Research Database (NHIRD) from 2001 to 2013. The colistin use was presented as DDDs/1000 bed days. The age-standardized in-hospital mortality rate was a weighted average of the age-specific mortality rates per 100 000 patients by using WHO standard population.

Results: The consumption of colistin was significantly increased after year 2006, although lower before 2005. The consumption of colistin were 0.01DDD/1000 bed days, 1.34DDD/1000 bed days, and 7.37DDD/1000 bed days in 2006, 2009, and 2013, respectively. Age-standardized of colistin used were 0.01DDD/1000 bed days, 2.41DDD/1000 bed days, and 2.95DDD/1000 bed days in 2006, 2009, and 2013, respectively. The elderly group accounted for the major consumption, which increased dramatically over the study years. (0.14DDD/1000 bed days in 2007, 12.9DDD/1000 bed days in 2013). The in-hospital mortality was increased with age, from 0.57

per 100 000 bed days (<20 years old) to 10.55 per 100 000 bed days (≥ 80 years old). Compared with patients who aged 50-59 years, adjusted rate ratio of in-hospital mortality was 1.73 (1.22-2.46), 2.88 (2.13-3.89), and 4.94 (3.78-6.46) in 60-69 y, 70-79 y, and ≥ 80 y, respectively.

Conclusions: There is an increasing trend toward consumption, while the quality use of colistin needs further investigation.

1098 | Reducing inappropriate supply of opioids at hospital discharge

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Background: Opioids are an area of global concern from a public health perspective. Between 2008 and 2014, there was an 87% increase in prescription opioid related deaths in Australia, with the greatest increase occurring in rural/regional Australia which saw a 148% increase. It is thought that inappropriate opioids prescribed at discharge from hospital are contributing to this epidemic. This study was conducted in an Australian tertiary hospital which utilises an electronic medicines management system (EMMS). To comply with regulatory requirements, Australian prescribers are required to write the quantity of opioids in words and figures on the prescription. A decision support alert (DSA) is provided on EMMS to remind prescribers of this requirement when they prescribe oxycodone IR on discharge.

Objectives: To determine if decreasing the example quantity within the DSA reduces the quantity of oxycodone IR prescribed at discharge.

Methods: A retrospective audit of prescriptions and dispensing data was used to analyse pre and post intervention data. During period 1 (01-15/06/2017), the DSA stated "please supply twenty (20) tablets" when prescribing oxycodone IR on discharge. The DSA was changed on the 28/08/2017 to "please supply ten (10) tablets." Post intervention data was examined in period 2 (01-15/11/2017). Proportion of discharges containing oxycodone IR, quantity provided and appropriateness of quantity supply was compared between the two time periods. Appropriateness was assessed by opioid use 48 h prior to discharge converted to a 3-day quantity of oxycodone IR by using a conversion table within Therapeutic Guidelines. Doses were rounded up to whole tablets; supply quantity was deemed appropriate if the supply was equal or less than the individually calculated 3-day requirement.

Results: 587 discharges were dispensed in period 1; 147 (25%) contained an opioid, with the most common being oxycodone IR, 130 (22%). In period 2, 633 discharges were dispensed with 176 containing an opioid (28%), 137 being oxycodone IR (22%). There was no significant change in the quantity of oxycodone IR provided in the two periods, 1584 vs 1552 ($p = 0.57$); the appropriateness of the quantity supplied (appropriate quantities for 43 patients vs 48,

$p = 0.74$); patients who were provided oxycodone IR on discharge after not receiving a dose of opioids 48 h prior to discharge, 32 vs 26 ($p = 0.26$).

Conclusions: A change to the DSA provided at the time of prescribing on discharge did not decrease the quantity or appropriateness of oxycodone IR supplied.

1099 | Evaluation of Antimicrobial Stewardship Programs implementation and outcomes using quasi experimental study design, in a selected hospital at Makkah, Kingdom of Saudi Arabia

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Background: Antimicrobial therapy for management of severe infections among critically ill patients is challenging due to unstable hemodynamic status of patients. Antimicrobial stewardship program is a collaborative effort to optimize antimicrobial use in health care institutions through evidence based quality improvement strategies.

Objectives: The aim of this research was to evaluate the impact of Antimicrobial Stewardship Programs (ASP) implementation in a critical care setting for improving antimicrobial use, cost, and clinical outcomes at selected hospital at Makkah region, Kingdom of Saudi Arabia.

Methods: A controlled interrupted time series analysis was used to compare outcomes in the 9 months before and after ASP implementation.

Results: Mean total monthly antimicrobial consumption measured as defined daily dose (DDD) per 100 bed days was reduced by 25 % (742.86 vs 555; $P = 0.1$) as compared with control group by 7 % (35 vs 38; $P = 0.735$). Total antimicrobials cost measured as total mean cost per 100 bed days was increased by 55% (38 723 vs 87 552; $P = 0.067$). The use of IV Ceftriaxone measured as defined daily dose per 100 bed days was decreased by 82 % (94 vs 17; $P = 0.008$), whereas oral Vancomycin use was increased by 84 % (27 vs 172; $P = 0.008$) in ICU.

Conclusions: Overall, based on the present study findings, involvement of higher administration in multidisciplinary ASP committees, daily audit, and feedback by clinical pharmacist and physicians with infectious diseases training and support from intensive care team are key sets of recommendations that can be made to enhance quality use of antibiotics in Saudi health care institutions.

1100 | Pharmacy closures and adherence to cardiovascular medications among older adults in the United States

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Background: It is unknown whether and how pharmacy closures affect medication adherence.

Objectives: To quantify the effect of pharmacy closures on adherence to statins, beta-blockers, and oral anticoagulants among adults aged 50 years or older in the United States.

Methods: Retrospective comparative interrupted time-series analyses using a nationally representative 5% sample of anonymized, individual-level pharmacy claims from IQVIA LRx LifeLink. Analyses were conducted on a continuously observed individuals from January 2011 through December 2015. Separate cohorts were derived for users of statins, beta-blockers, and oral anticoagulants, and the differential effect of closures was examined based on baseline adherence as well as pharmacy (eg, independent vs chain) and community (eg, low vs high pharmacy density) characteristics. Difference in monthly adherence, measured as proportion of days covered, during 12-month baseline and follow-up periods among patients using a pharmacy that closed (closure cohort) were compared with their counterparts (control cohort)

Results: Among 3.1 million individuals filling at least one statin prescription between January 2012 and December 2015, 3.0% (N = 106 150) filled at a pharmacy that subsequently closed. Monthly baseline adherence was similar in closure and control cohorts (71.3% vs 70.7%). In multivariable models, individuals filling at pharmacies that closed experienced, on average, a significant decline (−5.0% absolute change, 95% confidence intervals [CI] −5.19 to −4.79) in statin adherence when compared with their counterparts that persisted over a 12-month period. A similar decline in adherence was observed among closure cohorts when examining use of -blockers (−4.9%, CI −5.14 to −4.67) and oral anticoagulants (−4.5%, CI −5.10 to −4.61). The effect of pharmacy closures on adherence was greater among individuals using independent pharmacies, filling all their prescriptions at a single store or living in neighborhoods with fewer pharmacies.

Conclusions: Pharmacy closures are associated with persistent and clinically significant declines in adherence to essential cardiovascular medications among older adults in the United States. Efforts aimed at reducing barriers in access and adherence to prescription medications should consider the role of pharmacy closures, especially in patients at highest risk.

1102 | Hormonal contraceptive use in Norway, 2004-2016: A nationwide register-based study

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Background: Since 2002, public health nurses and midwives in Norway have had the right to prescribe oral contraceptives for women 16-19 years. This arrangement has been changed several times and from 2016 gave them the right to prescribe all contraceptives including long-acting reversible contraceptives (LARCs) to women over 16 years. In the last years, LARCs have been increasingly recommended in most countries.

Objectives: To examine how hormonal contraceptive use in Norway has developed during 2004-2016, including choice of contraceptive method (oral contraceptives or LARCs). In addition, we want to study what profession prescribes the different types of contraceptives.

Methods: Data on hormonal contraceptives (Anatomical Therapeutic Chemical [ATC] codes G03A, G02B, and G03HB) was provided by the nationwide Norwegian Prescription Database. All women who had been dispensed contraceptives at least once during 2004-2016 (N = 989 723) were included.

Results: In 2016, 393 978 (34% of the population) women 16-49 years of age received hormonal contraceptives at least once. The annual prevalence of use was stable during 2004-2016, ranging from 31 to 34%. The most commonly used contraceptive was combined oral contraception pills, 20% in 2016. Women 20-24 years old had the highest prevalence, ranging from 60-64%. From 2014 to 2016, the use of LARCs increased, especially among 16-19 year olds, where the prevalence increased from 1.6% to 7.7%. For women aged 16-19 years, 4.1% and 4.3% were prescribed LARCs by physicians in 2015 and 2016, respectively. In 2016, 3.4% women in the same age group were prescribed LARCs by public health nurses or midwives. The most commonly used LARCs for 16-24 years was subdermal implants, while for women over 25 years it was intrauterine devices.

Conclusions: The overall use of hormonal contraceptives was stable during 2004-2016. Use of LARCs increased especially in younger women. Public health nurses and midwives contributed to the increase in use of LARCs among young women in 2016.

1103 | Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions from the 6th month of pregnancy: Impact of health authorities' advice

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1101 | Abstract Withdrawn

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs. On June 2008 and February 2009, Dear Doctor Letters (DDL) were sent by French health authorities (AFSSAPS) to remind the risk of premature closure of the fetal ductus arteriosus with NSAIDs after 5 months of pregnancy.

Objectives: To evaluate the impact of Dear Doctor Letters on NSAIDs prescriptions during late pregnancy.

Methods: EFEMERIS is a French database including prescribed and reimbursed drugs during pregnancy and outcomes between 2004 and 2015. We performed a descriptive study and a "before-and-after" comparison of NSAIDs prescriptions between June 2, 2006, and June 3, 2008 ("before group"), and between March 1, 2010, and March 1, 2012 ("after group"). We realized Cochran Armitage trend test for checking whether NSAID exposed women's rates can be considered to vary linearly over time.

Results: We identified 1626 pregnant women ($n = 948$ [4.38%] in "before group" and $n = 678$ [2.73%] in "after group"; $P < 0.0001$) received at least one NSAID in late pregnancy. Between 2006 and 2012, morniflumate/niflumic acid (1.7% versus 0.9%; $P < 0.0001$), ibuprofene (0.8% versus 0.6%; $P = 0.01$), ketoprofen (0.7% versus 0.3%; $P < 0.0001$), acetylsalicylic acid (0.1% versus 0.05%; $P = 0.002$), and tiaprofenic acid (0.1% versus 0.05%; $P = 0.02$) dispensations decreased significantly after DDL, unlike flurbiprofene dispensations (0.03% versus 0.1%; $P = 0.03$). However, the prescriber's specialty was no difference between the two groups. Cochran Armitage trend test shows that the rate of women exposed to NSAID in late pregnancy decreased significantly during the study period ($P < 0.0001$). Sensitivity analysis found that the rate of women exposed to systemic NSAIDs decreased significantly after DDL (2.7% versus 1.7%; $P < 0.0001$).

Conclusions: The present study showed a significant decrease of the rate of women having a NSAID prescription in late pregnancy after DDL. This decrease does not affect a particular women's profile or a specialty of prescribers. These results are reassuring although the "before-and-after" design does not allow us to be sure of causal link.

1104 | A descriptive study of switching patterns among MS patients who started on Glatopa® therapy: A claims database analysis

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Background: Glatopa 20 mg/mL was introduced in April 2015 as a follow-on glatiramer acetate (FOGA) therapy for patients with multiple sclerosis (MS). However, little is known about patterns of Glatopa 20 mg/mL (FOGA) use since becoming commercially available.

Objectives: To describe the demographic characteristics and switching patterns of MS patients with FOGA use from a large US claims database.

Methods: The study sample included adult Medicare Advantage enrollees with Part D coverage (MAPD) meeting the following inclusion criteria: ≥ 1 pharmacy claim for FOGA between 01 Jun 2015 and 31 Jun 2016 (identification period). Index date was the date of the first pharmacy claim for FOGA during the identification period. Patients had continuous enrollment in a single health plan at least 6 months prior to index date and at least 3 months following index date. Discontinuation of FOGA was defined as a gap in therapy (ie, days without the medication) of at least 30 days. Therapies used by patients after discontinuation were also analyzed.

Results: A total of 95 subjects were included in the analysis (76% female, average age 61 years, average 428 days of follow-up). Eighty-four patients (88%) had a fill for Copaxone® 20 mg/mL (branded glatiramer acetate [GA]) once daily at some time prior to index date. Fifty-five patients (58%) were non-persistent on FOGA, either discontinuing with no evidence of another therapy or switching to another therapy. Overall, 31 patients (33%) switched to branded GA 20 mg/mL once daily, and 9 (9.5%) switched to branded GA 40 mg/mL three times weekly. Seventeen patients (18%) restarted FOGA after discontinuation or switch. The average length of FOGA persistence before switch or discontinuation was 112 days.

Conclusions: Although the study sample was small, and the exact reasons for switch need to be further investigated, this study highlights the importance of understanding patient persistence and switching behaviors when they start on a new MS therapy. Further studies are needed to confirm and further investigate these findings.

1105 | The effect of a regulatory action to prevent therapeutic duplication of respiratory drugs in Korea

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Background: In 2013, Korean regulatory announced respiratory drugs for which therapeutic duplication (TD) caution is provided to prescriber through the computerized system.

Objectives: To describe prescribing patterns of these drugs and estimate changes in TD prevalence after the announcement.

Methods: We conducted a time series analysis by using National Health Insurance Sampled data. Study drugs included 53 respiratory drugs (8 classes), and study subjects consisted of the patients prescribed any of these drugs at least once during their outpatient visits between January 2012 and December 2015. We used two definitions of TD: duplicative prescriptions overlapped for more than 30 days by the same prescriber and for more than 1 day by different prescribers. These definitions are identical to the conditions of providing caution information to prescribers through the system. We calculated relative differences (RD) and absolute differences (AD) in prevalence of TD

before and after the action and reviewed the distribution of the duplication period. Monthly rates were calculated and paired *t* test was conducted.

Results: In TD by the same prescriber, the decrease was found in non-decongestants, leukotriene receptor antagonists, xanthine bronchodilators, anti-allergic drugs, mucolytic agents, and cough suppressants, while increase were found in anti-histamines and beta-receptor agonists; the RD and AD (%) after the action were +10.28 and +0.053 in anti-histamines and +4.15 and +0.005 in beta-receptor agonists. In TD by different prescribers, the decrease was only found in xanthine bronchodilators (RD = -7.55, AD = -0.302), but seven out of eight classes were in increasing trend. (RD = +0.93, AD = +0.071 in anti-histamines; +4.14 and +0.155 in non-decongestants; +16.10 and +0.445 in leukotriene receptor antagonists; +27.07 and +1.418 in beta-receptor agonists; +7.69 and +0.084 in anti-allergic drugs; +11.16 and +0.669 in mucolytic agents; +15.64 and +0.515 in cough suppressants).

Conclusions: The 2013 regulatory action regarding respiratory drugs had little effect on the prevention of TD. More effective interventions should be developed to reduce TD of respiratory drugs.

1106 | Reducing the Drug Burden Index—A post hoc analysis of a randomised controlled trial using machine learning

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Background: In a randomised controlled trial, we did not find a significant difference in the proportion of patients with a decreased drug burden index between those who received and did not receive a medication review. A low burden of anticholinergic/sedative medication, measured by the drug burden index, is beneficial for older patients. Therefore, it is important to explore whether there was a subgroup of patients who may have benefitted from the medication reviews.

Objectives: In this post hoc analysis, we aimed to use machine learning techniques to identify classifiers to distinguish patients with a reduction in drug burden index from patients without reduction.

Methods: This was a post hoc analysis of data from a randomized controlled trial. The outcome was a decrease of at least 0.5 in the Drug Burden Index (DBI). This is the reduction of about one anticholinergic/sedative medication. Predictors were baseline medication data and several patient reported outcome measures including quality of life and the 7-minute screen as a measure of cognition. Data of the intervention and control groups were analysed separately using Bayesian binomial modeling and generalized matrix learning vector quantization (GMLVQ) both with backwards elimination. Receiver operating characteristic (ROC) curves and the corresponding area under curve (AUC) values were calculated.

Results: 157 patients, (75 intervention, 82 control), mean age 76.2 (SD, 6.9), 70.7% female were included. A higher than average age and a higher than average number of medications of the Anatomical Therapeutic Classes of Alimentary Tract and Metabolism (ATC-A)

and Genito Urinary System (ATC-G) and lower scores on the 7-minute screen test were predictors in the intervention group for a decrease in the DBI. AUC of the Bayesian binomial modeling was 0.82, AUC of the GMLVQ was 0.84. No predictors were identified in the control group data (AUC were about 0.5).

Conclusions: A subgroup of patients with older age, impaired cognition, and use of medications from ATC-A and G may have benefitted from the medication reviews. This suggests to target medication reviews to those patients in follow-up studies.

1107 | Drug utilisation patterns in older patients admitted to geriatric wards in Norway. Using network analysis to shed light on the changes in patterns

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Background: Network analyses have rarely been used to explore and visualize drug utilisation patterns. We believe that it has potential application in various studies, and we have applied it in a geriatric setting to show how it can be used.

Objectives: To describe changes in drug utilisation after a patient has been admitted to a geriatric ward in Norway.

Methods: The dataset contains prescriptions dispensed through pharmacies in Norway to persons first admitted to a geriatric ward in 2013. In order to look at drug utilisation before and after the hospital stay, we used a 120-day window before admission and 120 days after discharge. Any patients with additional hospital stays during these time windows were not included in the study population. The most prescribed substances during the time windows before and after were calculated and change were defined as the percentage increase/decrease in number of users. Networks of co-medication was created before, after, and using the change. Networks were formed using the nwcommands package in Stata 14.2 and the networks were visualised using Gephi version 0.9.2.

Results: Our study population consists of 1061 patients (mean age: 84 years [SD 7.9], 64% women). On average, a patient received 6.2 substances (SD 3.8) before admission and 6.1 substances (SD 4.3) after discharge. The five most commonly dispensed substances before is acetylsalicylic acid (375 pt), metoprolol (281 pt), zopiclone (240 pt), paracetamol (229 pt), and simvastatin (216 pt). The list only has one change after discharge with calcium now being the fifth most dispensed, replacing simvastatin.

Changes in drug utilisation patterns occur for analgesics where weak opioids and ibuprofen are removed while paracetamol and oxycodone is added. Similarly, benzodiazepines are removed while the antidepressant mirtazapine is added.

The network analyses show that combinations such as zopiclone and diazepam, codeine and tramadol and preventive therapies such as simvastatin in combination with losartan/hydrochlorothiazide and metformin were stopped.

Conclusions: The changes in drug utilisation patterns in older patients after staying at a geriatric ward seem to be related to improved pain

management and preventing falls. Further analyses into the patterns of co-medication might reveal additional interesting features and will be presented at ICPE 2018.

1108 | Preventing a rise in anticholinergic and sedative medication load: Feasibility of an innovative pharmacist-led intervention

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Background: Anticholinergic and sedative medications are commonly used by older individuals despite their negative effects on cognitive- and physical function. Effective interventions to reduce the load are urgently needed. Preventing a rise in load by taking action before chronic use of anticholinergic/sedative medications is established, may be the most promising approach.

Objectives: To test the feasibility and likely effectiveness of a pharmacist-led intervention for preventing a high anticholinergic/sedative load among older individuals.

Methods: A feasibility study in 50 community pharmacies in the Netherlands was conducted between September and December 2017. Potential patients were identified by screening electronic dispensing records for all persons aged ≥ 65 years, with a new anticholinergic and/or sedative medication which increased their total Drug Burden Index (DBI) to ≥ 2 (equals about 4 anticholinergic/sedative medications). Pharmacists selected 5-10 patients identified via the screening, evaluated medication use with the patient and discussed recommendations to reduce anticholinergic/sedative medication with the prescriber. Feasibility of the intervention was measured on several levels: patient screening, rate of agreement between pharmacist and prescriber on recommendations to change medication, and pharmacists' satisfaction with the intervention and time investment.

Results: Per pharmacy on average 18.1 (SD, 11.0, range 1-45) patients were identified with the screening tool. From the identified patients, 327 patients were selected by the pharmacist and included in the analysis: mean age 76.6 years (SD, 8.0), 62.4% female, mean 9.2 (SD, 3.4) medications, and mean DBI 3.6 (SD 1.3). Most common newly prescribed medications were oxycodone (16.5%), codeine (13.8%), and tramadol (12.5%). Recommendations to change medication were proposed for 59.6% of patients and agreement on change was reached for 33.3% of patients. 45 pharmacists (90%) were satisfied with the intervention (18 completely, 27 partly), and 36 pharmacists (72.0%) want to keep using the intervention. The median time investment per patient was 34 minutes (range 6.5-290).

Conclusions: The intervention was feasible and likely to be effective, as in one third of patients the rise in anticholinergic/sedative medication was prevented within reasonable time investment. Results can be used to refine screening criteria.

1109 | Prescriber agreement with pharmacists' recommendations to reduce anticholinergic/sedative load

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Background: Anticholinergic/sedative medications are commonly used by older individuals despite their negative effects on cognitive- and physical function. We found that a pharmacist-led intervention aiming at reducing a rising load in patients who recently had a newly prescribed anticholinergic/sedative medication was likely effective. It is unknown which patients benefitted mostly from the intervention.

Objectives: To determine the factors associated with agreement of a prescriber on pharmacists' recommendations to reduce anticholinergic/sedative load.

Methods: Feasibility study in 50 community pharmacies in the Netherlands conducted between September and December 2017. Potential patients were identified by screening electronic dispensing records for patients aged ≥ 65 years, with a new anticholinergic/sedative medication which increased their Drug Burden Index (DBI) to ≥ 2 (about 4 anticholinergic/sedative medications). Pharmacists selected 5-10 patients identified via screening, evaluated medication use with the patient, and discussed recommendations to reduce anticholinergic/sedative load with the prescriber. With logistic mixed effects models, we analyzed the association of patient characteristics, type of medication, type of recommendation, and type of communication between pharmacist/general practitioner (GP) with prescriber agreement on pharmacists' recommendations. We applied random effects on the level of pharmacy and patient.

Results: Pharmacists selected 327 patients (mean age 76.6 years [SD, 8.0], 62.4% female). For 195 patients (59.6%), 334 recommendations were proposed with on average 1.7 (SD, 0.9) recommendations per patient. Prescribers agreed with 149 (44.6%) recommendations. Agreement was more likely for recommendations on newly prescribed medication (OR 2.99, CI 1.58-5.66), medication prescribed by a specialist (OR 4.08, CI 1.71-9.71), cardiovascular medication (ATC C, OR 3.79, CI 1.61-8.92), respiratory medication (ATC R, OR 4.15, CI 1.60-10.78), alimentary tract medication (ATC A, OR 3.36, CI 1.35-8.37), and recommendations discussed in a face-to-face meeting with the GP (OR 2.16, CI 1.24-3.75). Agreement was less likely for

older patients (OR 0.97, CI 0.94–1.00) or recommendations for medication substitution (OR 0.34, CI 0.18–0.62).

Conclusions: Several factors were identified that increase the likelihood of agreement on pharmacists' recommendations to reduce anticholinergic/sedative load. Results can be used to refine the intervention.

1110 | Efficient selection of older patients for medication review: Development and validation of a selection algorithm

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Background: Performing medication reviews in older people with multiple medication can increase medication appropriateness as well as adherence. In the Netherlands, there are around 750 000 older people with at least 5 chronic medications, who may be eligible for medication reviews. To conduct such reviews efficiently, a suitable selection procedure is needed.

Objectives: To develop and validate an algorithm that is able to select complex patients most in need of a medication review.

Methods: We constructed an algorithm from 80 patient cases. An expert panel of 9 community pharmacists and 7 general practitioners rated the complexity of the cases in a modified Delphi method. Each case was judged by 8 experts. The median of the complexity rating for cases with consensus was used to develop the selection algorithm. We used backward stepwise linear regression with a minimum number of case characteristics to give good prediction (high adjusted R^2). The resulting algorithm was applied in 4 community pharmacies in the Netherlands to test its feasibility and validity. We selected a random sample of up to 5 complex and 5 simple cases per pharmacy, and compared these on (1) time needed for the review, (2) number of proposed and of implemented interventions, using t tests. We also compared the complexity rating of the algorithm with the rating of the community pharmacists using kappa statistics.

Results: The expert panel reached consensus on 75 cases. The cases had a mean age of 79 years, 48% were males, and mean number of prescribed drugs was 10. The final regression model predicted the complexity ratings significantly (adjusted $R^2 = 0.726$, $P < 0.0001$) and resulted in the following algorithm: "number of drugs" $\times 1$ + "number of prescribers" $\times 3$ + "recent fall incident" $\times 7$ + "does not collect own medication" $\times 4$. Applying this algorithm in 4 pharmacies resulted in a sample of 170 patients, of which 19 complex and 19 simple cases received a medication review. Medication reviews took on average 77 minutes in the complex and 66 minutes in the simple group ($P = 0.134$). No difference was found in the number of proposed ($P = 0.658$) or implemented ($P = 0.515$) interventions. The pharmacists agreed with the algorithm on complexity of the patients in 71% of the cases (kappa = 0.42).

Conclusions: We developed an easy to apply algorithm including four common case characteristics to identify complex patients for a medication review. The algorithm showed moderate agreement with judgments of community pharmacists.

1111 | Implications of Medicare Part D cost-sharing on disease-modifying therapy initiation among individuals with multiple sclerosis

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Background: Medicare beneficiaries with multiple sclerosis (MS) often face high out-of-pocket costs for disease-modifying therapies (DMTs). It is unclear how cost-sharing affects therapy initiation.

Objectives: To estimate the effects of patient cost-sharing on initiation of a DMT among newly diagnosed Medicare beneficiaries with MS.

Methods: Using Medicare claims data from 2010 to 2014, we identified a cohort of individuals with at least one inpatient or two outpatient diagnostic claims for MS. We restricted this group to beneficiaries with continuous Part A, B, and D coverage in the year before and after their initial diagnosis. Dual eligible were excluded. Beneficiaries with a Part D Low Income Subsidy (LIS) are shielded from cost-sharing. To estimate the effect of cost-sharing on time to DMT initiation, we compared beneficiaries with LIS to those without using multivariate Cox Proportional Hazards models adjusting for potential demographic and health-related confounders.

Results: There were 39 661 new diagnosed Medicare beneficiaries who met inclusion criteria; 3827 had full LIS benefits throughout the study period. Beneficiaries were predominately White (36 447, 91.9%) and female (29 406, 74.1%). LIS recipients were generally younger (55 vs 67 years, $p < 0.001$) and more likely to be enrolled through disability eligibility (79% vs 36%, $p < 0.001$). LIS recipients were also more likely to have chronic conditions indicating fibromyalgia, chronic pain, and fatigue (27% vs 15%, $p < 0.001$), depression (32% vs 23%; $p < 0.001$), and headache (10% vs 4%, $p < 0.001$). In the year after their index diagnosis, 434 LIS recipients initiated DMT versus 1682 non-LIS (11% vs 5%; $p < 0.001$). Among those who started a DMT, the average time to initiation was 115 days in those with LIS and 137 days for non-LIS ($p < 0.001$). After adjustment for covariates, individuals with LIS benefits were significantly more likely to initiate a DMT in the year following their diagnosis (adjusted hazard ratio 1.4, 95% CI 1.25 to 1.57).

Conclusions: Medicare beneficiaries with MS who are shielded from traditional cost-sharing are more likely to initiate a DMT in the year following their diagnosis. Future work should examine the effect of cost-related treatment delays on relapse rates and disability progression.

1112 | Tobacco cessation treatment utilization by Kentucky Medicaid recipients before and after Medicaid expansion and mandated tobacco treatment coverage: 2013-2015

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Background: Kentucky, and the Appalachian region in particular, faces disproportionate burden of tobacco-related morbidity and mortality. The Affordable Care Act (ACA) expanded Medicaid eligibility and required all health plans to cover two smoking quit attempts per year starting in 2013, where quit attempts are defined as four cessation counseling sessions and/or 90-day supply of any FDA-approved tobacco cessation medication.

Objectives: To describe tobacco use incidence and tobacco cessation treatment utilization in Kentucky, comparing by demographics and Appalachian status after ACA-mandated cessation treatment coverage in 2013.

Methods: The study design was a retrospective descriptive analysis of Kentucky Medicaid claims data from 2013 to 2015. Outcome measures were incidence of tobacco use and proportion of tobacco users receiving cessation treatment by year. Eligibility criteria included all Medicaid enrollees with (1) diagnosis of any tobacco use; and/or (2) procedure claim for tobacco cessation counseling; and/or (3) pharmaceutical claim for varenicline or nicotine replacement products (NRT). Chi square analysis was conducted for change in treatment utilization by year and treatment type.

Results: Tobacco use incidence increased from 52.11% (2013) to 63.97% (2015), likely due to an influx of male tobacco users in the enrollee population (30.39% in 2013 to 41.18% by 2015; $p < 0.001$). Tobacco cessation treatment utilization decreased overall (4.75% in 2013; 3.15% in 2015). Tobacco users receiving counseling decreased from 2.06% pre-ACA (2013) to 1.06% post-ACA (2015, $p < 0.001$), as did the proportion receiving NRT products post-ACA (1.99% in 2013 to 1.14% by 2015; $p < 0.001$). Less than 1% of tobacco users received varenicline during the study period, with significant post-ACA decrease (0.71% in 2013 to 0.41% by 2015; $p < 0.001$). More Appalachians received cessation treatment than non-Appalachians in 2013 (2.72% Appalachian; 2.03 non-Appalachian), but by 2015 non-Appalachians received more treatment (1.50% Appalachian; 1.65% non-Appalachian; $p < 0.001$).

Conclusions: Tobacco cessation treatment utilization, particularly varenicline, in Kentucky remained low despite Medicaid expansion, mandatory treatment coverage, and high tobacco use incidence. This suggests barriers to cessation treatment access such as lack of coverage information, inconsistent plan formularies, and prior authorization requirements.

1113 | Epidemiology and predictors of barriers to medication adherence using administrative claims and electronic health record data

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Background: Adherence to medications remains poor despite numerous efforts at predicting poor adherence. To our knowledge, none have attempted to predict patients' actual reasons for non-adherence using routinely-collected data from electronic health records (EHR) or administrative claims.

Objectives: To describe the epidemiology of barriers to adherence and identify key baseline predictors using EHR and claims data.

Methods: We used a linked EHR-claims dataset from a large pragmatic trial of poorly-adherent patients and uncontrolled cardiometabolic disease in the northeastern United States. This cohort included patients who completed a phone consultation with a trained pharmacist who classified patients with any of the following barriers: costs, forgetfulness/treatment complexity, health perceptions, low health literacy/knowledge, or side effects. Baseline demographic, clinical, and utilization factors were measured in the 12 months before the consultation in structured EHR (9 predictors) and claims data (16 predictors). We identified the most common clusters of barriers, defined as "phenotypes," and subsequently used logistic regression to identify key predictors of the most common adherence barrier phenotypes.

Results: In total, 1069 patients presented with 27 different adherence barrier phenotypes; 26.5% of patients had >1 barrier. The most common overall barrier was forgetfulness (39.0%); forgetfulness without other barriers was also the most prevalent phenotype (19.9%). Health perceptions without another barrier (9.3%), forgetfulness/health perceptions (8.0%), and experiencing side effects without another barrier (4.8%) were also common. Compared with other patients, distinguishing baseline factors of patients with the forgetfulness phenotype were fewer ER visits (Odds Ratio [OR]: 0.48, 95% CI: 0.23-0.98) and more office visits (OR: 1.06, 95% CI: 1.01-1.11). Patients with the health perceptions phenotype were less likely to speak English as their primary language (OR: 0.48, 95% CI: 0.23-0.93), were older (OR: 1.03, 95% CI: 1.00-1.06), and used fewer medications (OR: 0.89, 95% CI: 0.97-0.99).

Conclusions: The most common barrier to adherence was forgetfulness. Several baseline factors measurable in routinely-collected data, such as age, extent of medication use, and number of office visits or ER visits, were predictors of specific adherence barrier clusters. This information could inform future intervention or prediction efforts.

1114 | The emergency department pharmacist for improvement of under- and overtreatment with medication: An interim analysis

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Background: Drug-related problems can result in a substantial number of hospital admissions in The Netherlands. An important risk factor is polypharmacy and associated under- and overtreatment with medication. Medication reviews performed by emergency department (ED)-pharmacists may improve under- and overtreatment with medication in patients admitted due to drug related problems.

Objectives: To study the effect of medication reviews by ED-pharmacists on under- and overtreatment in ED-patients who are hospitalised due to drug related problems.

Methods: A prospective multicenter controlled intervention study was carried out. Patients admitted to the hospital after visiting the ED due to a drug related problem were included. Control patients were patients acutely admitted for another reason than a drug-related problem; they received routine care. For intervention patients, ED-pharmacists assisted in recognizing drug related problems and performed medication reviews. Primary outcome was the mean number of interventions in medication regarding under- and overtreatment (using the PCNE classification) after medication review performed by ED-pharmacists and by routine care. The difference between groups was analysed by the two-sample t-test.

Results: 64 intervention and 71 control patients were included. The mean number of interventions per patient regarding under- and overtreatment in control patients was 0.6 (SD±0.9) versus 2.3 (SD±2.1) in intervention patients ($p \leq 0.001$).

Conclusions: This interim analysis showed that medication reviews performed by ED-pharmacists contribute to additional interventions regarding under- and overtreatment in patients hospitalised due to a drug-related problem. The final study results are needed for more robust conclusions.

1115 | Community pharmacists' knowledge and practice toward non-prescription products used for weight control: A cross-sectional study

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Background: Obesity is considered as one of the major health problems with a rapid increase in its prevalence in Saudi Arabia. Previous

studies showed that most of obese people prefer using over-the-counter (OTC) slimming aids rather than non-pharmacological weight management methods (eg, exercise and diet). There is no data about the pharmacists' knowledge and practice toward weight loss products available in Saudi market.

Objectives: Assessment of knowledge and practices of community pharmacists in eastern region of Saudi Arabia toward non-prescription weight control products.

Methods: A cross-sectional study was conducted in the eastern region of Saudi Arabia from November 2013 to May 2014. A structured questionnaire was designed to identify the most commonly dispensed over-the-counter (OTC) products and assess community pharmacists' knowledge about their efficacy and safety. The evidence of safety and efficacy of the products identified from the questionnaire results was searched using Cochrane library, PubMed, and Google Scholar and then evaluated.

Results: Hundred pharmacists agreed to participate (Acceptance rate 92.59%). Their average practice experience was 7.48 ± 3.5 years. Participants dispensed 25 over-the-counter products for weight control, 50% of participants believed that these products do not have any serious side effects, and 65% of participants reporting asking the consumers about their medical history to avoid any disease-drug or drug-drug interactions. Green tea and its mixtures, Senna, and Chitosan were the most commonly OTC dispensed products (31%, 19.2%, and 8.8%, respectively) despite being not FDA approved and lack of consistent evidence of their efficacy and/or safety. While the FDA approved, Orlistat, was found to be dispensed in a lower rate (8%).

Conclusions: Majority of OTC products dispensed by community pharmacists for weight control lack evidence of efficacy and/or safety, and there is an obvious need to implement corrective educational and regulatory actions in this aspect.

1116 | Pharmacists' Involvement in rationalization of valganciclovir use in cytomegalovirus prophylaxis for renal transplant patients: A pilot single center study

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Background: Despite the proven efficacy of FDA and international consensus guidelines recommended valganciclovir regimens for cytomegalovirus (CMV) prophylaxis in renal transplant recipients, several centres implement regimens with lower doses and shorter durations due to accumulating evidence of cost-effectiveness.

The Armed Forces Hospital Southern Region Nephrology Centre, Khamis Mushait - Saudi Arabia, approved and implemented a protocol involving the use of valganciclovir 450 mg once daily for 3 months for CMV R+ recipients. A clinical pharmacist participated in the development of the protocol, and its implementation was monitored by AFHSR nephrology center pharmacists.

Objectives: Assessment of the clinical and economic outcomes of implementing AFHSR protocol of CMV prophylaxis in renal transplants.

Methods: Retrospective review of renal transplant recipients' charts from September 2016 till March 2017. The outcomes measured included number of pharmacists' recommendations and percentage of physicians' acceptance, days of therapy reduced and medication cost saving due to protocol implementation and pharmacists' interventions. Incidence of CMV infection and CMV related rejection was assessed by consultant nephrologist.

Results: Eighteen CMV R+ renal transplant recipients were included. Pharmacists interventions involved 7 of them (38.9%) with physicians' acceptance rate of 100%. All pharmacists' interventions were related to regimen duration. Compared with the FDA regimen, implementation of this protocol resulted in reduction of 1889 days of therapy (105 days/patient). For cost reduction, AFHSR protocol implementation resulted in medication cost saving of 519 116, 141 569 SR compared with FDA and guidelines regimens. Pharmacists' interventions resulted in reduction of 350 days of therapy (19 days/patient) and medication cost saving of 32 812 SR during the study period. For clinical outcomes, no patients developed CMV infection or CMV related rejection during a post-prophylaxis 6 months follow-up period.

Conclusions: Study findings suggest the cost-effectiveness of this regimen and pharmacists' involvement in its implementation.

1117 | The re-aim framework and REVLIMID REMS program: A methodology for REMS assessment using ISPE recommendations

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Background: To standardize the assessment approach to Risk Evaluation and Mitigation Strategy (REMS) programs, FDA, academia, and professional societies have recommended alternative evaluation models be considered. Traditionally, REMS Assessment Reports are based on FDA determined criteria. The RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) model, a public health program evaluation method, may be an applicable framework. In this study, we applied the RE-AIM framework to develop an alternative methodology for REVLIMID REMS[®] program assessment.

Objectives: To determine whether the RE-AIM framework could be applied successfully to the REVLIMID REMS program.

Methods: Using the International Society for Pharmacoepidemiology (ISPE) recommendations and the RE-AIM framework, we evaluated all REVLIMID REMS elements (Implementation Plan and 4 Elements to Assure Safe Use [ETASU]). Data availability, applicability of metrics/measurement criteria to each RE-AIM domain, and the model's overall ability to determine if the REMS program is meeting its goals were considered.

Results: Three proactive, required REVLIMID REMS ETASU, applicable to each REMS stakeholder type (prescribers, pharmacies, patients) were selected for evaluation. The Reach domain included the percentage of patients enrolled based on the number requesting enrollment. Effectiveness metrics included mandatory REMS stakeholder tasks (eg, prescriber and patient surveys, pharmacy dispense confirmation numbers, and pregnancy tests). The Adoption domain included certified prescribers and pharmacies who requested enrollment. Implementation metrics entailed the examination of enrollment processes, pharmacist REMS training compliance, and active REMS participation and compliance by enrolled stakeholders. For Maintenance, stakeholder compliance with REMS tasks over time, reduction in REMS burden (eg, percentage of stakeholders using the fastest channel to perform mandatory REMS tasks), and REMS participation adherence metrics (eg, percentage and times for flagged survey resolutions) were included.

Conclusions: We identified appropriate measurement criteria applicable to all 5 RE-AIM domains for the REVLIMID REMS program. Therefore, we believe that the RE-AIM framework could serve as a viable and quantifiable method for REMS program assessment. Risk management programs outside the United States could also potentially utilize the RE-AIM framework for program assessments.

1118 | Impact of the erythropoiesis-stimulating agents (ESAs) risk evaluation and mitigation strategy (REMS) on ESA administration and red blood cell (RBC) transfusion for chemotherapy (CT) induced anemia (CIA)

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Background: ESAs administered for CIA are associated with shortened overall survival and tumor progression or recurrence. The Centers for Medicare and Medicaid Services (CMS) issued a National Coverage Determination (NCD) in July 2007 to limit ESA coverage to patients with cancer meeting specific criteria (eg, Hgb < 10 g/dL). In 2010, FDA approved a REMS to mitigate the risks associated with ESA treatment of CIA. There is a need for evaluating the impact of REMS on appropriate ESA use.

Objectives: Compare ESA administration and RBC transfusion patterns before and after implementation of the NCD and ESA REMS.

Methods: We completed a retrospective cohort study (January 2006-September 2015) of patients ≥65 years enrolled in Medicare Fee-for-Service (± Part D) with a cancer diagnosis within 6 months prior to the first eligible CT claim. We divided study time into four periods demarcated by NCD issuance, REMS approval, and REMS implementation (pre-NCD, pre-REMS, grace period [1 year], and

post-REMS). Primary study outcomes were the proportion of CT episodes with (a) concomitant ESA administration and (b) post-CT ESA administration. The proportion of CT episodes with concomitant RBC transfusions was a secondary outcome. An interrupted time series with a log-linear model quantified the impact of NCD and REMS.

Results: We identified 1 441 548 beneficiaries receiving CT (22.6% lung cancer, 12.3% breast, 4.0% prostate, and 61.1% other cancers). Concomitant ESA administration and post-CT ESA administration decreased throughout the study period. After implementation of the NCD, concomitant ESA administration and post-CT ESA administration underwent an immediate, large decrease (12.5 percentage points [pp] and 4.0 pp, respectively). The decrease after implementation of the REMS was less pronounced, dropping 0.7 or 2.5 pp for concomitant ESA administration and 0 or 0.2 pp for post-CT ESA administration, depending on the method used to analyze the grace period. Concomitant ESA administration decreased faster in pre-REMS than in post-REMS period, 2.7% vs 1.2% per month. The fluctuation in concomitant RBC transfusions was less than 3 pp during the entire study period.

Conclusions: A large, nationally representative study showed that the NCD had a substantive effect on ESA administration, while the REMS had minimal impact on ESA administration and RBC transfusion patterns among patients ≥ 65 years with cancer treated for CIA.

1119 | Evaluation for disparities in erythropoiesis-stimulating agents (ESAs) administration in patients with cancer

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Background: Racial and gender disparities in quality of cancer care have been documented. We assessed if reimbursement (Centers for Medicare and Medicaid Services National Coverage Determination [NCD]) and regulatory (Risk Evaluation and Mitigation Strategy [REMS]) policies contributed to disparities in ESA use in patients treated for chemotherapy (CT)-induced anemia (CIA).

Objectives: To assess if trends in ESA administration after NCD and REMS differ by patient's race and sex.

Methods: Retrospective cohort study (January 2006–September 2015) of Medicare Fee-for-Service ($\pm$ Part D) beneficiaries ≥ 65 years with a cancer diagnosis claim within 6 months prior to the first CT claim. Study outcomes were (a) proportion of CT episodes with concomitant ESA administration and (b) proportion of CT episodes with concomitant red blood cell transfusions. We divided the study time into four periods demarcated by NCD issuance, REMS approval, and REMS implementation (preNCD, preREMS, grace period, and postREMS). We compared the mean monthly ESA administration and transfusions in each period by race and sex. To quantify impact of race

and sex subgroups on patterns of ESA administration, we used interaction terms of level (p_l) and trend (p_s) with subgroup in segmented log-linear regressions.

Results: Concomitant ESA administration in blacks was significantly higher than other races (preNCD: 35.6% vs 29.9%; preREMS: 13.6% vs 10.1%; post-REMS: 3.7% vs 2.8%). ESA administration was significantly higher in females than males prior to REMS approval (preNCD: 32.6% vs 27.6%, preREMS: 11.1% vs 9.5%) and converged postREMS (2.9%). Transfusions for CIA were similar by race (range: 7–8%; <1 percentage point [pp] difference) and sex (7%; <0.02 pp difference). The immediate decrease in ESA administrations after NCD ($p_l = 0.17$) and the subsequent monthly decline ($p_s = 0.47$) was similar in blacks and other races and likewise for sex ($p_l = 0.44$, $p_s = 0.22$). Immediate and long-term changes in ESA administration associated with REMS did not differ by race or sex.

Conclusions: Black patients on CT were more likely to be treated with ESAs than other races. Females were more likely to receive ESAs for CIA prior to REMS approval than males. Transfusions use for CIA were similar by race and sex. The NCD and REMS were not associated with racial or gender disparities in ESA administration in patients with cancer >65 years. In all subgroups, NCD coincided with immediate and long-term decreases in ESA administration with minimal impact of REMS on ESA trends.

1120 | Qualitative research: Another method to consider in the ongoing assessment of benefit-risk

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Background: Patients (pts) generally engage in a decision process when agreeing to take prescribed treatments. Pts' understanding of these decisions are usually supported by quantitative methods such as pt-reported measures of satisfaction and post-care experience. This study leveraged ethnography and empiricism to gain a deeper understanding of the social, physical, and mental drivers of pts with rheumatoid arthritis (RA) in deciding their treatment course.

Objectives: To evaluate the use of ethnography in understanding disease burden and benefit-risk in pts with RA.

Methods: Semi-structured in-home interviews were conducted with adult pts with RA living in the United States. Pts were observed in their lived environments and simultaneously interviewed regarding their RA journey and experiences with diagnosis, symptoms, treatment, and interactions with health care providers. The interviews were audio-recorded and transcribed verbatim. A code book was developed, and transcripts were analysed and coded to identify common themes relating to the guiding research question.

Results: A total of 18 pts participated and were interviewed (aged 27–80 years; 72.2% female; RA duration 4–40 years). Most pts framed their treatment experiences as being unpleasant but necessary. All pts described deep feelings of apprehension and displeasure towards

switching to a treatment that promised worse or more displeasing experiences. Four themes have emerged that should be examined further in subsequent qualitative and quantitative studies: 1. Pts expressed a mind-set of avoidance, meaning they evade in-depth discussions and dwell on the challenging or negative aspects of living with RA. 2. Pts stated that key motivators were whether treatment would positively affect their lives, relieve pain, stop progression, or alleviate symptoms. 3. Many pts perceived treatment options as "worth it" due to a belief that it will change their lives, allowing them to go to work and take on roles and responsibilities at work and at home. 4. Many pts stated the importance of a trusting relationship with their rheumatologist and that they will move forward with treatment if recommended by their clinician.

Conclusions: Benefit-risk evaluations generally rely on quantitative data and analyses. The integration of ethnography and qualitative methods could be an important tool to gain meaningful insights into the human condition and improve our understanding of how pts think about their treatment options.

1121 | Do people understand benefits and risks? Even ineffective treatments for delaying Alzheimer's disease are preferable to "doing nothing" for many older adults

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Background: Using a stated-preference study, we evaluated the relative value older adults placed on hypothetical treatments in delaying the onset of Alzheimer's disease (AD). Almost 1/3 of adults failed our dominated-pair validity test question, which was given to check understanding of the choice tasks.

Objectives: To understand why participants might value an active treatment for AD apart from specified treatment benefits and adverse-events.

Methods: 1004 older adults in the United States completed a web-enabled discrete-choice survey in which they were to suppose that they would develop AD in the future. Adults (ages ≥ 60) were presented with 8 choice tasks, with the option of no medication or a hypothetical AD treatment that would extend time prior to developing dementia. Each choice presented varying levels of efficacy and safety. A dominated-pair question was included, where the treatment alternative offered no additional benefit but offered significant risks relative to no treatment. Choices were analyzed using a random parameters logit model and a binomial probit model, including sensitivity of results to different assumptions about which respondents provided valid responses.

Results: On average, respondents were more concerned with preserving normal memory than risks from AD treatment. The maximum acceptable risk (MAR) of mortality for one more year of normal memory was 13% (95% CI: 9-17) for the entire sample, 19% excluding

those who never pick AD medication, and 7% excluding those who always chose AD medication and/or failed the validity test. These MARs suggest different risk tolerance groups, but also, the potential for a survey labelling effect among those who always chose treatment and/or failed the validity test. These adults may have interpreted the treatment vs no treatment choice as a choice between "doing something" vs "doing nothing" irrespective of benefits and risks presented. The number of times that treatment was chosen in 8 choice tasks was correlated with failing the validity test ($\rho = 0.89$). Adults always choosing the active treatment were 24% more likely to have provided recent AD care ($p = 0.006$).

Conclusions: In this study, adults may have understood benefit-risk concepts despite 30% of the sample picking an ineffective treatment in our validity test. The results suggest that some patients faced with a devastating condition may be hopeful that less effective treatments may work better in their case and are better than "doing nothing."

1122 | Measuring the impact of pharmacovigilance activities on public health; practical example of 3 signals

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Background: Measuring the effectiveness of pharmacovigilance activities is challenging but important.

Objectives: To investigate the feasibility of measuring impact of pharmacovigilance activities based on publically available data in the Netherlands for the safety signal of cyproterone acetate/ethinylestradiol (Diane-35) and the risk of developing venous thromboembolism, pergolide, and valvular heart fibrosis (VHF) and rosiglitazone and cardiovascular events.

Methods: No public datasets were available on the prevalence of either VTEs, moderate-to-severe valvular heart fibrosis (VHF), or cardiovascular events in diabetic patients. For Diane-35, the amount of prevented VTE cases in users after the pharmacovigilance (PV) activity in 2013 was estimated, taking into account possible switching to other combined oral contraceptives (COCs). For pergolide and rosiglitazone, a trend analyses for exposure using segmented regression analysis model was performed to estimate the risk for developing VHF or cardiovascular events in the exposed before and after the signal and PV activities.

Results: Estimation of the relative risk (RR) was based on estimates from the literature. An RR of 3.9, 3.8, and 2.8 for Diane-35, the 3rd/4th and 2nd COCs were used, respectively. The number of Diane-35 users decreased from 180 000 in 2012 to 44 000 users in 2015. 74 VTE cases/year were estimated as prevented due to overall change in hormonal contraceptive usage after 2013. The used RR of VHF for pergolide exposure was 2.3 and 29 915 pergolide users discontinuing treatment between 2003 and 2013,

resulting in an estimated 2752 prevented moderate-to-severe VHF cases. For RGZ, the available literature gave conflicting results regarding the increased risk of CV events—in general as well as compared with alternative medications. Therefore no estimation of decreased risk could be made. Although all PV signals caused a decrease in utilization of RGZ, the measured PV signals did not significantly change the utilization immediately after the PV signals were distributed.

Conclusions: Lack of data hampers assessment of the impact of PV signals for these three cases. A crude estimation of the impact was given for Diane-35 (74 VTE cases/year prevented) and Pergolide (2752 prevented moderate-to-severe VHF cases in 2003-2013), based on the RR from literature and change in use. For RGZ an estimation could not be made.

1123 | Patient-centered benefit-risk decision-making and the role of educational tools and psychological instruments in preference elicitation—Year 1 of IMI prefer

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Background: While researchers have developed a variety of methods for eliciting patient preferences, less attention has been focused on psychological instruments or educational tools that can help determine why patients form certain preferences and make certain decisions. If preferences are to be accurate expressions of trade-offs patients make when having properly understood benefit, harms, and other treatment attributes, then education and psychological measurements will be crucial.

Objectives: As a task in PREFER, a 5-year Innovative Medicines Initiative (IMI), we aimed to identify, describe, and assess the clinical feasibility of using scenario-based interactive tools (SBITs) and profile psychological variables that can affect the construction, elicitation, and interpretation of preferences.

Methods: As a first step, scoping and systematic reviews were performed. Based on that information, motivational factors and appraisal criteria were developed for selecting specific psychological measurements and educational features.

Results: Based on a systematic review of the available empirical evidence, 29 psychological constructs were identified with a theoretical basis for influencing preferences and decision-making. These constructs were sorted in three classes depending on the strength of evidence. Distinctions between psychological constructs that can be regarded as explanatory and those that can be regarded as formative were drawn. A scoping review on educational tools revealed that SBITs have largely not been developed and evaluated in a health care setting. Moreover, it was recognized that SBITs can be constructed with a wide variety of features. As such, preliminary

guidelines have been developed to chart how the characteristics of a particular case study relate to the selection of specific educational features.

Conclusions: There are some psychological instruments for which there is satisfying evidence and may explain preference heterogeneity or determine representativeness of the sample population. Further evidence is required to determine how useful other instruments are. SBITs are possibly useful in patient preference studies because they may (1) stimulate a more personal and subjective view and reflection about treatment options, (2) help motivate participants, and (3) help participants overcome cognitive challenges, inherent to many preference methods; but more research is needed.

1124 | Optimizing REMS counseling tools for prescribers and patients

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Background: As part of the REMS Integration Initiative under PDUFA V, the FDA developed a Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS. Key features of this framework, which was finalized in 2017, included that REMS drug counseling discussions between a health care professional (HCP) and patient should address both the benefits as well as the risks of the product. No guidance was provided, however, as to how to operationalize that framework for use in clinical practice. To address this need, we developed a REMS patient benefit-risk counseling tool that was based on the FDA Framework and which was guided by best practices in patient education material development and risk communication.

Objectives: Our study had two objectives: (1) to develop a REMS Benefit-Risk Counseling Guide (REMS B-R guide) based on the FDA Benefit-Risk Counseling Framework and (2) to pilot the B-R Guide in patients and health care professionals (HCPs) to determine its usability and feasibility in the context of real-world health care delivery.

Methods: The REMS B-R guide was tested with 12 prescribers of an osteoporosis drug and 12 patients with osteoporosis who were using the drug. Each participant was interviewed for 60 minutes either live interviews and/or virtual face-to-face. The B-R Guide in paper and website format were tested. Main outcome measures were understandability, actionability, relevance, usability, and clarity.

Results: In total, 12 patients and 12 HCPs were included in the pilot testing. 50% of patients were self-described as being low health literate. Both HCPs and patients were willing to use the B-R Guide for REMS communication. The patient B-R Guide was found to be clear, comprehensible, and usable by both HCPs and patients. The format of tables with "Information you should know" and "Action you can take" were found to be helpful by both HCPs and patients in communicating and understanding the risks. Patients with low health literacy performed equally well as those with average or high health literacy in terms of understanding the REMS B-R Guide content.

Conclusions: REMS B-R Guide may help HCPs in counseling patients and help them understand the benefits and risks of the treatment

and action that they can take to manage the risks. Patient involvement in the development process is essential to ensure understandability and usability.

1125 | Patient factors affecting clinician work intensity during opioid use discussions

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Background: Reducing opioid exposure requires potentially difficult conversations, but little attention has been paid to the work intensity or mental workload on clinicians

Objectives: Explore patient characteristics related to pharmacist workload intensity when discussing opioid tapering

Methods: As part of an RCT at Kaiser Permanente Northwest (KPNW), we adapted the NASA Task Load Index to assess self-reported clinician intensity in 5 domains: (1) mental demand, (2) temporal demand, (3) successfulness, (4) frustration, and (5) overall effort on a 0-100 scale (0 = least; 100 = most). Intensity was assessed among pharmacist clinicians with specialized training in communication techniques and opioid tapering who placed telephone calls aimed at helping patients reduce their post-surgical use of opioids. Patients were within 90 days of index total-hip or total-knee replacement (THR/TKR). Patient characteristics included age; sex; BMI; previous THR/TKR; dispenses of opioids, antidepressants, and muscle relaxants; diagnoses of substance use disorder, depression, and anxiety; a comorbidity index, number of outpatient visits, number of primary care providers, and predicted risk of persistent opioid use. We used OLS to assess whether work intensity was associated with patient's characteristics (with >10% prevalence, measured using KPNW electronic health records), controlling for all other characteristics

Results: Calls were made to 110 patients; mean age was 65 years with 59% female. Average clinician work intensity was low: mental demand = 26.0; temporal demand = 24.1; successfulness = 83.6; frustration = 8.6; and overall effort = 38.0. No characteristics tested were associated with intensity on temporal demand or overall effort. Patient anxiety was the only factor associated with increased mental demand (8.6% higher, 95% CI 0.6, 16.5). Anxiety was also associated with decreased perceived successfulness (12.3% lower, 95% CI -22.8, -1.9), while antidepressant exposure was associated with increased successfulness (10.1% higher, 95% CI 1.3, 18.8). Previous THR/TKR was associated with decreased frustration (11.2% lower, 95% CI -20.0, -2.6), as were more primary care contacts (-1.8%, 95% CI -3.6, -0.1)

Conclusions: Opioid tapering discussions with patients are associated with low clinical intensity among pharmacists trained on how to conduct these discussions. Few patient factors increase the intensity. Further work to examine variations in work intensity by patient complexity and clinician experience is warranted

1126 | Primary care physician, oncologist, and psychiatrist comfort levels with prescriptions written by themselves and peers for cancer comorbidities

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Background: Cancer is becoming a chronic condition as cancer survivorship increases, often accompanied by comorbidities that complicate treatment management. However, the roles and shared responsibilities of specialists in post-cancer care remain unclear.

Objectives: The objective of this study was to determine and compare primary care physicians (PCPs), oncologist, and psychiatrist comfort levels in prescribing medications that cancer patients frequently need during their care continuum.

Methods: A cross-sectional online survey of PCPs, oncologists, and psychiatrists was administered using Qualtrics Panels. Survey measures included (1) physicians' own comfort level in prescribing 23 categories of medications, (2) their level of comfort with other specialists prescribing to mutual patients, and (3) demographics. Responses were rated on a 7-point Likert scale. To ensure content and face validity, the survey was pre-tested with an independent sample of 12 health care providers and researchers. One-way ANOVAs and chi-square tests were used to analyze continuous and categorical variables, respectively.

Results: 150 physicians (50 oncologists, 50 PCPs, and 50 psychiatrists) completed the survey. The majority of respondents were male (78%), White race (66.4%), and non-Hispanic (93.9%). PCPs reported the highest overall personal comfort level in prescribing the most categories of medications; psychiatrists, the lowest. PCPs reported being less comfortable with oncologists prescribing antineoplastics and anticoagulants than oncologists were. Psychiatrists reported significantly lower comfort in having oncologists prescribe acute anti-infectives, antineoplastics, anticoagulants, and opioid and non-opioid analgesics than oncologists self-reported. However, both PCPs and psychiatrists reported being more comfortable with oncologists prescribing several categories of drugs than oncologists' own comfort level.

Conclusions: The treatment of cancer alongside chronic comorbid conditions requires a dynamic mix of providers. Our study sheds light on how PCP, oncologist, and psychiatrist comfort levels with prescribing for cancer and its comorbidities could influence the coordination of care for cancer patients with comorbidities.

1127 | A new analytic tool developed in the Sentinel System to assess adherence to FDA's safe use recommendations

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Background: The US FDA utilizes approved product labeling, safety communications, and risk mitigation strategies (eg, REMS) to mitigate serious risks of medical products and to provide recommendations on their safe use. Few population-based approaches have been developed to efficiently assess adherence to safe use recommendations or requirements.

Objectives: To develop a flexible, parameterized, reusable analytic tool for FDA's Sentinel System to assess adherence to FDA's safe use recommendations over time with two key capabilities: characterize adherence to patient monitoring recommendations for a drug and characterize concomitant medication use before, during, and/or after drug therapy.

Methods: We developed the tool, tested it, and applied it in the Sentinel Distributed Database to assess adherence to the labeled recommendation that patients treated with dronedarone should undergo electrocardiogram testing no less often than every 3 months. Measures of length of treatment, time to first ECG, number of ECGs, and time between ECGs were assessed. We also applied the tool to assess concomitant use of contraception among users of mycophenolate per label recommendations (concomitant use with contraception for the 4 weeks before initiation through 6 weeks after discontinuation of mycophenolate); we assessed the extent of overlap between episodes of dispensed contraceptive (oral, implant, patch, injection) and mycophenolate. Unadjusted results were stratified by age, month-year, and sex.

Results: We identified 21 457 new episodes of dronedarone use of ≥ 90 days from 7/2009 to 9/2015; 86% had ≥ 1 ECG, and 22% met the recommendation of an ECG no less often than every 3 months. We identified 21 942 new episodes of mycophenolate use among females 12-55 years from 1/2006 to 9/2015; 16% had ≥ 1 day of concomitant contraception dispensed, and 11.8% had concomitant contraception use for $\geq 50\%$ of the duration of mycophenolate therapy (4 weeks before initiation through 6 weeks after mycophenolate discontinuation); younger females had more concomitancy. These results may be underestimates, particularly of concomitant mycophenolate and contraception, because Sentinel is limited to treatment/care captured in claims data and we cannot assess need for contraception.

Conclusions: We developed a new publicly available analytic tool for use in databases formatted to the Sentinel Common Data Model that can assess adherence to safe use recommendations involving patient monitoring and concomitant drug use over time.

1128 | Redesigning prioritization methods using high-risk medicines for clinical pharmacists

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Background: Clinical pharmacist (CP) services are delivered to minimise the inherent risks associated with the use of medicines, increase patient safety, and optimise health outcomes. Traditional methods of distributing work for CPs include ward based (allocated beds) or a clinical unit-/team-based service. Due to resourcing constraints, CPs are unable to see all patients, so a prioritisation method may include identifying patients prescribed high-risk medicines. The study hospital currently allocates CPs to specific wards based on complexity of patient case-mix, bed turn over, and funding. Not all wards have an allocated CP.

Objectives: To determine if CPs are reviewing patients prescribed high-risk medicines using current allocation techniques.

Methods: A real-time snapshot audit over a 5-day period (29/1/18-2/2/18). Electronic Medicines Management System (EMMS) reports were run at an allocated time each day to determine the number of patients currently admitted and prescribed selected high-risk medicines. Three CPs reviewed a randomised sample of patients prescribed targeted high-risk medicines each day to determine which ward the patient was admitted (CP ward vs non-CP ward), proportion of medicines which were high risk on each ward, and if a CP had reviewed the high-risk medicine prescribed. The targeted high-risk medicines were opioids, vancomycin, and oral anticoagulants.

Results: Of the 19 wards within the study hospital, 2 were excluded as are not on EMMS. 11 of the 17 wards had an allocated CP. Over the 5-day period, 933 patients were identified via the EMMS report to be on a targeted high-risk medicine. A random sample of 202 (21%) was used for analysis. Within the sample of 202, 2344 individual medicines were prescribed (1339 CP wards vs 1005 non-CP wards), 305 were high risk medicines (169 CP wards vs 136 non-CP wards), $p = 0.57$ indicating no difference between the number of medicines prescribed as well as the ward distribution of patients on high risk medicines. All 17 wards had at least one prescription for a high-risk medicine (range 2-43). The two wards with the highest percentage of high-risk medicines prescribed were not allocated a CP, midwifery (24%), and hospice (31%) (range 10-31%). Both wards had high use of opioids, midwifery being a relatively low complex patient population. High-risk medicines were more likely to be reviewed if a patient was admitted on a CP ward (93 [55%] CP wards vs 20 [15%] non-CP wards).

Conclusions: The allocation of CPs to specific wards does not prioritise review of patients on high risk medicines.

1129 | Limitations in reporting “benefit-risk” across therapeutic areas in medical device literature

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Background: Throughout a medical product's life-cycle, decisions about its use are evaluated as a balance between patients' anticipated benefits and risks. While both qualitative and quantitative methodologies have been developed to assess benefit-risk, these methods may not be included in the abstracts of medical device literature, or studies may inappropriately designate findings as “benefit-risk.”

Objectives: To review the medical device literature and evaluate how benefit-risk is reported across various therapeutic areas.

Methods: Using MeSH terms for a broad capture, PubMed was searched for English language articles published in 2017 in which IMI-PROTECT benefit-risk methodologies were employed for medical devices.

Results: Among 218 abstracts, 96 (44%) were excluded due to inapplicability (not a primary study or not device research), and 64 (29%) were excluded because “benefit-risk” was mentioned only in the introduction or conclusion. A total of 58 abstracts across 13 therapeutic areas were identified as reporting a benefit-risk assessment. The majority (76%) used qualitative frameworks (22% quantitative). The predominant therapeutic areas were cardiovascular (CV, 50%) and oncology (10%). Oncology studies more often described quantitative frameworks (33%) compared with CV (21%) and other therapeutic areas (OTA, 22%). Oncology studies relied on registries, cohorts, and chart review (83%) more often than CV (72%) and OTA (50%). No oncology studies claiming to assess benefit-risk were randomized trials, while 20% of CV and 10% of OTA studies used randomized designs. The framework was inferred for all oncology studies. Conversely, 10% CV and 4% OTA sufficiently described methodology to define framework.

Conclusions: Current trends indicate the term “benefit-risk” is used broadly across medical device publications, with little context given to methodology. The lack of detail leaves the reader to wonder if and which benefit-risk assessment was conducted. Differences observed across therapeutic areas further limit interpretation. Oncology studies most often employed quantitative frameworks. CV studies provided more study design information and included more randomized studies, but also more often reported qualitative methodologies. Lack of standardization in reporting across therapeutic areas limits interpretation of “benefit-risk” for medical devices.

1130 | Sources of evidence supporting post-marketing pharmacovigilance regulatory actions since 2012

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Background: Major updates to the European Union (EU) pharmacovigilance (PV) legislation were implemented in July 2012. One objective of the update was “rapid and robust assessment of issues related to the safety of medicines.” Since PV legislation updates were applied, there have been no studies investigating sources of evidence and time to reach regulatory decision for products withdrawn, revoked, or suspended from EU market (“regulatory actions”). This study builds on previous DSRU research covering 1999-2001 and 2002-2011.

Objectives: To assess sources of publicly available evidence supporting regulatory actions due to safety reasons in the EU since 2012. To investigate time taken from authorisation to reach each regulatory decision.

Methods: Types of publicly available evidence, time to decision, and duration of marketing for each identified product were examined. We considered prescription products subject to regulatory action in the EU market (plus Norway, Iceland, and Liechtenstein) for safety reasons between 1 July 2012 and 31 December 2016 for inclusion. Evidence supporting each regulatory action was identified and categorised; frequencies and proportions were calculated. Median time to regulatory decision and duration of marketing prior to regulatory action were calculated. ANOVA was performed for time to regulatory decision.

Results: 18 medicinal products withdrawn, revoked, or suspended in the EU for safety reasons between 2012 and 2016 met our inclusion criteria. Case reports most frequently supported regulatory actions ($n = 17$, 94.4%). Epidemiological study designs were least commonly cited ($n = 8$, 44.4%). Multiple sources of evidence contributed to 94.4% of regulatory decisions ($n = 17$). Death most commonly led to regulatory action ($n = 5$; 27.8%), with four of these related to medication error or overdose. Median (IQR) time taken to reach a decision from the start of regulatory review was 204.5 days (143, 535 days) and fell across the study period ($p = 0.87$). Duration of marketing prior to regulatory action from each authorisation date increased between 2012 and 2016.

Conclusions: Sources of evidence supporting PV regulatory activities appear to have changed since implementation of updated EU PV legislation, particularly in favour of multiple supporting study designs. Case reports remain a common evidence source in regulatory decision-making, while epidemiological designs were least frequently cited. A small drop in time to reach regulatory decisions suggests better regulatory efficiency.

1131 | Impact of the 2012 pharmacovigilance legislation on the harmonisation of DHPCS in the EU

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Background: Direct health care professional communication (DHPC) is one of the most used measures to manage post-marketing drug risks in the EU. Previous research showed that there are substantial differences between countries for DHPCs published before 2013.

Objectives: The aim of the study was to analyse the content and timing of DHPCs sent out in Denmark and United Kingdom during January 2007-December 2016 in order to see if and how the

implementation of the new EU pharmacovigilance legislation in 2012 have had an impact on the publication practice between the countries.

Methods: All identified DHPCs were categorized as safety-related or not, and date of publication, drugs (ATC), EMA involvement, and authorisation type (central/national) were recorded. For safety letters, adverse events (AEs) involved and recommendations were recorded. Pairs of DHPCs published in both countries were identified based on ATC and publication date (<2 yr) and within pairs timing of publication, AEs and recommendations were compared. DHPCs on drugs marketed in one country only were excluded. T-tests were performed to determine differences before and after 2012 and between countries.

Results: Of the total of 228 Danish and 426 United Kingdom DHPCs letters 138 Danish (60.5%) and 215 United Kingdom (50.5%) were categorized as safety letters. Among the safety letters, a significant increase was observed with respect to the number of releases available in both countries before (38/103, 37%) and after (73/101, 72%) 2012 ($p < 0.0001$). With respect to content, 118/119 DHPC pairs concerned the same letters. As a result, no changes over time were observed in the proportion of same letters. Timing of these letters with a recorded exact publication date ($n = 91$) did not differ significantly ($p = 0.38$) before 2012 (DK letters published 9 days earlier than UK letters) and after 2012 (UK letters published 6 days earlier than DK letters).

Conclusions: The pharmacovigilance legislation impacted on number of identical releases available in both countries and has thereby led to more harmonization between these two European countries with respect to DHPC publications.

1132 | Pre/post effectiveness evaluation of the myozyme (alglucosidase alfa) safety information packet

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Background: The alglucosidase alfa (Myozyme) safety information packet ("previous SIP") was updated at the request of the European Medicines Agency to improve readability and content ("updated SIP").

Objectives: The study assessed and compared awareness, receipt, usage, and reading (whether the SIP was read), as well as knowledge and behavioural implementation of key messages (primarily around immunological testing) contained in the updated SIP and the previous SIP.

Methods: A two-wave pre-post multi-country (France, Germany, Italy, Spain, the UK, and Poland) survey was conducted among health care professionals (HCPs; nurses/physicians) who prescribed and/or monitored patients on alglucosidase alfa. Wave (W) 2 started 15 months after completion of W1 and after the implementation of the updated SIP. Both cross-sectional analyses within each wave and analyses of change between waves were conducted. Comparisons between W1 and W2 were considered statistically significant if $p < 0.05$.

Results: There were 46 (34 physicians/12 nurses) HCPs recruited in W1 and 52 in W2 (42 physicians/10 nurses); 22 participated in both waves. Although most HCPs filled out the survey questions on awareness (98%), usage (96%), and knowledge (70%), fewer had complete responses for the behaviour questions (51%). Most HCPs were from academic departments (67.4% W1; 80.8% W2) and belonged to neurology units (37.0% W1; 40.4% W2). Awareness (75.6% W1-82.4% W2) and receipt (77.7% W1-74.5% W2) of the SIP was high, though not significantly different in both waves. Among HCPs who reported receiving the SIP, there were not statistically significant increases in reading (88.6% W1-89.5% W2) and usage (88.2% W1-89.5% W2). The mean percentage of correct knowledge about immunological, urine, and skin testing was not statistically significantly higher in W2 than in W1 (61.1% vs 55.1%). Behavioural implementation around overall immunological testing was significantly higher in W2 than in W1 (50.3% vs 34.4%; $p = 0.024$) with a tendency to increase the appropriate performance of all specific types of testing in W2.

Conclusions: Both versions of the SIP showed relatively high awareness, receipt, reading, and usage. Although not statistically significant, there was an overall trend for most measures to improve numerically comparing the previous and updated SIP. This may represent a ceiling effect or inadequate power. The updated SIP did not require further improvement or evaluation by the EMA.

1133 | Benefit risk assessment for fibrinogen concentrate in the setting of complex cardiac surgery: Lessons learned using the CIRS-BRAT framework

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Background: Fibrinogen concentrate (FCH) has been successfully used in the setting of perioperative bleeding in complex cardiac surgery (CCS), as reported in several single center trials. CSL Behring conducted a multi-center, multi-national, placebo-controlled study (REPLACE) to demonstrate efficacy in this clinical setting to support a label expansion. Contrary to the single center studies, REPLACE did not show efficacy superiority over placebo, while the safety endpoints were favourable to FCH. Although the label expansion was not pursued, the company decided to conduct a thorough benefit-risk assessment (BRA) of FCH.

Objectives: To assess the benefit-risk profile of FCH in the clinical setting of CCS taking into account all available published evidence and completed clinical trials.

Methods: A CSL Behring cross-functional team was formed to conduct the BRA. The team followed the CIRS-BRAT framework to establish the decision frame, identify key benefits and risks, gather and interpret the data, and produce visualizations to display the results. A systematic literature review was conducted to identify relevant studies in addition to the data from REPLACE. Forest plots were generated to show the

benefits and risks of FCH compared to placebo or standard of care by each key outcome as well as by each study and by crude pooled analyses of identified placebo-controlled clinical trials.

Results: Eight studies were identified based on criteria established in the decision frame. Based on predefined criteria, 2 studies were excluded because information on key benefits and risks were not presented as binary data, and 1 observational study was described separately. The BRA of the 5 remaining studies showed that the evaluated benefits favored FCH in most studies and the evaluated risks were similar between FCH and the comparator. The benefit risk profile of FCH in the setting of complex cardiac surgery was determined to be favorable by the company; regulatory authorities agreed with the conclusion.

Conclusions: The use of a transparent structured approach (CIRS-BRAT framework) facilitated assessment and interpretation of a large volume of information in a complex situation and the positive benefit-risk profile for FCH in the setting of complex cardiac surgery was successfully communicated.

1134 | A decade of marketing approval of gene and cell based therapies in the United States, European Union, and Japan: A regulatory decision-making evaluation

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Background: There is a widely-held expectation of clinical advance with the development of gene and cell based therapies (GCTs). Yet establishing benefits and risks is highly uncertain due to the complex and idiosyncratic nature of therapies and small target populations. Furthermore, efficacy of novel modes of action and associated potential safety risks are uncertain, in particular over longer periods of time.

Objectives: We examine differences in decision-making for GCT approval and risk management between jurisdictions by comparing regulatory assessment procedures in the United States (US), European Union (EU), and Japan.

Methods: A descriptive cohort of 18 assessment procedures was analyzed by comparing assessment characteristics (eg, product characteristics, evidentiary support, and regulatory procedures), evidentiary and non-evidentiary factors considered in benefit/risk assessments, and post-marketing risk management strategies.

Results: Product characteristics are very heterogeneous, and only three products are marketed in multiple jurisdictions. Almost half of all approved GCTs were designated an orphan drug. Overall, confirmatory evidence or indications of clinical benefit were evident in the US and EU applications, whereas in Japan, approval was solely granted based on non-confirmatory evidence. Substantial post-marketing risk management activities were requested in the EU and Japan in

response to scientific uncertainties related to quality, safety, and efficacy (eg, risk minimization, assay validation, registries, observational studies, and clinical trials). EU and Japanese authorities often took unmet medical needs into consideration in decision-making for approval. These observations underline the effects of implemented legislation in these two jurisdictions that facilitate an adaptive approach to licensing. In the US, the recent assessments of two CAR-T cell products are suggestive of a trend towards a more permissive approach for GCT approval under recent reforms and under conditions of enhanced post-marketing safety risk management, in contrast to a more binary decision-making approach for previous approvals.

Conclusions: Our results indicate that all three regulatory agencies are currently willing to take risk by approving GCTs with scientific uncertainties and safety risks, urging them to pay accurate attention to post-marketing risk management and collection of confirmatory evidence.

1135 | Compendium of methods for measuring patient preferences in medical treatment

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Background: Patient preference studies are taking on an increasingly important role in the medical product lifecycle. While there are numerous industry, academic, regulatory, and patient group efforts addressing standards, quality, and proper application of preference studies, there is limited understanding of the range of methods to assess preferences and the trade-offs between them.

Objectives: To develop evidence-based recommendations to guide different stakeholders on how and when patient preference studies should be performed, we developed a comprehensive overview of patient preference exploration and elicitation methods.

Methods: We used a three-step approach to identify existing preference exploration (qualitative) and elicitation (quantitative) methods: (1) listing methods identified in previous preference method reviews; (2) conducting a systematic literature review on 4572 unique papers identified through multiple scientific databases, using English full-text papers published between 1980 and 2016; and (3) having discussions with international experts (n = 14) in the field of health preferences and/or medical decision making to validate the methods found.

Results: We identified 32 unique preference methods: 10 exploration and 22 elicitation methods. Consensus was reached among the experts interviewed to cluster exploration methods in three main groups: "Individual techniques," "Group techniques," and methods that were both "Individual and Group techniques." Elicitation methods were clustered in four groups: "Discrete Choice Based related techniques," "Threshold related techniques," "Rating related techniques," and "Ranking related techniques."

Conclusions: This study identified 32 unique methods for exploring and measuring patient preferences and reached consensus in clustering the methods. This compendium is a resource for researchers in the patient preference field and also serves as the basis to conduct additional studies that appraise the methods and determine which methods are most appropriate for measuring patient preferences in which phase of the medical product lifecycle to support patient-centric decision making.

1136 | Conditions and factors influencing application of patient preferences in benefit-risk and other assessments

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Background: The area of patient preferences research is at a crucial stage. An increasing number of activities are performed by industry, regulators, and health technology assessment (HTA) bodies to explore the use of patient preferences in decision making.

Objectives: To identify factors and conditions that influence the utility of patient preference studies for industry, regulators, and HTA bodies. In parallel, it was sought to identify the current applications of patient preferences in decision making.

Methods: A systematic literature search was conducted. Scientifically published literature and publicly available documents of health agencies and patient-centred initiatives were consulted. Semi-structured interviews were conducted in 7 European countries and the United

States. Interviewed stakeholders included patients, patient representatives, caregivers, industry representatives, regulators, HTA representatives, physicians, and academics. Focus group discussions were conducted with European industry representatives, European and US regulators, European HTA representatives, and patients from 4 European countries.

Results: A total of 744 publications were retrieved, and 87 were included. In addition, 143 semi-structured interviews and 8 focus groups were conducted. Major factors influencing utility of patient preference studies include cognitive burden, question framing, and participation of patients. Conditions under which patient preferences were found to be more useful include uncertain benefit-risk balance and new technologies. Evidence was found on possible applications of patient preferences in decision making, but current use is limited and structured processes to their integration are lacking. Patient preferences can be used in ideation, clinical development, benefit-risk assessment, and HTA. In benefit-risk assessment, patient preferences can be used to understand the importance of benefits and risks to patients and to weigh benefits and risks.

Conclusions: Although application of patient preferences in decision making is limited, they are gaining importance in different processes including benefit-risk assessment. However, many conditions and contextual factors have to be taken into account when designing and conducting a patient preference study in order to obtain valuable results that can be used in decision making. Funding: This work has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking PREFER grant no. 115966.

1137 | Stakeholder perspectives on the integration of patient preferences in the medical product life cycle

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Background: The patient perspective is increasingly considered essential on all levels of health care research and decision-making, including

benefit-risk assessments of medical products. A particular area of focus is the measurement and use of patient preferences.

Objectives: This study aimed to identify stakeholders' desires, expectations, concerns, and needs regarding the measurement and use of patient preferences throughout the medical product life cycle (MPLC).

Methods: A 3-step multimethod approach was used, including exploratory interviews ($n = 16$), a literature review and semi-structured interviews ($n = 143$) with patients, informal caregivers, patient representatives, physicians, regulators, reimbursement agency representatives, health technology assessment (HTA) representatives, industry representatives, and academics from 8 countries (7 EU, USA).

Results: The exploratory interviews revealed the heterogeneity with which interviewees defined patient preferences. The majority of interviewees agreed that there is value in measuring and using patient preferences in all stages of the MPLC. The literature review showed numerous roles for patient preferences to inform industry, marketing authorization, HTA, and reimbursement decision-making. The semi-structured interviews showed that although the majority of interviewees were positive towards the general concept of patient preferences in the MPLC, mixed opinions exist regarding the implementation of patient preferences in industry, regulatory marketing authorization, HTA, and reimbursement decision-making. Stakeholders recognized a need for more awareness, acceptance and education on the concept, measurement, and use of patient preferences throughout the MPLC. The most recurring concerns among stakeholders were a lack of standardization and consensus on methodological aspects of methods to measure patient preferences due to the novelty of this field of research.

Conclusions: This study identified key stakeholder desires, expectations, concerns, and needs regarding the measurement and use of patient preferences, which highlight important areas of further preference research aiming to inform decision-making throughout the MPLC, including benefit-risk assessments.

Funding: This work has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking PREFER grant no. 115966

1138 | Health care professional survey to assess the effectiveness of abatacept (Orencia®) patient alert cards in rheumatoid arthritis patients

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Background: Patient alert cards (PACs) for intravenous (IV) and subcutaneous (SC) abatacept (ORENCIA®) are designed to inform patients and health care professionals (HCPs) about the risk of infections and to enhance communication between the HCP and patient. A HCP survey was conducted to assess the effectiveness of the PACs in rheumatoid arthritis patients. A patient survey and retrospective chart review

was also conducted. This was part of a post-marketing commitment to the European Medicines Agency (EMA).

Objectives: To assess awareness, access, distribution, utilization/utility of the PAC, and knowledge and behavioural implementation of key messages by HCPs.

Methods: Cross-sectional survey of HCPs (rheumatologists and nurses) conducted in France, Germany, Spain, Sweden, and the United Kingdom. HCP questionnaires were completed online. Results are provided overall, separately for HCPs who had access to the PAC versus those who did not, and by HCP type (physicians and nurses).

Results: The recruitment rate (completers/eligible) was 74%. The survey was completed by 79 HCPs; 50 physicians and 29 nurses. The majority belonged to academic centres (60%) with a median of 21.0 patients treated with Orencia in the previous year. A total of 90% of HCPs were aware of the PAC, and 68% reported having accessed the tool, of whom 72% had also read it. More nurses than physicians were aware (93% vs 88%), reported access (72% vs 65%), and read the PAC (90% vs 60%), distributed it (81% vs 67%), and explained the content (94% vs 43%) to their patients. Knowledge about the risk of infections was demonstrated in 91% of HCPs who had access to the PAC versus 73% of those who did not ($p = 0.053$) and was similar in nurses and physicians (86% vs 84%). The mean level of utility of the PAC was 71%.

Conclusions: The study results demonstrated the effectiveness of the Orencia PAC. HCP survey results showcased the central role of nurses in the provision and handling of the PAC. The results suggest that distribution of the PAC to patients could be improved, despite already being included inside the Orencia product packaging. Nurses should be the target of any strengthened distribution efforts, where feasible, emphasizing the need to discuss the information contained in the PAC with the patient as well as providing it for both the SC and IV formulations.

1139 | Development of an evidence-based implementation strategy for digital risk minimization measures

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Background: Implementation strategies that are well planned and executed are critical for ensuring the adoption of additional risk minimization measures (aRMMs). Although sponsors have gained considerable experience in implementing traditional, paper-based aRMMs, there is less precedent for implementing digital aRMMs, especially in a global context. Herein we describe an implementation strategy for an innovative digital aRMM platform. This tool, an interactive, web-based application ("app") was developed to train pharmacists in the admixing process and preparation of an oncology drug. The app was designed as a bifurcated platform tool comprised of an internal content-control portal and an external user interface for published content.

Objectives: (1) To describe the process for developing and executing a global implementation strategy for a digital risk minimization tool and (2) to describe lessons learned in the execution of that strategy.

Methods: Guided by emerging best practices from the implementation science health care services research literature and Diffusion of Innovation theory, a global strategy was developed for the implementation of a risk minimization tool. The global strategy incorporated multiple elements which were collectively selected to promote early adoption, implementation, sustainability, and scale-up of the risk minimization tool.

Results: Through close cross-functional collaboration and comprehensive stakeholder training, a plan was created to address the challenges inherent in the global rollout of a digital risk minimization tool for an oncology drug. Iterative feedback between the local affiliates and global stakeholders led to dynamic training sessions, facilitated execution of the implementation plan, and generated platform design specifications. As a result, the platform was successfully launched to international affiliates and pertinent sites in that locale. The core implementation strategy and local implementation plan will be replicated for mass distribution of the global platform solution to additional geographies. The use of the tool will be tracked and provide feedback on the success of implementation process.

Conclusions: The development of a robust implementation strategy is critical to the successful launch of a digital risk minimization tool, especially when the aim is to implement the aRMM globally. Such a strategy, at least in the current regulatory environment, may be more complex than those required to implement paper-based aRMMs.

1140 | Quantitative analysis of survey studies assessing the effectiveness of risk minimisation measures: State of the art

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Background: GVP XVI Annex 1 provides guidance on the methodology to be used in surveys evaluating the effectiveness of additional RMMs (EU RM Survey Studies). This guidance is general and can be widely interpreted.

Objectives: To assemble evidence from RM Survey Studies conducted in ≥ 1 EU country. Data on participation, receipt, usage, reading (ie, whether materials were read), knowledge, behavior, and consequences are described and pooled where possible.

Methods: This is a quantitative review of EU RM Survey Studies. The EU PAS Register was used to identify completed survey studies with study report available, obtained either through the Register or from sponsors, up to 26 May 2017. PRAC Assessment Reports were used to obtain regulatory consequences. Data on study characteristics, participation, study results (receipt, use including reading, knowledge, and behaviour), and consequences were extracted and summarised

by counts and percentages. Where appropriate study results were synthesized and pooled together in Forest Plots.

Results: From 1084 studies in the EU PAS Register up to 26 May 2017, 47 were surveys, 16 had reports available, and two were obtained from sponsors. Drugs assessed mainly were in the anti-neoplastic/immunomodulating (17%) and nervous system (39%) groups. Additional RMMs were evaluated in ~90% of studies: patient cards (38%), dear health care professional communications (31%), health care professional brochures (81%), and patient brochures (25%). Three quarters of the surveys had one-wave designs. Prescribers were most frequently included (89% specialists; 50% general practitioners) and patients only in 29%. Almost all studies assessed knowledge. For completers/invited, the pooled response rate was 5% (95% CI: 4%-8%), whereas for completers/eligible, the estimate was 93% (95% CI: 87%-98%). Receipt was reported as less than 50% in over half of the results for receipt. Usage was in the range of 50%-70% in 80% of results reporting usage. Reading achieved greater than 50% in more than half the reported results. The percentage of correct responses to knowledge questions among HCPs and patients was >80% and 30-50%, respectively. "No changes to the materials" was the main regulatory consequence.

Conclusions: This quantitative review provides data to drive recommendations for the conduct and reporting of EU RM Survey Studies. The ENCePP Special Interest Group on Measuring the Impact of PV Activities is one forum which may consider using these results for developing guidance

1141 | Evaluation of patient knowledge of safety and safe use information for aflibercept

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Background: As part of the risk-management plan for aflibercept (an intravitreal antineovascularisation agent with several indications), Bayer developed materials to educate physicians and patients on the key safety information for aflibercept and distributed them to ophthalmology practices to increase awareness and understanding.

Objectives: To measure whether patients received the aflibercept patient booklet, patient information leaflet, and audio CD and evaluate their knowledge of the key safety information.

Methods: An observational, cross-sectional study was conducted in the United Kingdom, Germany, France, Spain, and Italy. A diverse sample of ophthalmology practices was recruited among known aflibercept prescribers identified by Bayer. Geographic location was evaluated to ensure diversity. Physicians invited patients who had received an aflibercept injection in the last 6 months to complete an interviewer-administered questionnaire. Data analyses were descriptive.

Results: Of the 851 eligible patients, 776 were interested, 774 consented, and 773 were included in the analysis (completed at least one knowledge question in full). Thirty-eight percent of patients reported receipt of the aflibercept patient booklet; 23% the aflibercept audio CD; and 35% the aflibercept patient information leaflet. Patients' knowledge of health conditions to discuss with a doctor before an aflibercept injection was high, from 85% (95% CI, 82%-87%) to 92% (95% CI, 90%-94%) on 8 of 9 items. Knowledge was lower, 52% (95% CI, 48%-55%), on the one item related to pregnancy and breastfeeding, likely because this condition is less salient in the aflibercept patient population given the patients' ages (99% of patients in the study were ≥ 46 years). Knowledge about possible side effects varied by item, with the highest correct response proportion (74% [95% CI, 70%-77%]) for "eye pain" and the lowest (42% [95% CI, 39%-46%]) for "detachment of the gel-like substance inside the eye from the retina." Most patients (78% [95% CI, 75%-81%]) knew they should speak to their health care provider immediately if they think they might be having a side effect from their aflibercept injection.

Conclusions: Levels of patient knowledge were as expected, with highest knowledge on less complex concepts (eg, conditions to discuss with the physician and easily identified side effects) and lower knowledge on more complex concepts and issues less salient to the patient population (eg, more complex side effects and issues pertaining to women of childbearing potential).

1142 | Risk management of medication errors in the EU

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Background: The EU-Risk minimization plan (EU-RMP) describes important identified risks, important potential risks, and missing information for

medicines and strategies to limit these risks. Medication errors (MEs) can be recognized pre-authorization as an important risk and included in the EU-RMP with routine or additional risk minimization measures (aRMM).

Objectives: This study aims to describe the risk management of MEs for centrally authorized products (CAPs) in the EU.

Methods: The online European Public Assessment Reports at the time of authorization for all originator CAPs authorized between 1 January 2010 and 31 December 2015 were reviewed. The following data were collected: ATC code, safety concerns, implementation of routine or aRMM, studies to evaluate the effectiveness of RMM. Safety concerns were converted into the most appropriate *preferred terms* using the Medical Dictionary for Regulatory Activities (MedDRA[®]) version 19.0. ME safety concerns were identified using the narrow Standard MedDRA query and classified by ATC code, year of authorization, type of ME, routine or aRMM, type of RMM, and population targeted by aRMM.

Results: During the study period 231 CAPs were approved in the EEA, of which 60 had at least one ME safety concern. The proportion of CAPs with ME safety concerns increased from 21.1% in 2010 to 32.7% in 2015. In total 67 ME safety concerns were identified, of which 23 with aRMM. All aRMM consisted of educational material targeted at health care professionals (87.0%), patients (47.8%), or both (34.9%). ME safety concerns were most frequently categorized as important potential risks (74.6%) with more aRMM imposed when categorized as important identified risk (66.7% vs 28.0%). Anti-infectives for systemic use had most ME safety concerns (16.4%) but never aRMM. Cardiovascular medications had the highest proportion of additional RMM (4/5). The type of medication errors was highly variable: *medication error* (41), followed by *drug administration error* (5) and *accidental exposure to product* (5). For 83.6% of the aRMM for ME, effectiveness studies were requested.

Conclusions: The increased proportion of CAPs with ME safety concerns may be an indicator of increased awareness of the risk of medication errors, or increasingly complicated therapies and medicines. Further research is needed to evaluate the effectiveness and continuing need for aRMM for ME