# Prevalence of drug-drug interactions of warfarin prescriptions in South Africa

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# ABSTRACT

**Title:** Prevalence of drug-drug interactions of warfarin prescriptions in South Africa.

**Keywords:** Warfarin, drug-drug interactions, anticoagulant, vitamin K antagonist, drug utilisation review, private health care sector, prescribed daily dose (PDD), pharmaceutical benefit management company.

**Background:** Warfarin is an anticoagulant that is used for the prophylactic and therapeutic treatment for a wide range of thrombo-embolic disorders. The prescribing and monitoring of warfarin therapy is challenging due to the fact that warfarin exhibits numerous interactions with other drugs and a variety of factors that influence the dosing of warfarin.

**Objective:** The general objective of this study was to investigate the prevalence of drugs prescribed with warfarin that may have a potential drug-drug interaction (DDI) with warfarin.

**Methods:** This was a cross-sectional, observational or qualitative study that was conducted on medicine claims data of a pharmaceutical benefit management company for patients receiving warfarin therapy for a six year period, ranging from 1 January 2005 to 31 December 2010. Drug products that were co-prescribed with warfarin were also identified from the medicine claims database. The total number of prescriptions for all drug products during the study period were analysed and compared to the warfarin dataset. This was done by means of the SAS 9.1® computer package (SAS Institute, 2004). The total number of prescriptions and medicine items claimed from the database during the study period were respectively 49 523 818 and 118 305 941. Potential DDIs between warfarin and co-prescribed drugs were identified and classified according to a clinically significant rating. The clinically significance ratings of potential DDIs are described in three degrees of severity, identified as major, moderate and minor (Tatro, 2011:xiv).

**Results:** The database consisted of 427 238 warfarin prescriptions and 427 744 warfarin medicine items, which represented 0.9% of the total number of prescriptions and 0.4% of total number of medicine items. The total number of patients who claimed warfarin prescriptions through the database represented 0.9% (n=68 575) of the total number of patients who claimed prescriptions in the total database (2005-2010). General practitioners prescribed the highest frequency of warfarin medicine items, representing 58.3% (n=249 202) of the total number prescribed. The age group that claimed the highest

frequency of warfarin prescriptions (n=327 592, 76.6%) and the highest frequency of warfarin medicine items (n=327 984, 76.7%) was age group 4 (consisting of patients 59 years and older). The distribution between females and males regarding warfarin prescriptions claimed (n=205 999, 48.2%; n=221 117, 51.8%) and warfarin medicine items claimed (n=206 232, 48.2%; n=221 390, 51.8%) were almost equal. General practitioners prescribed the highest average PDD (7.01 mg ± 9.86 mg) of warfarin medicine items. Paediatric cardiologists prescribed the lowest average PDD (4.61 mg ± 1.29 mg) of warfarin medicine items. A d-value of 0.1 indicates that there is no practical difference of the average PDD between general practitioners and paediatric cardiologists. The average PDD of warfarin medicine items between females (6.60 mg ± 9.06 mg) and males (6.74 mg ± 8.41 mg) was almost equal. The age group who was prescribed the highest average PDD was age group 2 (consisting of patients 20 years to 39 years old) (7.42 mg ± 7.42 mg). Age group 4 (consisting of patients 59 years and older) (6.50 mg ± 8.90 mg) was prescribed the lowest average PDD of warfarin medicine items. A d-value of 0.1 indicates that there is no practical difference of the average PDDs of warfarin medicine items between these two age groups.

The results revealed that drugs with a significance rating (SR) of 1 (n=155 066, 43.3%), 2 (n=30 128, 8.4%), 4 (n=137 144, 38.3%), and 5 (n=36 144, 10.1%) were co-prescribed with warfarin in the six year study period. The five drugs that was co-prescribed with warfarin most frequently was aspirin (n=48 903, 13.6%), thyroxine (n=33 954, 9.5%), amiodarone (n=25 056, 7.0%), simvastatin (n=19 070, 5.3%) and celecoxib (n=10 794, 3.0%). These five drugs have a SR of 1.

**Conclusions:** This study showed that the top five drugs most frequently prescribed with warfarin are aspirin, thyroxine, amiodarone, simvastatin and celecoxib. These drugs can potentially interact with warfarin. The potential interactions of these drugs are rated with a significance rating of 1. This concludes that drugs that can potentially cause life threatening effects and permanent damage are commonly co-prescribed with warfarin. Clinical data concerning the INR or PT must be obtained in order to evaluate whether or not warfarin therapy is changed when a potentially interacting drug is co-prescribed. The age of the patients as well as the duration of warfarin treatment should also be obtained in order to assess whether warfarin treatment is changed with the progression of age.

# OPSOMMING

**Titel:** Voorkoms van geneesmiddelinteraksies op warfarien voorskrifte in Suid-Afrika

**Sleutelwoorde:** Warfarien, geneesmiddel-geneesmiddelinteraksies (GGI), antikoagulante, vitamiene K antagoniste, medisyneverbruikevaluering, private gesondheidssorgsektor, voorgeskrewe daaglikse dosering (VDD), farmaseutiese voordele bestuursmaatkappy.

**Agtergrond:** Warfarien is 'n antikoagulant wat gebruik word vir die profilaktiese en terapeutiese behandeling van 'n wye verskeidenheid trombo-emboliese toestande. Die voorskryf en kontrolering van warfarinterapie is uitdagend vanweë die feit dat warfarien verskeie interaksies met ander geneesmiddels kan hê en 'n wye verskeidenheid van faktore die dosering van warfarien beinvloed.

**Doelwit:** Die algemene doelwit van die studie is om die voorkoms van moontlike interaksies met geneesmiddels wat saam met warfarien voorgeskryf word te ondersoek.

**Metodes:** 'n Deursnee-, waarnemings- of kwalitatiewe studie is onderneem met betrekking tot die medisyne-eisdata van 'n farmaseutiese voordele bestuursmaatskappy vir pasiënte wat warfarienterapie ontvang het tydens 'n ses jaar periode vanaf 1 Januarie 2005 tot 31 Desember 2010. Geneesmiddels wat saam met warfarien voorgeskryf is is ook uit die medisyne-eisdatabasis geidentifiseer. Die totale hoeveelheid voorskrifte vir alle medisyne-items gedurende die studietydperk is ook geanaliseer en met die warfarien datastel vergelyk. Dit is gedoen met behulp van die SAS 9.1® rekenaarpakket (SAS Instituut, 2004). Die totale hoeveelheid voorskrifte en medisyne-items wat ge-eis is vanaf die databasis gedurende die studietydperk was onderskeidelik 49 523 818 en 118 305 941. Potensiële GGI tussen warfarien en mede-voorskrewe geneesmiddels is geidentifiseer en geklassifiseer met 'n kliniese beduidende gradering. Die kliniese beduidende graderings of potensiële GGI is beskryf na gelang van drie grade van erns naamlik belangrik, gemiddeld en onbelangrik (Tatro, 2011:xiv).

**Resultate:** Die databasis het 427 238 warfarien voorskrifte en 427 744 warfarien medisyne-items opgelewer, wat 0.9% van die totale hoeveelheid voorskrifte verteenwoordig het, en 0.4% van die totale hoeveelheid medisyne-items. Die totale hoeveelheid pasiënte wat warfarien voorskrifte deur die databasis ge-eis het verteenwoordig 0.9% (n=68 575) van die

totale hoeveelheid pasiënte wat voorskrifte ge-eis het in die totale databasis (2005-2010). Algemene praktisyns het die meeste warfarien medisyne-items voorgeskryf, naamlik 58.3% (n=249 202) van die totaal. Die ouderdomsgroep wat die meeste warfarien voorskrifte ge-eis het (n=327 592, 76.6%) en die meeste warfarien medisyne-items ge-eis het (n=327 984, 76.7%) is ouderdomsgroep 4 (bestaande uit pasiënte 59 jaar en ouer). Die verspreiding tussen vroue en mans met betrekking tot die warfarien voorskrifte wat ge-eis is (n=205 999, 48.2%; n=221 117, 51.8%) en die warfarien medisyne-items wat ge-eis is (n=206 232, 48.2%; n=221 390, 51.8%) was byna dieselfde. Algemene praktisyns het die hoogste gemiddelde VDD (7.01 ± 9.86) van warfarien geneesitems voorgeskryf. Pediatriese kardioloë het die laagste gemiddelde VDD (4.61 ± 1.29) van warfarin medisyne-items gehad. 'n D-waarde van 0.1 dui aan dat daar geen praktiese verskil is met betrekking tot die gemiddelde VDD tussen algemene praktisyns en pediatriese kardioloë nie. Die gemiddelde VDD van warfarien medisyneitems tussen vroue (6.60 ± 9.06) en mans (6.74 ± 8.41) was byna gelyk. Die ouderdomsgroep wat die hoogste gemiddelde VDD gehad het was ouderdomsgroep 2 (7.42 ± 7.42). Ouderdomsgroep 4 (6.50 ± 8.90) het die laagste gemiddelde VDD van warfarien medisyne-items ge-eis. 'n D-waarde van 0.1 dui geen praktiese betekenisvolle verskil in die gemiddelde VDD's van warfarien medisyne-items tussen hierdie twee ouderdomsgroepe nie.

Die resultate het getoon dat geneesmiddels met 'n beduidendheidsgradering (BG) van 1 (n=155 066, 43.3%), 2 (n=30 128, 8.4%), 4 (n=137 144, 38.3%), en 5 (n=36 144, 10.1%) saam met warfarien voorgeskryf is gedurende die ses jaar periode. Die vyf geneesmiddels wat saam met warfarien voorgeskryf is sluit in aspirien (n=48 903, 13.6%), tiroksien (n=33 954, 9.5%), amiodaroon (n=25 056, 7.0%), simvastatien (n=19 070, 5.3%) en celecoxib (n=10 794, 3.0%). Hierdie vyf middels het elk 'n BG van 1.

**Gevolgtrekkings:** Hierdie studie het gewys dat die vyf geneesmiddels wat die meeste saam met warfarien voorgeskryf is die volgende insluit: aspirien, tiroksien, amiodaroon, simvastatien en celecoxib. Hierdie geneesmiddels kan potensieel met warfarien reageer, met 'n potensiële interaksiegradering met 'n beduidendheid van 1. Dit beteken dat geneesmiddels wat potensieel lewensbedreigende effekte of permanente skade kan doen algemeen saam met warfarin voorgeskryf word. Kliniese data met betrekking tot die Internasionale Genormaliseerde Verhouding of protrombientyd moet bekom word om te evalueer of warfarienterapie aangepas word wanneer 'n geneesmiddel wat 'n potensiele interaksie met warfarien het, saam met warfarien voorgeskryf word. Die ouderdom van die pasiënt en die duur van warfarienterapie moet ook bekom word om te assesseer of warfarien terapie aangepas word soos wat die pasiënt ouer word.