

**A drug utilisation review of the concept of metabolic syndrome using
a South African medicines claims database**

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ABSTRACT

A drug utilisation review of the concept of metabolic syndrome using a South African medicines claims database

The aim of the study was to determine the prevalence, medicine prescribing patterns and direct treatment cost associated with the metabolic syndrome and its components in the private health care sector of South Africa. A two-dimensional research method was employed, consisting of a literature review and an empirical investigation. The objective of the literature review was to provide background to the study by conceptualising the metabolic syndrome and the components forming part thereof. The empirical investigation consisted of a descriptive, quantitative, retrospective drug utilisation review study, utilising medicine claims data sourced from a South African Pharmaceutical Benefit Management (PBM) company for the period January 1, 2005 to December 31, 2008. Data for a total 246 122 patients from 2005, 252 080 from 2006, 208 632 from 2007 and 196 242 from 2008, receiving at least one medicine item from the pharmacological medicine classes of antihypertensives (including diuretics, MIMS® classifications 7.3 and 16.1), hipolipidaemics (MIMS® classification 7.7) and antidiabetics (MIMS® classification 19.1) were analysed. Metabolic syndrome was defined according to the American Heart Association/National Heart, Lung and Blood Institute criteria, as patients with claims for ≥ 1 medicine item(s) per year from *each* of these drug classes.

Seventy one per cent ($n = 261\ 036$) of patients from 2005 met one risk selection criterion for the metabolic syndrome, compared with 69.9% from 2006 ($n = 269\ 452$), 66.6% ($n = 226\ 264$) from 2007 and 64.9% ($n = 214\ 109$) from 2008 (male:female ratio 1:1.5 for 2005-2008; age peak $>45, \leq 60$ year). A total 60 683 (4.0%, $n = 1\ 509\ 621$) of patients from the 2005 dataset met at least two risk criteria for the metabolic syndrome. This number of patients increased to reach 63 835 (4.1%, $n = 1\ 558\ 090$) in 2006, thereafter decreasing to 57 992 (4.9%, $n = 1\ 178\ 596$) in 2007 and 57 220 (5.9%, $n = 974\ 497$) in 2008. A total 5.7% ($n = 246\ 122$) of patients in 2005 met inclusion criteria for the metabolic syndrome, increasing to 6.5% ($n = 252\ 080$) in 2006, 7.8% ($n = 208\ 632$) in 2007 and 8.3% ($n = 196\ 242$) in 2008 (male to female ratio for 2005 - 2008:1.2:1). In general, prevalence increased from $\sim 0.1\%$ of patients aged $>0, \leq 15$ years to $\sim 0.3\%$ in those $>15, \leq 30$ years, $\sim 6\%$ in patients $>30, \leq 45$ years, $\sim 40\%$ in patients aged $>60, \leq 75$ years and $\sim 20\%$ in patients >75 years. The average prevalent age appeared earlier in males than in females by 2 years.

The average pill burden per prescription for patients from the 2005-metabolic syndrome

category was 2.6 ± 1.43 , compared with 2.6 ± 1.47 in 2006, 2.7 ± 1.52 in 2007 and 2.7 ± 1.53 in 2008, with a maximum of 16 items claimed per patient in 2005, 14 in 2006 and 2007, respectively and 19 in 2008. Antidiabetics, hipolipidaemics and antihypertensives were claimed in a ratio of 1:1:2 across the 4-year study period. A prescribing index of 20 medicine items (active substances) based on prescribing volume was established for metabolic syndrome patients; the 5 most claimed medicine items on this index was metformin, simvastatin, atorvastatin, insulin and gliclazide.

A total of 17 716 different treatment regimens was identified for patients from the 2008-metabolic syndrome category, containing from one to 12 different active substances per regimen. Overall 90.7% ($n = 17\ 716$) of treatment regimens contained between 3 and 7 different active substances per prescription; a further 3.3% contained ≥ 8 active substances each. The combination of indapamide and perindopril with amlodipine, or simvastatin and/or metformin had the highest prevalence among those regimens containing ≥ 3 active substances.

The total direct medicine treatment cost from the metabolic syndrome category amounted to R71.7 million in 2005, increasing to R94.7 million in 2008. Medical aid schemes contributed 90.0% ($n = R71\ 724\ 445.88$) towards these costs in 2005, decreasing to 86.0% ($n = R94\ 690\ 393.54$) in 2008. The average scheme contribution was $R131.14 \pm 135.64$ (median R103.12) per medicine item in 2005, compared with $R126.63 \pm 133.65$ (median R101.24) in 2006, $R128.39 \pm 141.69$ (median R101.35) in 2007 and $R122.45 \pm 143.97$ (median R94.27) in 2008. Patients paid the excess 10% (2005) to 14% (2008) of costs out-of-pocket for co-payments on medicine items at an average cost of $R14.55 \pm 34.26$ (median R0.00) per item for 2005, compared with $R15.80 \pm 38.04$ (median R0.00) during 2006, $R16.61 \pm 38.01$ (median R0.00) in 2007 and $R19.95 \pm 40.06$ (median R2.28) in 2008. The average annual direct medicine treatment cost for a patient from the metabolic syndrome category summed to $R4\ 809.20 \pm 4\ 057.46$ (median R3 850.67) in 2005, compared with $R5\ 053.34 \pm 4\ 033.85$ (median R4 041.16) in 2006, $R5\ 503.88 \pm 4\ 348.67$ (median R4 357.79) in 2007 and $R5\ 300.03 \pm 4\ 433.93$ (median R4 100.06) in 2008.

A total 7 050 patients (39.5%, $n = 17\ 866$) or approximately every third patient from the metabolic syndrome category had at least one other Chronic Disease List (CDL) condition during 2008. An average chronic disease count of 1.4 ± 0.63 (median 1) (range: 1-5) per patient was calculated. Diseases that co-occurred most were hypothyroidism (22.7%, $n = 7\ 050$), coronary artery disease (13.6%, $n = 7\ 050$), cardiac failure (10.7%, $n = 7\ 050$), asthma (7.3%, $n = 7\ 050$) and glaucoma (4.5%, $n = 7\ 050$).

In conclusion, this study established base-line estimates on the prevalence, medicine

prescribing patterns and associated direct medicine treatment cost of patients with metabolic syndrome and/or those at risk for the development thereof in the private health care sector of South Africa, as defined by surrogate measures of criteria from the American Heart Association and National Blood Institute. Recommendations for future extensions and diversifications to the study were made.

‘n Medisyneverbruiksevaluering van die konsep van metaboliese sindroom deur gebruik te maak van ‘n databasis van Suid-Afrikaanse medisyne-eise

Die doel van die studie was om die voorkoms, medisynevoorskryfpatrone en direkte medisynebehandelingskoste van die metaboliese sindroom en sy komponente in die private gesondheidsorgsektor van Suid-Afrika te bepaal. ‘n Tweedimensionele navorsingsmetode is gebruik, bestaande uit ‘n literatuuroorsig en ‘n empiriese ondersoek. Die doel van die literatuuroorsig was om die metaboliese sindroom en die komponente wat deel daarvan vorm te konseptualiseer ten einde ‘n agtergrond vir die studie te skep. Die empiriese ondersoek het bestaan uit ‘n beskrywende, kwantitatiewe retrospektiewe medisyneverbruiksevalueringstudie deur van medisyne-eisedata, wat vanaf ‘n Suid-Afrikaanse Farmaseutiese Voordele Bestuursmaatskappy verkry is, gebruik te maak. Data vir die periode 1 Januarie 2005 tot 31 Desember 2008 is verkry. Data vir 246 122 pasiënte uit 2005, 252 080 uit 2006; 208 632 uit 2007 en 196 242 uit 2008, wat ten minste een medisyne-item uit die farmakologiese medisyneklasse van antihipertensiewe middels (insluitende diuretika, MIMS® klassifikasie 7.3 en 16.1), hipolipidemiese (MIMS® klassifikasie 7.7) en antidiabetiese middels (MIMS® klassifikasie 19.1) ontvang het, is geanaliseer. Metaboliese sindroom is gedefinieer van kriteria afkomstig van die Amerikaanse Hartvereniging en Nasionale Bloed- en Long-Instituut, as pasiënte met ‘n eis vir ≥ 1 medisyne-item(s) per jaar vanuit elk van hierdie medisyneklasse.

Een-en-sewentig persent ($n = 261\ 036$) van pasiënte uit 2005 het aan een selekteringskriterium vir metaboliese sindroom voldoen, teenoor 69.9% uit 2006 ($n = 269\ 452$), 66.6% ($n = 226\ 264$) uit 2007 en 64.9% ($n = 214\ 109$) uit 2008 (in ‘n verhouding van 1:1.5 vir manlik:vroulik vir 2005-2008; voorkomspiek 46-60 jaar). Altesaam 683 ($n = 261\ 036$) pasiënte uit 2005 het altesaam aan twee van die selekteringskriteria vir metaboliese sindroom voldoen, teenoor 63 835 ($n = 269\ 452$) uit 2006, 57 992 ($n = 226\ 264$) uit 2007 en 57 220 ($n = 214\ 109$) uit 2008 (in verhouding van 1:1 vir manlik:vroulik vir 2005-2008). Altesaam 5.7% ($n = 246\ 122$) van pasiënte uit 2005, 6.5% ($n = 252\ 080$) in 2006, 7.7% ($n = 208\ 632$) in 2007 en 8.3% ($n = 196\ 242$) in 2008 (in ‘n verhouding van 1.2:1 vir manlik:vroulik vir 2005-2008) het aan die selekteringskriteria vir metaboliese sindroom voldoen. Voorkoms het oor die algemeen verhoog vanaf $\sim 0.1\%$ in pasiënte met ouderdomme $>0, \leq 15$ jaar, tot $\sim 0.3\%$ in diegene $>15, \leq 30$ jaar, $\sim 6\%$ in pasiënte $>30, \leq 45$ jaar, $\sim 40\%$ in pasiënte $>60, \leq 75$ years, en $\sim 20\%$ in pasiënte >75 jaar. Die gemiddelde voorkomsouderdom was 2 jaar vroeër in manlike as in vroulike pasiënte.

Die gemiddelde tabletas per voorskrif vir 2005 was 2.6 ± 1.43 , teenoor 2.6 ± 1.47 in 2006, 2.7 ± 1.52 in 2007 en 2.7 ± 1.53 in 2008. 'n Maksimum van 16 items is per pasiënt geëis in 2005, teenoor 14 in 2006 en 2007 onderskeidelik, en 19 in 2008. Antidiabetiese, hipolipidemiese en antihipertensiewe medikasie is in 'n verhouding van 1:1:2 oor die vierjaarstudieperiode geëis. 'n Voorskrifindeks, gebaseer op voorskryfvolume, is daargestel vir pasiënte met metabooliese sindroom; die vyf medisyne-items wat die meeste uit hierdie indeks geëis is, was metformien, simvastatin, atorvastatin, insulien en gliklasied.

Altesaam 17 716 verskillende behandelingsregimens, bevattende tussen een en twaalf verskillende aktiewe stowwe per regimen, is geïdentifiseer vir pasiënte van die 2008-metabooliesesindroom-kategorie. Altesaam 90.7% ($n = 17\ 716$) van hierdie behandelingsregimens het tussen 3 en 7 verskillende aktiewe stowwe per voorskrif bevat en 'n verdere 3.3% van regimen het ≥ 8 aktiewe stowwe elk bevat. Die kombinasie bestaande uit indapamied en perindopril tesame met amlodipien, of simvastatin en/of metformien, het die hoogste voorkoms gehad tussen die regimen wat ≥ 3 aktiewe stowwe bevat het.

Die totale direkte medisynebehandelingskoste vir pasiënte van die metabooliesesindroom-kategorie het in 2005 R71.7 miljoen beloop en vermeerder tot R94.7 miljoen in 2008. Mediese fondse het 90.0% ($n = R71,724\ 445.88$) bygedra tot hierdie koste in 2005 wat in 2008 na 86.0% ($n = R94\ 690\ 393.54$) afgeneem het. Die gemiddelde mediese fondsebydrae was $R131.14 \pm 135.64$ (mediaan R103.12) per medisyne-item in 2005, teenoor $R126.63 \pm 133.65$ (mediaan R101.24) in 2006, $R128.39 \pm 141.69$ (mediaan R101.35) in 2007 en $R122.45 \pm 143.97$ (mediaan R94.27) in 2008. Pasiënte het die uitstaande koste van 10% (in 2005) tot 14% (in 2008) uit die sak betaal as bybetalings op medisyne-items, teen 'n gemiddelde koste van $R14.55 \pm 34.26$ (mediaan R0.00) per item in 2005, teenoor $R15.80 \pm 38.04$ (mediaan R0.00) gedurende 2006, $R16.61 \pm 38.01$ (mediaan R0.00) in 2007 and $R19.95 \pm 40.06$ (mediaan R2.28) in 2008. Die gemiddelde jaarlikse direkte medisynebehandelingskoste vir 'n pasiënt van die metabooliesesindroom-kategorie het $R4\ 809.20 \pm 4\ 057.46$ (mediaan R3 850.67) in 2005 beloop, teenoor $R5\ 053.34 \pm 4\ 033.85$ (mediaan R4 041.16) in 2006, $R5\ 503.88 \pm 4\ 348.67$ (mediaan R4 357.79) in 2007 en $R5\ 300.03 \pm 4\ 433.93$ (mediaan R4 100.06) in 2008.

Altesaam 7 050 pasiënte (39.5%, $n = 17\ 866$) of ongeveer elke derde pasiënt uit die metabooliesesindroom-kategorie het ten minste een ander "Chronic Disease List (CDL)" toestand gedurende 2008 gehad. 'n Gemiddelde chroniesesiekte-telling van 1.4 ± 0.63 (mediaan 1) (reeks: 1-5), per pasiënt is bereken. Siektes wat die meeste voorgekom het, was hipotiroïdisme (22.7%, $n = 7\ 050$), koronêre hartvatsiekte (13.6%, $n = 7\ 050$), hartversaking (10.7%, $n = 7\ 050$), asma (7.3%, $n = 7\ 050$) en gloukoom (4.5%, $n = 7\ 050$).

Ter samevatting: Hierdie studie het basislynberamings neergelê rakende die voorkoms, medisynevoorskryfpatrone en direkte medisynebehandelingskoste vir pasiënte met metabooliese sindroom en/of diegene wat 'n risiko loop om die sindroom te ontwikkel, in die private gesondheidsorgsektor van Suid-Afrika, soos gedefinieer deur surrogaatmetings van kriteria afkomstig van die Amerikaanse Hartvereniging en Nasionale Bloed- en Long-Instituut. Aanbevelings vir toekomstige uitbreiding en diversifisering van die studie is gemaak.

KEYWORDS/TREFWOORDE

Keywords: Metabolic syndrome, antidiabetics, antihypertensives, hipolipidaemics, retrospective drug utilisation review, medicine claims data, prevalence, direct medicine treatment cost, prescribing index, chronic disease count

Trefwoorde: Metaboliese sindroom, antidiabetiese middels, antihipertensiewe middels, hipolipidemiese middels, retrospektiewe medisyneverbruiksevaluering, medisyn-eise data, voorkoms, direkte medisynbehandelingskoste, voorskrifindeks, chroniesesiekte-telling

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*I dedicate this thesis to my mother and late father,
who have been my role-models for hard work
and perseverance and who taught me
the importance of education.*

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LIST OF ABBREVIATIONS AND ACRONYMS

A

ACE	Angiotensin-converting enzyme
ACE /AACE	American College of Endocrinology/ American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AHA	American Heart Association
AHA/NHLBI	American Heart Association/National Heart, Lung And Blood Institute
apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease

B

BMI	Body mass index
BP	Elevated blood pressure

C

CAD	Coronary artery disease
CDL	Chronic Disease List
CER	Cost-effectiveness ratio
CETP	Cholesteryl ester transfer protein
CHD	Coronary Heart Disease
CPI	Cost prevalence index
CVD	Cardiovascular disease
CRP	C-reactive protein

D

DASH	Dietary Approaches To Stop Hypertension
DECODE	Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe
DECODA	Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Asia
DGAT2	Hepatic diacylglycerol acyltransferase 2
DM	Diabetes mellitus
d-ROMs	Derivates of the reactive oxidative metabolites
DUR	Drug utilisation review

E

EASD	European Association for the Study Of Diabetes
ECS	Endocannabinoid system
EGIR	European Group for Study of Insulin Resistance
ESC	European Society of Cardiology

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

H

HbA _{1c}	Glycated haemoglobin test
HDL	High-density lipoprotein
HMG-COA	Hydroxymethylglutaryl-coenzyme A reductase
HR	Hazard ratio

I

IAS	International Atherosclerosis Society
IASO	International Association of the Study Of Obesity
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
ICUR	Incremental cost-utility ratio
IDLS	Intermediate-density lipoproteins
IGT	Impaired glucose tolerance
LCDS	Low-calorie diets
IL	Interleukin

J

JNC	Joint National Commission

L

LCAT	Lecithin:Cholesterol Acyltransferase
LDL	Low-density lipoprotein
LP(A)	Lipoprotein(a)
LRCF	Lipid Research Clinics Prevalence Mortality Follow-Up Study

M

MIMS	Monthly Index of Medical Specialities
MRFIT	Multiple Risk Factor Intervention Trial

N

NAD	Nicotinamide adenine dinucleotide
NCEP/ATP III	National Cholesterol Education Program—Third Adult Treatment Panel
NEFAS	Non-esterified free fatty acids
NFCS	The National Food Consumption Survey
NHANES	National Health And Nutrition Examination Survey
NIH	National Institute of Health
NNT	Number needed to treat

O

OGTT	Oral glucose tolerance test

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

P

PAI	Plasminogen activator inhibitor
PBM	Pharmaceutical benefit management
PMB	Prescribed minimum benefits
PPAR	Peroxisome proliferator-activated receptor
PROCAM	Prospective Cardiovascular Munster Study
PROCEED	Prospective Obesity Cohort of Economic Evaluation and Determinants

Q

QALY	Quality-Adjusted Life Years

R

RAAS	Renin-angiotensin-aldosterone system

S

SA	South Africa
SAA	Serum amyloid A protein
SADHS	South African Demographic and Health Survey
SAHS	Southern African Hypertension Society
SAS	Statistical Analysis System
SASSO	South African Society for the Study of Obesity

T

TC	Total cholesterol
TLC	Therapeutic lifestyle changes
TNF	Tumour necrosis factor

U

UKPDS	United Kingdom Prospective Diabetes Study

V

VLCD	Very-low-calorie diets
VLDL	Very-low density lipoprotein

W

WHF	World Heart Federation
WHO	World Health Organization
WHR	Waist-to-hip-ratio

Y

YLL	Years of Life Lost

LIST OF SYMBOLS

α	Alpha
β	Beta
δ	Delta
γ	Gamma
$<$	Less than
$\leq$	Less-than or equal to
$>$	More than
$\geq$	More-than or equal to
$\pm$	Plus minus
®	Registered
™	Trademark
mm Hg	Millimeters of mercury
mg/mL	Milligram per milliliter
mg/dL	Milligrams per deciliter
mmol/L	Millimol per liter
4S	Scandinavian Simvastatin Study
95% CI	95% Confidence Interval

ASSOCIATED PRESENTATIONS

The following conference presentations relevant to the thesis were produced during candidature:

Burger, J.R., Serfontein, J.H.P. & Lubbe, M.S. 2010. The metabolic syndrome: estimates of prevalence in the South African private healthcare sector. Podium presentation at the Biennial Congress of the Southern African Hypertension Society, Gauteng, South Africa, 19-22 January 2010.

Burger, J.R., Serfontein, J.H.P. & Lubbe, M.S. 2010. Cost analysis of the medicine treatment of South African patients with metabolic syndrome. Poster presentation at the ISPOR 13th Annual European Congress, Prague, Czech Republic, 6-9 November 2010.

Burger J.R. 2011. Metabolic syndrome: call for treatment guidelines. Invited speaker at the HMR Africa Healthcare Summit, Isando, Gauteng, South Africa, 19-22 January 2011.

Burger, J.R., Lubbe M.S. & Serfontein J.H.P. 2011. Longitudinal analysis of medicine prescribing patterns for metabolic syndrome patients in South Africa. Poster presentation at the European Association for Clinical Pharmacology and Therapeutics (EACPT) conference, Budapest, Hungary, 26-29 June 2011.

Burger, J.R., Serfontein, J.H.P. & Lubbe, M.S. 2011. Pill burden in South African patients with multiple risk factors for metabolic syndrome. Poster presentation at the ISPOR 14th Annual European Congress, Madrid, Spain, 5-8 November 2011.

Burger, J.R., Lubbe, M.S. & Serfontein, J.H.P. 2011. Identifying South African patients with metabolic syndrome using medicine claims data. Poster presentation at the EuroDURG/ISPE conference, Antwerp, Belgium, 30 November to 3 December 2011.

CHAPTER 1

Introduction and Study Overview

This chapter represents the introduction and overview of the study. It contains an overview of the background to, and the rationale for the study, the significance of the study, the research questions, purpose (aim) of the study and method of study to be employed. The chapter concludes with the general division of chapters in the thesis.

1.1 BACKGROUND AND RATIONALE FOR THE STUDY

The South African health care market is divided between two systems viz., the public and private sectors. The private sector, administered largely by health insurance schemes (provided by medical aid schemes), serves less than 20% of the population's needs, leaving the bulk of the population (mainly the uninsured and poor) to be subsidized *via* general tax revenue. Yet the private sector consumes more than 50% (maybe as high as 80%) of the total health care expenditure in South Africa or approximately seven times more *per capita* than the public sector (Still, 2009:28).

The past decade in the private South African health care sector was recognised by costs of care that escalated at a rate exceeding the inflation rate, with diminishing growth in the number of medically insured people. During the 2010/11 financial year, total benefit expenditure in this sector reached R84.7 billion, with private hospital expenditure R31.1 billion and medicine R14.0 billion (~17% of total benefits paid) (CMS, 2011:161). Over the past decade, private health care costs in South Africa have been driven by hospital cost and the cost of medicines, with a lesser contribution also by the cost of treatment by medical specialists (Still, 2009:28). In response to the developments in the private sector, the Government enacted a range of regulations - in particular, the Medical Schemes Act (Act 131/1998) as amended - to ensure *inter alia* fair access to private health services and to control the cost escalation (Leon & Mabope, 2005:34). Legislation moving towards a national health care system in South Africa has also been applied i.e., the regulatory role of the Council for Medical Schemes (CMS) in overseeing the application of Prescribed Minimum Benefits (PMBs) of the Chronic Disease List (CDL) (Bester *et al.*, 2005:1).

The private health care sector (medical aid schemes) of South Africa engage in the reform by employing various strategies to contain costs, i.e. by moving towards managed health care, the employment of the principles of drug utilisation review (DUR), pre-authorisation processes, the development of disease management plans, generic substitution, and health economics in funding and pricing decisions (Bester *et al.*, 2005:1; Butkow, 2005). The concept of PMBs was first introduced by the Medical Schemes Act in 1998 (Act 131/1998) as a new medical schemes legislation to provide cost-effective and essential health care and to expand access to those previously excluded from cover (Anon., 2004:31). PMBs are minimum benefits (including provision for the diagnosis, treatment and care costs) which must be provided to all members of medical aid schemes, for a range of conditions specified in the regulations (CMS, 2011:29). The most common of these conditions include cardiovascular conditions (*inter alia* cardiac failure, coronary artery disease and hypertension) and metabolic/endocrine conditions (*inter alia* diabetes mellitus types 1 and 2, and hyperlipidaemia).

Cardiovascular disease (CVD) was notorious as the main cause of morbidity and mortality in the developed world during the 19th century (Lopez *et al.*, 2006:21; Wilmoth, 2000:1118, World Health Organization, 2002a:81). Despite the introduction of guidelines for its prevention and treatment, cardiovascular disease and type 2 diabetes mellitus continue to be leading causes of mortality in the world today. For example, based on statistics from the World Health Organization (WHO, 2011), cardiovascular diseases accounted for 17.3 million (or 30%) of deaths worldwide in 2008. By 2030, however, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke. Roglic and Unwin (2010:16) further estimated an excess global mortality of 4 million persons attributable to diabetes for the year 2010.

The burden of cardiovascular disease in sub-Saharan Africa is also increasing, to such an extent that it is now considered a public health problem (De-Graft Aikins *et al.*, 2010; Kengne *et al.*, 2005:3592). In the year 2000, 9.2% of the total deaths in this region could be ascribed to cardiovascular diseases (WHO, 2005:1-2). Projections from the Global Burden of Disease Project suggest that the burden of CVD faced by African countries will double from 1990 to 2020, whereas diabetes will become notably more prevalent in the African Region (WHO, 2005:2). Already in the late 1990s, Barry and Wassenaar (1996:29) estimated that South Africans had the highest incidence of coronary heart disease in the world. More recently Bradshaw and co-workers (2003:12;14) determined cardiovascular diseases (in particular hypertensive disease and ischaemic heart disease) and diabetes to both rank under the top 20 specific causes of premature mortality in the country.

Cardiovascular disease and diabetes have a major socio-economic impact on individuals, families and societies in terms of health care costs, absenteeism and national productivity

(Delpont, 2006:3; Simpson *et al.*, 2003:1666). This is further compounded by the fact that a high proportion of CVD and diabetes burden occurs earlier among adults of working age in developing countries, impacting negatively on these country's economic viability (Gaziano, 2005:3547; Sullivan, 2007:S1). In 1991 an estimated 2-3% of South Africa's gross national income, or roughly 25% of South African health care expenditures, was devoted to the direct treatment of CVD (Pestana *et al.*, 1996:679). According to Gaziano (2005:3547) expenditures in developed countries i.e. the United States (US) can serve as an indication of possible future expenditure in developing countries. Based on estimates by Heidenrich *et al.* (2011:3), between 2010 and 2030, real (2008 US\$) total direct medical costs of CVD are projected to triple from US\$273 billion to \$818 billion, whereas real indirect costs for all CVD are estimated to increase by 61% from \$172 billion in 2010 to \$276 billion in 2030.

Several risk factors contribute to the incidence of CVD as well as the development of type 2 diabetes mellitus (NIH, 2002:3207,3212). The simultaneous presence of these risk factors is now recognised as a disease entity by some - the so-called "metabolic syndrome" or "syndrome X" (Grundy & Cleeman *et al.*, 2005:2735). These terms have become some of the most frequently used in the field of medical science over the past few years (Sarafidis & Nilsson, 2006:621).

The American Diabetes Association and National Heart, Lung and Blood Institute use the term "metabolic syndrome" to describe a constellation of metabolic abnormalities or risk factors that identifies a person at increased risk for atherosclerotic cardiovascular disease (ASCVD) and/or type 2 diabetes mellitus (Grundy & Cleeman *et al.*, 2005:2737). There are, however, a number of unresolved questions causing controversies surrounding the syndrome. For example, there is controversy about whether the metabolic syndrome is a true syndrome or a mixture of unrelated phenotypes. Ding *et al.* (2010:485) and Khan (2007:1807) argue that the term "syndrome" is inappropriate because the combination of parameters yields no more information than analysing the individual parameters. In contrast, Grundy (2006e:1689) is of the opinion that "risk clustering cannot be explained by chance occurrence alone" stating that "if the metabolic syndrome is defined as multiple risk factors that are metabolically interrelated, then the syndrome certainly exists".

Furthermore, there is controversy about the pathogenesis of the syndrome; there are no well-accepted criteria for the diagnosis of the metabolic syndrome, and there is uncertainty about the clinical utility of the metabolic syndrome. For example, Bayturan *et al.* (2010:483), Hadaegh *et al.* (2012:430), Reaven (2005:931), and Woodward and Tunstall-Pedoe (2009:210) argue that other protocols for predicting cardiovascular disease and diabetes are equal or better diagnostic tools than the metabolic syndrome criteria. In contrast, Alberti *et al.* (2009:1640), Duvnjak *et al.*

(2008:83), Whayne (2009:648), and Spellman and Chemitiganti (2010:S21) are of the opinion that the metabolic syndrome represents a useful and simple clinical concept which allows for earlier detection of type 2 diabetes and cardiovascular disease, and is therefore highly relevant for prevention efforts at both the individual and population level. Notwithstanding this controversy surrounding the term “metabolic syndrome”, a diagnosis thereof may be useful, if only for the fact that it highlights a patient with multiple atherogenic risk factors that may benefit by receiving coordinated care.

The presence of one component of the metabolic syndrome heightens the possibility of having more of the other components of the syndrome (Smith *et al.*, 2005:e137). The probability of an individual having the metabolic syndrome thus rises when diseases such as diabetes, hypertension and atherogenic dyslipidaemia are present, and even more so when one or more of these diseases occur simultaneously. According to Mackinnon and co-workers (2003:161), a minimum of 70% of all adults have at least one component of the metabolic syndrome, of which 5-10% may progress to diabetes on an annual basis (Laakso, 2005:365). It is furthermore estimated that the metabolic syndrome affects between 10-30% of adult populations worldwide, especially populations in developed countries or urban areas of developing countries (Wild & Byrne, 2005:4). One in eight children might have three or more risk factors for the metabolic syndrome (CDC, 2004:4). The detection and management of underlying diseases/risk factors are thus of utmost importance to prevent CVD and its morbidity and mortality (WHO, 1999:32), and essential in preventing cardiovascular disease and diabetes becoming a future major health care burden (Sarti & Gallagher, 2006:122).

Prevalence rates of the metabolic syndrome in sub-Saharan Africa are uncertain due to a paucity of information (Ntyintyane *et al.*, 2006:51). Only a few studies have been published on the prevalence of the metabolic syndrome *per se* in Africa – the majority thereof are reports on the prevalence of the individual components in scattered populations (Mbanya, 2005). High prevalence rates of hypertension, diabetes, hyperlipidaemia and obesity in sub-Saharan African countries and specifically in South Africa, however, might be an indication of the prevalence of the syndrome (Bester *et al.*, 2005:15; CMS, 2005:25; Fezeu *et al.*, 2007:70; Gan, 2003:9; Okeahialam, 2005:14; Puoane *et al.*, 2002:1038).

Management of the metabolic syndrome generally includes lifestyle modifications as first-line defence (Tuomiletho, 2005:30). About 50% of people with the metabolic syndrome, however, do not reach treatment goals with life-style interventions only and thus require pharmacological intervention (Hanefeld & Schaper, 2005:390). There are two possible therapeutic approaches to the metabolic syndrome. One approach is to identify and treat each risk factor independently (disparate to its clustering with other risk factors) or alternatively, to target multiple or all of the

risk factors with single therapies (Grundy, 2006d:296). At present, however, there are no approved medicines that can reliably reduce all of the metabolic risk factors over the long term - resulting in the treatment of individual risk factors through a combination of lipid-lowering agents, antihypertensives and antihyperglycaemics (Grundy, 2006d:297). Pharmacological treatment in patients with the metabolic syndrome thus typically leads to polypharmacy - especially in those patients with type 2 diabetes or dyslipidaemia, where treatment with ten or more different kinds of agents is second nature (Hanefeld & Schaper, 2005:383). The majority of these treatments are usually directed against risk factors of the syndrome, but various other agents might also be necessary to treat complications of the risk factors or closely related conditions, exacerbating the polypharmacy quandary. As the number of substances required to better control risk factors and complications increase, so do the possibilities of untoward effects – drug side effects, drug-drug interactions, non-adherence, medication errors and increased risk of hospitalisation - and so does the cost of therapy (directly mainly due to medication and indirectly due to the cost of treating adverse events) (Rollason & Vogt, 2003:820-821).

There is also limited information in the literature about health resource use and cost attributable to the metabolic syndrome in South Africa, and up to date no studies have been conducted assessing the economic impact of the metabolic syndrome in South Africa; especially in the private health care sector. Estimates derived of the cost of treatment in other Sub-Saharan African countries, indicate that the total cost for medications needed to treat all risk factors (high blood pressure, diabetes and dyslipidaemia) in the entire population of patients with cardiovascular risk factors (with a metabolic syndrome prevalence of 22.1%) amount to US \$84.6 *per capita* per year, with cost for minimal follow-up medical care and laboratory test to amount to \$22.6 (Bovet *et al.*, 2006:1). In addition, patients with the metabolic syndrome have significantly higher short-term disability costs, an increased mean number of inpatient admissions and increased cost per admission, a longer length of hospital stay and an increased number of outpatient visits per patient compared with those without the syndrome (Hivert *et al.*, 2009; Schultz & Edington, 2009:464-465).

Research has shown that prevention or detection of illness before a crisis occurs, provides better outcomes related to chronic illness (Rolland, 2002:286; Woolf, 2008:2437). Historically, health care providers followed a treatment philosophy instead of one of prevention. As the South African population ages, however, a delivery model that endeavours to provide a preventive orientation must be sought and organisational health care delivery systems must also be shifted. The rapidly escalating cost of drug therapy, though, is a concern to health care providers throughout the world, particularly as new pharmacological agents often offer only marginal improvements over existing therapies but at significantly higher costs (Vuorenkosi *et al.*, 2008:2). In the interim, the gap between the supply and demand for health care is growing

(McDonald & Wally, 2004). No health care system in the world (public or private) can, however, afford and/or finance all the health services from which its population can potentially profit. This implies some tough choices for policy-makers and trustees of medical schemes by whom health services, diagnostic modalities and/or pharmacological agents should be provided and/or funded (Henderson, 2009:111).

Health payers and policy makers need information about the cost and effectiveness of medical treatments. Economic evaluations can provide health care decision-makers with such valuable data, allowing optimal distribution of scarce resources (Arenas-Guzman *et al.*, 2005:34). Moreover, according to Van Velden *et al.* (2005:1076) economic evaluations can play an important role in different types of health care decision-making, i.e., formulary decisions, reimbursement decisions and/or price and prescribing at macro, meso and micro level. Alternatively, economic evaluation can also have a behavioural effect, involving the instrumental use of research findings, with a subsequent powerful influence on health care decision-making.

Managed care organisations can play an important role in maintaining health and reducing the cost of health care by successful intervention before the development of clinically recognised diabetes, coronary artery disease and cardiovascular disease (Fine, 2007:S2). These organisations employ *inter alia* drug utilisation reviews to ensure that the appropriate risk population and high costs due to the continuing treatment of chronic medical conditions can be accurately predicted and controlled (thus help to better ways to allocate limited resources) through disease management programmes (Fine, 2007:S1; Russell *et al.*, 1996:10; Zhao *et al.*, 2003:389).

1.2 SIGNIFICANCE OF THE STUDY

From the aforementioned discussion, it is evident that the metabolic syndrome is an evolving disease process that must be addressed pro-actively by health care providers and decision makers. Decision makers, however, require evidence on the cost, effectiveness and impact of health care interventions to facilitate transparent decision-making. Managed care organisations also need to be able to estimate the prevalence of health states to manage health care appropriately – especially for conditions that are carrying a high disease burden such as the metabolic syndrome (Hollenbeak *et al.*, 2007:S4). Effective strategies for metabolic syndrome disease management can be developed and resource allocation planned when it is clear how the syndrome and the clustering of risk factors translate into health care utilisation at a population level (Boudreau *et al.*, 2009:306).

According to Burns and Grove (2009:85), research is conducted to provide information that can

lead to research-based care. This study will provide a baseline cost and impact information. Economic research conducted on the metabolic syndrome in the private health care sector of South Africa could furthermore therefore potentially facilitate and/or add to the

- effective targeting of intervention strategies and thereby minimise the risk of progression to chronic disease; and
- identification of future high cost users of medical care associated with morbidity and mortality attributable to subsequent cardiovascular disease and diabetes mellitus.

1.3 RESEARCH QUESTIONS

Two major research questions were formulated for this study, namely:

- What does the term “metabolic syndrome” entail, and what is the impact thereof in the private health care sector of South Africa?
- How can economic analysis and drug utilisation review as tools assist in the decision-making process regarding the treatment of the metabolic syndrome and its components in the private health care sector of South Africa?

1.4 RESEARCH METHOD

In order to answer the above-stated research questions, a two-dimensional research procedure, consisting of a literature study followed by an empirical investigation was initiated.

1.4.1 Literature review

According to Neuman (2005:89), literature studies (the use of relevant books, journals and articles) provide a background to the study being proposed, and are used to establish the context of the topic, to discover important variables relevant to a topic and to gain a new perspective and to rationalise the significance of the problem.

Several books and articles were used for the literature study. This literature review presented in the second chapter of this thesis and focuses on the concept of metabolic syndrome. In this chapter, emphasis is directed towards the origin of the syndrome, the prevalence and diagnosis thereof, the burden of disease, associated risk factors and their propensity of developing cardiovascular disease and diabetes mellitus, as well as their impact on the use of scarce resources and health care service utilisation. Thereafter a discussion of the management of these risk factors ensues. Chapter 2 concluded with a discussion on the treatment of metabolic syndrome, *per se*.

1.4.2 Empirical research

The empirical phase of the study consisted of a quantitative, non-experimental (exploratory-descriptive), retrospective drug utilisation review, using medicine claims data from a leading South African Pharmaceutical Benefit Management Company (PBM). This method employed, is discussed in detail in chapter 3.

1.5 STUDY AIM

The aim of the study was identified by the following overall goal and specific objectives for each phase of the research process.

1.5.1 Research goal

The goal of this study is to determine the prevalence and impact (resource utilisation and direct treatment cost) associated with the metabolic syndrome and its components in the private health care sector of South Africa.

1.5.2 Research objectives

Research objectives are a formulation of the purpose of the research in measurable defined terms. The specific research objectives of the literature study aimed at achieving the goal of this study are to:

- Conceptualise what the “metabolic syndrome” and its components entails.
- Determine how prevalent the “metabolic syndrome” is worldwide and in South Africa.
- Determine the impact of metabolic syndrome and these components on the utilisation and cost of health care services.
- Determine the treatment for metabolic syndrome and its components.

These specific literature objectives were further subcategorised into several topics. These are further detailed in chapter 2.

The specific research objectives of the empirical investigation phase of the study relate to the drug utilisation review conducted on medicine claims data obtained from a leading South African Pharmaceutical Benefit Management Company (PBM), for the period January 1, 2005 to December 31, 2008 (except were explicitly stated otherwise). The specific objectives were to:

- Review the prevalence and demographic profile of patients on the respective datasets (empirical objective #1).

- Review claims patterns (prescriptions and medicine items) for patients from the datasets, stratified by age and gender (empirical objective #2).
- Review cost associated with prescriptions and medicine claims claimed for patients from the datasets, stratified by age and gender (empirical objective #3).
- Review the prevalence and demographic profile of patients considered “at risk” for the development of metabolic syndrome, stratified by age and gender (empirical objective #4).
- Review claims patterns (prescriptions and medicine items) for patients considered “at risk” for the metabolic syndrome, stratified by age and gender (empirical objective #5).
- Review the associated cost of medicine claims for patients considered “at risk” for the development of the metabolic syndrome, stratified by age and gender (empirical objective #6).
- Determine the prevalence and demographic profile of metabolic syndrome patients (empirical objective #7).
- Review claims patterns (prescriptions and medicine items) for metabolic syndrome patients, stratified by age and gender (empirical objective #8).
- Determine the direct medicine treatment cost of metabolic syndrome patients, stratified by age and gender (empirical objective #9).
- Determine a prescribing index for metabolic syndrome patients based on prescribing volume and cost of medicine items (empirical objective #10).
- Determine the prescribing volume, nature and direct cost of the most claimed treatment regimens used for metabolic syndrome patients from the period January 1, 2008 to December 31, 2008 (empirical objective #11).
- Determine the prevalence of chronic conditions co-occurring in metabolic syndrome patients from the period January 1, 2008 to December 31, 2008 (empirical objective #12).

1.6 CHAPTER DIVISION

This thesis is divided into 5 chapters. Chapter 2 entails a comprehensive literature review of the metabolic syndrome and its components. Chapter 3 incorporates a discussion of the method employed in the empirical investigation phase of the study, as well as the research design while Chapter 4 consists of the data analysis and interpretation of results. Chapter 5 opens with an overview of the thesis content, and provides summaries of the most significant findings of the study. Chapter 5 also highlights the strengths and weaknesses of the study, and provide recommendations for future extensions and diversifications to the study.

1.7 CHAPTER SUMMARY

In this chapter, cardiovascular disease (CVD) and diabetes was established as main causes of global and local morbidity and mortality. The metabolic syndrome was identified as a major risk factor for both CVD and type 2 diabetes. A brief literature review was given to support the purpose of the study, the choice of method and to establish a framework for the study. The goal was spelt out together with the specific research objectives. The potential value of the study was explained. The next chapter contains a discussion on the concept of metabolic syndrome and its components.

CHAPTER 2

Literature Review

Chapter one of this thesis provided an introduction and overview of the study, also stating the specific objectives for the study. This present chapter contains the background information gathered during the literature review phase of this study. The specific objectives of this review were to conceptualise the metabolic syndrome, to determine how prevalent metabolic syndrome is and which components form part thereof. The impact of these components and the metabolic syndrome *per se* on the utilisation and cost of health care services further needed to be determined, and the treatment thereof, as well as for the metabolic syndrome needed to be. To attain these objectives, several sources were consulted, and a number of topics were addressed. The chapter has been arranged under these headings.

2.1 SOURCES EMPLOYED DURING THE LITERATURE REVIEW

To attain the specific objectives of the literature review, several books, websites and articles from different fields of research and practices i.e. pharmacology (therapeutics and diseases), pharmacy practice (disease management, managed health care, drug utilisation review, pharmacoepidemiology, evidence-based medicine) and economics (pharmacoeconomics) were consulted. Databases that were employed during the literature search included Ebsco Host, Scopus, ISI web of Knowledge, RSAT, Science Direct, Nexus, SACat, ProQuest and Google Scholar.

Several older references were included in the review because of their significance in terms of their original contribution to the subject of metabolic syndrome and to establish a timeline for the development of the concept, such as Kylin (1923), Vague (1947), Avogaro and Crepaldi (1965), Avogaro *et al.* (1967), Gofman *et al.* (1966), Hanefeld (1973), Haller (1977), Singer (1977), Reaven (1988) and Kaplan (1989). Secondary references (e.g. Magliano *et al.*, 2008) were used when the original reference (e.g. Beijer *et al.*, 1991; Morgagni, 1765) were not available/obtainable. Abstracts (e.g. Mamedov *et al.*, 2003 and Moraes *et al.*, 2009) were used when original articles were not available in English.

2.2 HISTORICAL OVERVIEW OF THE METABOLIC SYNDROME CONCEPT

The concept of the metabolic syndrome dates back to the 15th century, when a Dutch physician, Nicolaes Tulp, linked hypertriglyceridaemia and the ingestion of saturated fatty acids, obesity and bleeding tendency in the documentation of a syndrome he coined the “hypertriglyceridaemia syndrome” (Beijer *et al.*, 1991, quoted by Magliano *et al.*, 2008:31). In the mid of the 17th century, Giovanni Morgagni (celebrated as the father of the modern anatomical pathology), described central obesity, hypertension, hyperuricaemia, atheroma and sleep apnoea as a cluster of conditions commonly found together (Morgagni, 1765, as quoted by Magliano *et al.*, 2008:31). Eskil Kylin, a Swedish physician, thereafter added abnormal glucose metabolism to this description, describing a syndrome involving hypertension, hyperglycaemia and hyperuricaemia (Kylin, 1923:124). Approximately two decades later Vague (1947:340) reported a relationship between diabetes, obesity and fat distribution (particularly in the upper body) and cardiovascular disease (CVD). A number of researchers subsequently reported the frequent co-occurrence of metabolic risk factors in individuals at high coronary disease risk (CAD) *inter alia* Avogaro and Crepaldi, 1965; Avogaro *et al.*, 1967; and Gofman *et al.*, 1966, thereby strengthening the case for a relationship between the clustering of metabolic syndrome risk factors and cardiovascular disease.

Gofman and colleagues (1966:691) established that dyslipidaemia associated with the increased CAD risk was characterised by an abundance of small, dense, triglyceride rich, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). In the early 1970s, Hanefeld (1973) extended the earlier observations, underlying the high risk for atherosclerosis in those presenting with the cluster of disorders. Haller (1977:124) and Singer (1977:129) were the first to use the term “*metabolische syndrom*” (i.e. metabolic syndrome) in the late 1970s to describe the clustering of type 2 diabetes mellitus, hyperinsulinaemia, obesity, hypertension, hyperlipidaemia, hyperuricaemia and thrombophilia.

The modern era began in 1988 with Reaven (1988:1605) showing strong associations between insulin resistance, hypertension, glucose intolerance, low high-density lipoprotein (HDL) cholesterol and raised VLDL triglycerides in single patients. Reaven placed emphasis on the effects of genetic and environmental factors on the severity of insulin resistance, also indicating the increased risk for atherosclerosis in individuals with this cluster of risk factors he coined the “Syndrome X”. A year later Kaplan (1989:1519) added “central adiposity” to the syndrome as described by Reaven, summarising the main characteristics of the syndrome as four components: central adiposity, impaired glucose tolerance, hypertriglyceridaemia and hypertension. Kaplan coined this syndrome as the “deadly quartet”, again emphasising the risk for the development of cardiovascular disease. In the early 1990s, Ferrannini and co-workers

(1991:420) described the same clustering of abnormalities in this cardiovascular and metabolic syndrome as being caused by insulin resistance and concluded that “insulin resistance syndrome” should be the appropriate name for this condition.

Many names have since been used over the years to describe the concept of metabolic syndrome, including the terms “syndrome of affluence”, “(dys)metabolic syndrome X”, “obesity dyslipidaemia syndrome”, “metabolic cardiovascular syndrome”, “plurimetabolic syndrome”, “syndrome X”, the “DROP syndrome (Dyslipidaemia, insulin Resistance, Obesity and elevated blood Pressure)”, “Luxus Syndrome” and “Reaven’s syndrome” (Dandona *et al.*, 2005:1448; Han & Lean, 2006:537; Rassman & Gupta, 2005:30; Sarafidis & Nilsson, 2006:622). No single term has been universally accepted, although the terms “insulin resistance syndrome”, “metabolic syndrome” and “syndrome X” are currently the most used. The metabolic syndrome (as a multiple-component condition) can also be called a “multiplex cardiovascular risk factor” (Grundy, 2007:399).

According to Churilla and Zoeller (2008:119) and Grundy (2006e:1689), the term “metabolic syndrome” is realistic to employ as the most “appropriate label” by clinical and research communities given the “metabolic” nature of the syndrome, and the fact that it is largely accepted in both cardiovascular and diabetes fields, and does not commit to a particular pathogenesis. Because the scope of this research project is on medicine use and not on the particular pathogenesis or origin of the syndrome, the term “metabolic syndrome” will be used throughout this thesis, recognising however, that there is still a debate as to whether the metabolic syndrome is simply a clustering of risk factors or a true syndrome.

2.3 DEFINITION AND COMPOSING RISK FACTORS

The term “metabolic” originally derives from the modern Latin, from Greek *metabolē*, meaning change (OED, 2011), whereas the term “syndrome” also deriving from the Greek *sundromē*, from *sun*, literary means “together” and *dromē* or *dromos* from *dramein* meaning “to run” (OED, 2011). The Oxford English Dictionary (2011) also describes the term metabolic as “*the chemical processes that occur within a living organism in order to maintain life*” and syndrome as “*a group of symptoms which consistently occur together, or a condition characterized by a set of associated symptoms*”. Stedman’s medical dictionary (2006) adds that a syndrome is a “*symptom complex of unknown aetiology*” (that is) “*associated with any morbid process*”...“*constituting together the picture of the disease*”. Thus, the concept “metabolic syndrome” can be described as a group of modifiable risk factors or as a symptom complex occurring in the same individual. These factors or this symptom complex constituting the picture of the disease occurs more often together than by chance alone and appears to be

linked through a common underlying metabolic mechanism of unknown origin. The American Diabetes Association and National Heart, Lung and Blood Institute use the term “metabolic syndrome” to describe a constellation of metabolic abnormalities or risk factors that identifies a person at increased risk for atherosclerotic cardiovascular disease (ASCVD) and/or type 2 diabetes mellitus (Grundty & Cleeman *et al.*, 2005:2737).

The National Cholesterol Education Programme's third Adult Treatment Panel (NCEP/ATP III) (NIH, 2002:3182) distinguishes between underlying, major and emerging risk factors of the metabolic syndrome. Major risk factors include cigarette-smoking, hypertension, elevated LDL-cholesterol, low high-density lipoprotein (HDL) cholesterol, family history of premature coronary heart disease and aging. Underlying risk factors (factors giving rise to the metabolic risk factors) include abdominal obesity, genetic- and other factors such as physical inactivity, hormonal factors and an atherogenic diet (Grundty & Brewer *et al.*, 2004:433; Grundty & Cleeman *et al.*, 2005:2735). Emerging risk factors are elevated triglycerides, small, dense LDL-cholesterol particles, glucose intolerance and/or insulin resistance and a prothrombotic- and pro-inflammatory state (Miranda *et al.*, 2005:34; Shah *et al.*, 2006:343; Shen *et al.*, 2003:701). Several novel features were added over time to the metabolic syndrome based on frequent association therewith, including elevated lipoprotein(a), homocysteine, micro-albuminuria and creatine concentrations (Dandona *et al.*, 2005:1448; Fan, 2007:233; Tamakoshi *et al.*, 2003:444), and serum calcium levels (Saltevo *et al.*, 2011:433). Figure 2.1 depicts some of the risk factors of the metabolic syndrome and their characteristics.

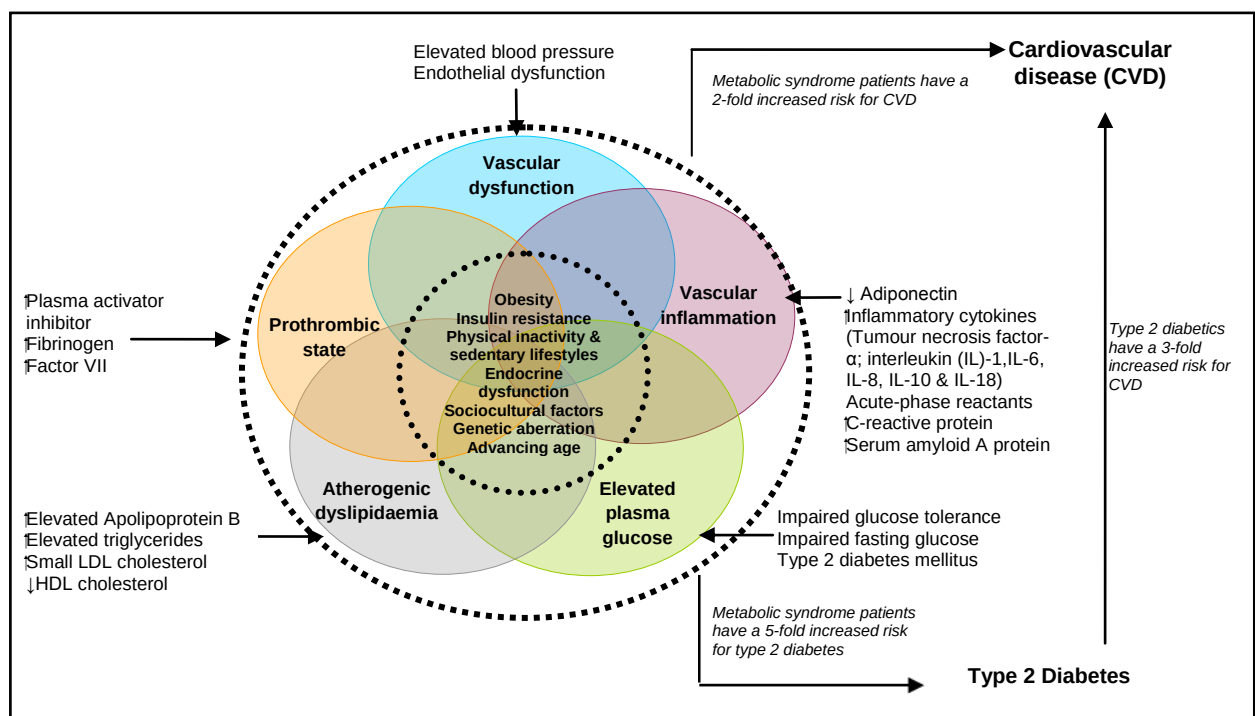


Figure 2.1: Risk factors for the metabolic syndrome (constructed from Hanefeld & Schaper, 2005:382; Grundty, 2006c:1248; Grundty, 2006d: 296; and Reaven, 1995:474)

Even without diabetes, the metabolic syndrome conveys a doubling of relative risk for ASCVD (Grundy & Cleeman *et al.*, 2005:2735-2752). With diabetes, this risk increases to approximately 5 times (Alberti *et al.*, 2009:1641) (refer to Figure 2.1).

A number of expert groups have attempted to set forth simple diagnostic criteria for use in clinical practice to identify patients who manifest the multiple components of metabolic syndrome. These criteria vary to some extent, but commonly include a combination or cluster of both underlying and metabolic risk factors i.e. a certain set of factors that increases cardiovascular risk [atherogenic dyslipidaemia, elevated blood pressure, elevated glucose, a prothrombotic state, and a pro-inflammatory state (Grundy & Cleeman *et al.*, 2005:2735)].

2.4 DEFINING CRITERIA FOR THE DIAGNOSIS OF METABOLIC SYNDROME

The defining criteria for the diagnosis of the metabolic syndrome in adults and children are discussed here. Aspects of the defining criteria for diagnosis in South Africa follow thereafter.

2.4.1 Defining criteria for metabolic syndrome diagnosis in adults

There are currently seven “definitions” that set the criteria for the diagnosis of metabolic syndrome in adults. A comparison between these different definitions is made in subsequent paragraphs, these being from the

- World Health Organization (WHO, 1999:33);
- European Group for Study of Insulin Resistance (EGIR) (Balkau & Charles, 1999:442);
- National Cholesterol Education Programme –Third Adult Treatment Panel (NCEP/ATP III) (NIH, 2001:2487);
- American College of Endocrinology and the American Association of Clinical Endocrinologists (ACE/AACE) (Bloomgarden, 2003:933);
- American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) (Grundy, 2005:2243; Grundy & Cleeman *et al.*, 2005:2735);
- International Diabetes Federation (IDF, 2005); and the
- Joint interim definition for clinical diagnosis of the metabolic syndrome; statement by the IDF, the NHLBI, the AHA, the World Heart Federation (WHF), the International Atherosclerosis Society (IAS) and the International Association of the Study of Obesity (IASO) (Alberti *et al.*, 2009:1642).

A consultation group on the definition of diabetes for the World Health Organization (Alberti & Zimmet, 1998:539) proposed the first formalised definition of the metabolic syndrome in 1998. The main purpose of this report was to update the classification and diagnostic criteria of

diabetes mellitus (WHO, 1999:32). The definition was therefore based on the assumption that insulin resistance is one of the major underlying contributors to the metabolic syndrome and featured impaired glucose regulation [impaired glucose tolerance (IGT), measured by an oral glucose tolerance test, diabetes or insulin resistance] as its centre (Alberti, 2005:D3). Apart from insulin resistance, the diagnosis of the syndrome requires the presence of at least two additional risk factors, from hypertension, obesity [measured by waist/hip ratio (WHR) or body mass index (BMI)], raised triglycerides or low HDL-cholesterol and micro-albuminuria (WHO, 1999:33). According to Kim and Reaven (2004:69), it was the view of the WHO Consultation Group that each component conveyed increased CVD risk, but that the combination thereof was more powerful.

A year later, specialists from the European Group for the study of Insulin Resistance (EGIR) proposed a modified version of the WHO definition for use in non-diabetic subjects only (Balkau & Charles, 1999:443). They suggested that the syndrome included non-metabolic features, and proposed the name “insulin resistance syndrome” as suggested by earlier studies. This definition required the presence of insulin resistance plus two or more of the following: central obesity, dyslipidaemia (high triglycerides or low HDL-cholesterol), hypertension and fasting plasma glucose ≥ 6.1 mmol/L^a (Alberti *et al.*, 2005:1059; Balkau & Charles, 1999:442). The EGIR proposed the use of fasting insulin levels to estimate insulin resistance and impaired fasting glucose as a substitute for impaired glucose intolerance of the WHO definition (Alberti, 2005:D4).

The third effort at defining the metabolic syndrome to assist diagnosis in clinical practice was incorporated in the recommendations for dyslipidaemia testing and management of the National Cholesterol Education Programme Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult treatment Panel III) (NIH, 2001:2486). As with the WHO report, the main purpose of this report was not to define the metabolic syndrome but to update clinical guidelines for the diagnosis and administration of cholesterol, focusing on the primary prevention in individuals with several risk factors. With these goals in mind, the panel introduced the metabolic syndrome as the presence of three or more of five clinically identifiable interrelated risk factors that raise CVD risk, from central obesity, raised triglycerides, low HDL-cholesterol level, hypertension and an elevated fasting glucose level (Alberti, 2005:D4; Alberti *et al.*, 2005:1061).

The American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) proposed a further set of clinical criteria to identify insulin-resistant individuals, also referring to it as the “insulin resistance syndrome” (Bloomgarden, 2003:933).

^a To convert to mg/dL: mmol/L x 18 (Berne & Campbell, 2011:51).

Their position statement described a list of four factors (so-called identifying abnormalities) known to predict the development of CVD or type 2 diabetes, including elevated triglycerides, reduced HDL-cholesterol, elevated blood pressure and elevated fasting and post-load glucose (Bloomgarden, 2003:933). The criteria (a hybrid of those of the NCEP/ATP III and WHO definitions for the syndrome) differed from the NCEP/ATP III criteria in that patients, whose degree of hyperglycaemia fulfilled the diagnostic criteria for type 2 diabetes mellitus, were excluded (Sarafidis & Nilsson, 2006:624). Other risk factors recognised by the ACE/AACE included polycystic ovary syndrome, prior gestational diabetes, sedentary lifestyle, age and ethnicity (Einhorn *et al.*, 2003:238).

In 2005, the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF) attempted to combine the different clinical definitions. The definition of the AHA/NHLBI (Grundy & Cleeman *et al.*, 2005:2735) as a revision of the NCEP/ATP III definition, maintained NCEP/ATP III criteria except for minor modifications, i.e. the threshold for IFG was reduced from 110-100 mg/dL^b and abdominal obesity as mandatory component was dropped (Grundy, 2005:2243; Grundy & Cleeman *et al.*, 2005:2738). Present diagnostic criteria thus require the presence of any three from five defining criteria, i.e. abdominal obesity (measured as a waist circumference), hypertension (or pharmacological treatment of previously diagnosed hypertension), raised triglycerides (or pharmacological treatment for elevated triglycerides), low HDL-cholesterol (or pharmacological treatment for reduced HDL-cholesterol) and elevated fasting plasma glucose (insulin resistance) or (pharmacological treatment for elevated fasting glucose).

The IDF dropped the WHO requirement for insulin resistance but included central obesity as a prerequisite, with particular emphasis on waist circumference as screening tool (IDF, 2005); the remainder of the criteria were essentially identical to those provided by the NCEP/ATP III. In essence, the IDF definition required the presence of any two additional risk factors, from hypertension (or treatment of previously diagnosed hypertension), raised triglycerides (or specific treatment for this lipid abnormality), low HDL-cholesterol (or specific treatment for this lipid abnormality) and raised fasting plasma glucose or previously diagnosed type 2 diabetes (IDF, 2005). Ethnic-specific waist circumference cut-offs have also been incorporated into the definition. The definition therefore moved in quite a different direction from the earlier definitions putting “central obesity” forward as the necessary factor for identification of the syndrome.

In a recent attempt to resolve the remaining differences between definitions of the metabolic syndrome, the IDF, the NHLBI, the AHA, the World Heart Federation (WHF), the International Atherosclerosis Society (IAS) and the International Association of the Study of Obesity (IASO)

^b To convert to mmol/L: mg/dL ÷ 18 (Berne & Campbell, 2011:51).

agreed in a joint interim statement (JIS) that abdominal obesity should not be a prerequisite for diagnosis (Alberti *et al.*, 2009:1642). Obesity is therefore one in five criteria, so that the presence of any three of five risk factors constitutes a diagnosis of the syndrome. Measures in this definition include population- and country-specific definitions for elevated waist circumference (IDF cut points for non-Europeans and either IDF or AHA/NHLBI cut points for Europeans), elevated triglycerides (or specific treatment for this lipid abnormality), reduced HDL-cholesterol (or specific treatment for this lipid abnormality), elevated blood pressure (or treatment of previously diagnosed hypertension) and raised fasting glucose or treatment thereof. By this latter criterion, most patients with type 1- and type 2 diabetes will have the metabolic syndrome (Alberti *et al.*, 2009:1642).

Table 2.1, constructed from Alberti *et al.* (2009:1642); Balkau and Charles (1999:442); Bloomgarden (2003:933); Grundy (2005:2243); Grundy and Cleeman *et al.* (2005:2735); the International Diabetes Federation (2005); the NIH (2001:2487) and the World Health Organization (1999:33), summarises the different definitions proposed by the various organisations for the clinical diagnosis of metabolic syndrome in adults.

Several differences can be identified comparing the different definitions. For example, the positioning of the predominant causes of the syndrome and the specific cut-points employed in particular differ between the various definitions. The WHO and NCEP/APT III definitions both include the four major clinical characteristics of the syndrome, although their focuses differ. Clinical use of these definitions would not thus result in major differences in the identification of individuals with the syndrome (Sarafidis & Nilsson, 2006:624). Another potential disadvantage of the WHO criteria is that, at least in some cases, special testing beyond routine assessment may be needed (Grundy & Brewer *et al.*, 2004:433) which means that this criteria have been applied less frequently to large epidemiological or clinical studies in which often only the fasting glucose level is measured (Ritchie & Connell, 2007:320; Wild & Byrne, 2005:4). The NCEP/ATP III criteria, however, were developed for application in the outpatient setting, contain no mandatory diagnostic criteria and are considered as the most applicable set of criteria in every day practice (Gazi *et al.*, 2004:244).

Criticism towards the EGIR definition includes that it did not meet wide international use, as it differed little from the WHO definition to which it was proposed as an alternative (Sarafidis & Nilsson, 2006:624). Similar to the WHO definition, these criteria may be less applicable to large epidemiological or clinical studies (Ritchie & Connell, 2007:320; Wild & Byrne, 2005:4). According to Sarafidis and Nilsson (2006:624), the use of the ACE/AACE definition in epidemiological studies is also limited because a defined number of the risk factors in the definition were not specified - diagnosis of the metabolic syndrome in patients is therefore left

up to clinical judgement.

The IDF definition, although it relies on the “easy to perform” measurements in everyday practice, compromises the diagnostic limits for the various components of the other definitions proposed (Sarafidis & Nilsson, 2006:625). Chen and Pan (2007:1097) also showed that the IDF definition failed to identify a number of individuals (~4-5% of their study population) who had more than three metabolic syndrome components, but a small waistline. Data from a study by Assmann and co-workers (2007:541) moreover indicated that the IDF definition yielded a lower predictive power of coronary events compared with the ATP III definition. Criticism towards the AHA/NHLBI statement includes that it makes only minor changes to the NCEP/ATP III definition (Skilton *et al.*, 2007:417), whereas the new joint definition only changes population- and country-specific cut points for waist circumference (Alberti *et al.*, 2009:1642).

In spite of the differences identified between the existing definitions used for identifying individuals with the metabolic syndrome, Reaven (2002:286) believes that the conceptual importance of the diagnosis is to show that the “abnormalities” are more likely to occur together than alone.

Table 2.1: Defining criteria for the diagnosis of metabolic syndrome in adults

	WHO ^A	NCEP/ATP III ^B	EGIR ^C	ACE/AACE ^D	IDF ^E	AHA/NHLBI ^F	JIS ^G
Requirements	Impaired glucose regulation or diabetes and/or insulin resistance plus ≥ 2 of the following:	≥ 3 of the following:	Hyperinsulinaemia (fasting insulin concentration above the upper quartile for the non-diabetic subjects) plus ≥ 2 of the following:	Not applicable	Central obesity (based on ethnic specific WHR) plus ≥ 2 of the following:	≥ 3 of the following 5:	≥ 3 of the following 5:
Blood pressure	$\geq 140/90$ mmHg	$\geq 130/85$ mmHg	$\geq 140/90$ mmHg and/or treatment for hypertension	$\geq 130/85$ mmHg	$\geq 130/85$ mmHg or treatment of previously diagnosed hypertension	≥ 130 mmHg systolic blood pressure or ≥ 85 mmHg diastolic blood pressure or an antihypertensive pharmacological treatment in a patient with a history of hypertension	≥ 130 mmHg systolic blood pressure or ≥ 85 mmHg diastolic blood pressure or an antihypertensive pharmacological treatment in a patient with a history of hypertension
TGs	≥ 1.7 mmol/l (150 mg/dl)	≥ 1.7 mmol/l (150 mg/dl)	> 2.0 mmol/l (180 mg/dl) and/or treatment for dyslipidaemia	≥ 1.69 mmol/l (150 mg/dl)	≥ 1.7 mmol/l (150 mg/dl) or specific treatment for this lipid abnormality	≥ 1.7 mmol/l (150 mg/dl) or pharmacological treatment for elevated triglycerides	≥ 1.7 mmol/l (150 mg/dl) or pharmacological treatment for elevated triglycerides
HDL-C	Men: < 0.9 mmol/l (35 mg/dl); Women: < 1.0 mmol/l (39 mg/dl)	Men: < 1.0 mmol/l (40 mg/dl); Women: < 1.3 mmol/l (50 mg/dl)	< 1.0 mmol/l (40 mg/dl) and/or treatment for dyslipidaemia	Men: < 1.04 mmol/l (40 mg/dl); Women: < 1.29 mmol/l (50 mg/dl)	Men: < 1.03 mmol/l (40 mg/dl); Women: < 1.29 mmol/l (50 mg/dl) or specific treatment for this lipid abnormality	Men: < 1.0 mmol/l (40 mg/dl); Women: < 1.3 mmol/l (50 mg/dl) or pharmacological treatment for reduced HDL-cholesterol	Men: < 1.0 mmol/l (40 mg/dl); Women: < 1.3 mmol/l (50 mg/dl) or pharmacological treatment for reduced HDL-cholesterol
Central obesity	BMI > 30 kg/m ² and/or: Men: WHR > 0.90 ; Women: WHR > 0.85	Men: waist circumference ≥ 102 cm; Women: waist circumference ≥ 88 cm	Men: waist circumference ≥ 94 cm; Women: waist circumference ≥ 80 cm	BMI ≥ 25 kg/m ²	Men: waist circumference ≥ 94 cm; Women: waist circumference ≥ 80 cm; with ethnicity specific values for other groups)	Men: waist circumference ≥ 102 cm; Women: waist circumference ≥ 88 cm	Non-Europeans: Men: waist circumference ≥ 94 cm; Women: waist circumference ≥ 80 cm; Europeans: Men: waist circumference ≥ 102 cm; Women: waist circumference ≥ 88 cm

Table 2.1: Defining criteria for the diagnosis of metabolic syndrome in adults (*continued*)

	WHO ^A	NCEP/ATP III ^B	EGIR ^C	ACE/AACE ^D	IDF ^E	AHA/NHLBI ^F	JIS ^G
MAU	Urinary albumin excretion rate ≥ 20 $\mu\text{g}/\text{min}$ or albumin:creatinine ratio ≥ 30 mg/g	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Fasting glucose	Not applicable	≥ 6.1 mmol/l (110 mg/dl)	≥ 6.1 mmol/l [≥ 110 mg/dl; ≥ 5.6 mmol/l (101 mg/dl) for venous or capillary whole blood]	100-126 mg/dl; 2-hour post-glucose challenge >140 mg/dl	≥ 5.6 mmol/l (100 mg/dl) or previously diagnosed type 2 diabetes	≥ 100 mg/dl or on pharmacological treatment for elevated plasma glucose (insulin resistance)	≥ 100 mg/dl or on pharmacological treatment for elevated glucose
Other risk factors	Not applicable	Not applicable	Not applicable	Family history of type 2 diabetes, hypertension, or CVD, polycystic ovary syndrome, sedentary life-style, advancing age, ethnic groups having high risk for type 2 diabetes or CVD.	Ethnic-specific waist circumference cut-offs	Not applicable	Not applicable

WHR = Waist-to-hip ratio; TGs = Triglycerides; HDL-C = HDL-cholesterol; BMI = Body Mass Index; MAU = Micro-albuminuria

^A(WHO, 1999:33); ^B(NIH, 2001:2487); ^C(Balkau & Charles, 1999:442); ^D(Bloomgarden, 2003:933); ^E(IDF, 2005); ^F(Grundy, 2005:2243; Grundy & Cleeman *et al.*, 2005:2735); ^G(Alberti *et al.*, 2009:1642).

2.4.2 Defining criteria for metabolic syndrome diagnosis in children and adolescents

Due to a lack of a universally accepted definition of the metabolic syndrome in children and adolescents, the criteria used in early paediatric studies up till recently have been variably adapted from adult standards with the use of gender- and age-dependent normal values (Ford & Li, 2008b:160; Lambert *et al.*, 2004:834; Rodríguez-Morán *et al.*, 2004:2517; Weiss *et al.*, 2004:2372). The International Diabetes Federation published a first definition of the metabolic syndrome in children and adolescents in 2007, based on percentile definitions that are standard across age ranges: 6<10, 10<16 and ≥ 16 years (IDF, 2007). The American Heart Association (Steinberger *et al.*, 2009:636) also published a guideline for children and adolescents 12-19 years. Table 2.2 summarises the proposed definitions of the metabolic syndrome in children and adolescents.

Table 2.2: Diagnosis of the metabolic syndrome in children and adolescents (adapted from Steinberger *et al.*, 2009:636 and Zimmet *et al.*, 2007:2060)

Ages (years)	AHA criteria 12-19	6<10	IDF criteria 10<16	≥ 16
Requirements	≥ 3 of the following:	Abdominal obesity	Central obesity plus ≥ 2 of the following:	Central obesity (based on ethnic specific WHR) plus ≥ 2 of the following:
Obesity (WHR)	$\geq 90^{\text{th}}$ percentile for age, sex, and race/ethnicity	$\geq 90^{\text{th}}$ percentile	$\geq 90^{\text{th}}$ percentile or adult cut-off if lower	94 cm for Europid males and ≥ 80 cm for Europid females (ethnic-specific values for other groups)
TGs	≥ 1.23 mmol/L (≥ 110 mg/dL)	≥ 1.7 mmol/L (150 mg/dL)	≥ 1.7 mmol/L (150 mg/dL)	≥ 1.7 mmol/L (150 mg/dL) or specific treatment for high triglycerides
HDL-C	$\leq 10^{\text{th}}$ percentile for race and sex	< 1.03 mmol/L (40 mg/dL)	< 1.03 mmol/L (40 mg/dL)	Males: < 1.03 mmol/L (40 mg/dL); Females: < 1.29 mmol/L (50 mg/dL) or specific treatment for this lipid abnormality
Blood pressure	$\geq 90^{\text{th}}$ percentile for age, sex, and height	≥ 130 mmHg systolic blood pressure or ≥ 85 mmHg diastolic blood pressure	≥ 130 mmHg systolic blood pressure or ≥ 85 mmHg diastolic blood pressure	≥ 130 mmHg systolic blood pressure or ≥ 85 mmHg diastolic blood pressure or treatment of previously diagnosed hypertension
Fasting glucose	≥ 5.6 mmol/L (100 mg/dL)	≥ 5.6 mmol/L or known type 2 diabetes mellitus	≥ 5.6 mmol/L or known type 2 diabetes mellitus	≥ 5.6 mmol/L or known type 2 diabetes mellitus

WHR = Waist-height-ratio; TGs = Triglycerides; HDL-C = HDL-cholesterol

Table 2.2 shows that waist circumference is assessed by percentiles in both the IDF and AHA guidelines, with cut-offs for metabolic and blood pressure variables defined only for those older than the age of 10 years. Abdominal or central obesity is essential for diagnosis in all three age groups from the IDF definition, whereas the AHA guidelines have no specific requirements. Although it is unnecessary to diagnose the metabolic syndrome as an entity in children below the

age of 10 years, both guidelines stress weight reduction.

2.4.3 Diagnosis of metabolic syndrome in South Africa

South Africa has adopted the ICD-10 (International Statistical Classification of Diseases and related Health Problems, 10th revision) as a diagnosis coding standard for the country (both public and private sector) in 1995. The process of implementation, however, only started at the beginning of 2004 with the formation of a National Task Team on ICD-10 implementation (Matshidze & Hanmer, 2007:95).

In the South African public health care sector, the Standard Treatment Guidelines and Essential Drugs List (EDL^c) of the Essential Drugs Programme, published by the South African Department of Health for primary health care providers to manage conditions, employs the ICD code “E66.9” (i.e. “unspecified obesity”) to signify metabolic syndrome (The National Essential Drugs List Committee, 2008:152). The guidelines further list the following risk factors as part of the metabolic syndrome: impaired glucose metabolism, central obesity, dyslipidaemia and hypertension. The thresholds stipulated for the diagnosis for these risk factors are as follows:

- Abdominal obesity: waist circumference >102 cm in men and >88 cm in women; or BMI 25- to 29.9 kg/m² (overweight), 30- to 39.9 kg/m² (obese), >40 kg/m² (extremely obese).
- Fasting plasma triglycerides >1.70 mmol/L.
- HDL-cholesterol <1.04 mmol/L in men and < 1.30 mmol/L in women.
- Blood pressure >130/85 mmHg.
- Fasting blood glucose >6.5 mmol/L (Department of Health, 2008:152).

In the private health care sector of South Africa, the implementation of the ICD-10 code was only formally introduced in 2005 (Matshidze & Hanmer, 2007:95). Medical aid schemes (as the main means of financing private health care in South Africa), administrators, health care providers and other parties use the ICD-10 coding system *inter alia* for speedy and appropriate reimbursement of providers. This code, though, does not provide for the metabolic syndrome [unlike the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), which uses code X277.7 for the syndrome] (CDC, 2010). Therefore, the Council for Medical Schemes of South Africa (2007a) developed the first standardised ICD-10 coding system to assist clinical coders in the South African private health care environment in 2007. Based on this classification system, the metabolic syndrome is symbolised as “I10/E78.5/E66.9/E11.9”, where “I10” signifies essential hypertension as primary diagnosis, “E78.5” unspecified hyperlipidaemia, “E66.9”

^c Essential drugs are medicines that satisfy the needs of the majority of the population. The South Africa National EDL serves to guide procurement and supply of medicines as a medicines formulary in the public health care sector.

unspecified obesity and “E11.9” non-insulin-dependent diabetes mellitus without complications as sub-diagnoses. This coding standard is updated on a yearly basis, but is not yet fully implemented in practice. The code is also not without controversy, for example the code only provides for non-insulin-dependent diabetes mellitus without complications. Patients with type 1 diabetes are therefore excluded, as is those with non-insulin-dependent diabetes mellitus with other specified complications or non-specified hyperglycaemia/prediabetes and impaired glucose tolerance. Based on the most recent definition for diagnostic criteria in metabolic syndrome patients [i.e. the joint interim statement (JIS)], however, most adult patients with type 1 and type 2 diabetes will have the metabolic syndrome (Alberti *et al.*, 2009:1642).

2.5 PREVALENCE AND EPIDEMIOLOGY OF METABOLIC SYNDROME

A discussion of the prevalence and epidemiological trends of metabolic syndrome in worldwide populations is provided here. A discussion of the prevalence in Sub-Saharan Africa and the South African population proceeds thereafter.

2.5.1 General trends and prevalence rates

Various surveys document the prevalence of metabolic syndrome in worldwide populations; many of these aim at the coincident comparison of prevalence rates by applying diagnostic criteria from more than one definition. The absence of a homogeneous and clear definition of the metabolic syndrome makes prevalence estimates not only difficult to calculate, but also to compare (Adams *et al.*, 2005:2778; Sarti & Gallagher, 2006:125; Santos & Barros, 2007:327). Prevalence rates can furthermore be affected by a multitude of both modifiable and non-modifiable interlinked factors, i.e. differences in genetic background, age, gender, ethnicity, lifestyle factors such as diet, levels of physical activity, obesity, use of alcohol and smoking, levels of over- and under-nutrition, birth weight, co-morbidity, economic and social status, level of education and place of residence (Adams *et al.*, 2005:2778; Rheeder *et al.*, 2002:640; Santos *et al.*, 2008; Wild, 2007:132-135).

The lack of a reliable, accepted definition of metabolic syndrome in children and adolescents, as with adults, complicates the estimation of prevalence in this population too, with prevalence varying widely according to the definition used. Golley *et al.* (2006:854), Kelishadi (2007:64) and Steinberger *et al.* (2009:629) list the following reasons for the lack of a reliable, accepted definition in children and adolescents:

- The use of adult cut points or a distinct set of cut points for all ages during childhood.
- Disturbances seen in the metabolic indicators in most children are only quantitatively moderate.
- The lack of a normal range for insulin concentration across childhood.

- The physiological insulin resistance of puberty.
- The lack of waist cut points linked to obesity, morbidity or metabolic syndrome for children.
- Differences in baseline lipid levels among various races.

The metabolic syndrome is nonetheless a common condition in the general adult population of developed countries, or urban areas of developing countries where lifestyle changes towards a western urbanised pattern. At least one-fourth of the adults in the Americas and Europe carry the syndrome (Grundy, 2008:634), whereas in developing countries such as Mexico, a prevalence rate of 13.6% was observed when using the WHO definition and 26.6% when using NCEP/ATP III criteria (Aguilar-Salinas *et al.*, 2004:79). Prevalence rates of 19% have also been measured in Brazil, 23.6% in Greece, 41.4% in India, 33.7% in Iran, 20.7% in Ireland, 32.2% in Turkish males and 31.2% in Venezuela (Batsis *et al.*, 2007:520). In general, about 15-30% of apparently healthy adults are affected (Scuteri *et al.*, 2005:886), compared with 45% of individuals with known cardiovascular disease (Gorter *et al.*, 2004:367). Almost half of people over the age of 50 years (Blumenthal, 2005:S497; Mehta & Reilly, 2004:187; Kuk & Ardern, 2010:2459) and 42% to 60% of individuals 70 years or older are affected (Haslam & James, 2005:1198; Prabhakaran & Anand, 2004:56).

Consistent inferences from studies on the prevalence of the metabolic syndrome around the world (Cameron *et al.*, 2004:373; Eckel *et al.*, 2005:1416; Ervin, 2009:3-4; Ferrari, C.K.B., 2008:88; Morley & Sinclair, 2009:496; Procopiou & Philippe, 2005:3; Wild & Byrne, 2005:4) suggest that among adults

- the prevalence of the metabolic syndrome is consistently and highly obesity dependent;
- the prevalence of the metabolic syndrome is highly age-dependent;
- a trend of higher prevalence of the metabolic syndrome is evident among men (in some cases, the prevalence may be up to double or more that among women), especially when using the WHO definition;
- a wide variation in prevalence is apparent in both men and women within the same age range (based on the NCEP/ATPIII definition) i.e. 10-25% for men and 10-15% for women; and
- prevalence rates of both the metabolic syndrome and its constitutional components vary within same ethnic population groups.

As with the adult population, paediatric literature shows an increase in the prevalence of the metabolic syndrome (or a related construct with a meaning similar to that in adult disease) in children and adolescents. For example, in 2003, Cook *et al.* (2003:825) reported a prevalence of 4.2% in the US adolescent population. A more recent analysis by Jolliffe and Janssen (2007:896) indicated a prevalence of 7.6% and 9.6%, respectively measured with NCEP/ATP III and IDF

criteria in the same population. According to Moraes *et al.* (2009), the prevalence of the metabolic syndrome in worldwide adolescent populations (i.e. those 10-19 years) may be as high as 15.4% (as measured by NCEP/ATP III criteria) to 38.7% (based on IDF-criteria).

Gender diversity in the manifestation of metabolic syndrome and/or its components reaches beyond its prevalence. For example, Hwang and colleagues (2007:904) showed that lipid components appeared the earliest in both genders, whereas the first isolated components appeared earlier in females than in males (mean age 43.4 vs. 45.6 years). On the contrary, the mean prevalent age of metabolic syndrome appeared earlier in men than in women by 4.9 years (mean age 51.3 vs. 56.2 years). The variations in prevalent age from the appearance of any isolated component to metabolic syndrome were 12.8 years in women and 5.7 years in men, respectively. Hwang *et al.* furthermore showed the difference in prevalent age from the isolated component to metabolic syndrome in physically active males with a BMI <23 kg/m² to be 15.4 years longer than for their female counterparts. Based on a study by Ervin (2009:3-4) there was also diversity in the prevalence of abdominal obesity, hypertriglyceridaemia, hypertension and hyperglycaemia by age group for different gender groups. For example, the prevalence of each of these risk factors increased with each consecutive age group in females, whereas for males, this pattern was only true for hypertension and hyperglycaemia. In his study, Ervin showed that older males were more likely than younger individuals to have abdominal obesity, but there was no increase in the prevalence of abdominal obesity with age in males older than 40 years. Older males were also more likely than younger males to have hypertriglyceridaemia (Ervin, 2009:3-4).

2.5.2 Sub-Saharan Africa and South Africa

The prevalence of the metabolic syndrome in sub-Saharan Africa is uncertain due to a paucity of information. Available studies, nevertheless, report high prevalence rates in specific populations, for example, Longo-Mbenza and co-workers (2010:32) determined a prevalence rate of 3.6% in Kinshasa Hinterland (Central Africa region). Bovet *et al.* (2006:7) measured a prevalence of 22.1% in the population of the Seychelles (aged 25 to 64) in 2004. Makuyana and co-workers (2004:27) reported a prevalence rate of 43% among urban Africans in Zimbabwe. Isezuo and Ezunu (2005:560) indicated a prevalence of 54.3% among native Nigerians (aged 35-80 years) with type 2 diabetes, whereas Fezeu *et al.* (2007:75) reported prevalence rates of 1.8% in rural women (5.9% in urban areas) vs. 1.9% in rural men (7.9% in urban areas) of Cameroon. Garrido and colleagues (2009:333) determined a prevalence rate of 34% amongst health care workers in Botswana, with another 34% at high risk for developing the syndrome. Njelekela and colleagues (2009) also determined that at least 38% (n = 209) of participants between the ages of 44 and 66 years in Tanzania had metabolic syndrome. In their study, Njelekela *et al.* also showed women to

have a more than three-fold greater odds of having metabolic syndrome than their male counterparts.

The prevalence and impact of the metabolic syndrome on the South African population are also largely unknown (Ker *et al.*, 2007:30; Schwellnus *et al.*, 2009:178). Furthermore, according to Motala *et al.* (2009:S2.9) and Jennings *et al.* (2009:50), no population-based research on the prevalence of the syndrome in South Africa has been conducted to date. Studies of populations where the prevalence of the metabolic syndrome or its components was measured (either as primary or secondary outcomes of the study) generally show large gender and inter-ethnic diversity in its manifestation. For example, results of the POWIRS study (Schutte & Olckers, 2007:651) indicate that the metabolic syndrome occurs less frequently amongst African (24.8%, $n = 102$) than Caucasian women (30.4%, $n = 115$). Kalk and Joffe (2008:249) reported similar results, furthermore showing more severe metabolic syndrome (defined as the presence of diabetes plus 3 to 4 additional risk factors) in African men and those from Caucasian origin (both male and female) compared with African women. The prevalence of the metabolic syndrome is moreover substantially lower in diabetic African men compared with their female- and Caucasian counterparts, because these men are significantly less insulin resistant (Kalk & Joffe, 2007:110). This in turn can be ascribed to smaller waist circumference measurements for African men compared with African females and Europeans of both sexes (Kalk & Joffe, 2008:250). Africans further appear to have a reduced amount of pancreatic β -cells, with a subsequent less significant insulin response compared with their Caucasian counterparts (Ntyintyane *et al.*, 2009b:27; Rubenstein *et al.*, 1969:749).

Adult Caucasian women further demonstrate a larger mean waist circumference, whereas the women from African ethnicity present with a significantly larger sagittal abdominal diameter (Schutte *et al.*, 2008:530). Similar racial differences were also reported by Matsha and co-workers (2009:363-364) in adolescents from the Western Cape. In addition, Caucasian women have higher triglycerides, plasminogen activator inhibitor-1 activity and cortisol levels compared with African women (Greyling *et al.*, 2007:503), whilst African women have a significantly higher blood pressure, leptin, fibrinogen, C-reactive protein and higher odds ratios for having the metabolic syndrome with regard to HDL-cholesterol, blood pressure and fasting glucose, than Caucasians (Schutte & Olckers, 2007:651; Schutte *et al.*, 2008:528-536). Individuals from African ancestry furthermore have a significantly lower level of uric acid compared with their Caucasian counterparts (Palmer *et al.*, 2007:680; Palmer *et al.*, 2010:643).

There are moreover ethnic differences in lipid profiles – the lipid profile is less atherogenic in the African population compared with the European population, with lower triglycerides and LDL-cholesterol levels and higher HDL-levels (Punyadeera *et al.*, 2001:763; Schutte *et al.*, 2008:528-

536). Adiponectin levels in normal weight African women are furthermore marginally lower compared with their Caucasian counterparts (Schutte *et al.*, 2007:186).

In the early 1980s, Seedat and Seedat (1982:68) showed that hypertension was highest in urban Africans of the Zulu tribe, intermediate in Europeans and lowest in ethnic Indians and rural Africans. The prevalence was also higher in females compared with males in the African and Indian population, unlike in the Europeans. According to Opie and Seedat (2005:3564), the higher prevalence in urban Africans may be ascribed to multiple causes, *inter alia*, lower plasma renin levels, sodium abnormalities, epithelial sodium changes, altered genes regulating the renin-angiotensin-aldosterone system, increased peripheral vascular resistance, increasing obesity, socio-economic stress and an underweight phenotype.

In an attempt to assess the prevalence of the metabolic syndrome in South Africa over the last 10 years, a tailored Boolean search was carried out by the researcher using the search terms ("South Africa" OR "Suid-Afrika" OR "SA" OR "RSA") AND ("metabolic syndrome" OR "metaboliese sindroom" OR "syndrome X" OR "sindroom X" OR "insulin resistance syndrome" OR "insulienweerstandigheidsindroom") in titles or abstracts. The following databases were searched during September 2010 to June 2011 to identify relevant citations:

- Ebsco Host^d (2001-2009)
- Scopus [2000-2010 (Jun)]
- ISI web of Knowledge (2000-2009)
- RSAT (2000-2009)
- Science Direct (2000-2009)
- Nexus (2000-2009)
- SACat [2000-2011 (Jun.)]
- ProQuest (2000-2009)
- Google Scholar [2000-2011 (Jun.)]

The search was limited to the English and Afrikaans languages. Twenty-five papers/ dissertations/theses fulfilled the criteria for inclusion. Details of the authors, inception year and setting of the study, geotype, the number, age and gender, ethnic group of the subjects, the diagnostic criteria used and the measured prevalence reported in these publications are given in Table 2.3 by setting of the study and publication year.

^d Databases within the Ebsco Host® search engine that was searched included Academic Search Premier, MasterFILE Premier, Medline and Health Source: Nursing & Academic.

Table 2.3: Description of papers and samples identified in the Boolean search

Province/ Location		Inception year	Sample size <i>n</i>	Ethnicity and geotype	Average age (years) and gender	Diagnostic criteria	Measured Prevalence (%)	Author and year
North-West Province	Potchefstroom	1996–1998	426	African (THUSA-study)	15-65 193 M; 233 F	WHO	25% M; 32% F	Kruger, 2001 (Thesis)
	Potchefstroom	March–April 2003, August 2004	101	African (POWIRS study)	20-50 F	NCEP/ATP III	15.8%	Kotze, 2004 (Dissertation)
	Potchefstroom	Not stated	100	African (urban) (POWIRS study)	19-50 F	NCEP/ATP III	Obese: 38%; Overweight: 8%	Jonker, 2004 (Thesis)
	Potchefstroom	March–April 2003, August 2004	102	African (urban) (POWIRS study)	20-50 F	NCEP/ATP III	Obese: 37.3%; Overweight: 25%	Schutte <i>et al.</i> , 2005
	Potchefstroom	March–April 2003, August 2004	209	95 African 114 Caucasian (urban) (POWIRS study)	20-55 F	NCEP/ATP III	Caucasian: 26%; African: 15.8%	Greyling <i>et al.</i> , 2007.
	Potchefstroom	March–April 2003, August 2004	217	102 African 115 Caucasian (urban) (POWIRS study)	F	IDF	Caucasian: 30.4%; African: 24.8%	Schutte & Olckers, 2007
	Potchefstroom	1996-1998	448	African (THUSA-study)	15-70 205 M; 243 F	IDF	~10%	Reimann <i>et al.</i> , 2008
	Potchefstroom	March–April 2003, August 2004	102	African (urban) (POWIRS study)	20-50 F	WHO, EGIR, NCEP/ATP III, ACE and IDF	EGIR: 5.4%; NCEP/ATP III: 15.7% WHO: ≥ 19.4%; IDF: 24.8% ACE: 25.5%	Schutte <i>et al.</i> , 2009
	Potchefstroom	1996-1998	608	African (THUSA-study)	16-70 269 M; 339 F	WHO	Active copers: 10.45% Passive copers: 9.15%	Malan <i>et al.</i> , 2008
Gauteng	Johannesburg	Not stated	159	Not stated	Not stated	IDF	23.3%	Distiller <i>et al.</i> , 2010
	Mamelodi, Pretoria	Not stated	124	African (urban)	56.9 ± 11.0 F	WHO	42%	Rheeder <i>et al.</i> , 2002
	Johannesburg	1994 – 2002	754	500 African 254 Caucasian	>30 African: 209 M; 291 F Caucasian: 135 M; 119 F	IDF, NCEP/ATP III	IDF: M: African (46.5%), Caucasian (74.1%) F: African (85.2%), Caucasian (86.6%) NCEP/ATP III: M: African (55.0%), Caucasian (74.1%); F: African (82.5%), Caucasian (84.0%)	Kalk & Joffe, 2008

Table 2.3: Description of papers and samples identified in the Boolean search (*continued*)

Province/ Location		Inception year	Sample size <i>n</i>	Ethnicity and geotype	Average age (years) and gender	Diagnostic criteria	Measured Prevalence (%)	Author and year
Gauteng	Soweto	Not stated	40	African	55.3 ± 8.1 33 M; 7 F	NCEP/ATP III	60% 82.5% M; 17.5% F	Ntyintyane <i>et al.</i> , 2006
	Soweto	January 2003, June 2006	60	African	54.1 ± 8.8 CAD patients: 33 M; 7 F Control: 13 M; 7 F	IDF	NCEP/ATP III: 60%; IDF: 57.5%	Ntyintyane <i>et al.</i> , 2009a
Western Cape	Gugulethu	May 2005 - Jul. 2006	334	African	114 M; 220 F	NCEP/ATP III	33.5%	Okpechi <i>et al.</i> , 2007
	Not stated (107 schools)	Not stated	1 272	446 African 130 Caucasian 696 Coloured	10-16 African: 158 M; 288 F Caucasian: 57 M; 73 F Coloured: 281 M; 415 F	NCEP/ATP III IDF definition for children	IDF: 1.9%; NCEP/ATP III: 6.5%	Matsha <i>et al.</i> , 2009
	Stellenbosch University	Not stated	266	Not stated	Not stated 88 M; 178 F	IDF	6% males, 3% females	Smith & Essop, 2009
Free State	Mangaung/ QwaQwa	Not stated	1 611	African 853 semi-rural 758 urban	≥25 Semi-rural: 279 M; 574 F Urban: 290 M; 468 F	WHO	Semi-rural: 30.7% M: 28.1%; F: 33.9% Urban: 30.5% M: 26.3%; F: 33.9%	Mollentze, 2003
KZN	Durban	May 1999-June 2005	389	Indian	≤45 338 M; 51 F	NCEP/ATP III IDF	NCEP/ATP III: 60%; IDF: 57%	Ranjith <i>et al.</i> , 2007
	Ubombo district	3 month period Not stated	947	African (rural)	>15 189 M; 758 F	JIS IDF NCEP/ATP III	JIS: 26.5%; IDF: 23.3%; NCEP/ATP III: 18.5% JIS: M: 11.6%; F: 30.2%	Motala <i>et al.</i> , 2011
Other (not specified)	Not stated	Not stated	228	African (urban)	18-45 F	IDF	12%	Evans <i>et al.</i> , 2007
	Not stated	Not stated	1 392	93 African	30-60 1 367 M; 25 F	NCEP/ATP III	Overall: 31% African: 30%	Ker <i>et al.</i> , 2007.
	29 sites (not stated)	Nov 2005 – Nov 2006	1 201	986 Caucasian 126 Indian 73 Coloured 8 African	18-80 (58.3 ± 11.4) 668 M; 533 F	AHA/NHLBI	53.3%	Ramjeeth <i>et al.</i> , 2008

Table 2.3: Description of papers and samples identified in the Boolean search (*continued*)

Province/ Location		Inception year	Sample size <i>n</i>	Ethnicity and geotype	Average age (years)	Diagnostic criteria	Measured Prevalence (%)	Author and year
Other (<i>continued</i>)	Not stated	Not stated	225	African (urban)	18-45 F (122 obese; 103 normal weight)	IDF, NCEP/ATP III	IDF: 13.1%, NCEP/ATP III: 9.9% (normal-weight: IDF= 3.8%, NCEP/ATP III = 0%), obese: IDF = 18.5%, NCEP/ATP III = 18.1%	Jennings <i>et al.</i> , 2009
	Not stated	Not stated	600	Africans 300 HIV+ 300 HIV-	Not stated	NCEP/ATP III, IDF	IDF: 21.1% HIV+ 22.6% HIV- NCEP/ATP III: 15.2% HIV+ 11.5% HIV-	Fourie <i>et al.</i> , 2010

AHA/NHLBI = American Heart Association/National Heart, Lung and Blood Institute; CAD = Coronary Artery Disease; F = Female; HIV = Human Immunodeficiency Virus; IDF = International Diabetes Federation; JIS = Joint interim statement; KZN = Kwa-Zulu Natal; M = Male; NCEP/ATP III = National Cholesterol Education Programme –Third Adult Treatment Panel; WHO = World Health Organization

Based on Table 2.3, studies seemed to be carried out sporadically, with relatively small sample sizes in defined high-risk groups of patients, such as those with type 2 diabetes, obesity and coronary artery disease. Most studies were conducted among urban African women. Only one paper reported prevalence rates among children/adolescents aged 10-16 years. In this particular study (Matsha *et al.*, 2009:364) an overall prevalence of 6.5% was reported, similar to rates reported in the US [e.g. Jolliffe and Janssen (2007:896), refer to paragraph 2.5.1]. Other deductions from Table 2.3 were:

- The prevalence was highly obesity-dependent.
- Most studies were of African study participants, with emphasis on urban, obese women.
- Most authors used NCEP/ATP III or IDF criteria for diagnosis, in small populations.
- The prevalence of the metabolic syndrome in adult populations varied according to definition used (with high variety within same age and gender groups), and a lower prevalence as measured with the IDF criteria compared with NCEP/ATP III criteria.
- The metabolic syndrome is more prevalent in South African Caucasians when compared with their African counterparts.

Based on area/study location, it seems that most of the studies were based in certain provincial or municipal areas. Five studies were conducted in the estimated six metropolitan areas in South Africa, e.g. City of Tshwane metropole (Rheeder *et al.*, 2002), the City of Johannesburg metropole (Ntyintyane *et al.*, 2006), City of Cape Town metropole (Okpechi *et al.*, 2007) and the eThekweni metropole (Motala *et al.*, 2011; Ranjith *et al.*, 2007). A further 11 studies were conducted in the estimated 231 municipalities in South Africa: 9 in North-West Province, one in the Western Cape (Smith & Essop, 2009) and one in the Free State (Mollentze, 2003). The location was unknown in a further five studies.

It seems that most studies listed in Table 2.3 that measured prevalence based on gender, indicated a higher prevalence among females (i.e. Kruger, 2001; Kalk & Joffe, 2008; Mollentze, 2003 and Motala *et al.*, 2011) compared with their male counterparts (i.e. studies by Ntyintyane *et al.*, 2006 and Smith & Essop, 2009). All of these studies (with the exception of the study by Kalk & Joffe), however, were conducted on individuals from African descent. Kalk and Joffe (2008), indicated prevalence in both African and Caucasian patients, using the IDF and NCEP/ATP III criteria. Based on their study, the prevalence of metabolic syndrome was also higher in females by both defining criteria.

2.6 THE SIGNIFICANCE OF METABOLIC SYNDROME

The clinical significance and consequences of the metabolic syndrome are discussed here. A discussion on the impact of the metabolic syndrome on disease burden ensues in section 2.6.2.

2.6.1 Clinical significance and consequence

There is some controversy over the clinical value of metabolic syndrome, with inconsistent findings from various studies. For example, the San Antonio Heart Study (Hunt *et al.*, 2004:1251) proved the metabolic syndrome inferior to established predicting models for both type 2 diabetes and cardiovascular disease. Lorenzo and workers (2007:10) in contrast, showed that the metabolic syndrome is associated with a significant cardiovascular disease risk particularly in men aged ≥ 45 years and women aged ≥ 55 years and predicts diabetes beyond glucose intolerance alone. A year later Sattar and co-workers (2008:1932) showed that the syndrome is strongly associated with the development of diabetes in middle-aged and elderly individuals but has either a negligible, or weak association with the development of cardiovascular disease. Regardless of this apparent incongruity in clinical utility, the diagnosis of metabolic syndrome presents an opportunity to rationalise health services delivering coordinated care to those with one or more risk factors for the metabolic syndrome (Cameron, 2010:119; Taslim & Tai, 2009:32). Some of these risk factors, as such, are major and independent risk factors for diabetes and CVD, each directly promoting atherosclerosis (refer to section 2.9).

Strong co-existence of multiple metabolic syndrome risk factors that complement each other results in a higher risk burden. The magnitude of this increased risk burden varies according to which components of the syndrome are present in an individual (Grundy, 2006b:1095), as well as to the number of components present (ADA, 2005:888; Scholze *et al.*, 2020). The presence of one component of the metabolic syndrome furthermore heightens the possibility of having more of the other components of the syndrome. For example, individuals with diabetes are more likely to have hypertension and/or dyslipidaemia than the general population (Fagot-Campagna *et al.*, 2000:A79). Likewise, half of patients with hypertension are insulin-resistant (Reaven *et al.*, 1996:374; Lima *et al.*, 2009:109); hypertensive patients also have a 2-fold higher prevalence of diabetes and obesity compared with normotensive people (Kaplan, 1989:1516; De Simone *et al.*, 2010:359). The timing and presentation of hypertension differ between type 1 and type 2 diabetes. For example, in patients with type 1 diabetes, hypertension normally develops after a number of years, ultimately affecting approximately 30% of individuals with the disease (Rovira, 2002:162). In patients with type 2 diabetes, hypertension may be present at the time of diagnosis or even before the development of hyperglycaemia, eventually developing in 20-60% of patients (Grossman & Messerli, 2008:84). Hypertensive patients are furthermore more likely to have hypertriglyceridaemia and low HDL-cholesterol levels and *vice versa* (Kannel, 1993:S36; Wong *et al.*, 2006:206). Obese men and women, respectively have a 7.7-fold and 5.3-fold increased risk for developing hypertension compared with lean individuals (Williams, P.T., 2008:2542) and up to 60% of obese individuals have hypertension (Mokdad *et*

et al., 2003:76). In the Nurses' Health Study, the relative risk for diabetes for women with a BMI of 25.0- to 29.9 kg/m² increased 8-fold compared with those with a normal BMI, whereas the risk increased 20-fold for those with a BMI 30- to 34.9 kg/m² and 39-fold for those with a BMI of 35 kg/m² or greater (Colditz *et al.*, 1997:60). An excess adiposity is furthermore associated with the release of adipokines (cytokine-like molecules of adipose tissue origin e.g., leptin, resistin and adiponectin) that may up-regulate inflammatory cytokines (e.g. tumour necrosis factor- α and interleukin-6), contributing to an increase in the levels of C-reactive protein (CRP) – a persistent low-grade inflammation that favours atherosclerosis (De la Sierra & Ruilope, 2007:210). An increased CRP level has recently been recognised as a cardiovascular risk factor (Capuzzi & Freeman, 2007:16).

Besides presenting a twofold risk for cardiovascular disease [including a 2.5-fold risk for coronary artery disease, a 2-fold risk for stroke (Fitch *et al.*, 2007:S24), and a 2.5-fold risk for heart failure (Voulgari *et al.*, 2011:1345)] and a fivefold risk for diabetes mellitus (refer to Figure 2.1), the metabolic syndrome *per se* relates to an amplified risk for a variety of disease outcomes. These include:

- A 9-fold risk for sleep apnoea (Kono *et al.*, 2007:1390; Vgontzas *et al.*, 2005:222).
- A 5-fold risk for chronic renal failure (Lucove *et al.*, 2008:27).
- A 3-fold risk for fatty liver and non-alcoholic steatohepatitis (Abdeen *et al.*, 2006:39).
- A 6-fold risk for colorectal cancer (Chan *et al.*, 2007:1418).
- A 2 to 3-fold risk for endometrial carcinoma (Rosato *et al.*, 2010) and breast carcinoma (Xue & Michels, 2007:s834).
- A 4-fold risk in polycystic ovary syndrome (Cussons *et al.*, 2008:2357).
- A 3-fold risk in gallstones and kidney stones (Méndez-Sánchez *et al.*, 2005:1656).

Other diseases frequently associated with metabolic syndrome are asthma-like symptoms (Lee *et al.*, 2009:341), reduced lung function (Yeh *et al.*, 2011:2310), sub-threshold depression (Vanhala *et al.*, 2009:141), psoriasis (Love *et al.*, 2011:421), high normal thyroid-stimulating hormone levels (Ruhla *et al.*, 2010:700) and cognitive decline in old age (Dik *et al.*, 2007:2659; Raffaitin *et al.*, 2011:523).

A favourable cardiovascular risk profile is coupled with a higher quality of life, health-related quality of life and a lesser risk for diseases in old age (Daviglius *et al.*, 2003:2467). Subsequently, individuals with metabolic syndrome are more likely to have fair or poor health. For example, Ford and Li (2008a:167) demonstrated that patients with the metabolic syndrome experienced more mentally unhealthy days (OR, 1.97; 95% CI: 1.28 - 3.02) and activity-limitation days (OR, 3.20; 95% CI: 1.46 - 7.02) than those without the syndrome. Miettola and colleagues (2008:1059) further showed that individuals with the metabolic syndrome had a

significantly lower mobility, hearing, breathing, discomfort and symptoms, vitality and erectile dysfunction and male hypogonadism compared with those without the syndrome. Early detection and management of the metabolic syndrome or individual components are thus critical from a value perspective, for the prevention or delay of type 2 diabetes mellitus, heart disease and the development of other health complications (Blumenthal, 2005:S500).

2.6.2 Metabolic syndrome disease burden

The concomitant presence of dyslipidaemia, hypertension and diabetes (particularly in obese patients), results in increased medical expenditure and lost productivity. For example, Sullivan and co-workers (2008:2157) showed that obese individuals with diabetes, dyslipidaemia or hypertension had significantly greater medical expenditures than those without the respective conditions, at US\$7,986, \$7,636 and \$6,197, respectively. The presence of these conditions in obese patients furthermore resulted in a greater number of missed work days, i.e. 8.7, 5.5 and 4.5 days respectively, for patients with diabetes, dyslipidaemia or hypertension (overall ~179% more work days lost); subsequently resulting in greater productivity lost (US\$1,217, \$763 and \$622, respectively). Individuals with cardiometabolic risk factor clusters furthermore spent (on top of lost workdays), 147% more days in bed than those without any risk factors (Sullivan *et al.*, 2007:446). In addition, lower adherence to healthy lifestyle habits (i.e. diet, exercise, maintaining a healthy weight, not smoking and a moderate alcohol use), is associated with a significant higher use of antihypertensives, lipolipidaemics and antihyperglycaemics (King *et al.*, 2009:1130).

The high prevalence associated with the metabolic syndrome carries an important economic consequence in terms of the medical cost of diabetes and cardiovascular disease, as well as morbidity and mortality, in addition to higher health care utilisation rates (i.e. more frequent hospitalisations, higher utilisation of outpatient and physician services) and greater product expenditure. For example, according to Mottillo *et al.* (2010:1130) the metabolic syndrome carry an increased risk of cardiovascular disease (RR, 2.35; 95% CI: 2.02 - 2.73), CVD mortality (RR, 2.40; 95% CI: 1.87 - 3.08), all-cause mortality (RR, 1.58; 95% CI: 1.39 - 1.78), myocardial infarction (RR, 1.99; 95% CI: 1.61 - 2.46), and stroke (RR, 2.27; 95% CI: 1.80 - 2.85). Schultz and Edington (2009:464-465) determined that patients with the metabolic syndrome had significantly higher health care (US\$3 340 vs. \$1 788), pharmacy (\$570 vs. \$270) and short-term disability (\$106 vs. \$59) costs, compared with those without the syndrome. Similar findings were reported by Hivert and colleagues (2009), in addition to an increased mean number of inpatient admissions (0.35 ± 1.20), an increased cost per admission (US \$5,057), a longer length of hospital stay (6 ± 3 days) and an increased number of outpatient visits per patient (10.4 ± 2.5 visits) compared with those without the syndrome. Boudreau *et*

al. (2009:310) furthermore added that the average annual total costs of subjects with the metabolic syndrome were 1.6 times higher and 1.3 times higher when stratified by diabetes. In the study by Boudreau and co-workers, patients with the metabolic syndrome also had a higher utilisation of inpatient stay and cost (2.1 and 2.2 times, respectively), higher primary care visits and cost (both 1.3 times), higher other outpatient visits, i.e. speciality and mental health (1.2 and 1.3 times, respectively) and higher pharmacy services (1.8 times). The indirect costs associated with the treatment of patients with metabolic syndrome were further estimated to be 13 to 17 times higher than direct pharmacotherapeutic costs (Turek *et al.*, 2010:538).

Schultz and Edington (2009:464) further determined that the average number of conditions per person with the metabolic syndrome was significantly higher than that of a person without the syndrome. For example, in their study the average number of conditions per person was 1.01 vs. 0.68 for those without metabolic syndrome. According to studies by Thorpe and Howard (2006:w385) and Curtis *et al.* (2007:2556) the most significant predictors of long-term costs in patients with the metabolic syndrome are hypertension (accounting for 22% of long-term costs in patients), hyperlipidaemia (accounting for 20% of long-term costs in patients with low HDL-cholesterol and 15% of patients with high triglycerides for 15%) and serum glucose (accounting for 16% of costs). Overall, annual costs associated with the metabolic syndrome increase by an average of 24% per additional risk factor (Boudreau *et al.*, 2009:308). Early detection and management of the metabolic syndrome are thus critical from a cost perspective as well.

2.7 THE AETIOLOGY OF METABOLIC SYNDROME

The origin of the metabolic syndrome is a subject of intense scrutiny and considerable controversy. Two schools of thought currently exist: firstly, the “early”/“foetal” origins hypothesis (also called thrifty phenotype) and secondly, the original thrifty genotype hypothesis. Extensive discussion of the thrifty pheno- and genotype hypotheses is beyond the scope of this research project – a short summary therefore follows. Other determinants that may play a role are also briefly mentioned. This section concludes with a brief description of the evidence for the origin of the metabolic syndrome in South Africa (refer to paragraph 2.7.4).

2.7.1 The thrifty phenotype hypothesis

The thrifty phenotype hypothesis, also known as Barker’s Hypothesis, describes a hypothesis that was originally put forward in the early 1990s by Hales and Barker (1992:595), who postulated that certain structures of the organs have their functions primed during embryonic and foetal life. Environmental factors, particularly nutrition, act in early life to programme the risks for the early onset of cardiovascular and metabolic disease later in adult life and

consequently, premature death (Hales & Barker, 1992:595; Hales & Barker, 2001:5).

This phenotype hypothesis thus suggests that there is an adaptive response when the foetal environment is poor, which optimises the development of key body organs to the disadvantage of others and leads to a distorted post-natal metabolism, designed to augment post-natal survival under conditions of intermittent or poor nutrition (Wells, 2007:144; Sebert *et al.*, 2011:1953S). Based on this hypothesis, small size at birth in full-term pregnancies and/or greater post-natal weight gain are linked with a subsequent development of major features of the metabolic syndrome, namely glucose intolerance, increased blood pressure, dyslipidaemia and increased mortality from cardiovascular disease (Barker *et al.*, 1993:62; Wells, 2007:170). A recent analysis by Efstathiou *et al.* (2012:907) confirmed this hypothesis, showing that the co-existence of low birth weight, small head circumference and parental history of overweight or obesity, predicted metabolic syndrome in adolescents with a sensitivity of 91% and specificity of 98%.

2.7.2 The thrifty genotype hypothesis

According to Speakman (2006:7), individuals have a genetic inclination towards certain diseases/conditions; these are mainly expressed in a modern, maladaptive environment. In the early 1960s, Neel suggested that “thrifty” genes were selected during evolution at a time when food resources were sparse which resulted in a fast insulin trigger and thus a superior capacity to store fat, which placed the individual at risk for obesity and type 2 diabetes (Neel, 1962:353; Neel, 1999:S2). Based on Neel’s hypothesis, such a genotype would be particularly beneficial for ancient populations exposed to periods of starvation, because it would allow them to deposit fat stores efficiently and thus endure succeeding periods of food crisis. This thrifty genotype, albeit, proves detrimental in modern civilisation where food is more readily available, because it promotes efficient storage of fat in preparation for a period of shortage that never materialises (Speakman, 2006:7). Many recent papers promote this original idea as a plausible evolutionary scenario, *inter alia*, Isomaa (2003:2399); Groop and Orho-Melander (2001:106); Hegele and Pollex (2005:R663); Moller and Kaufman (2005:49), Tiffin *et al.* (2008:55) and Sebert *et al.* (2011:1954S).

Although certain family studies (Groop *et al.*, 1996:1591; Henneman *et al.*, 2008:576; Ho *et al.*, 1990:33) advocate that the heritability of the metabolic syndrome is between 10-24%, in most cases, individual components have higher heritability than does the syndrome (Lusis *et al.*, 2008:819). For example, Lin and co-workers (2005:2009) estimated that when components were treated as continuous traits, the heritability varied from 16% for systolic blood pressure, to 60% for HDL-cholesterol. As discrete traits, the estimated heritability varied from 27% for large

waist circumference to 51% for low HDL-cholesterol levels. The inheritance of some of the common features of the metabolic syndrome identified in the literature is depicted in Table 2.4.

Table 2.4: The inheritance of some components of the metabolic syndrome

Component	Evidence supporting heritability
Obesity & Abdominal fat	– 25-40% of variation in body fat is attributed to genetic factors (Argyropoulos <i>et al.</i>, 2005:402; Bouchard & Perusse, 1993:346). – 25-60% of BMI and 40-55% of abdominal obesity is heritable (Argyropoulos <i>et al.</i>, 2005:402). – Distribution of subcutaneous (SC) fat in truncal area exhibits a genetic effect of about 20% (relative to SC fat in limbs) (Bouchard & Perusse, 1993:346). – 60% of the variance in abdominal fat in post-menopausal women is genetic (Lara-Castro <i>et al.</i>, 2002:873).
Hypertriglyceridaemia & HDL-cholesterol	– Heritability of HDL-cholesterol is stronger than heritability of triglycerides (Lehtovirta <i>et al.</i>, 2000:285). – Heritability is associated with insulin-resistance (Nieves <i>et al.</i>, 2003:172). – Familial and sporadic atherogenic dyslipidaemia identifies predisposition for the metabolic syndrome (Bao <i>et al.</i>, 1997:1749; Wyszynski <i>et al.</i>, 2005:197). – 25-60% of triglycerides and LDL-cholesterol, 30%-80% HDL-cholesterol and 50-60% of total cholesterol is heritable (Argyropoulos <i>et al.</i>, 2005:402).
Hypertension	– 40%-50% heritable (Groop & Orho-Melander, 2001:107). – Systolic blood pressure is 20-70% heritable compared with 10%-50% for diastolic blood pressure (Argyropoulos <i>et al.</i>, 2005:402). – Homeostasis-related traits are 20-60% heritable (Argyropoulos <i>et al.</i>, 2005:402). – Micro-albuminuria is 30% heritable (Argyropoulos <i>et al.</i>, 2005:402). – Associated with insulin-resistance (Srinivasan <i>et al.</i>, 2006:38). – Associated with pre-mature atherosclerotic cardiovascular disease (Srinivasan <i>et al.</i>, 2006:39; Bao <i>et al.</i>, 1997:1749).
Insulin resistance	– Insulin resistance cluster in families (Groop <i>et al.</i>, 1996:1585; Ho <i>et al.</i>, 1990:31). – 45% of first-degree relatives of patients with type 2 diabetes are insulin resistant (compared with 20% of individuals without a family history) (Beck-Nielsen & Groop, 1994:1714). – First-degree relatives of patients with type 2 diabetes have an increased waist-to-hip ratio compared with those without a family history of the disease (Groop <i>et al.</i>, 1996:1585). – 10-75% of fasting glucose, 20-55% of fasting insulin and 46%-90% of insulin resistance or type 2 diabetes mellitus are inherited (Argyropoulos <i>et al.</i>, 2005:401).

2.7.3 Other determinants for metabolic syndrome

Abdominal adiposity and physical inactivity (to a lesser degree) are strong determinants of insulin resistance (Racette *et al.*, 2006:674-675; Raitakari *et al.*, 1994:244), the metabolic syndrome (Després & Lemieux, 2006:882) and cardiovascular disease risk (Arsenault *et al.*, 2010:342). This effect is more pronounced in middle-aged individuals, especially women (Hu *et al.*, 2004:2217; Li *et al.*, 2006:502).

Other environmental determinants of CVD are also associated with the metabolic syndrome, for example, tobacco exposure and aging. Smoking impairs insulin action and induces insulin resistance (Bergman *et al.*, 2009:2223; Gupta *et al.*, 2006:287). Smoking may further increase the risk for heart attack or stroke at least threefold in hypertensive and diabetic patients (Fagard, 2009:S430; Primates *et al.*, 2001:191), whereas aging predisposes individuals to the

metabolic syndrome (Morley & Sinclair, 2009:494;496).

The aetiology of diseases such as obesity, diabetes and CVD is furthermore heavily influenced by environmental factors. These factors may cause disease states by acting either alone or in combination with specific genetic factors. Among selected subgroups, their genes may modify the susceptibility to a given environment. Current evidence therefore suggests that both genetic and environmental factors and their interactions play an etiological role in the pathogenesis of metabolic syndrome (Prentice & Moore, 2005:430).

A few other determinants of the metabolic syndrome in developing countries in particular, include the transition in demographics (i.e. shift to low fertility, low mortality, higher life expectancy) and the transition in epidemiology (i.e. from widely prevalent infectious diseases to a pattern of high prevalence of chronic lifestyle related non-communicable diseases) caused by a transition in socio-economics (i.e. developing countries become more resourceful). These transitions in turn cause considerable changes in dietary and physical activity patterns (i.e. nutrition and lifestyle transitions, and stress), ultimately leading to significant effects on body composition and metabolism, often resulting in increase in body mass index, excess adiposity (generalised and abdominal), evidence of ectopic fat, and an increase in dyslipidaemia and diabetes. Other factors include physical inactivity, socio-economic and sociocultural factors. Each type of transition has a significant effect on the development of obesity and metabolic risk factors, of which urbanisation, nutrition transition and increasing affluence are the most important determinants. The thrifty geno- and phenotype also play a role in the development of obesity and type 2 diabetes seen in certain ethnic groups in developing countries (Misra & Khurana, 2008:S21-S22).

2.7.4 Evidence for the origin of metabolic syndrome in South Africa

According to Levitt and Lambert (2002:179), there is compelling evidence in South Africa that supports the thrifty phenotype theory, with the Birth-to-Ten Cohort study and the study of full-term offspring of primiparous women from Cape Town as most important contributors to this body of evidence. The Birth-to-Ten Cohort study - a study of the determinants of growth, development and health in children - dating back to the early 1990s (Yach *et al.*, 1991:230), showed that systolic blood pressure in children at the age of 5 years was inversely related with weight at birth, independent of weight, height, gestational age, maternal age or socio-economic status (Levitt *et al.*, 1999:266). Levitt and co-workers (2002:179) also showed systolic blood pressure to decrease with 3.0 mmHg (95% CI: 1.0 - 5.0) for every 1 000 g increment in study participants' birth weight. This study therefore established that influences early in childhood and subsequent growth might increase the effect of birth-weight on blood pressure in South African

populations.

Metabolic studies undertaken in a smaller representative subgroup of the Birth-to-Ten Cohort study population also showed an inverse association between birth weight and the 30-minute plasma glucose concentration, and the quantity of insulin secreted within the first 30 minutes and the last 90 minutes of the oral glucose tolerance test (Crowther *et al.*, 1998:1165). According to Levitt *et al.* (2001:A246) and Levitt and Lambert (2002:179), this verifies the correlation between poor foetal growth as measured by birth weight in conjunction with rapid childhood weight gains, and glucose tolerance and insulin resistance later in life.

The study of full-term descendants of primiparous women from Cape Town examined the association between low birth weight and glucose intolerance, blood pressure and dyslipidaemia (Levitt *et al.*, 2000:4611). Data from this study showed that young adults (20 years) who had a low birth weight for gestational age (<10th centile) had significantly higher systolic and diastolic blood pressures compared with those who had a normal birth weight (25th to 75th centiles). The low-birth weight group also had an 11.9% prevalence of glucose intolerance (impaired glucose tolerance and diabetes) in contrast to none reported in the normal birth weight group (Levitt *et al.*, 2000:4615). A more recent re-analysis of this data (Levitt *et al.*, 2005:1122) showed that adult size altered the low-birth weight effect on these outcomes. For example, only the group who was above the current median for BMI or total fat or abdominal fat accumulation, showed the low-birth weight phenotype of higher systolic blood pressure, higher plasma triglyceride concentrations and insulin resistance as measured by the homeostasis assessment model and post-oral glucose tolerance test insulin concentrations. A study by Gray and colleagues (2002:4253) in preterm neonates of African descent further showed that those who were small for gestational age and had the greatest post-natal gain in weight had the greatest insulin resistance.

The proposed mechanisms underlying the development of the metabolic syndrome are reviewed in the subsequent section.

2.8 THE PATHOPHYSIOLOGY OF METABOLIC SYNDROME

A number of pathophysiological pathways have been proposed in recent years to describe the cause of the metabolic syndrome. For example, at the outset of the development of the concept, insulin resistance and/or hyperinsulinaemia were thought the main etiological process because most individuals with the syndrome featured either one or the other defect (Reaven, 1988:1595). Many recent papers also promote this original idea as a main etiological scenario, *inter alia*, Liao *et al.* (2004:980), Stolar (2007:200-201), Potenza and Mechanick (2009:562) and

Salazar *et al.* (2011:115). Most factor analyses though, show obesity as a common risk factor in two different association paths – that of obesity and hypertension and another encompassing alteration in obesity, dyslipidaemia and glycaemic control (Lawlor *et al.*, 2004:1016; Meigs *et al.*, 1997:1598). On the other hand, Franco and co-workers (2009:1949) suggest that there are mainly two trajectories and combinations of components that patients enter the metabolic syndrome with – both paths show high blood pressure as a central factor, one additionally has central obesity and hyperglycaemia, and the other is characterised by dyslipidaemia. As such, the pathophysiology remains a subject matter of abiding controversy.

The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD) (Rydén *et al.*, 2007:97) suggested a causal relationship with insulin resistance and visceral adiposity as the main pathophysiological pathway. Eckel *et al.* (2005:1421) likewise proposed a model that assumes that excessive fatty acids creates insulin resistance by the added substrate availability and by modifying downstream signalling upon reaching insulin sensitive tissues.

Extensive discussion of the pathophysiology of the metabolic syndrome is beyond the scope of this literature review, a brief description of the role of the various underlying mechanisms in this process (risk factors for the development of the metabolic syndrome) therefore follows. The model proposed by Eckel *et al.* (refer to Figure 2.2) is used as basis for this overview, however, recognising that not all of the associations between the different components of the metabolic syndrome can be ascribed to insulin resistance and/or obesity or the causal relationship between these two factors. For example, research has shown that just 60-78% of patients with the metabolic syndrome present with insulin resistance (Han & Lean, 2006:538; McLaughlin *et al.*, 2003:803). In addition, only about 60% of obese individuals have the metabolic syndrome (Citrome, 2005:86; Park *et al.*, 2003:434); in fact even lean individuals with or without central weight gain can have the metabolic syndrome (Alexander *et al.*, 2003:1210; Janssen, 2005:1315). Furthermore, not all overweight or obese patients are insulin resistant (Ruderman *et al.*, 1998:711). These opinions suggest that there may be “metabolically obese” individuals, who have an equally high risk of developing diabetes or cardiovascular disease as those who are obese or insulin resistant.

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Diagram A of Figure 2.2 illustrates how a greater amount of (non-esterified) free fatty acids (NEFAs) are released from an expanded mass of adipose tissue (mainly through the action of the cyclic AMP-dependent enzyme hormone sensitive lipase) into muscle and liver cells (Eckel *et al.*, 2005:1418). The excessive influx of NEFAs into muscle results in insulin resistance, predisposing the individual to hyperglycaemia (Boden, 2011:139; Shah *et al.*, 2008:642). The various mechanisms postulated for this action include that

- excess fatty acids inhibit glucose oxidation (glucose-fatty acid cycle) (Randle *et al.*, 1963:786) with subsequent associated defects such as a reduction in glucose partitioning to glycogen and increased lipid accumulation in triglycerides) (Eckel *et al.*, 2005:1421);
- muscle levels of diacylglycerol are raised, stimulating the serine phosphorylation of the insulin receptors and thereby inhibits normal insulin signalling (Shulman, 2000:172); and
- excess circulating fatty acids and glucose increases pancreatic insulin secretion ultimately resulting in hyperinsulinaemia (Eckel *et al.*, 2005:1421).

Hyperinsulinaemia subsequently results in hypertension *via* the following mechanisms:

- Direct vascular effects, impairment of insulin-mediated vasodilatation, or vasoconstriction (Dorresteijn *et al.*, 2011; Tripathy *et al.*, 2003:2882). Additionally, cellular cation transport may be altered in patients with insulin resistance; also promoting vasoconstriction (Smith, 1993:327).
- Hyperinsulinaemia driving sodium retention. Insulin enhances renal sodium retention (Kotchen, 2010:1171; Moller & Kaufman, 2005:53). Vasoactive cytokines and hormones, such as angiotensin II, endothelin-1 and cyclo-oxygenase and lipo-oxygenase produced by adipose tissue in insulin resistant individuals act in part by reducing sodium excretion by the kidney *via* activation of the renin-angiotensin-aldosterone system (RAAS) (Gorzelnjak *et al.*, 2002:965; Sowers & Fronlich, 2004:69), thereby increasing the blood volume and therefore blood pressure (James *et al.*, 2004:497). High leptin levels may also activate the pro-opiomelanocortin pathway and sympathetic nervous system, thereby increasing blood pressure (Aneja *et al.*, 2004:169).
- Hyperinsulinaemia driving central nervous system activity. Insulin resistance and hyperinsulinaemia increase the tone of the sympathetic nervous system control of the arterioles which increase blood pressure (Dorresteijn *et al.*, 2011; Korhonen *et al.*, 2008:945). Activation of the central nervous system may also contribute to the elevation of blood pressure through its effects on vasculature and renal handling of sodium and water (Hall, 2000:140; Huggett *et al.*, 2004:850).
- Insulin resistance may also yield an action directly on small blood vessels, leading to high blood pressure (Eckel *et al.*, 2005:1421; Salazar *et al.*, 2011:115).

The influx of excess NEFAs into the liver increases the triglyceride content of the liver *in sync* as it does in muscle, so doing producing insulin resistance. Reduction in insulin action in liver then allows for enhanced gluconeogenesis and increased hepatic glucose output, accentuating hyperglycaemia in those patients who have reduced insulin secretory capacity (Ritchie & Connell, 2007:319). Increased fat in the liver further promotes the development of atherogenic dyslipidaemia by interfering with the exogenous and endogenous lipid pathways at a number of key steps (Eckel *et al.*, 2005:1419).

The various mechanisms postulated for the interference of insulin-resistant states with the exogenous lipid pathway:

- The activity of lipoprotein lipase tends to decrease in insulin-resistant individuals (Semenkovich, 2006:1813).
- The increased concentrations of chylomicrons and their remnants are accompanied by an increase in the exchange of triglycerides for cholesteryl ester from HDL, resulting in triglyceride enriched HDL particles, depleted of cholesteryl ester (Borggreve *et al.*, 2003:1064; Grundy, 2006a:2597).
- Subsequent hydrolysis of the HDL triglyceride by hepatic lipase leads to the formation of smaller and denser (than usual) HDLs (Chapman, 2003:4).

The development of an insulin-resistant state interferes with the endogenous lipid pathway as follows:

- In insulin-resistant states, normal suppression of lipolysis in adipocytes by the post-prandial increase in plasma insulin levels is reduced, causing a continued release of free fatty acids (even throughout the post-prandial state) with subsequent amplified production of triglycerides and thus of VLDLs (Barter, 2005:S9).
- The increased production of triglyceride and VLDLs results in an increase in the concentration of VLDLs (in combination with a reduced activity of lipoprotein lipase). This subsequently leads to an increase in the rate of CETP-mediated exchange of triglyceride and cholesteryl esters between HDLs and VLDL, and thus an increased cholesteryl ester content of VLDLs and an increase in triglyceride content of HDLs (Barter, 2005:S9; Bays, 2003:358).

A similar CETP-mediated exchange of triglyceride and cholesteryl esters between VLDLs and LDLs results in the configuration of triglyceride-rich LDL particles (Sacks & Campos, 2003:4526). The triglyceride in both the HDLs and LDLs is then hydrolysed by hepatic lipase to result in smaller and denser LDL and HDL particles, contributing to the increased risk for atherosclerosis in insulin-resistant populations (Gropper *et al.*, 2005:143).

There are several potential mechanisms whereby low HDL levels are anti-atherogenic, *inter alia* enhanced reverse cholesterol transport, anti-oxidation and anti-inflammatory properties and the ability to protect against LDL modification (Mackness *et al.*, 2000:383). HDL also has antithrombotic effects including antiplatelet actions and protein-C activation. Such actions of HDL then lead to the removal of excess cholesterol from the artery wall and prevent leukocyte adhesion to the endothelium, with subsequent metabolism in the liver (Whayne, 2009:644). HDL is also a marker for the presence of other lipid and non-lipid risk factors; for example, obese patients with metabolic syndrome and atherogenic dyslipidaemia usually have low HDL levels (Mackness *et al.*, 2004:682).

Diagram B (Figure 2.2) illustrates the paracrine and endocrine effect of the pro-inflammatory state, which is superimposed on and causal to the insulin resistance created by excessive FFA. An increased amount of interleukin-6 (IL-6), tumour necrosis factor alpha (TNF- α) and protein kinase C is secreted by the various cells in adipose tissue i.e. adipocytes and monocyte-derived macrophages (Grundy & Brewer *et al.*, 2004:434; Pi-Sunyer, 2006:S15). These cytokines – which are key mediators of the prothrombotic and pro-inflammatory states (Garg, 2006:S10) – “derail” the insulin signalling pathway (Rassman & Gupta, 2005:32), resulting in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFA. The levels of IL-6 and other cytokines are also increased in the circulation and may add to the production of hepatic glucose, VLDL by the liver and insulin resistance in muscle. The increase in adipocyte mass is furthermore associated with an increased expression of angiotensinogen, fibrinogen and other anti-inflammatory adipokines such as adiponectin, leptin and resistin by the liver that complements the overproduction of plasminogen activator inhibitor-1 by adipose tissue, with a resulting prothrombotic state (Garg, 2006:S10; Miranda *et al.*, 2005:39). This prothrombotic state may encourage both atherogenesis and thrombosis, each contributing to clinical coronary disease.

2.9 THE COMPONENTS OF METABOLIC SYNDROME

An overview of elevated waist circumference/obesity, (atherogenic) dyslipidaemia, elevated blood pressure, elevated plasma glucose, a prothrombotic state and a pro-inflammatory state as components of the metabolic syndrome stipulated by the AHA/NHBL criteria (refer to Table 2.1) is provided in this section.

2.9.1 Elevated waist circumference/obesity

The NCEP/ATP III (NIH, 2002:3182) considers obesity as an underlying risk factor for CVD, whereas the AHA/NHLBI and others term obesity as a metabolic risk factor (Grundy & Brewer *et*

al., 2004:433). A discussion concerning the classification and prevalence of waist circumference/obesity and risk of metabolic syndrome, diabetes and CVD, and the treatment thereof is provided in this sub-section.

2.9.1.1 Definition of elevated waist circumference/obesity

According to the US National Institutes of Health and the National Heart, Lung, and Blood Institute Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (NIH, 1998:27) obesity is a “*complex multifactorial chronic disease that develops from an interaction of genotype and the environment*”. The World Health Organization (2000:6) and DiPiro (2009:663) furthermore describe obesity as a disease state of excess body fat stores that accumulate to “an extent that health may be adversely affected”. The abdominal or visceral, male or android type of obesity is the form most strongly associated with the metabolic syndrome (Grundy & Brewer *et al.*, 2004:433).

Markers for obesity include *inter alia* the measuring of the body mass index (BMI) or Quetelet's index (a height/weight formula with strong correlation to body fat content), the waist circumference (WC) or the waist-to-hip ratio (WHR) (that measures abdominal fat distribution) and body fatness (Kullberg *et al.*, 2007:150). Obesity for adults is classified as a BMI ≥ 30 kg/m², which can be subdivided into five classes (Poirier *et al.*, 2009:87). For example, class 1 obesity is represented by a BMI of 30-34.9 kg/m², class 2 by a BMI of 35.0 – 39.9 kg/m², class 3 by a BMI ≥ 40 kg/m² (severe, extreme or morbid obesity), class 4 by a BMI ≥ 50 kg/m², and class 5 obesity by a BMI ≥ 60 kg/m² (Poirier *et al.*, 2009:87). Obesity in children between the ages of 2 and 18 years is defined as a BMI at the 95th percentile or ≥ 30 kg/m², whichever is lower. Severe obesity in those 2 to 18 years of age is defined as a BMI at 99th percentile, or a BMI ~ 30 -32 kg/m² for those 10-12 years of age, and a BMI 34 kg/m² for adolescents 14-16 years of age (Barlow, 2007:S168).

Table 2.5 shows international recommendations proposed for thresholds of abdominal obesity according to waist circumference.

Table 2.5: Recommended waist circumference thresholds for abdominal obesity (adapted from Alberti *et al.*, 2005:1059)

Population	Recommended waist circumference threshold	
	Men	Women
Europid	≥94 cm	≥80 cm
Caucasian	≥94 cm (increased risk) ≥102 cm (still higher risk)	≥80 cm (increased risk) ≥88 cm (still higher risk)
United States	≥102 cm	≥88 cm
Canada	≥102 cm	≥88 cm
European	≥102 cm	≥88 cm
Asian (including Japanese)	≥90 cm	≥80 cm
Asian	≥90 cm	≥80 cm
Japanese	≥85 cm	≥90 cm
China	≥85 cm	≥80 cm
Middle east, Mediterranean	≥94 cm	≥80 cm
Sub-Saharan Africa	≥94 cm	≥80 cm
Ethnic Central and South American	≥90 cm	≥80 cm

2.9.1.2 Prevalence and epidemiology of elevated waist circumference/obesity

The prevalence of overweight and obesity is rising at an alarming rate worldwide, and is often described as “being of epidemic proportions” (Low *et al.*, 2009:60; Kanekar & Sharma, 2010:105; Wang, 2001:1129; Yusuf *et al.*, 2005:1647). According to Finucane and co-workers (2011:564) approximately 1.46 billion adults worldwide had a BMI of 25 kg/m² or greater in 2008, of these 205 million males and 297 million females were obese. An estimated 43 million children worldwide in 2010 were considered either obese or overweight (De Onis *et al.*, 2010:1262) with another 92 million at risk of becoming overweight. According to Rocchini (2002:854) and the WHO (2003:2), about 18-22 million (12%-14%) of overweight children are under the age of five years.

De Onis and colleagues furthermore estimated the prevalence of overweight and obesity by region, as follows: Africa, 8.5%; Asia, 4.9%; Latin America and the Caribbean, 6.9%; Oceania 3.5%; developed countries (Europe, North America, Australia, New Zealand, and Japan), 11.7%; and developing countries, 6.1%. Approximately 68% of the adult population in the US (i.e. 72.3% among men and 64.1% among women) are either overweight or obese (Flegal *et al.*, 2010:238). A further 10.4% of American children aged 2 to 5 years, 19.6% of children aged 6-11 years and 18.1% of children aged 12-19 years were also above the 95th percentile of BMI for age in 2007-2008 (Ogden *et al.*, 2010:245). Abdominal overweight in the English population aged 18-67 years rose from 44.9% to 62.3% in men, and from 46.6% to 66.8% in women between 1993 and 2008, while abdominal obesity rose from 19.2% to 35.7% in men, and from 23.8% to 43.9% in women (Howel, 2011).

Obesity rates in Africa vary based on the stage of transition of each country (Misra & Khurana, 2008:S12; Prentice, 2006:94), reflecting incidences similar to that of the US (Asfaw, 2006:262). The prevalence of obesity in South Africa is higher than that reported in other African countries (especially amongst poorer women) (Goedecke *et al.*, 2006:65; Haslam & James, 2005:1197). Based on data from the first South African Demographic and Health Survey (SADHS) in 1998, 56.6% of women and 26.9% of men older than 15 years were either overweight or obese (Puoane *et al.*, 2002:1041). The mean body mass index for adolescent women in this survey was also greater than that for their male counterparts, at 23.0 kg/m² vs. 21.0 kg/m² (Department of Health, 2002). The 2003-SADHS showed no changes in the prevalence of obesity and overweight in adults since 1998 (at 55% for women and 30% for men) (Department of Health, 2007), also estimating an obesity prevalence rate of 24% for adolescent women and 9% for their male counterparts. Based on the Health of the Nation Study (Armstrong *et al.*, 2006:442) a further 3.2% of males and 4.9% of females aged 3 to 16 years nationally were classified as obese during 2001-2004, with a further 14% of males and 17.9% of females classified as overweight. About one in five children aged 1 to 4 years in rural South Africa is currently stunted, of whom one in three at the age of 1 year (Kimani-Murage *et al.*, 2010).

According to the United States Department of Health and Human Services (2007), overweight adolescents have a 70% chance of becoming overweight adults, increasing to 80% if one or both parents are overweight or obese. Obesity and/or overweight in general can be attributed mainly to two major risk factors, namely plentiful supplies of inexpensive foods and a sedentary lifestyle (Grundy, 2006a:2595). Obesity in children particularly, is caused by multiple aetiologies i.e. genetic and metabolic factors (e.g. leptin deficiency or medical causes such as hypothyroidism and growth hormone deficiencies), high socio-economic status, residence in metropolitan cities, marketing by transnational food companies, false beliefs about nutrition and “risky behaviour” (e.g. an increase in dietary fat and energy intake and a decrease in physical activity) and female gender (Dehghan *et al.*, 2005; Gupta *et al.*, 2012:68). In addition, several other (main) causes for obesity and overweight pertaining to South Africa were identified *inter alia*:

- Rapid and unplanned urbanisation and globalisation.
- Psychosocial, psychological and low socio-economic factors.
- Level of education.
- Cultural factors.
- Perceptions and beliefs about body weight (Ali & Crowther, 2010:193; Goedecke *et al.*, 2006:70-73; Kruger *et al.*, 2005:492-494; SASSO, 2001:2).

2.9.1.3 Elevated waist circumference/obesity as risk factor

Obesity, particularly of the abdominal type and sedentary life style, may induce excessive CVD morbidity and mortality through several mechanisms. Firstly, obesity seems to advance the development of several morbid conditions that are autonomous risk factors for CVD, including hypertension, elevated cholesterol, hypertriglyceridaemia and impaired glucose tolerance (Alberti, 2005:D3). Secondly, obesity seems to promote the clustering of these risk factors, thus increasing the risk exponentially (Nugent, 2004:40; Prabhakaran & Anand, 2004:56), and thirdly, obesity has an effect on the cardiovascular system (that seems independent of diabetes, hypertension and dyslipidaemia). The last mechanism is ascribed to the opinion that fat creates a metabolically active organ (Laclaustra *et al.*, 2007:126) and is responsible for the secretion of a number of different substances including *inter alia* non-esterified free fatty acids, cytokines and vasoactive substances (such as PAI-1, adiponectin and angiotensin II). These substances exacerbate the risk for cardiovascular disease (Grundy & Brewer *et al.*, 2004:434; Opie, 2007:e32, Lavie & Milani *et al.*, 2009:1930).

The risk for CAD increases even with a mild increase in BMI (Dudina *et al.*, 2011:740; James *et al.*, 2004:498; Yusuf *et al.*, 2005:1644). Different gender groups, however, show different cut points for the definition of overweight status as it relates to CAD risk. For example, Manson *et al.* (1995:683) and Rimm *et al.* (1995:1119) established that in middle-aged women, a BMI more than 23 kg/m² (but less than 25 kg/m²) indicates a 50% increase in risk for a non-fatal/fatal CAD, whereas a BMI more than 25 kg/m² (but less than 29 kg/m²) indicates a 72% increase in risk in middle-aged men. Age also plays an important role in the relative risk associated with obesity – according to Baron (2006b:1267) the risk declines with ageing up to the age of 75 years, where after weight is no longer a risk factor. The duration of obesity also influences associated health risks i.e. the longer the duration, the greater the increased health risks (Caterson *et al.*, 2004:e478).

According to Rosenbaum *et al.* (2012) waist circumference is further a strong and independent determinant of the distribution of HDL subfractions toward denser particles in overweight patients with one or more cardiovascular risk factors, from hypertension, dyslipidaemia, diabetes mellitus, current smoking, age >60 years for females or >50 years for males. A waist circumference ≥92 cm, independently of BMI, may also predict the clustering of risk factors for cardiovascular disease as shown by Charlton and colleagues (2001:145) in a sample of older South Africans with mixed ancestry.

The risk for developing diabetes increases in a dose-dependent manner in answer to increases in BMI. For example, compared with an individual with a normal BMI (18.5-24.9 kg/m²), the

prevalence of type 2 diabetes is 3-7 times higher in a person with a BMI of 30-34.9 kg/m², to 20- (Field *et al.*, 2001:1584; Mokdad *et al.*, 2003:77) to 40 times (Chan *et al.*, 1994:966; Colditz *et al.*, 1995:484) in an individual with a BMI of ≥ 35 kg/m². Power and Thomas (2011:1989) furthermore found that BMI gains in child- and adulthood are associated with higher HbA_{1c} levels, for example, they showed that for every SD of 5-year BMI increase from 0 to 7 years, there was a 75% (95% CI: 1.42 - 2.16) increased risk of HbA_{1c} ≥ 7 , increasing to a 4.7-fold (95% CI: 3.12 - 7.00) risk for the interval 23-33 years. Power and Thomas also found that duration of obesity was associated with HbA_{1c} levels, compared with an individual that had never been obese, those with childhood onset had a 23.9-fold risk (95% CI: 13.5 - 42.1) of HbA_{1c} $\geq 7\%$. Weight gain after 18 years in women and after the age of 20 years in men *per se* increases the risk for type 2 diabetes (Caterson *et al.*, 2004:e479).

The development of insulin resistance is regarded as the dominant mechanism whereby weight gain leads to the development of type 2 diabetes (James *et al.*, 2004:549; Stolar, 2002:S3). Type 2 diabetes develops when the capacity of the pancreas to generate insulin cannot sustain the markedly bigger requirement induced by insulin resistance (ADA, 2007:S4). Insulin resistance is affected/induced by various factors, i.e.: (1) increases in weight (particularly if the extra energy is stored in abdominal, i.e. visceral fat); (2) dietary composition (Vessby *et al.* 2001:315; Willet *et al.*, 2002:274S); (3) cytokines secreted by visceral adipose tissue (*inter alia* interleukin-6 and tumour necrosis factor) (Borst, 2007:283); and (4) reduced levels of adiponectin (Furler *et al.*, 2006:230; Kantartzis *et al.*, 2005:1683). Physical inactivity also contributes to insulin resistance (in particular patients with hypertension) (Hwu *et al.*, 2004:359).

Based on data of the San Antonio Heart Study, adult patients with a baseline BMI ≥ 30 kg/m² were 3- to 8-fold more likely to develop the metabolic syndrome than individuals with a BMI < 25 kg/m² or small waist circumference (Han *et al.*, 2002:929). This risk is also different for the respective gender groups, for example Ervin (2009:4) showed that overweight males were more than six times as likely as underweight and normal weight males to meet the criteria for metabolic syndrome (OR, 6.17; 95% CI: 3.96 - 9.62), whereas obese males were nearly 32 times as likely to meet this criteria (OR, 31.92; 95% CI: 20.06 - 50.78). Overweight females were nearly 5.5 times as likely as underweight and normal weight females to meet the criteria for metabolic syndrome (OR, 5.48; 95% CI: 3.75 - 8.02), whereas obese females were more than 17 times as likely to meet this criteria (OR, 17.14; 95% CI: 12.54 - 23.44) (refer to section 2.8 for the underlying mechanisms linking intra-abdominal obesity to development of the metabolic syndrome.) Other disease risks besides cardiovascular disease that increase significantly with BMI levels above 25.0 kg/m² are sleep apnoea, osteoarthritis, complications during anaesthesia and reproductive abnormalities (Ali & Crowther, 2005:56; Haslam & James, 2005:1199-1202).

Obesity is one of 10 foremost risk factors for high cardiovascular mortality in developing and developed countries (measured by disability-adjusted life years), which adds to the burden of disease (WHO, 2002b:7). Mortality associated with excess weight increases linearly with the build-up in the degree of obesity and overweight (i.e. for each increase of 1 kg in body weight, the risk for coronary mortality increased by 1-1.5%) (Caterson *et al.*, 2004:e476-e477).

2.9.1.4 Elevated waist circumference/obesity disease burden

Wolf (2002:60S) gave an elaborate description of the economic consequences of the obese patient. Based on his publication and that of Finkelstein and co-workers (2004:22), overweight and obesity and associated health problems have a significant economic impact on health care systems in several developed countries, accounting for approximately 6% of total US medical expenditure. An updated estimate of this analysis shows that the increase in obesity prevalence was responsible for almost a \$40 billion increase in medical spending through 2006 (Finkelstein *et al.*, 2009:w829). Van der Merwe (2007:5) estimated that the health care expenses carried by obesity and its related illnesses in South Africa to be as high as 8% of South African annual medical expenditure.

The relationship between obesity and the use of medical care and cost is consistent and generally dose-responsive. Finkelstein *et al.* (2004:23) estimated that Americans spent over US\$75 billion dollars a year on medical expenses attributed to obesity. Approximately \$33 billion of this amount (i.e. 44%) is spent on weight-reducing products (Klein-Schwartz, 1998:1). In South Africa, more than R44 million is spent each year on registered diet treatments, with about three-quarters of this spent on over-the-counter (OTC), or non-prescription products (SASSO, 2001:18).

Pronk *et al.* (1999:1541) found that there was a 1.9% increase in median costs for every one-unit increase in BMI; which, although it did not translate into large increases in cost at the individual patient level, could become quite significant at population level. A similar study by Oster *et al.* (2000:684) determined that for every one health care dollar spent, 41 cents would be attributable to health care cost due to obesity. A 9-year retrospective cohort study conducted on the relationship between obesity and future health care costs by Thompson and co-workers (2001:216) furthermore indicated that individuals with a BMI of 25-29.9 kg/m² (overweight) and ≥30 kg/m² (obese) had (relative to individuals with a normal BMI of 20-24.9 kg/m²) a

- 10% and 36% (respectively) higher total annual health care costs;
- 37% and 105% (respectively) higher pharmacy cost; and
- a 13% and 39% (respectively) higher number of outpatient visits to primary care

providers.

High waist circumferences are also associated with higher annual health care costs compared with a low waist circumference. For example, Pendergast *et al.* (2010:408) showed that the annual health care cost was 16-18% higher in Germany and 20-30% higher in the US for subjects with a high waist circumference compared with subjects with a low waist circumference. Similar findings were reported earlier by Højgaard *et al.* (2008) in a Danish population.

According to Pearson *et al.* (2009), obese individuals received on average 3.1 medications during a visit to a provider, compared with 2.5-2.6 medications for overweight to normal weight patients. In 2001, Thompson *et al.* (2001:214) established that overweight and obese individuals, respectively had 1.5 times (95% CI: 0.54 - 6.77) and 6.1 (95% CI: 2.88 - 27.78) the number of filled prescriptions for antihyperglycaemics and 2 (95% CI: 1.54 - 2.72) and 3.4 (95% CI: 2.57 - 4.65) times the number of cardiovascular medications relative to individuals with a normal BMI. Overweight individuals with abdominal obesity furthermore have a 13% higher prevalence of diabetes compared with overweight individuals without abdominal obesity (Wolf *et al.*, 2008:1251). Wolf and co-workers also determined that the associated health care cost of the overweight and obese patients in this study was significantly higher compared with those of patients with normal BMI values (i.e. US\$456 ± 937 for a person with a normal BMI vs. \$1,084 ± 3,531 for an overweight individual and \$1,186 ± 2,808 for the obese). Findings from an earlier study by Thorpe *et al.* (2004:483) support these findings. In their study, Thorpe and co-workers showed that the medical spending for overweight/obese adults above the age of 65 years was about 60% higher compared with those individuals of normal weight. The higher medical spending in older obese patients may be ascribed to the chronic nature of obesity-attributable diseases among obese adults above the age of 65 years compared with non-elderly obese individuals (Finkelstein *et al.*, 2003:219).

Obesity furthermore carries a significant indirect cost in terms of impact on the quality of a patient's life and life expectancy. According to Hossain *et al.* (2007:213A), a higher body mass index may account for up to 16% of the global burden of disease (expressed as disability-adjusted life-years). Obese individuals, especially women, are also more likely to be absent from work and experience restrictions in mobility and activity (Fontaine *et al.*, 2003:187). According to Muennig and co-workers (2006:1662), overweight males and females, respectively lost 270 000 and 1.8 million quality-adjusted life years due to being overweight relative to their normal-weight counterparts, whereas obese males and females lost 1.9 million and 3.4 million quality-adjusted life years, respectively, per year due to obesity. Being obese at age 40 years additionally reduces life expectancy by 7.1 years for women and 5.8 years for men (Peeters *et*

al., 2003:31).

Younger adults generally have a greater expected number of years of life lost (YLL) due to overweight and obesity than older adults. This effect is also more pronounced among men. For example, Fontaine *et al.* (2003:192) showed a maximum YLL of 13 years for men aged 20-30 years with a severe level of obesity (BMI >45 kg/m²), representing an approximate 22% reduction in the expected remaining lifespan of a man. Women of the same age and BMI category in this study lost 8 years due to obesity. Based on prediction, current adolescent overweight will result in 161 million life-years complicated by obesity, diabetes mellitus or CHD and 1.5 million life years lost (Lightwood *et al.*, 2009:2235).

The significant cost of obesity is largely due to associated co-morbidities (Owens, 2003:163), functional limitations and disabilities (Alley & Chang, 2007:2025). By reducing the incidence and severity of obesity, the indirect costs attributed to obesity may also be reduced besides the risk in health disease. For example:

- The risks of co-morbidities may reduce (Anderson & Konz, 2001:332S).
- Quality of life improves (Halford, 2006:8; Karlsson *et al.*, 1998:124).
- There is a reduction in the number of days of sick leave (1.4 to 2.4 times) (Karason *et al.*, 2000:1800; Van der Merwe, 2007:5).
- Total cost of loss of productivity reduces (Van der Merwe, 2007:5).
- Disability pension reduces (1.5-2.8 times) (Van der Merwe, 2007:5).

With regard to clustering of cardiovascular risk factors typically found in patients with the metabolic syndrome, estimates from the Scottish Intercollegiate Guidelines Network (2011) indicated a 10 kg body weight loss could increase HDL-cholesterol by 8% whilst reducing systolic and diastolic blood pressure by 10 mmHg and 20 mmHg respectively, fasting plasma glucose by 50%, total cholesterol by 10%, LDL-cholesterol by 15%, and triglycerides by 30%.

2.9.1.5 Treatment of elevated waist circumference/obesity

A number of potentially effective weight loss interventions were identified for the reduction of weight in the US, including: (1) diet, (2) exercise, (3) behavioural strategies, (4) the foregoing three interventions in combination, (5) restricted use of pharmaceutical interventions in conjunction with strategies to alter lifestyle, and (6) surgery for certain morbidly obese individuals (Roux *et al.*, 2006:1093; Whitlock *et al.*, 2010:e399). Similar interventions were proposed by the Southern African Society for the Study of Obesity (Van der Merwe, 2007) for use in the treatment of adults in South Africa by medical and other health care practitioners (refer to Figure A.1 and Table A.1, Annexure A for algorithm). Guidelines for the treatment of

obesity in South African pre-adolescent children without complications (aged 2-7 years) furthermore propose a slowing down in the rate of weight gain (Department of Health, 2003a:10). Weight loss may also be indicated in pre-adolescents whose weight-for-age or BMI is >95th percentile and who have complications (Department of Health, 2003a:10). The recommended treatment for children and adolescents includes a moderately reduced calorie intake whilst maintaining a well-balanced diet (Pacifico *et al.*, 2011:456). Physical activity in children should also be increased. The ultimate goal of effective weight loss methods in adults (i.e. to have measurable effects on outcomes) is to reduce body weight by 7-12% over a 6- to 12-month period, followed by a long-term alteration of behaviour and maintenance of increased physical activity (Banning, 2005:165; Orzano & Scott, 2004:362).

2.9.1.5.1 Dietary advice, exercise and behavioural therapy

Dietary interventions for obesity are intended to create a negative energy balance (i.e. calories ingested should be less than calories expended) by reducing daily energy intake below energy requirements - the greater the energy deficits, the greater the weight loss (Fabricatore & Wadden, 2003:70).

There is some controversy surrounding which diets are the most effective for weight reduction - those that emphasise protein, those that emphasise carbohydrates or those that emphasise fat. Low-calorie diets (LCDs) are diets designed to create energy deficits of 500-1 000 kcal/day (Orzano & Scott, 2004:363), whereas very-low-calorie diets (VLCDs) are diets that provide 200-800 kcal/day, with large amounts of protein (70-100 g/day) to preserve lean body mass (Wadden & Osei, 2002:229). Low-calorie diets induce a weight loss of 0.5-1 kg/week (Orzano & Scott, 2004:363), whereas very-low-calorie diets produce weight losses of 15-25% in 8- to 16 weeks (Wadden & Osei, 2002:229). Very-low-calorie diets are usually recommended for patients with a BMI ≥ 30 kg/m² who have failed to lose weight using an LCD (Wadden & Osei, 2002:229) or for those whose weight is 35% more than that expected (Tsai & Wadden, 2006:1285). Combined evidence from several studies (Cox *et al.*, 2003:114; Dansinger *et al.*, 2005:51; Ross *et al.*, 2004:797) suggests that each kilogram of weight loss due to calorie restriction is associated with approximately 1 cm reduction in waist circumference. Larger decreases in calorie intake will therefore generally report greater reductions in waist circumference alongside larger decreases in body weight and ultimately alleviate all risk factors associated with the metabolic syndrome. In a recent comparison of weight-loss diets with different compositions of fat, protein and carbohydrates, Sacks *et al.* (2009:871), however, suggested that any type of diet could be effective in the elevation of obesity when non-nutritional influences were minimised. Janiszewski *et al.* (2008:101) were likewise of the opinion that the reduction in abdominal obesity is influenced primarily by dietary adherence and the duration and

severity of calorie restriction, rather than dietary composition.

Nonetheless, according to Hanefeld and Schaper (2005:389) the probability of long-term success increases significantly if the reduction in weight can be sustained over a longer period of time (e.g. more than 2 years). A mean weight loss of 10% of total body weight over a 1-year period also reduces the probability of weight regain (Wing & Hill, 2001:340). Diet alone achieves a greater weight loss compared with physical activity alone, whereas increased physical activity alone is associated with maintaining weight loss better than diet alone (Skender *et al.*, 1996:344; Vuori, 2004:29).

Behavioural therapy usually consists of behaviour modification directed towards diet and exercise, and involves the counselling of the patient regarding stimulus control, goal setting, cognitive restructuring, self-monitoring and contracts to reward behaviour (Foster, 2003:275; Hanefeld & Schaper, 2005:385; Poirier *et al.*, 2006:971). This approach typically yields a 10% reduction in body weight during the first 6 months of treatment (Foster, 2003:275). Without continued contact, patients normally regain one-third of their weight within 1 year and usually experience a total regain within 5 years (Wadden & Foster, 2000:441). Physician counselling plus weekly or bimonthly counselling from other professional counsellors may be the most effective behavioural therapy method (McTigue *et al.*, 2003:947; Pignone *et al.*, 2003:90).

A systematic review evaluating the major commercial weight loss programs in the US indicated that most diets are associated with high costs and attrition rates (Tsai & Wadden, 2005:64). Based on findings from Orzano and Scott (2004:363), nine patients would require dietary treatment for one patient to successfully lose and maintain a 10-pound (~4½ kilogram) decrease in weight. Their analysis also showed that exercising only would require “treating” 17 patients to effectively have one patient lose and maintain this decrease in weight compared with diet alone. The combination of diet and exercise (in comparison to both alone), required only seven patients to treat to effectively have one patient lose and maintain this decrease in weight (Orzano & Scott, 2004:364). In addition, Roux and co-workers (2006:1099) proved a three-component intervention of diet, exercise and behaviour modification more cost-effective than a regimen of diet and pharmacotherapy alone. In situations where a calorie-reduced diet and lifestyle changes do not promote weight loss after 12 weeks, the use of anti-obesity agents as an adjunct to diet and exercise modification should be considered (O’Connell, 2004:116, SASSO, 2001:19).

2.9.1.5.2 Pharmacotherapy of elevated waist circumference/obesity

Obesity is considered more an underlying risk factor that should be treated with diet and lifestyle

change. However, most guidelines and consensus documents universally recommend the use of pharmacological agents as adjunctive therapy whenever an adult patient has a BMI greater than 30 kg/m² and fails to achieve weight loss with diet and exercise alone (Coutinho, 2009:263). In the presence of associated conditions such as type 2 diabetes, hypertension and dyslipidaemia, the cut-off point for the pharmacological treatment recommendation is further lowered to 27 or even 25 kg/m² (NIH, 1998:70). However, no pharmacological agent has been shown safe and effective for use in children and adolescents (Pacifico *et al.*, 2011:456).

Monotherapy with weight reduction products has not been particularly effective for the treatment of obesity in adults. For example, dinitrophenol, an uncoupler of mitochondrial oxidative phosphorylation, showed severe toxicity (Harper *et al.*, 2001:255), whereas amphetamine-like agents had addictive properties (Kolanowski, 1999:119). Fenfluramine, a racemic compound, and dexfenfluramine its dextrorotary stereoisomer that stimulate the release of serotonin, were also withdrawn from the market because of serious adverse events such as cardiac valvular fibrosis and pulmonary hypertension (Kolanowski, 1999:119; Yanovski & Yanovski, 2002:591). Comparable complications had been encountered earlier with aminorex (an indirect sympathomimetic agent) (Fishman, 1999:159; Rothman *et al.*, 1999:873).

Although there are several approaches to obtain an anti-obesity effect, agents generally prescribed for weight loss can be divided into two categories based on their presumed mechanisms of action, i.e. centrally acting (agents that suppress appetite, increase satiety, or increase thermogenesis), or peripherally acting (agents that block intestinal fat absorption) (Hofbauer *et al.*, 2007:567; Li *et al.*, 2005:533). Peripherally acting agents currently available include orlistat and cetilistat (lipase inhibitors). Central acting agents can be further sub-divided based on the neurotransmitters they affect into noradrenergic agents (i.e. benzphetamine, diethylpropion and phentermine - that increase levels of norepinephrine), serotonergic agents (i.e. dexfenfluramine and fenfluramine) and agents with combined serotonergic, noradrenergic and dopaminergic action (i.e. sibutramine) (Dunican *et al.*, 2007:1445).

At least two medications have been approved for the long-term management of obesity and overweight (up to 2 years), namely orlistat and sibutramine (Klein, 2004:163S; SASSO, 2001:19). Both these agents have been shown to produce weight losses of 5-10% in body mass at two years (Halford, 2006:9). Sibutramine, though, has since been withdrawn from the American market because of increased cardiovascular risk (FDA, 2010b; Hitt & Wood, 2010).

A recent systematic review of economic evaluations of weight loss products comparing incremental cost-effectiveness ratios (Neovius & Narbro, 2008:1761) showed that orlistat and sibutramine are within the range of what is generally regarded as "cost-effective". Short

discussions on orlistat and sibutramine, and other medicine and new developments used for the treatment of obesity follow in the subsequent sub-section. A brief discussion on bariatric surgery is also presented.

- **Orlistat**

Orlistat - a potent selective inhibitor of pancreatic, carboxyl ester and gastric lipases, acting locally in the gut lumen – is currently the only lipase inhibitor approved for weight loss in adults (Curran & Scott, 2004:2847). The efficacy of orlistat to induce a 1-year weight loss of 5% in adults in excess of placebo has been evaluated in various studies *inter alia* Guy-Grand *et al.* (2004:381) and Hertzman (2005:1018). Studies by Sjöström *et al.* (1998:170) and Davidson and Hauptman *et al.* (1999:240) furthermore showed that four patients needed to be treated with orlistat to achieve this 5% reduction in weight. Orlistat furthermore enhances reductions in waist circumference of 7-9 cm (Wirth, 2004:21). Several recent studies have also established efficacy in weight reduction among obese adolescent and paediatric populations, *inter alia* Chanoine *et al.* (2005:2882), Czernichow *et al.* (2010:156), Dunican *et al.* (2007:1449), Kanekar and Sharma (2010:106), Ozkan *et al.* (2004:739), Whitlock *et al.* (2010:e416) and Rogovik *et al.* (2010:344). The FDA approved orlistat in 2003 for obesity treatment of US patients aged 12 to 16 years, based on the results of the study by Chanoine and co-workers (2005:2882). In addition, orlistat treatment lowers heart rate, systolic and diastolic blood pressure, dyspnoea and glycaemia successfully and improves atherogenic dyslipidaemia (Cocco *et al.* 2005:68, Dimitrov *et al.*, 2005:127; Griffith, 2007; Rissanen *et al.*, 2003:108). Rucker *et al.* (2007:1197) also indicated a significantly reduced waist circumference, BMI and HbA_{1c} concentrations in patients with diabetes, high total cholesterol, LDL-cholesterol and low HDL-cholesterol concentrations. Similar findings were also reported in the XENDOS trial (Torgerson *et al.*, 2004:160), suggesting that orlistat might also be effective in the treatment of obesity in patients with the metabolic syndrome. Data from studies by Kelley *et al.* (2002:1036) and Berne (2005:616) furthermore indicated a significantly reduced requirement of hypoglycaemic medication (respective to placebo) after orlistat treatment.

According to Iannazzo and co-workers (2008:63), orlistat shows a good pharmacoeconomic profile, in particular, the strategy of a screening programme to identify and treat patients with impaired glucose tolerance. In their study Iannazzo *et al.* showed that the programme had a cost-utility value of about €10,000/QALY. Lacey *et al.* (2005:975) studied the cost-effectiveness of a 1-year orlistat treatment plus a calorie-controlled diet, compared with a calorie-controlled diet alone among overweight or obese Irish adults without diabetes, showing that after one year, the incremental cost per year was €478 compared with diet alone, with a number needed to treat to gain one QALY estimated at 35. From a health system perspective, the incremental

cost per QALY gained, was within the range considered cost-effective at €16,954 (Lacey *et al.*, 2005:979). In a similar study, Hertzman (2005:1009) analysed the cost-effectiveness of orlistat among Swedish patients without type 2 diabetes mellitus. The outcomes of this study showed an incremental gain in QALY of 3.04 at an additional cost of \$5,187 for 100 average orlistat-treated patients.

The main adverse effect of orlistat is related to gastro-intestinal disturbances (Choussein *et al.*, 2009:653; Klein, 2004:165S). Post-marketing reviews, though, show rare cases of severe liver damage with orlistat (FDA, 2010a). The rate of serious adverse effects attributable to orlistat could be as high as 2-3 per 10 000 (Li & Maglione *et al.*, 2005:537; Shekelle *et al.*, 2004).

- **Sibutramine**

Sibutramine – a derivative of the amphetamine precursor β -phenethylamine – exhibits its pharmacological action by selectively inhibiting the serotonin and norepinephrine re-uptake by the presynaptic nerves (Dunican *et al.*, 2007:1445; Klein, 2004:163S), thereby increasing satiety and reducing appetite (Halford *et al.*, 2010:107). In addition, it enhances satiety signals and potentiates energy expenditure by stimulating thermogenesis *via* an increase in efferent sympathetic activity (Karthikeyan & Niveditha, 2009:72).

Sibutramine-treated patients are three times more likely to achieve a 5-10% weight loss than placebo-treated patients who received the same diet and exercise advice (Hansen *et al.*, 1999:1018). Product-associated weight loss with sibutramine also enhances reductions in waist circumference; for example, treatment has consistently reduced waist measurements by 3-10 cm more than that of diet alone, which corresponds with a reduction of 500-1 000 g in intra-abdominal adipose tissue (Day & Bailey, 2002:392). Therapy with sibutramine would require eight patients to treat with the 10 mg dose, compared with four patients with the 15 mg dose to achieve a 10% reduction in body weight (Smith & Goulder, 2001:510). According to Fabbrini and Klein (2008:43), intermittent therapy with sibutramine may be just as effective as continuous daily therapy in achieving weight loss. Weight regain, however, occurs rapidly once treatment is stopped (James *et al.*, 2000:2123). Sibutramine has also been evaluated for use in adolescents. Based on an analysis by Dunican and co-workers (2007:1450), sibutramine significantly reduced weight up to 5.6 kg/m² from baseline in overweight adolescents. Sibutramine furthermore significantly reduces fasting plasma glucose, insulin and triglyceride levels in severe obese patients (compared with placebo plus dietary intervention) (Arterburn *et al.*, 2004:1001; Barkeling *et al.*, 2003:699; Viner *et al.*, 2010:600).

Common adverse effects of sibutramine include a dry mouth, constipation, insomnia and an

increase in heart rate and blood pressure (Tziomalos *et al.*, 2009:450). According to Arterburn *et al.* (2004:1001) a dose of 10 mg/day to 15 mg/day increased heart rate by approximately 4 to 6 beats/minute and increased both diastolic and systolic blood pressure by about 2-4 mmHg, respectively. This rate of serious adverse effects with sibutramine could be as high as eight (Shekelle *et al.*, 2004) to 15 per 10 000 individuals (Arterburn *et al.*, 2004:1001). Recent findings from the Sibutramine Cardiovascular Outcome (SCOUT) trial (James *et al.*, 2010:915) demonstrated a 16% increase in the risk for serious heart events, including non-fatal heart attack, non-fatal stroke, the need to be resuscitated once the heart stopped and death, in a group of patients given sibutramine, compared with placebo. Based on the results of the SCOUT Trial, the advisory committee for the European Medicines Agency recommended suspension of marketing authorisation of sibutramine within the European Union (Hitt & Wood, 2010), whereas the FDA withdrew the product from the US market on October 8th, 2010 (FDA, 2010b). Sibutramine was withdrawn voluntarily from the South African market in October 2010, but reintroduced in 2011 under the brand name CiplatrimTM.

O'Meara *et al.* (2002:78) estimated the cost-effective ratios (CERs) of using sibutramine for treating obese patients without co-morbidities for one year at \$8,400/QALY. Warren *et al.* (2004:17) furthermore determined the cost per quality-adjusted life year (QALY) of 1 year's treatment with sibutramine combined with diet and lifestyle advice at an incremental cost per QALY of £4,780.

- **Other medicine and new developments**

A number of older therapeutic agents (of which most belong to the class of sympathomimetic agents) are still available for short-term use in the treatment of obesity, i.e. benzphetamine, diethylpropion, phendimetrazine and phentermine [anorectic agents that stimulates norepinephrine (and possibly dopamine) release], and mazindol (an anorectic agent that blocks norepinephrine reuptake, stimulate thermogenesis and delay gastric emptying) (Haddock *et al.*, 2002:262; Moyers, 2005:950). The appetite-suppressing effects of these agents tend to diminish after a few weeks and they are therefore only useful as an adjunct treatment during the first few weeks of a weight loss programme (Rossiter, 2010:67). Moreover, Haddock *et al.* (2002:268) examined 108 studies of pharmacotherapy for obesity collected from the 1950s to illustrate the efficacy of anorexic products. According to this review by Haddock and colleagues, no agent included in the study (i.e. amphetamine, dexamphetamine, benzocaine, benzphetamine, dexfepramine, diethylpropion, fenfluramine, fluoxetine, mazindol, methamphetamine, phendimetrazine, phentermine, phenylpropanolamine, or sertraline), produced a weight loss in excess of 4% (around 1 BMI point) above and beyond the placebo over a year. Haddock and co-workers furthermore found that "no drug, nor class of drug,

demonstrated any clear superiority over any other”.

Numerous over-the-counter products, including homeopathic preparations, are available for weight reduction in various countries. These products are widely used despite inadequate documentation of their safety and efficacy (Dulloo, 2004:405; Greenway & Heber, 2004:329). The majority of non-prescription (OTC-) products available for suppressing appetite contain amphetamine-like substances, usually norpseudoephedrine or other ephedrine derivatives or phenylpropanolamine (Rossiter, 2010:67). These amphetamine-like agents have been shown to be more effective than placebos in promoting weight loss; however, long-term weight loss has not been demonstrated unless these agents are taken continuously (Bray, 1993:711). Major symptoms and adverse effects may include heart palpitations, anxiety, insomnia, light-headedness, nausea, dizziness, dry mouth, mood changes, irritability and raised blood pressure (Westfall & Westfall, 2007). Products containing pseudoephedrine, d-norpseudoephedrine and ephedrine have subsequently been reclassified and rescheduled in South Africa to Schedule 6 status in 2008, i.e. available *via* a prescription only (MCC, 2008).

Other new developments that enhance energy expenditure (e.g. therapeutic agents that cause energy uncoupling in muscle) also used for the treatment of obesity include: 3-adrenoceptor agonists, thyroid hormone receptor β -subtype agonists, 5-HT_{2c} receptor agonists such as lorcaserin (Astrup, 2010:289), melanin concentrating hormone 1 (MCH-1) antagonists, metformin, peroxisome proliferator-activated receptor-gamma agonists (PPAR γ) agonists such as pioglitazone (Desilets *et al.*, 2008:824), and agents that reduce gastric emptying such as pramlintide (Nisoli & Carruba, 2004:463), liraglutide and exenatide (Cannon & Kumar, 2009:63). Cetilistat, a novel benzoxazinone inhibitor of gastro-intestinal and pancreatic lipases still under development, also produced a clinically and statistically significant weight loss in obese patients over a 12-week period (Kopelman *et al.*, 2007:497). The Food and Drug Administration furthermore approved orlistat 60 mg capsule (ALLI®) as a weight loss aid for over-the-counter marketing in the US in February 2007 (CDER, 2007). ALLI® also became available as OTC product in South Africa in 2010 (Anon., 2010b:58).

- **Bariatric or weight reduction surgery**

Individuals with morbid obesity, unmanageable by other weight-reduction interventions are usually treated by bariatric or weight reduction surgery (Orzano & Scott, 2004:365). This type of surgery involves restriction procedures (e.g. gastric banding and vertical gastropasty) to reduce the absorption of food, or bypassing procedures (e.g. Roux-en-Y or biliopancreatic diversion) to eliminate the presence of food in the proximal small intestine (Encinosa *et al.*, 2005:1039; Poirier *et al.*, 2011:1685). Patients with a BMI of more than 40 kg/m² or a BMI of 35-39.9 kg/m²

with obesity-related medical co-morbidities are eligible for surgical treatment (NIHCDCP, 1991:956; Zalesin *et al.*, 2010:114).

Although surgical treatments for obesity are associated with a risk for peri- and post-operative complications such as wound infections, breakdown of the surgical wound site and abdominal wall hernia (Banning, 2005:166), they commonly realise more profound and long-lasting weight loss and improve or resolve most co-morbidities of severe obesity. For example, Encinosa *et al.* (2005:1039) and Lee *et al.* (2004:1090) showed that bariatric surgery in patients with the metabolic syndrome achieves permanent (follow-up of more than 14 years) and significant weight loss (above 50% of excess body weight) in more than 90% of patients. A meta-analysis by Buchwald *et al.* (2004:1728) indicated an average weight loss of 60% of excess weight (or 23-28 kg more) (at a two-year follow-up) compared with individuals using conventional methods. Gastric bypass surgery furthermore improved (if not resolved) essentially all the metabolic complications classically associated with mortality in obese patients (Schauer *et al.*, 2000:517; Vogel *et al.*, 2007:225). For example, gastric bypass surgery produces

- a 96% improvement in dyslipidaemia (resolution in 63%);
- an 88% improvement in hypertension (resolution in 70%);
- a 100% improvement in diabetes (return to normoglycaemia without medication in 82%), and
- a 93% improvement in sleep apnoea (resolution in 74%) (Schauer *et al.*, 2000:517).

A life expectancy benefit model of gastric bypass surgery developed by Pope *et al.* (2006:268) predicted that gastric bypass surgery, for 40 year-old females with a BMI of 40 kg/m², would increase life expectancy by 2.6 years (~7%), from 36.2 years to 38.7 years. Life expectancy for 40-year-old male patients with a BMI of 40 kg/m² would increase by 3.3 years from 29.1 to 32.4 years. Systematic reviews furthermore concluded that weight-loss surgery was a cost-effective intervention calculated at fewer than US\$50,000/QALY (Salem *et al.*, 2005:276), with equivocal outcomes between the different types of surgery (Avenell *et al.*, 2004:159; Clegg *et al.* 2003:1175; Picot *et al.*, 2009:iv). According to Orzano and Scott, (2004:366) gastric bypass surgery provided a greater weight loss than other treatments with number needed to treat values of two and three per individual, respectively. Surgical management is therefore more costly than non-surgical management, but provides improved outcomes.

2.9.1.6 Summary of elevated waist circumference/obesity

Obesity is an independent risk factor for hypertension and dyslipidaemia as well as cardiovascular disease, which is the major cause of death in individuals with diabetes. Overweight and obesity are also strongly linked to the development of type 2 diabetes and can

complicate its management.

There is a dramatic increase in the prevalence and incidence of overweight (BMI >25 kg/m²) and obesity (BMI >30 kg/m²) throughout the world, with high prevalence rates in South Africa (refer to section 2.9.1.2). The prevalence of obesity is thus a necessary component of strategies to prevent not only heart disease and stroke but their major risk factors as well (Caterson *et al.*, 2004:e478).

In the early 1990s, Weintraub (1992:642) suggested that obesity needed to be treated more as a chronic condition that might need prolonged use of medications (long term weight management) for appropriate control. Several other researchers share this opinion *inter alia* Meyer *et al.* (2006:15), Moyers (2005:957) and Bartlett (2003:36). According to South African researchers, Kruger *et al.* (2005:496) and Van der Merwe (2007:9), this would reduce the need for other products that are often prescribed for the complications of obesity, such as analgesics, lipid lowering, antihypertensive and oral antidiabetic agents. Effective treatment of obesity will also improve all risk factors associated with the metabolic syndrome, subsequently reducing the risk for type 2 diabetes and CVD risk (Padwal & Majumdar, 2007:71) (refer to section 2.9.1.5). A reduction in obesity would furthermore bring about significant benefits in monetary terms for health care expenditure (refer to section 2.9.1.4).

Obesity in children, adolescents and adults should essentially be treated with diet and lifestyle change (refer to paragraph 2.9.1.5.1). Still, whenever an adult patient has a BMI greater than 30 kg/m² and fails to achieve weight loss with diet and lifestyle change, or has co-morbid conditions such as type 2 diabetes, hypertension and dyslipidaemia, adjunctive therapy with pharmacological agents may be necessary (refer to paragraph 2.9.1.5). Among the anti-obesity agents, orlistat have been shown relatively cost-effective and potentially effective in the treatment of obesity in patients with the metabolic syndrome. Weight loss surgery results in substantial weight loss (McDonald, 2007:1109), but is more costly than non-surgical management (refer to paragraph 2.9.1.5.2).

2.9.2 (Atherogenic) dyslipidaemia

Elevated triglycerides and small, dense LDL-particles are considered emerging risk factors for the metabolic syndrome, whereas elevated LDL-cholesterol and low HDL-cholesterol levels are considered major risk factors (Grundy, 2006a:2596). A discussion concerning the classification, prevalence and risk for (atherogenic) dyslipidaemia for metabolic syndrome, diabetes and CVD is provided here. A discussion on the treatment of (atherogenic) dyslipidaemia ensues in paragraph 2.9.2.5.

2.9.2.1 Definition of (atherogenic) dyslipidaemia

The term dyslipidaemia is an umbrella term referring to a “*clinically significant alteration in the circulating complexes of lipids and proteins known as lipoproteins predisposing to coronary heart disease and related disorders*” (Berger & Marais, 2000:164). According to Goldberg (2008), dyslipidaemia has been coined to define subjects with isolated high levels of LDL-cholesterol, or triglycerides, or low HDL-cholesterol. “Hyperlipidaemia” accentuates an excess amount of lipids, whereas “hypercholesterolaemia” refers to a high level (i.e. ≥ 5 mmol/L) of plasma cholesterol (Butler, 2009:28). A short description of each of the different types of lipoproteins is depicted in Table 2.6.

Table 2.6: Lipoprotein concentrations and classification (compiled from Department of Health, 2003b; Miller *et al.*, 2011:2318; NIH, 2002:3164 and Schwinghammer, 2009:101)

Lipoprotein	Concentration	Classification
Total cholesterol	<4.5 mmol/L (175 mg/dL)	Optimal
	4.5 – 6.1 mmol/L (175-239 mg/dL)	Borderline-high
	≥ 6.2 (240 mg/dL)	High
LDL-cholesterol	<2.6 mmol/L (100 mg/dL)	Optimal
	2.6 - 3.3 mmol/L (100-129 mg/dL)	Above-optimal
	3.4 - 4.1 mmol/L (130 to 159 mg/dL)	Borderline high
	4.2 - 4.9 mmol/L (160 to 189 mg/dL)	High
	>5.0 mmol/L (190 mg/dL)	Very high
Serum triglycerides	<1.2 mmol/L (100 mg/dL)	Optimal
	<1.7 mmol/L (150 mg/dL)	Normal
	1.7 - 2.2 mmol/L (150 to 199 mg/dL)	Borderline high
	2.3 - 5.7 mmol/L (200 to 499 mg/dL)	High
	>5.7 mmol/L (500 mg/dL)	Very high
HDL-cholesterol	<1.0 mmol/L (40 mg/dL)	Low
	≥ 1.6 mmol/L (60 mg/dL)	High

Non-HDL-cholesterol is defined as the difference between total cholesterol and HDL-cholesterol (Wagner *et al.*, 2003:2048) or simply the sum of LDL-cholesterol and VLDL-cholesterol (Havel & Frost, 2000:2105). Non-HDL-cholesterol approximates the concentration of apolipoprotein (Apo) B (Talbert, 2003:S5), lipoprotein(a), IDL and VLDL remnants (Cui *et al.*, 2001:1414), thus encapsulating the total risk from atherogenic lipoproteins in patients with the metabolic syndrome in whom LDL-cholesterol and triglycerides concentrations are modestly elevated (Sattar *et al.*, 2004:2688). Non-HDL-cholesterol treatment goal is 20 mg/dL (Havel & Frost, 2000:2107) to 30 mg/dL (Szapary & Rader, 2004:212) above a patient’s LDL-cholesterol goal.

Insulin-resistant states, such as type 2 diabetes and the metabolic syndrome, are associated with a distinctive atherogenic profile, designated as the “atherogenic lipoprotein phenotype” or

“atherogenic dyslipidaemia” (Athiros *et al.*, 2011: 24; Haffner *et al.*, 2000:977; Kolovou *et al.*, 2005:360). This phenotype is characterised by the following components:

- A borderline high-risk for small, dense LDL-cholesterol [130-159 mg/dL (3.4-4.1 mmol/L), lipid-depleted LDL].
- Moderately raised (often-high normal) triglycerides [$\geq$ 150 mg/dL (1.7 mmol/L)].
- Low HDL-cholesterol (especially HDL₂ cholesterol) below 40 mg/dL (1.0 mmol/L).
- Raised apolipoprotein A-1 and apolipoprotein B-100 levels (Grundey & Brewer *et al.*, 2004:434; Hayden, 2006:168; Kathiresan *et al.*, 2006:27).

2.9.2.2 Prevalence and epidemiology of (atherogenic) dyslipidaemia

The prevalence of dyslipidaemia fluctuates according to study population and the definition of dyslipidaemia used. This prevalence is in general highest in patients with premature CHD (i.e. clinically evident disease occurring before 55 years of age in men and before 65 years in women) (Rosenson *et al.*, 2010). For example, in the early 1990s Genest *et al.* (1992:2031) showed the prevalence of dyslipidaemia to be as high as 80-88% in patients with coronary disease compared with approximately 40-48% in age-matched controls without CHD. Similar findings were reported more recently by Steinhagen-Thiessen and co-workers (2008).

Approximately 80% of the world's population has suboptimal levels of total serum cholesterol (i.e. in excess of 150 mg/dL) (Vasan *et al.*, 2008:35). Findings from the 2005-2006 NHANES suggest an overall prevalence for high LDL-cholesterol of 21.2% in the US population, compared with 9.4% for low HDL-cholesterol (Kuklina *et al.*, 2009:2106). According to the United States National Center for Health Statistics (2009:7), 24% of women, aged 65-74 years had high serum cholesterol levels in 2005-2006, compared with 11% among their male counterparts. Similar findings were reported in the 2010-Health Statistics for the United States (NCHS, 2011:25).

In general, approximately 10% of adolescents aged 12-19 years have abnormal cholesterol levels (with cholesterol levels higher in females than in males). As both sexes age, LDL-cholesterol rises, with less severe levels experienced in males. Triglyceride concentrations also continuously increase throughout puberty (i.e. in those 11-14 years of age) (Bertrais *et al.*, 2000:320). At the age of 55 years, women's LDL-levels exceed that of men. Regardless of gender, males older than 45 years and females older than 55 years have increased levels of high cholesterol risk (Irons *et al.*, 2002:1616).

Dyslipidaemia is also quite common in westernised, industrialised, (and developing) communities such as South Africa. Over a decade ago, Steyn *et al.* (1996:482) estimated the

overall prevalence of familial hypercholesterolaemia in South Africa as 1:72 compared with 1:500 worldwide. Later in 1998, a survey of 200 private practices across the country described the detection and management of hypercholesterolaemia in about 13 000 patients (Steyn *et al.*, 1998:1572). More recently, Maritz (2006:101) calculated the total number of South Africans (30 years and older) with hypercholesterolaemia (cut off point for total cholesterol of 5 mmol/L or 193 mg/dL) in the region of 5.7 million people (~12% of the country's population in 2006). In contrast to general prevalence rates, Maritz also determined that the prevalence of hypercholesterolaemia was lower among females than in males in younger South African groups, equal in the middle age groups and higher in females in old age.

Atherogenic dyslipidaemia is more prevalent than isolated high LDL-cholesterol (Vega, 2004:525), affecting up to 60% of high-risk patients (Szapary & Rader, 2004:212). Findings from the recent HeartSCORE and IndiaSCORE studies (Mulukutla *et al.*, 2008:416) furthermore showed that there were significant population variations in atherogenic dyslipidaemia, for example, the prevalence of small-dense LDL-cholesterol and of TG/HDL ratio >3 was greatest among Asian Indians and smallest among patients from African descent. Compared with Caucasians, the adjusted odds for Indians having an atherogenic dyslipidaemic cholesterol pattern was 2.06 and TG/HDL ratio >3 were 9.42. The adjusted odds of having an atherogenic dyslipidaemic cholesterol pattern (OR, 0.39) or TG/HDL ratio >3 (OR, 0.41) was lower in patients from African descent compared with Caucasians.

Little is known about the prevalence of atherogenic dyslipidaemia in South African populations. Similar to the studies by Mulukutla and colleagues, Maritz (2006:101) indicated that a high TG/low HDL-cholesterol pattern of dyslipidaemia was also common in the South African Indian population. Maritz also calculated a high TG/low HDL-cholesterol ratio of dyslipidaemia in the coloured population of the Western Cape.

2.9.2.3 (Atherogenic) dyslipidaemia as risk factor

Dyslipidaemia is not only considered the hallmark of the metabolic syndrome (Ascaso *et al.*, 2011:177; Vinik, 2005:29) but is also widely recognised as an independent risk factor for cardiovascular disease (Blumenthal, 2005:S500; Genest, 2000:3A). Worldwide, 56% of ischemic heart disease mortality and disease burden were attributable to total cholesterol levels of more than 3.8 mmol/L, translating to 3.6 million deaths in the year 2000 (Lawes *et al.*, 2004:391). Estimates for that same year in South Africa (Norman, Bradshaw & Steyn *et al.*, 2007:712) showed that high cholesterol levels (≥ 3.8 mmol/L) caused 24 144 (95% CI: 22 404 - 25 286), or approximately 5% of all deaths in South Africa. Overall, approximately 29% of ischemic stroke and 59% of ischemic heart disease in adults older than 30 years were

attributable to a cholesterol level ≥ 3.8 mmol/L in 2000 (Norman, Bradshaw & Steyn *et al.*, 2007:712).

Elevated serum cholesterol, low HDL-cholesterol and hypertriglyceridaemia are furthermore autonomously (and significantly) related with myocardial infarction/stroke in patients with metabolic syndrome. According to Manninen *et al.* (1992:43) patients with triglyceride levels >200 mg/dL (2.3 mmol/L) and a LDL:HDL-cholesterol ratio $>5:1$ carried a 3.8-fold higher risk for cardiac events. Low HDL-cholesterol, in addition to high fasting glucose, has a primary predictive ability for coronary heart disease (Hsia, 2003:241).

Large-scale epidemiologic studies such as the Framingham study (Castelli *et al.*, 1986:2837), the Multiple Risk Factor Intervention Trial (MRFIT) (Stamler *et al.*, 1986:2826) and the Seven Countries study (Keys *et al.*, 1984:152) established an exponential relationship between higher cholesterol levels (and lower HDL levels) and the degree of atherosclerosis and CVD risk. The slope of this relation is greater among younger than older people, with a CVD risk for approximately 2% for each 1% raise in total cholesterol in patients of middle age (Boden, 2000:20L; Durrington, 2003:722). Middle-aged men whose serum cholesterol levels are in the highest quintile for age (above 230 mg/dL) thus have a 10% risk for coronary death before the age of 65; compared with men in the lowest quintile (below 170 mg/dL) (the latter have a risk for 3%). The cause of death from CHD before age 65 years is also less common in women, with equivalent risks one-third those of men (Baron, 2006a:1240).

Dyslipidaemia occurs commonly in patients with type 2 diabetes, increasing the risk for cardiovascular disease. For example, according to Nesto (2008:9) more than 50% of type 2 diabetics have a borderline-high to high total cholesterol. Results of the Botnia Study furthermore showed that the prevalence of low HDL-cholesterol in men and in women and/or elevated plasma triglycerides were up to three times higher in those with diabetes and two times higher in those with impaired fasting glucose, compared with those with normal glucose tolerance (Isomaa *et al.*, 2001:687). Two landmark studies, i.e. the MRFIT- (Stamler *et al.*, 1993:434) and the Seven Countries study (Keys *et al.*, 1984:152) demonstrated that increases in total cholesterol levels in patients with diabetes were coupled with an increase in the incidence of coronary artery disease. Although the slope of the relation between coronary artery disease mortality and cholesterol in individuals with diabetes is similar to that in individuals without diabetes (Wilson, 2001:879), the incidence of coronary artery disease in diabetics is increased 2- to 4-fold for any given rise in cholesterol level (Steiner, 2000:B51). The subsequent rate of atherogenesis is proportional to the severity of ambient risk factors including serum cholesterol levels (Vega, 2001:1109). The influences of the different lipoproteins on CVD and diabetes are briefly described in subsequent paragraphs.

2.9.2.3.1 Elevated serum triglycerides as risk factor

The atherogenic effect of the triglycerides can be attributed to the presence of triglyceride-rich lipoproteins that contain small, dense LDL particles and their remnants (i.e. VLDL and IDL). These particles contribute directly to the formation of arterial-wall foam cells (Grundey, 1998a:21B; Yuan *et al.*, 2007:1117).

Clinical trials provide evidence of a linear relationship between plasma triglyceride levels and cardiovascular disease (Ginsberg, 2001:1178; Sarwar *et al.*, 2007:456). A one mmol/L (38.7 mg/dL) increase in triglyceride levels significantly increases the relative risk for CAD by 30-32% in men and 75-78% in women (Austin *et al.*, 1998:8B; Cullen, 2000:947).

Hyperinsulinaemia or insulin resistance and obesity are, at least in part, responsible for increased hepatic VLDL triglyceride production (refer to section 2.8). Elevated levels of total plasma and very-low-density-lipoprotein triglyceride levels are also often observed in patients with type 2 diabetes (Taskinen, 1992:12; Vergès, 2010:358). These serum triglycerides in type 2 diabetics increase about 1.5-3 times that of gender, age and body weight matched non-diabetic controls (Shah & Karmarkar, 1991:27). Laakso *et al.* (1993:1421) furthermore indicated that high levels of total cholesterol (>2.3 mmol/L or 150 mg/dL) increased the risk for CHD death or all CHD events 2-fold in patients with non-insulin dependent diabetes.

2.9.2.3.2 Elevated LDL-cholesterol as risk factor

According to Jeppesen *et al.* (2006:373), the metabolic syndrome is associated with a similar risk for CVD when compared with a LDL-cholesterol level of more than 5.02 mmol/L (195.8 mg/dL). The positive relationship between serum cholesterol levels and the development of first or subsequent attacks of CHD occurs over a broad range of LDL-cholesterol levels, the higher the level, the greater the risk (Szapary & Rader, 2004:219). Accordingly, Baigent *et al.* (2010:1673), showed a 10% reduction in all-cause mortality per 1.0 mmol/L LDL reduction (RR, 0.90; 95% CI: 0.87 - 0.93) in a meta-analysis of 26 trials. This reduction in mortality largely reflected reductions in deaths due to coronary heart disease (RR, 0.80; 99% CI: 0.74 - 0.87) and other cardiac causes (RR, 0.89; 99% CI: 0.81 - 0.98).

Small dense LDL might also be more atherogenic than buoyant LDL because: (1) it is more toxic to the endothelium; (2) it is more able to transit through the endothelial basement membrane; (3) it adheres well to glycosaminoglycan; (4) it has increased susceptibility to oxidation; and/or (5) it is more selectively bound to scavenger receptors on monocyte derived macrophages (Carmena *et al.*, 2004:III-2; Gazi *et al.*, 2006; Hirano *et al.*, 2004:561). Moreover,

the total number of lipoprotein particles in the LDL-fraction is usually augmented in the presence of small LDL-particles and subsequently also the atherogenic potential (Blake *et al.*, 2002:1935).

According to Laakso (2002:59), newly or previously diagnosed type 2 diabetes patients usually have normal to slightly elevated total and LDL-cholesterol levels when compared with normoglycaemic controls. These are possibly ascribed to an elevation in VLDL in these patients (Vergès, 2010:358).

2.9.2.3.3 Low levels of HDL-cholesterol as risk factor

Low plasma HDL-cholesterol levels [35 mg/dL (0.9 mmol/L)] are independent risk factors for coronary heart disease (Muntner *et al.*, 2010:174). El Harchaoui and colleagues (2009:87-88) also established HDL- particle concentration as an independent CAD risk factor. According to Jacobs *et al.* (1990:37), a 10 mg/dL (0.3 mmol/L) decrease in HDL bestowed the same risk for CAD as 30 mg/dL (0.8 mmol/L) increase in LDL. Roze *et al.* (2006:2554) showed similar results in a health economic modelling study. The presence of high levels of LDL or increased plasma triglycerides amplify this risk for CHD attributable to a low level of HDL-cholesterol (Vega, 2001:1110). For example, in the Prospective Cardiovascular Munster (PROCAM) study population, authors showed that low HDL-cholesterol (in association with a cluster of risk factors, such as the metabolic syndrome) was associated with a risk that increased by 2- to 3-fold above the risk for isolated low HDL (Assmann & Schulte, 1988:1713). Majeed and Miller (2008:179) reported similar findings in a more recent review.

Women have, on average, HDL-cholesterol levels approximately 10 mg/dL (0.3 mmol/L) higher compared with those of men (Meagher, 2004:427). Each 1% increase in HDL-cholesterol is thus associated with a 2% reduction in the risk for CHD in men vs. a 3% reduction in women (Bays, 2003:358; Boden, 2000:20L). With menopause, though, LDL-cholesterol levels increase; this levels out the difference in risk for cardiovascular disease in different gender groups (Jackson, 2008:14; Vitale *et al.*, 2007:17).

The increased risk for CHD seen in patients with low HDL-cholesterol seems even more pronounced among patients with diabetes. For example, results of the United Kingdom Prospective Diabetes Study (UKPDS, 1998a:173) illustrated that the relative risk for CVD that accompanied a low HDL-cholesterol level in individuals with diabetes, increased by 1.15 for each 0.1 mmol/L (3.9 mg/dL) decrement in HDL-cholesterol. This reduction in plasma cholesterol can be ascribed to a decrease in HDL₂ subfraction (Laakso, 1997:138; Tovar & Schering, 2006:64).

In summary, although there is evidence that each component of the lipid triad (low HDL, small LDL-cholesterol particles and remnant lipoproteins) is individually atherogenic, the National Cholesterol Education Programme Expert Panel (NIH, 2002:3173) is of the opinion that the relative quantitative contribution of each cannot be determined. For this reason, the lipid triad should be viewed as a whole as a risk factor. The underlying mechanisms linking atherogenic dyslipidaemia to development of the metabolic syndrome were described in section 2.8.

2.9.2.4 (Atherogenic) dyslipidaemia disease burden

Dyslipidaemia is a significant contributor to cardiovascular morbidity and mortality in the industrialised world (Tovar & Schering, 2006:63). This impact ensures that dyslipidaemia carries a high cost in terms of human life and health care expenditures. For example, a higher-than-optimal blood cholesterol level can contribute to about 17% of deaths in a given population (Turley *et al.*, 2006:255), whilst the cost of not treating high levels of cholesterol can result in twice as higher cost of cardiovascular-related inpatient care and even significantly higher total care costs (Carlsson *et al.*, 2004:32). Severe hypertriglyceridaemia, *per se*, is associated with 33-38% greater medical costs per annum, independent of resource-intensive conditions such as cardiovascular disease, heart failure, hypertension and diabetes (Nichols *et al.*, 2011:227). The benefit of treating lipid disorders thus lies in the ability of lipid-lowering products to avoid costs associated with expensive health care resources such as hospitalisation or surgical procedures (Zowall & Grover, 2003:275). For example, data from the Scandinavian Simvastatin Study (4S) indicated the following reductions of health care resource consumption with lipid modifying treatment (Scandinavian Simvastatin Study Group, 1994:1383):

- Reduced hospitalisation for acute cardiovascular disease (including revascularisation) (i.e. 26%).
- Reduced hospitalisations for coronary heart disease events (32%).
- Reduced number of revascularisations (32%), and
- days spend in hospital for the above events (34%).

The 4S study furthermore indicated a significant reduction in the risk for all-cause- and coronary mortality associated with lipid modifying treatment, as well as a saving of seven myocardial infarctions for every four lives treated over a 6-year period (Scandinavian Simvastatin Study Group, 1994:1383). Stamler *et al.* (2000:316) furthermore determined that men with favourable baseline serum cholesterol levels had an estimated greater life expectancy of 3.8-8.7 years. A low LDL- and total cholesterol is therefore not only associated with an increased longevity, but also a better quality of life. Based on calculations by Norman, Bradshaw and Steyn *et al.* (2007:712) high cholesterol levels accounted for 222 923 or 1.4% of 16.2 million DALYs (95% CI: 1.3 - 1.4) in South Africa for the year 2000.

Cholesterol lowering agents (especially the statins) currently constitute some of the most dynamic segments of the total prescription medicine market in the world. In terms of retail expenditure by therapeutic category, total revenues of cholesterol-lowering agents exceeded US\$16.9 billion in 2010 (Kale *et al.*, 2011:1857). Based on the Mediscor Medicines' Review of 2010, cholesterol lowering agents featured among the top five therapeutic groups in the South African private health care market since 2004, accounting for 4.5% of medicine expenditure in 2010 (Badenhorst *et al.*, 2010:11).

2.9.2.5 Treatment of (atherogenic) dyslipidaemia

The South African lipid guidelines developed by the South African Medical Association and the Lipid and Atherosclerosis Society of South Africa (LASSA), are based on the revised American NCEP/ATP III guidelines for treatment of atherogenic dyslipidaemia (Raal *et al.*, 2004:53). Comparable interventions to the American guidelines are therefore proposed for use in the treatment of adults by South African medical and other health care practitioners (refer to Annexure A.2 for algorithm). The goals of the 2006-LASSA guidelines include:

- Recommending lipid lowering pharmacological treatment for patients with severe genetic dyslipidaemia, established vascular disease and for those at high risk for CVD (i.e. a 10-year risk for an acute coronary event $\geq 20\%$).
- A target^e for LDL-cholesterol of ≤ 2.6 mmol/L (2.5 mmol/L in patients at high risk of CVD and those with established disease).
- A target for total cholesterol < 4.5 mmol/L for those with severe genetic lipid disorders (< 5 mmol/L for asymptomatic, apparently healthy patients).
- A minimum target of at least a 45% reduction in LDL-cholesterol for those patients with severe dyslipidaemia but who were unable to meet the target of ≤ 2.6 mmol/L (Department of Health, 2003b; SAMA/LASSA, 2000:164).

The objectives of the South African lipid guidelines are thus to reduce the incidence of first or recurring events due to coronary heart disease, ischemic stroke and peripheral artery disease, by focusing on the prevention of disability and premature death. *Per se*, the guidelines deal with the role of lifestyle changes, the management of major cardiovascular risk factors and the use of prophylactic therapies in the deterrence of CVD.

The approach to the patient with atherogenic dyslipidaemia concentrates primarily on therapeutic lifestyle changes (TLC) (Szapary & Rader, 2004:212). Pharmaceutical interventions in conjunction with strategies to altered lifestyle should, however, be considered if lifestyle

^e The Council for Medical Schemes Guideline for the treatment of hyperlipidaemia was published in 2003 (Department of Health, 2003b). This guideline still uses the LDL cholesterol goal of < 3 mmol/L as the new guideline (with target goal of 2.6 mmol/L) is still awaiting approval (Van Schoor, 2010:47).

changes are not successful for those at high risk for developing CAD, or for those who currently have CAD, a CAD risk equivalent^f, or continual atherogenic dyslipidaemia (Tenenbaum *et al.*, 2006; Wild & Byrne, 2006:21). The treatment of dyslipidaemia in children and adolescents with metabolic syndrome focus primarily on behavioural change – i.e. weight management and exercise (Pacifico *et al.*, 2011:457).

2.9.2.5.1 Therapeutic lifestyle changes of (atherogenic) dyslipidaemia

A number of potentially effective therapeutic lifestyle changes (TLC) were identified for the reduction of atherogenic dyslipidaemia in patients with the metabolic syndrome or type 2 diabetes, including:

- A reduced intake of saturated fats and dietary cholesterol.
- An intake of dietary options to enhance lowering of low-density lipoprotein cholesterol [e.g. plant stanols/sterols and increased viscous (soluble) fibre].
- Weight reduction.
- Increased regular physical activity (Bays, 2003:358; Krauss *et al.*, 2000:2286; Meagher, 2004:428).

A short discussion on dietary modification as primary focus of TLC therapy to lower LDL-cholesterol, and weight reduction and physical activity as part of TLC therapy follows subsequently.

• Reduced intake of saturated fatty acids, trans-fatty acids and dietary cholesterol

Increases in LDL-total and cholesterol are closely associated with increased dietary intake of saturated fatty acids, trans-fatty acids and increased serum cholesterol (NIH, 2002:3260; Siri & Krauss, 2005:458).

Saturated (non-essential) fatty acids decrease LDL-receptor expression and as a result increase LDL-cholesterol levels (Kreisberg & Oberman, 2003:2449). Every 1% increase in total calories of dietary saturated fatty acids correlates to a 2% increase in LDL-cholesterol (Griel & Kris-Etherton, 2006:260). Equally, a 1% decrease in calories of dietary saturated fatty acids has been shown to decrease LDL-cholesterol with 2% (NIH, 2002:3261). In contrast to earlier studies indicating a positive correlation between saturated fat and the risk for CVD (e.g. Yu-Poth *et al.*, 1999:632), Siri-Tarino and co-workers (2010b:544) reported no significant evidence indicating that dietary saturated fat is associated with an increased risk for CHD or CVD.

^f Patients with CAD risk equivalents are considered to have the same 10-year CHD risk of a coronary event as patients who have established CHD. The patients thus qualify for the same insistent treatment (NIH, 2002:3143; Talbert, 2003:S4).

Substitution of saturated fat by monounsaturated fatty acids yields a modest reduction in both LDL- and HDL-cholesterol (Lichtenstein, 2003:112; Siri-Tarino *et al.*, 2010b:508). Substitution with polyunsaturated fatty acids (i.e. omega-3 fatty acids e.g. α -linoleic acid) yields an even higher decrease in LDL-cholesterol levels. Most omega-3 fatty acids derived from marine- and plant sources (i.e. dietary α -linoleic acid) are associated with a reduction in CHD mortality (Harris, 2005:375; Lee & Lip, 2003:477). The cardioprotective benefits may be attributed to prevention of arrhythmias, decreased thrombogenicity, and improved endothelial function and reduced triglyceride levels (Hartweg *et al.*, 2009:30; Kris-Etherton *et al.*, 2002:2747). Three to five grams of fish oil per day has also been shown to reduce triglyceride levels up to 30%.

Substitution of dietary carbohydrates with polyunsaturated or monounsaturated fats also show that the ratios of total- to HDL- and LDL-cholesterol decline (Mensink *et al.*, 2003:1148). For example, by substituting a 1% of energy in the form of saturated fatty acids with an equal percentage of monounsaturated or polyunsaturated fatty acids, HDL-cholesterol is lowered by 0.002 mmol/L (0.08 mg/dL). Equally, the ratio of total cholesterol to HDL- and LDL-cholesterol increases when carbohydrates are replaced with trans-fatty acids (Siri-Tarino *et al.*, 2010a:508). Trans-fatty acids are furthermore associated with a considerable increased risk for coronary heart disease. For example, a 2% increase in energy intake from trans-fatty acids is associated with a 23% increase in the incidence of coronary heart disease (Howard *et al.*, 2006:664; Mozaffarian *et al.*, 2006:1601).

- **Intake of dietary options to enhance lowering of LDL-cholesterol**

The NCEP/ATP III guidelines recommend plant stanols and sterols for patients with high serum cholesterol because these plant components have been shown to reduce LDL-cholesterol levels (NIH, 2002:3260). According to Vuorio *et al.* (2000:504), Lichtenstein and Deckelbaum, (2001:1178) and Hendriks *et al.* (2003:690) plant-derived stanols/sterol esters at dosages of 2-3 grams/day lower LDL-cholesterol levels by 6-15% with a maximum LDL-lowering effect occurring with dosages of 2 g/day. Plant sterols have also proved to be efficacious in lowering non-HDL-cholesterol (Lau *et al.*, 2005:1354).

A meta-analysis by Brown *et al.* (1999:35) indicated that diets high in fibre decreased total- and LDL-cholesterol. Results of this analysis also indicated that daily intake of 3 g soluble fibre could decrease total cholesterol by 0.129 mmol/L (5 mg/dL), or approximately 2%, correlating to 4% decrease in the incidence of coronary artery disease (Jenkins *et al.*, 2002:837). Anderson *et al.* (2000:477) furthermore reported a reduction in the ratio of apolipoprotein B to apolipoprotein A-1 by 6% in response to fibre intake adjunctive to dietary therapy.

- **Weight reduction and increased regular physical activity**

The NCEP/ATP III guidelines emphasise the treatment of overweight and obesity in patients as part of their LDL-lowering therapy to decrease the patient's risk for CHD (NIH, 2002:3190). A 12-week trial of dietary changes to reduce LDL-cholesterol is suggested before introducing weight-loss interventions as a means of reducing the risk for metabolic syndrome (NIH, 2002:3190).

According to Raal (2003:379) a patient who achieves and maintains ideal body weight ($\text{BMI} < 27 \text{ kg/m}^2$) following a prudent lipid-lowering diet, could experience an average reduction of up to 20% in LDL-cholesterol levels i.e. a decrease in LDL-cholesterol of 1-2 mmol/L (38.7-77.4 mg/dL). Foster *et al.* (2003:2088) furthermore showed that a low-carbohydrate, high-protein trial (i.e. the Atkins diet) consistently reduces triglycerides by up to 20% and in some cases raises HDL-cholesterol by 20%. In general, for every 4.5 kg of constant weight loss, triglycerides are decreased by 6 mg/dL (0.07 mmol/L) while HDL-cholesterol levels are increased by about 2 mg/dL (0.05 mmol/L) (Van Gaal *et al.*, 2005:L25).

Regular physical activity is also emphasised in the National Cholesterol Education Programme Guidelines because of its significance in the management of metabolic syndrome. This and other guidelines recommend that physical activity be introduced to dyslipidaemic patients when TLC therapy is initiated and to support the concept when treatment emphasis shifts to management of metabolic syndrome (NIH, 2002:3254; Kelly, 2010:1100). Increasing regular physical activity has been shown to reduce LDL-cholesterol levels, very low-density lipoprotein cholesterol and triglycerides by 4-5% and increase high-density lipoprotein cholesterol levels by approximately 5% (Durstine *et al.*, 2009:146).

Aerobic exercise, independent of weight loss, increases HDL-cholesterol levels modestly and reduces triglycerides in a dose-dependent manner. Patients with atherogenic dyslipidaemia furthermore derive greater benefit from aerobic exercise than those with isolated low HDL-cholesterol (Mestek, 2009:281; Szapary *et al.*, 2003:488). Endurance exercises on the other hand significantly decrease total cholesterol, triglycerides and LDL-cholesterol and decrease the particle concentrations for large, small and very small low-density lipoprotein particles. Endurance exercises moreover increase HDL-cholesterol by 3.3 mg/dL (0.09 mmol/L) (Halverstadt *et al.*, 2007:448).

Dietary approaches tend to lower total cholesterol, LDL-cholesterol and triglyceride levels, whereas exercise tends to raise HDL-cholesterol and decrease triglyceride levels. Combining these interventions may therefore render additive, or synergistic effects, and provides benefit to

the adult patient with atherogenic dyslipidaemia. Weight control and exercise are advocated for children as both these measure lowers plasma triglyceride levels successfully. They are, however, less effective in increasing HDL-cholesterol levels; a change in dietary composition (e.g. fat restriction) is thus promoted in children (Pacifico *et al.*, 2011:457).

2.9.2.5.2 Pharmacotherapy of (atherogenic) dyslipidaemia

The South African lipid guidelines are based on the revised American NCEP/ATP III guidelines for treatment of atherogenic dyslipidaemia (Raal *et al.*, 2004:53). The NCEP/ATP III recommend a two-step approach to cholesterol management – step one focuses on attaining the goal for LDL-cholesterol, whereas step two focuses on the management of the metabolic syndrome and other lipid risk factors (NIH, 2002:3247).

Step one of the management approach centres primarily around therapeutic lifestyle changes to attaining the goal for LDL-cholesterol (Szapary & Rader, 2004:212) (refer to section 2.9.2.5.1). Pharmaceutical interventions in conjunction with strategies to alter lifestyle in adults should be considered if lifestyle changes are not successful for those at high risk for developing CAD, or for those who currently have CAD, a CAD risk equivalent or continual atherogenic dyslipidaemia (Tenenbaum *et al.*, 2006; Wild & Byrne, 2006:21). No guidelines have been issued for the treatment of atherogenic dyslipidaemia in children; however, as reduction in LDL-cholesterol has been shown to prevent cardiovascular events in adulthood, treatment for children should primarily centre on lowering LDL-cholesterol (Pacifico *et al.*, 2011:457).

To achieve the goal for LDL-cholesterol in adults, treatment is generally initiated with a LDL-lowering agent (usually a statin, although bile acid sequestrants or nicotinic acid can also be used); dosages dependent on the baseline LDL-cholesterol level (NIH, 2002:3304). Doses should be maintained if the treatment goal has been achieved in about 6 weeks; otherwise, LDL-lowering therapy can be intensified, either by increasing the dose of the statin or by adding a bile acid sequestrant (NIH, 2002:3304).

In the presence of atherogenic dyslipidaemia, first-line therapy should focus on weight reduction and increased physical activity, with three classes of medicines - statins and nicotinic acid and fibrates as secondary line of treatment. Pharmacological treatment for atherogenic dyslipidaemia in childhood should be reserved for those older than the age of 10 years, who either have LDL-cholesterol levels persistently >190 mg/dL or have LDL-cholesterol levels >160 mg/dL and either a strong family history of premature CVD or two or more additional risk factors from: HDL-cholesterol <40 mg/dL, tobacco use, high blood pressure, obesity or insulin resistance (Pacifico *et al.*, 2011:457). The American Heart Association, the

Atherosclerosis, Hypertension, and Obesity in Youth Committee, the Council of Cardiovascular disease in the Young, and the Council on Cardiovascular Nursing furthermore advocate that pharmacological treatment be initiated at Tanner stage 2 in males or after the onset of menses in females (McGrindle *et al.*, 2007:1959).

According to Gryskiewicz *et al.* (2005:691) the variable that most significantly drives cost-effectiveness when a smaller decrease in LDL-cholesterol is required (less than 40%), is the cost of a product. When larger LDL-cholesterol reductions are required, LDL-cholesterol lowering capacity is the single most important factor in determining cost-effectiveness of the lipid-lowering therapies. There are currently several major classes of lipid-modulating agents available for the therapeutic reduction of lipoprotein levels – i.e. hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), peroxisome proliferator-activated receptors (PPAR) agonists, bile acid sequestrants, cholesterol absorption inhibitors, nicotinic acid and derivatives and other cholesterol and triglyceride modifiers (Rossiter, 2010:165). A short discussion on each of the therapeutic classes that can be used in the treatment of dyslipidaemia follows in subsequent sections.

- **3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors**

The 3-hydroxymethylglutaryl-coenzyme A reductase inhibitors or statins are considered the agents of choice for patients with higher than optimal to high LDL-cholesterol levels (Balbisi, 2006:RA36; Sharma *et al.*, 2009:622). Statins also have the best ability to decrease levels of all atherogenic apolipoprotein-containing-lipoproteins, and can thus (potentially) improve the three major lipid imbalances characteristic of hypercholesterolaemic patients with metabolic syndrome (Chapman & Caslake, 2004:A45; Grundy, 2000:viii; LaRosa *et al.*, 1999:2344). In addition, statins could add two years to a person's life (Mehta *et al.*, 2006:1598), and significantly reduce the risk for major cardiovascular events (Brugts *et al.*, 2009:b2376). Statins are the best tolerated of the currently available hypolipidaemic agents (Insull *et al.*, 2007:549) and have the highest level of patient adherence among available agents (Tsuyuki & Bungard, 2001:580). Based on a current scientific statement from the American Heart Association, statins should be initiated as treatment of familial hypercholesterolaemia in children at age ≥ 10 years in males and after the onset of menses in females (McGrindle *et al.*, 2007:1959).

Statins act *via* at least two mechanisms in patients with dyslipidaemia. Firstly, they exert their action by lessening VLDL production in the liver and inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme, thus directly inhibiting cholesterol biosynthesis (Sadowitz *et al.*, 2010:243). Secondly, statins promote the up-regulation of LDL-receptor expression consequential from enzyme inhibition, thus enhancing the clearance of the entire

spectrum of apolipoprotein-B-containing lipoproteins, reducing the potential impact of these lipoproteins in initiating and progression of atherosclerotic lesions (Crisby *et al.*, 2001:931; Mukhtar *et al.*, 2005:250). Vaughn and Gotto (2004:886) also suggested that statins could mediate intracellular processes that involve cell signal trafficking and protein synthesis indirectly by inhibiting the synthesis of prenylated proteins such as geranyl-geranyl pyrophosphate and farnesyl-farnesyl pyrophosphate. Blocking the production of prenylated proteins stops the activation of certain regulatory proteins that promote cell maintenance, cell growth and cell communication and attenuating apoptosis (Arnaud *et al.*, 2005:130). Apoptosis attributable to statins could thus decrease the enlargement of atherosclerotic plaques by regulating smooth muscle cell proliferation (Vamvakopoulos, 2005:145).

Although statins share a universal mechanism of action, their crystallographic differences govern water solubility, which sequentially influences absorption, distribution, metabolism and excretion (Schachter, 2005:117) and finally, also their lipid-modifying efficacy (Istvan & Deisenhofer, 2001:1163). Statins can be sub-classified into first-generation, or fermentation products (lovastatin, pravastatin and simvastatin); second-generation, synthetic, but racemic mixtures, of which fluvastatin is the only current member; and third-generation, which are pure enantiomers, such as cerivastatin, atorvastatin, rosuvastatin and pitavastatin (Stein, 2001:14). [Cerivastatin (Baycol®, Lipobay®) has been withdrawn from the market since 2001 due to the high rate of serious adverse effects (Clark, 2003:388; Furberg & Pitt, 2001:206)].

Lovastatin and pravastatin are both about equal in efficiency with about 10 mg achieving a 20% reduction in LDL-cholesterol. Fluvastatin, on the other hand, requires 20 mg and is the least potent of all the statin agents (Chapman & Caslake, 2004:A46; Jones *et al.*, 1998:585). Simvastatin is about twice as potent and only 5 mg is needed for a 20% reduction. Atorvastatin and rosuvastatin have a vastly greater effectiveness (Jones, 2004:S11-S12), with rosuvastatin being significantly superior in its potency effect, requiring 10 mg to produce a 47% reduction in LDL-cholesterol (Davidson *et al.*, 2002:268). Within the range of daily doses from 1-4 mg, the efficacy of pitavastatin as a lipid-lowering agent seems similar, or potentially superior, to that of atorvastatin, pravastatin and simvastatin (Sasaki *et al.*, 2008:1098; Stender & Hounslow, 2009:e945; Yokote *et al.*, 2008:350), with a LDL-cholesterol reduction capability of 40-45% (Hayashi *et al.*, 2007:2316; Lee *et al.*, 2007:2368). The statins are furthermore able to increase HDL-cholesterol on average by 5% (LaRosa *et al.*, 1999:2344), so doing also reducing the risk for CHD mortality by about 27-30% (Ebrahim *et al.*, 1999:22; Gordon, 2000:304).

Statins also show pleiotropic effects (CRP-lowering and mono-suppressing actions) in patients with impaired fasting glucose (Krysiak *et al.*, 2010:2268). The British National Formulary for Children (Costello, 2006:157) furthermore indicates that atorvastatin may be used for the

treatment of hyperlipidaemia (including familial hypercholesterolaemia) in children 10-17 years of age, whereas pravastatin is licensed for use in children over 8 years. Avis *et al.* (2007:1808-1809) showed atorvastatin (10-20 mg) to reduce LDL-cholesterol levels by 39% (95% CI: -44% to -35%) in children, compared with pravastatin (20 mg), that reduced LDL-cholesterol by 30% (95% CI: -37% to -22%). Simvastatin may be used from the age of 5-10 years in dosages of 5-20 mg daily (Costello, 2006:158), reducing LDL-cholesterol levels in children by 34% (García-de-la-Puente *et al.*, 2009:1209).

The efficacy of a selected dose of statin can be observed within 3-4 weeks. The dose response for all statins is predictable, with an additional LDL-cholesterol reduction of 6% for each doubling of a dose of a given statin in both children and adults (Kreisberg & Oberman, 2003:2459; McCrindle *et al.*, 2007:1957). Doubling the dose, though, increases the cost of statins almost 2-fold (Jacobson *et al.*, 1998:1986) except in countries where there is level pricing.

Cost-effectiveness is directly associated with baseline population risk and inversely linked to product cost per unit of LDL-cholesterol lowering (NIH, 2002:3222). As baseline risk increases and effective product cost decreases, cholesterol lowering with statins becomes more cost-effective. According to Jacobson and co-workers (1998:1986) the cost of higher-dosage statins is thus even greater when indexed to a 1% reduction in LDL-level. More recent reports by Killilea and Funk (2006:S329) and Gryskiewicz *et al.* (2005:690) depicted that, for a low-to-moderate reduction (30-40%), the agents lovastatin (10-, 20- and 40 mg) and fluvastatin (80 mg) provided the lowest cost per 1% reduction (i.e. US\$12-19 per percentage reduction). For a more pronounced lowering of the LDL-cholesterol level (35-50%), greater potency statins, such as simvastatin (80 mg), atorvastatin and rosuvastatin are the most cost-effective alternatives. According to Hirsch *et al.* (2005:255), rosuvastatin (10 mg) proved even more cost-effective than the same dose of atorvastatin in terms of cost per 1% LDL-cholesterol reduction achieved (i.e. €1.85 vs. €2.37, respectively, per 1% reduction). The selection of a statin should, however, not only be based on the extent of LDL-cholesterol reduction that is desired; cost and whether the statin has been shown to reduce clinical CHD events should also be considered (Chong *et al.*, 2001:398; NIH, 2002:3218). Lovastatin, pravastatin, simvastatin and rosuvastatin have been shown to prevent clinical CVD events in randomised control trials (Kreisberg & Oberman, 2003:2460).

Adverse effects of the statins are usually mild. Attention should be paid to transaminase levels, to creatine kinase and to symptoms of muscle pain and stiffness. Rhabdomyolysis is a rare complication that may be precipitated by the concurrent administration of fibrates, immunosuppressive medicines and erythromycin. Patients may also occasionally complain of

gastro-intestinal intolerance, headache, insomnia and other vague symptoms (Samson, 2008:355-356). Pitavastatin appears to have a similar safety profile compared with the older statins, but is associated with a lower incidence of drug-drug interactions because it is minimally metabolised by the cytochrome P-450 iso-enzymes (Ahmad & Cheng-Lai, 2010:266). Statin therapy is furthermore linked to a slightly increased risk for worsening glucose tolerance/developing insulin resistance and type 2 diabetes (Byrne & Wild, 2011; Rajpathak *et al.*, 2009:1928; Sattar *et al.*, 2010:741). In a recent meta-analysis of 5 statin trials with 32 752 participants without diabetes at baseline, Preiss *et al.* (2011:2563) calculated that 8.4% of participants receiving intensive therapy with atorvastatin or simvastatin (80 mg/daily) compared with moderate-dose therapy (daily atorvastatin 10 mg, simvastatin 20 mg, or pravastatin 40 mg) developed diabetes during a mean follow-up of 4.9 years (OR, 1.12; 95% CI: 1.04 - 1.22). Compared with moderate-dose statin therapy, the risk for diabetes was higher by 12% in the intensive-dose group, with a number needed to harm per year of 498. Based on a study by Her *et al.* (2010:170) this effect is less pronounced during treatment with rosuvastatin or the combination of atorvastatin and ezetimibe. These findings however suggest that older patients on statin therapy must be monitored closely for signs of dysglycaemia (Lewis, 2011:533).

- **Peroxisome proliferator-activated receptor (PPAR) agonists**

Peroxisome-proliferator activated receptors (PPARs) are ligand activated transcription factors belonging to the nuclear hormone receptor super family (Liu *et al.*, 2008:1078). Three isoforms, encoded by separate genes, have been identified, i.e. PPAR α , PPAR δ (also known as PPAR β) and PPAR γ , each displaying distinct tissue and developmental expression patterns (Davis, 2008:S22). PPAR α is highly expressed in tissues with a high oxidative capacity, such as the heart, skeletal muscle, kidney and liver tissue, whilst the PPAR γ isotype is highest expressed in adipose tissue (Gilde *et al.*, 2006:A24). PPAR δ is almost ubiquitously expressed in greater amounts than α or γ in almost all tissues, especially the skeletal muscle and small and large intestine (with the exception of adipose tissue) (Michalik & Wahli, 1999:564).

PPARs can be activated by an array of natural (endogenous) ligands, ranging from long chain fatty acids to eicosanoids, as well as synthetic ligands, such as peroxisome proliferators, hypolipidaemic agents, anti-inflammatory and insulin-sensitising products (Gilde *et al.*, 2006:A24). PPARs transactivate gene expression on ligand binding *via* heterodimerisation with the retinoic X receptor. This composite then binds to a direct repeat sequence designated PPAR-responsive element (Tan *et al.*, 2005:99). PPARs are also able to down-regulate or transrepress gene expression *via* a signal-transduction disrupting mechanism independent of DNA binding (Staels & Koenig *et al.*, 1998:790); they therefore have diverse roles in regulating

lipid homeostasis (Bishop-Bailey & Wray, 2003:1; Cho *et al.*, 2008). More targeted modulation of PPAR signalling may therefore have potential in the prevention of atherosclerosis (Jandeleit-Dahm *et al.*, 2009:24).

– ***PPAR α agonists***

PPAR α is the mostly characterised of the three PPAR subtypes and is highly expressed in the liver and relatively expressed in the heart, kidney, skeletal muscle, intestinal mucosa and brown adipose tissue (Fazio & Linton, 2004:148; Opara, 2005:170). Activators of PPAR α include a variety of endogenous present fatty acids and clinically used medications, such as those of the fibrate class (Bishop-Bailey & Wray, 2003:2).

Fibrates (or derivatives of fibric acid) are the second oldest class of lipid-lowering agents, having been used for more than four decades in clinical practice due to their significant triglyceride decreasing ability. Fibrates are also able to increase HDL-cholesterol levels (Tenenbaum & Fisman, 2004). Their ability to reduce LDL-cholesterol is, however, variable and highly dependent on baseline triglyceride levels (Stein, 2001:15). As a consequence, these active substances are not normally accepted as primary agents for LDL-cholesterol lowering, but considered excellent prospective candidates for reducing the risk for cardiovascular events (particularly myocardial infarction) in subjects with the metabolic syndrome and/or diabetes because of the beneficial effects on glucose and lipid metabolism (Elkeles, 2011:7; Spratt, 2009:S4). This class of agents should be used preferentially for children with severe elevations in triglyceride levels who are at risk for pancreatitis (Pacifico *et al.*, 2011:457).

The PPAR α form mediates fibrate action on HDL-cholesterol levels *via* transcriptional induction of synthesis of the major HDL apolipoproteins (Apo A-1 and Apo A-2) (Hersberger & Von Eckardstein, 2005:620). Fibrates also lower hepatic apolipoprotein C-3 production and increase lipoprotein lipase-mediated lipolysis *via* PPAR. In addition, fibrates stimulate cellular fatty acid uptake, conversion to acyl-CoA derivatives and catabolism by the β -oxidation pathways, which, combined with a reduction in fatty acid and triglyceride synthesis, result in a decrease in VLDL production (Raal, 2009:86). To summarise, both the enhanced catabolism of triglyceride-rich particles and the reduced secretion of VLDL underlie the hypertriglyceridaemic effect of fibrates, whereas their effect on HDL metabolism is associated with changes in HDL apolipoprotein expression (Staels & Dallongeville *et al.*, 1998:2088).

Clofibrate was the first fibrate approved for the treatment of dyslipidaemia in the early 1960s (Stein, 2001:15), with subsequent-generation approved agents such as gemfibrozil and fenofibrate (Kloer, 1987:3), bezafibrate (Goa *et al.*, 1996:725) and ciprofibrate (Turpin &

Bruckert, 1996:S83). As a group, fibrates may reduce plasma levels of triglycerides by 30-50% and typically increase levels of HDL-cholesterol by 5-15% depending on lipid phenotype and baseline concentration (Chapman, 2003:2; Mittal, 2008:185; Tenenbaum *et al.*, 2006). Fibrates may also reduce LDL-cholesterol by up to 15-20% (Steiner, 2005:204) and show pleiotropic effects (CRP-lowering and mono-suppressing actions) in patients with impaired glucose tolerance (Krysiak *et al.*, 2010:2266). Additionally, fibrates may also reduce the risk for cardiovascular disease. For example, Birjmohun *et al.* (2005:195) showed a 25% (95% CI: 10 - 38%) reduction in the risk for major coronary events with fibrates.

Hay and Sterling (2005:139) estimated that (when using a societal cost-effectiveness threshold of US\$50 000 per QALY), primary prevention of CHD in patients with low HDL-cholesterol levels using generic gemfibrozil therapy was cost-effective for all age and sex categories, in contrast to fenofibrate therapy, which was cost-effective for males, but not for females at baseline risks levels. In this study, gemfibrozil was more cost-effective than fenofibrate because of the assumed equal efficacy and the greater fenofibrate product cost. In the base-case scenario, because of their greater CHD lifetime risk, it was more cost-effective to treat males than females with either gemfibrozil or fenofibrate. The cost per QALY furthermore decreased with age for most age intervals in both males and females.

The adverse effects of the fibrates are normally mild and do not necessitate therapy cessation. The most common adverse effects are a mild, non-specific gastro-intestinal symptom complex including dyspepsia and nausea, whilst the most severe adverse effect encompass the ability of the fibrates to increase cholesterol in the bile, which can lead to an increase in gallstone formation (Kohlman-Trigoboff, 2005:75). Hepatic and muscle toxicity are uncommon with monotherapy, although it has been seen with increased incidence when combined with other agents such as the statins (Gau & Wright, 2006:467). Gemfibrozil, in particular, inhibits the glucuronidation of statins (especially cerivastatin) and may therefore increase blood levels of any active statin (Bottorff, 2006:28C). Fenofibrate does not share this characteristic to the same degree and may therefore be a hypothetical better “partner” with statins in combination therapy (Bergman *et al.*, 2004:1060; Keating, 2011:228) (refer to “combination therapy with lipolipidaemics”). Clofibrate is currently rarely used because of an increased mortality associated with its use (Toutouzas *et al.*, 2010:1670).

– **PPAR γ agonists**

PPAR γ plays important roles in the regulation of proliferation and differentiation of several cell types, including adipose cells (Bishop-Bailey & Wray, 2003:5). It has the ability to bind a variety of small lipophilic compounds derived from both metabolism and nutrition. These ligands, in

turn, determine co-factor recruitment to PPAR γ , regulating the transcription of genes in a variety of complex metabolic pathways. PPAR γ is highly expressed in adipocytes, where it mediates differentiation, promotes lipid storage and, consequently, is thought to indirectly improve insulin sensitivity and enhance glucose disposal in adipose tissue and skeletal muscle (Argmann *et al.*, 2005:82; Lazar, 2005:9). A number of ligands can activate PPAR γ , including docosahexaenoic acid, linoleic acid, a number of lipids, including oxidised LDL-cholesterol, azoyle-PAF and eicosanoids, the prostanoids and thiazolidinediones (Bishop-Bailey & Wray, 2003:5).

The thiazolidinediones (TZDs or glitazones) are synthetic PPAR γ ligands, that includes the compounds troglitazone, ciglitazone, rosiglitazone, pioglitazone (Bishop-Bailey & Wray, 2003:5), and a novel component, rivoglitazone (Kong *et al.*, 2011:806). These agents have well-recognised effects on the glucose metabolism, and are therefore primarily indicated for the treatment of type 2 diabetes mellitus (refer to paragraph 2.9.4.5.2). Thiazolidinediones also have a multitude of other therapeutic effects including anti-inflammatory effects and the amelioration of hypertension (refer to paragraph 2.9.3.5.2), micro-albuminuria and hepatic steatosis. According to Goldberg *et al.* (2005:1552) and Deeg *et al.* (2007:2462) both rosiglitazone and increase HDL-cholesterol levels (14.9% with pioglitazone vs. 7.8% with rosiglitazone, respectively). Pioglitazone furthermore increases total, large and medium HDL particles whilst decreasing small HDL concentration, whereas rosiglitazone, in contrast, decreases total, large and small HDLs whilst increasing medium HDL particle concentration.

One of the most common adverse effects of thiazolidinediones is fluid retention, which can result in, or exacerbate, oedema and congestive heart failure (CHF) (FDA, 2011a; Gale, 2011:5; Hollenberg, 2003:113S; Rosen, 2010:805). Patients with dyslipidaemia at high risk for myriad morbid complications who are taking a thiazolidinediones should therefore be monitored for signs and symptoms of CHF, with possible discontinuation of the agent in cases with CHF exacerbation. The FDA (2011e) also recently issued a warning for the use of pioglitazone in patients with active bladder cancer or those with a prior history of bladder cancer because of the potential increased risk. The first agent in this class, troglitazone, was banned because the risk for idiosyncratic hepatotoxicity outweighed its potential benefits (Graham *et al.*, 2003:304), and the agent, ciglitazone, was also never used as medication. Other adverse effects include weight gain and anaemia (Stojanovska *et al.*, 2007:69).

Patients on rosiglitazone furthermore have a 43% excess risk for myocardial infarction and 64% excess risk for cardiovascular death (Nissen & Wolski, 2007:2459). The effects on fasting triglycerides are divergent with pioglitazone therapy associated with a reduction in fasting triglycerides (attributable to the decrease in large VLDL and intermediate density lipoproteins), whereas rosiglitazone is associated with increased triglycerides (due to an increase in both

large- and medium-sized VLDL and IDL concentrations). Pioglitazone furthermore decreased whereas rosiglitazone increased apolipoprotein C-3 (Deeg *et al.*, 2007:2462; Goldberg *et al.*, 2005:1552). Pioglitazone has also been shown to have no effect on serum apolipoprotein A-1 levels compared with rosiglitazone that was associated with a decrease in apolipoprotein A-1 levels (Deeg & Tan, 2008). Both rosiglitazone and pioglitazone elevate LDL-cholesterol; the increase is, however, significantly greater with rosiglitazone compared with pioglitazone (12.3% and 21.3%, respectively) (Deeg *et al.*, 2007:2462; Goldberg *et al.*, 2005:1552). Rosiglitazone is therefore generally not suitable for metabolic syndrome patients. A discussion on the role of the TZDs on glucose metabolism and their cost-effectiveness follows in paragraph 2.9.4.5.2.

– **Dual PPAR α / γ agonists**

Simultaneous activation of PPAR α and PPAR γ activators might, through a complementary mechanism of action, alter the tissue distribution of fatty acids by stimulating their uptake and utilisation in adipose tissue, liver and skeletal muscle (Gregoire *et al.*, 2007). Another complementary mechanism of combined activation of PPAR α and PPAR γ in improving obesity-induced insulin resistance involves the induction of adipose tissue adiponectin receptors by PPAR α and adiponectin by PPAR γ , resulting in decreased infiltration of macrophages into adipose tissue, thereby ameliorating tissue inflammation and improving obesity-induced insulin resistance (Tsuchida *et al.*, 2005:3359). In their study, the authors proposed novel mechanisms by which activation of PPAR α and/or PPAR γ ameliorates insulin resistance, focusing on adipose tissue, such as:

- Activation of PPAR α that suppresses inflammation and adipose hypertrophy in adipose tissue.
- Dual activation of PPAR α and - γ enhances the action of adiponectin by increasing both adiponectin and adiponectin receptor expression Tsuchida *et al.*, 2005:3361).

Several dual PPAR α / γ agonists have been developed in an attempt to combine the therapeutic effects of both PPAR α and PPAR γ selective agonists, amongst which compounds, belonging to the glitazar class, have been advanced to clinical development. The glitazars also belong to the class of potential antidiabetic agents (refer to paragraph 2.9.4.5.2).

Glitazars show predominant significant PPAR γ activity, although their affinity for PPAR α is greater than that of fenofibric acid (DeFronzo, 2005:22). Several clinical trials established superior efficacy of these compounds in improving lipid homeostasis to a larger extent than did selective PPAR-agonists. For example, Buse *et al.* (2005:1193), and Kendall *et al.* (2006:1021) found that muraglitazar monotherapy improved triglycerides, HDL-cholesterol, apolipoprotein B and non-HDL-cholesterol levels in patients with type 2 diabetes. In a more recent trial, Rubin *et*

al. (2009:207-209) reported similar results, and established that the rates of treatment-related adverse effects and discontinuations caused by these adverse effects were similar for muraglitazar compared with pioglitazone 15 mg (approximately 20%). In the Glucose and Lipid Assessment in Diabetics (GLAD) study, tesaglitazar reduced plasma triglycerides and increased HDL-cholesterol levels “quantitatively greater” than those achieved with pioglitazone (Goldstein *et al.*, 2006:2588). Tesaglitazar also improved the fasting lipid profile (by decreasing triglycerides, non-HDL-cholesterol and fatty acids and increasing HDL-cholesterol levels) and plasma apolipoprotein A-1, -B and -C-3 levels in the Study in Insulin Resistance (SIR) (Fagerberg *et al.*, 2005:1723). Ragaglitazar has been shown to decrease the levels of triglycerides and fatty acid concentrations to the same extent to that of pioglitazone in patients with type 2 diabetes, but only ragaglitazar (not pioglitazone) increased HDL-cholesterol and decreased apolipoprotein B levels (Saad *et al.*, 2004:1327). The emergence of several different types of toxic effects, however, has resulted in the failure of these glitazars to progress beyond phase III development. For example, development of tesaglitazar was discontinued in 2006 because of indications that it could cause renal impairment (Hamrén *et al.*, 2008:861). Muraglitazar was linked with cardiovascular safety issues and therefore suspended in 2006 (Nissen *et al.*, 2005:2584), whereas ragaglitazar, MK-0767 and naveglitazar were found to be associated with an increased incidence of both bladder cancer and hyperplasia in animal studies and therefore discontinued (Long *et al.*, 2008:228).

The latest dual PPAR α / γ agonist, aleglitazar, is distinguished from muraglitazar (which might have a greater affinity towards PPAR γ) and tesaglitazar, (which might have a greater affinity towards PPAR α) in that it is a balanced high-affinity ligand for both PPAR α and PPAR γ (Bénardeau *et al.*, 2009:2471). Compared with placebo, aleglitazar increased HDL-cholesterol levels in a dose-dependent manner by up to 28% and reduced triglyceride levels by as much as 38%. Aleglitazar also significantly reduced LDL-cholesterol levels, although by a lesser magnitude than the other lipid fractions (Cavender & Lincoff, 2010:214). According to Henry *et al.* (2009:133), the overall toxicity profile from non-clinical safety studies with aleglitazar is consistent with that of pioglitazone; the most relevant findings are reversible and show an adequate safety margin.

– **PPAR δ (β) agonists**

PPAR δ (also referred to as PPAR β) agonists controls the expression of genes involved in fatty acid uptake, beta-oxidation and energy uncoupling and is therefore implicated in the regulation of the fatty acid burning capacities of skeletal muscle and adipose tissue (Bedu *et al.*, 2005:861; Coll *et al.*, 2009:51). By controlling the number of oxidative myofibers, which induce and enhance fatty acid catabolism in muscular tissue, PPAR δ is also implicated in the adaptive

metabolic response of skeletal muscle to endurance exercise (Berger *et al.*, 2005:244; Fredenrich & Grimaldi, 2005:23). Ligand activation of these receptors may also be associated with improved insulin sensitivity and elevated HDL levels, thus demonstrating promising potential for targeting PPAR δ in the treatment of obesity, dyslipidaemia, type 2 diabetes (Burdick *et al.*, 2006:9) and the metabolic syndrome (Barish *et al.*, 2006:596).

PPAR δ is activated by a more restricted range of natural ligands, for example various saturated and unsaturated fatty acids (FA), eicosanoids, prostacyclin and retinoid acids (Bishop-Bailey & Wray, 2003:4; Shaw *et al.*, 2003:41589).

- **Bile acid sequestrants (resins)**

According to Kraemer and Miller (2000:562), bile acid sequestrants or resins were the first agents successfully developed for the treatment of severe hypercholesterolaemia. Results of the Lipid Research Clinics Coronary Primary Prevention Trial also provided evidence that the bile acid sequestrants can reduce the risk for coronary events in men with up to 19% (Rifkind, 1984:33C). In addition, resins may reduce glucose levels in patients with type 2 diabetes mellitus (Staels, 2009:25).

There are three bile acid sequestrants in clinical use, i.e. cholestyramine and colestipol (first generation agents or non-absorbable cationic polymer resins) and colesevelam (a second-generation agent). The primary mechanism of action of the first generation of bile sequestrants involves the non-covalent binding to negatively charged bile acids in the small intestine (Insull, 2006:260), depleting the bile acid pool by about 40% (Goldberg, 2009:12). This binding reduces the entero-hepatic circulation of bile acids, influencing the hepatic metabolism of cholesterol. Three key enzyme systems are affected: cholesterol 7 α -hydroxylase, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and phosphatidic acid phosphatase. The activation of hepatic cholesterol 7 α -hydroxylase promotes the conversion of intracellular cholesterol to bile acids. The resulting decrease in hepatocyte cholesterol content enhances LDL-receptor expression, which in turn lowers serum LDL-cholesterol concentrations in a dose-dependent manner (Golan *et al.*, 2008:433). Activation of phosphatidic acid phosphatase promotes hepatic triglyceride synthesis, induces secretion of triglyceride-rich, VLDL-cholesterol particles and consequently, increases plasma triglyceride levels. Bile acid sequestrants also promote apolipoprotein A-1 synthesis by an unknown mechanism and tend to raise HDL-cholesterol levels, primarily by increasing plasma HDL₂ concentrations (Neal, 2008:S36).

Although colesevelam acts in the same way as do cholestyramine and colestipol it was

developed to have enhanced specificity, greater affinity and greater capacity for binding bile acids than cholestyramine or colestipol (Goldberg, 2009:16). Colesevelam is therefore at least 4-6 times more potent on a weight basis than either cholestyramine or colestipol (Steinmetz, 2002:937).

First generation bile-acid sequestrants are able to reduce LDL-cholesterol by 15-30% (Golan *et al.*, 2008:433) and raise high-density lipoprotein cholesterol by 3-5% (Neal, 2008:S36). Unfortunately, it can also increase triglycerides by approximately 13.5% (Tovar & Schering, 2006:73). The second-generation agent, colesevelam, has been shown to reduce total and low-density lipoprotein cholesterol levels significantly and dose-dependently by up to 19% and increased HDL-cholesterol by 8-9% (Insull *et al.*, 2001:980). Colesevelam moreover has a favourable effect on apolipoprotein B levels and increases apolipoprotein A-1 as well (Florentin *et al.*, 2008:995) in addition to having anti-inflammatory properties (e.g. reduces high sensitivity CRP concentrations) (Florentin *et al.*, 2008:996). Colesevelam furthermore gained FDA approval in 2008 as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. According to Brunetti and Campbell (2011), colesevelam (as add-on therapy with metformin, sulphonylureas, and insulin) is able to reduce HbA_{1c} levels by 0.50-0.54%. Colesevelam furthermore causes only slight increases in triglyceride levels (Davidson & Dillon *et al.*, 1999:1897).

Hilleman *et al.* (1995:190) found resin therapy alone significantly less cost-effective than statins alone or in combination with a statins - primarily because of the lower reduction in LDL-cholesterol compared with that observed with the statins. Lower-dose resin therapy was further more cost-effective than higher-dose resin therapy due to a fairly flat dose-response with therapy. Earlier studies showed similar results with colestipol (Superko *et al.*, 1992:138; Schrott *et al.*, 1995:38).

The use of bile acid sequestrants (with the exception of colesevelam that shows an improved tolerability) is limited by patient adherence as these agents commonly cause gastro-intestinal adverse effects, especially constipation and flatulence and require large and frequent dosing (Bays & Goldberg, 2007:568). Because of their effect on triglyceride levels and other adverse effects, the use of bile acid sequestrants should further be limited to a select group of patients with type 2 diabetes who have an isolated increase in LDL-cholesterol and normal serum triglyceride levels (Tenenbaum *et al.*, 2006).

- **Cholesterol absorption inhibitors (ezetimibe)**

Ezetimibe is the first of the 2-azetidinone compounds, a novel class of lipid modifying agents,

which potentially inhibit the absorption of biliary and dietary cholesterol and related phytosterols from the small intestine without affecting the absorption of fat-soluble vitamins, triglycerides or bile acids (Kosoglou *et al.*, 2005:467). It is primarily indicated as an addition to statin treatment in patients with LDL-cholesterol levels above target and because ezetimibe prevents the intestinal absorption of the non-cholesterol sterols (sitosterol and campesterol) it might be the agent of choice in cases of sitosterolaemia (Salen *et al.*, 2004:970). The addition of ezetimibe consequently becomes most cost-effective when larger LDL reductions are required (Gryskiewicz *et al.*, 2005:690).

Ezetimibe has a mechanism of action that is unique compared with other available lipid-lowering agents and is complementary to that of the HMG-CoA reductase inhibitors, resulting in synergistic cholesterol-lowering effects when these agents are used in combination (Aschenbrenner, 2008:463). Ezetimibe localises in the brush border of the small intestinal enterocytes and reduces the uptake of cholesterol and phytosterols into the enterocytes by interfering with the Niemann-Pick C1-like 1 protein 1 (NPC1L1) (Denke, 2003:13). This has the net effect of inhibiting cholesterol absorption by keeping the cholesterol in the intestinal lumen, allowing it to be excreted (Drazen *et al.*, 2008:1507). Consequently, this results in a reduction of hepatic cholesterol stores and an increase in the blood clearance of cholesterol (Hou & Goldberg, 2009:88). A compensatory increase in cholesterol synthesis occurs when ezetimibe is given as monotherapy (Nutescu & Shapiro, 2003:1465); with on-going therapy, however, the net effect of ezetimibe monotherapy is to reduce total cholesterol by 13%, LDL-cholesterol by 18% and apolipoprotein B by 16% in patients with hypercholesterolaemia (Van Heek & Davis, 2002:J8). The agents' ability to reduce triglycerides (8%) or to lower HDL-cholesterol (1%) is less prominent (Van Heek & Davis, 2002:J8). The effects of ezetimibe are increased when combined with statins, with an amplified 25% decrease in LDL-cholesterol, 14% decrease in triglycerides and 3% increase in HDL-cholesterol (Gau & Wright, 2006:467). Ezetimibe add-on therapy furthermore significantly improves apolipoprotein B levels (18%) and derivatives of the reactive oxidative metabolites (d-ROMs) (11%), as well as the LDL-cholesterol to HDL-cholesterol ratio (28%) and apolipoprotein B to apolipoprotein A-1 ratio (22%) (Yamaoka-Tojo *et al.*, 2009) (refer to "combination therapy with hypolipidaemics").

Based on a systematic review by Ara *et al.* (2008:3), ezetimibe is a cost-effective treatment for individuals with high baseline LDL-cholesterol values, for patients with diabetes and for individuals with heterozygous familial hypercholesterolaemia. Amongst combination products, simvastatin (40 mg) plus ezetimibe (10 mg) proved the most cost-effective for lowering of LDL-cholesterol more than 40% (Gryskiewicz *et al.*, 2005:692; Perkerson *et al.*, 2005:20).

Ezetimibe monotherapy (compared with placebo) is well tolerated. The most commonly

reported adverse events are musculoskeletal disorders and upper respiratory tract infections. Other common adverse events include headache, back pain and gastro-intestinal adverse events (Ara *et al.*, 2008:30).

- **Nicotinic acid and derivatives (acipimox)**

Niacin (Vitamin B₃) is a water-soluble vitamin that occurs in two forms: nicotinic acid and nicotinamide. Both nicotinic acid and nicotinamide are dietary precursors for the synthesis of nicotinamide adenine dinucleotide, NAD(H) and related coenzymes, NADP(H). When given in pharmacological doses nicotinic acid favourably affects all lipids and lipoproteins. It is regarded as the most potent HDL raising agent among lipid lowering agents (Roze *et al.*, 2007:416) and is not only effective at raising HDL-cholesterol but also effectively reduces key atherogenic lipid components including triglyceride-rich lipoproteins (mainly very low-density lipoproteins and VLDL remnants), LDL-cholesterol and lipoprotein(a) (Aschenbrenner, 2008:463). Nicotinic acid therapy is therefore ideal (either alone or in combination with a statin – refer to “combination therapy with hypolipidaemics”) for treating the principal features of the atherogenic lipid profile that typically occurs in patients with the metabolic syndrome (Chapman *et al.*, 2004:1266; McGovern, 2004:72). Poldermans and co-workers (2008:319) also recently established that the use of prolonged-release nicotinic acid reduced cardiovascular risk score by about 3.3 points. Duggal and colleagues (2010:163) found similar results with regular niacin therapy, additionally showing a small (although non-significant) decrease in coronary and cardiovascular mortality.

Several reports published earlier and in recent years suggested multiple potential mechanisms that would contribute to the lipid modulating effects of nicotinic acid. Suggestions that have been made, include the decrease in the fractional catabolic rate of apolipoprotein A-1 *via* reduction in hepatocytes uptake (increasing apolipoprotein A-1 would facilitate greater reverse cholesterol transport (RCT) by making apolipoprotein A-1 more bioavailable to remove excess cellular cholesterol from the arterial wall macrophage) (Bodor & Offermanns, 2008:S70; Jin *et al.*, 1997:2020); the inhibition of hepatic diacylglycerol acyltransferase 2 (DGAT2) which is a key enzyme in the synthesis of triglycerides destined for VLDL-cholesterol (Ganji *et al.*, 2004:1835); the inhibition of adipose tissue hormone-sensitive lipase, leading to decreased free fatty acid flux to the liver and a resulting decrease in hepatic production of triglyceride-rich lipoproteins (Tunaru *et al.*, 2003:352; Zhang *et al.*, 2005:732); and also an increase in the expression of peroxisome proliferator activated receptor- γ , together with an enhancement of peroxisome proliferator-activated receptor- γ transcriptional activity in macrophages (Knowles *et al.*, 2006:653).

Nicotinic acid increases HDL-cholesterol levels by 15-30% (Vega & Grundy, 1994:80) and

decreases triglycerides by 20-50%, depending on the dose (Almeda, 2007:202). These changes tend to be curvilinear; thus, smaller doses of nicotinic acid still produce significant increases in HDL or reductions in triglyceride with fewer adverse effects (Knopp *et al.*, 1998:1102; Taylor *et al.*, 2004:3516). The degree of LDL-cholesterol lowering by nicotinic acid vary, however, according to Illingworth *et al.* (1994:1593) reductions of 5%, 16% and 23% in LDL-cholesterol are noted with daily doses of 1.5, 3.0 and 4.5 grams, respectively. High doses of nicotinic acid may lower lipoprotein(a) by 30% (Owada *et al.*, 2003:351).

In 1990, Schulman *et al.* (1990:3031) proved niacin the most cost-effective medication for lowering cholesterol, costing US\$139 per 1% reduction in LDL-cholesterol levels compared with other agents such as cholestyramine, lovastatin, colestipol, gemfibrozil and probucol. In the study by Schulman and colleagues, the cost per 1% reduction for the other agents was approximately two to three times that of niacin. Nicotinic acid seems the most effective treatment modality for favourably modifying all the lipoprotein abnormalities associated with atherogenic dyslipidaemia among lipid-lowering agents (Roze *et al.*, 2007:416).

The tolerability of nicotinic acid has previously been the major barrier to its wider clinical use; though, this has been greatly improved by the development of a new prolonged release (PR) formulation (McCormack & Keating, 2005:2719). Major adverse effects of niacin include flushing and sensations of heat and cutaneous discomfort (Berger & Marais, 2000:174; Birjmohun *et al.*, 2005:189). A report on the Arterial Disease Multiple Intervention Trial (ADMIT) population of patients with peripheral vascular disease (Elam *et al.*, 2000:1268) furthermore showed high dose niacin (up to 3 g/day) associated with three other major adverse effects: hyperglycaemia (increased insulin resistance and deterioration of glycaemic control), hyperuricemia/gout and hepatotoxicity. The risk for hepatotoxicity seems greater with the sustained-release preparations (Al-Mohaissen *et al.*, 2010:206).

Acipimox - a long-acting synthetic derivative of nicotinic acid - is 20 times more potent, better tolerated and has a longer duration of action as compared with nicotinic acid (Lorenzen *et al.*, 2001:351). Similar to the mechanism of action postulated for nicotinic acid, it is suggested that the mechanism of action of acipimox is to inhibit peripheral lipolysis reducing plasma non-esterified fatty acid (NEFA) levels. The potential beneficial effect acipimox may have on glucose metabolism in patients with type 2 diabetes is a result of lowering plasma and possibly skeletal muscle concentrations of NEFA (Shih *et al.*, 1997:118). In hyperlipidaemic subjects, the effects of acipimox include decreases in plasma triglycerides and cholesterol with possible increases in high-density lipoprotein cholesterol.

- **Cholesteryl ester transfer protein (CETP) inhibitors**

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that plays a critical role in cholesterol metabolism, exchanging cholesteryl esters and triglycerides between lipoproteins. CETP mediates the transport of cholesteryl esters from HDL to apolipoprotein B containing lipoproteins, with a balanced transfer of triglycerides in the opposite direction. Inhibition of CETP therefore results in an accumulation of cholesteryl esters in HDL (and thereby an increase in HDL-cholesterol) (Hunt & Lu, 2009:420), and a decreased level of VLDL-cholesterol and LDL-cholesterol (Van der Steeg *et al.*, 2004:632). The CETP inhibitors also show potential as anti-atherosclerotic agents by blocking the transfer of cholesterol esters from HDL-cholesterol to VLDL, LDL and small dense LDL-cholesterol. This effect has a remarkable potential for atherosclerosis control, particularly with the increase in metabolic syndrome with high triglycerides and small dense LDL-cholesterol (Gau & Wright, 2006:469).

Several classes of CETP inhibitors were developed and advanced to clinical development including *inter alia*, the 1,2,3,4-tetrahydroquinolines (e.g. dalcetrapib, torcetrapib and anacetrapib) (Hunt & Lu, 2009:419; Sikorski, 2006:9). The first of these agents, dalcetrapib resulted in a 34% increase in HDL-cholesterol with a 7% reduction in LDL-cholesterol levels (De Grooth *et al.*, 2002:2164). In combination with pravastatin, dalcetrapib caused a 28% increase in HDL (Derks *et al.*, 2009:892). Stein and co-workers (2009:86) also reported an increase of up to 16% in apolipoprotein A-1 with dalcetrapib. When administered as a monotherapy torcetrapib produced a 46-106% increase in HDL (Brousseau *et al.*, 2004:1513). When given in addition to atorvastatin (20 mg/day), an increase in plasma HDL-cholesterol concentration of 61% was observed in addition to a 20% relative decrease in LDL-cholesterol concentration (Zareba, 2006:96). Millar and co-workers (2006:1351) furthermore reported significant reductions in apolipoprotein B levels with torcetrapib with no major effect on plasma triglycerides. Anacetrapib produced dose-dependent lipid-altering effects with peak lipid-altering effects of 129-138% increase in HDL-cholesterol and a 38-40% decrease in LDL-cholesterol in patients with dyslipidaemia (Cannon *et al.*, 2010:2413; Krishna *et al.*, 2009:85).

Reported adverse effects of the CETP inhibitors include the elevation of hepatic transaminases, an increase in systolic blood pressure of 4.6 mmHg (with torcetrapib) and abdominal symptoms (Oram & Heinecke, 2008:166). Elevated CETP concentration in conjunction with elevated triglyceride levels are associated with increased odds (~25%) for cardiovascular events (Stein *et al.*, 2009:88; Van der Steeg *et al.*, 2004:635). This effect is less pronounced with anacetrapib, as indicated by a predictive probability (confidence) of 94% (Cannon *et al.*, 2010:2413).

- **Combination therapy with hypolipidaemics**

Treatment guidelines recommend aggressive combination lipid-lowering therapy in patients at high risk for cardiovascular disease, i.e. patients who have familial hypercholesterolaemia or familial combined hyperlipidaemia (Durrington, 2003:719) or where patients have not reached target LDL-cholesterol levels of fewer than 70 mg/dL (1.8 mmol/L) with monotherapy (Tannock, 2008:369). The justification for combination therapy is that agents with synergistic/additive mechanisms of action can provide complementary effects on the lipid profile (Venkataraman *et al.*, 2004:978).

Nicotinic acid (niacin) and fibrates are suggested as the most suitable option for patients with atherogenic dyslipidaemia because they reduce triglycerides, raise HDL-cholesterol and convert small, dense, triglyceride rich LDL-particles to larger, more buoyant ones (Talbert, 2003:S7). According to the National Cholesterol Education Programme (Birjmohun *et al.*, 2005:194) these agents can be used either as monotherapy in the absence of elevated LDL-cholesterol or in combination with a LDL-cholesterol lowering agents.

Statins are considered the agents of choice for patients with high or higher than optimal LDL-cholesterol levels (Balbisi, 2006:RA36; Gau & Wright, 2006:452). Maximum statin doses may, however, be associated with an increase in frequency of tolerance problems, particularly myopathy (Luh & Karnath, 2003:888; Phillips & Haas, 2008:975). In situations where the highest tolerated statin dose does not achieve the target LDL-cholesterol, agents from different classes that mediate LDL lowering via different mechanisms and sites of action than the statins, may then be added to produce the desired result and possibly ameliorate some of the tolerance problems, for example the bile acid sequestrants or ezetimibe.

The following section entails a description of the rationale for some of the most common combinations employed.

- ***Statins plus bile acid sequestrants***

Above and beyond the decrease in CHD event rates achieved by both medicine classes, adding a bile acid sequestrant (resin) to statin therapy can provide a further 10-25% reduction of LDL-cholesterol (Ballantyne, 2005:19K) and is therefore ideal to reach LDL-cholesterol goals in patients who cannot tolerate high statin doses. The combination of a resin and low-dose statin may render a similar reduction in LDL-cholesterol than that obtained from single therapy with a high dose statin. For example, Hunninghake *et al.* (2001:409) showed that colesevelam plus atorvastatin (10 mg) reduced LDL-cholesterol levels by 48% compared with a 53% reduction

achieved with atorvastatin (80 mg) monotherapy.

Although the combination of resins and statins may not be ideal in patients who have high triglyceride levels (because of their effect on VLDL-cholesterol levels), it may offer advantages in type 2 diabetes mellitus patients because of the reduction in blood glucose and glycated haemoglobin (Zieve *et al.*, 2007:76) (refer to “bile acid sequestrants”).

– ***Statins plus ezetimibe***

The rationale for the combination of ezetimibe and a statin resides in their complementary mechanisms of action that affects cholesterol metabolism, e.g. ezetimibe inhibits cholesterol absorption within the intestine, whereas the statins inhibit cholesterol biosynthesis in the liver (Guyton *et al.*, 2011:161). According to Gau and Wright (2006:467), the combination of ezetimibe with statins results in an amplified decrease in LDL-cholesterol and triglycerides and increase in HDL-cholesterol. For example Rotella *et al.* (2010) and Robinson *et al.* (2009:1696) respectively showed the combination of simvastatin and ezetimibe to increase HDL-cholesterol significantly more than did a doubling of a dose of simvastatin and/or monotherapy with atorvastatin.

Tomassini and co-workers (2009:858) furthermore showed the combination of simvastatin and ezetimibe to significantly reduce intermediate-density lipoprotein cholesterol, very low-density lipoprotein cholesterol and remnant-like lipoprotein cholesterol from baseline more than did statin monotherapy in patients with type 2 diabetes and hypercholesterolaemia. This effect is even more pronounced with higher doses of potent statins; Ballantyne *et al.* (2007:678), showed the combination of rosuvastatin (40 mg) and ezetimibe (10 mg) to reduce LDL-cholesterol by up to 70%, whereas the combination of simvastatin (20 mg) and ezetimibe (10 mg) decreased LDL-cholesterol levels by 37.4% (Chirinos *et al.*, 2010:918e4).

– ***Statins plus nicotinic acid***

This combination is particularly useful in high-risk patients who need increases in HDL-cholesterol levels as well as reductions of LDL-cholesterol and triglyceride levels. For example, Brown *et al.* (2001:1590) showed that treatment with simvastatin (10 mg) and niacin (1 000 mg twice daily) resulted in a reduction in a 42% LDL-cholesterol level, a 36% decrease in triglycerides and a 26% increase in HDL-cholesterol level from baseline. Similar effects were also shown for niacin (2 000 mg) in combination with less potent statins, e.g. lovastatin (40 mg) (Kashyap *et al.*, 2002:677). In addition, Kashyap and co-workers also showed reductions of 25% and 24%, respectively, in lipoprotein (a) and C-reactive protein levels. This effect is dose-

dependent.

– ***Statins plus fibrates***

The combination of statin and fibrate decreases triglycerides and increases HDL-cholesterol to a level greater than achieved with either agent alone and is therefore useful for patients who have metabolic syndrome, diabetes and other forms of mixed dyslipidaemia (Hou & Goldberg, 2009:90). Grundy and Vega *et al.* (2005:466) showed the combination of fenofibrate (160 mg/day) and simvastatin (20 mg/day) therapy to reduce triglycerides by 23.6% and VLDL-cholesterol by 25.1% in patients with combined hyperlipidaemia. The fenofibrate/simvastatin combination furthermore increased HDL-cholesterol by 18.6% compared with that at baseline; this increase was double that observed with simvastatin monotherapy. A more recent study by Kipnes *et al.* (2010:57) showed sustainable improvements in HDL-cholesterol (17.4%) and decreases in triglycerides and LDL-cholesterol of 46.4% and 40.4% respectively, with long-term treatment (≥ 2 years) with fenofibrate and moderate-dose statins (e.g. rosuvastatin 20 mg, simvastatin 40 mg and atorvastatin 40 mg) in patients with mixed dyslipidaemia.

The combination of most statins with gemfibrozil increases the incidence of myopathy, including rhabdomyolysis (Bottorff, 2006:28C). This phenomena is less prominent with fenofibrate (refer to “PPAR α agonists”).

– ***Bile acid sequestrants plus nicotinic acid***

Nicotinic acid and the bile acid sequestrants are some of the earlier substances used in the lowering of LDL-cholesterol levels. This combination had been used long before the arrival of the HMG-CoA reductase inhibitors, particularly in high-risk patients (Antonios & Silliman, 2009: 42; Hou & Goldberg, 2009:90). Angelin *et al.* (1986:393) showed the combination of cholestyramine and nicotinic acid to reduce LDL-cholesterol levels by 32% and LDL/HDL ratios by 40%. The combination of acipimox and cholestyramine has also been shown to reduce serum LDL-cholesterol by 27%, and to increase HDL-cholesterol levels (Gaw *et al.*, 1995:45).

– ***Nicotinic acid plus fibrates***

The addition of nicotinic acid to fibrates produces a shift from a predominance of small, dense LDL-cholesterol particles to larger, more buoyant ones, often in conjunction with a reduction in triglycerides (Saely *et al.*, 2010:693). The concurrent use of these products therefore produces an even greater beneficial effect on the dyslipidaemia typically found in patients with familial combined hyperlipidaemia (Gaddi *et al.*, 2007:885).

Superko and co-workers showed the combination of gemfibrozil and nicotinic acid to reduce fasting triglycerides by 61%, total cholesterol by 21% and LDL-cholesterol levels by 20%. This treatment combination also resulted in a 71% reduction in IDL mass; reductions in dense LDL-II and LDL-III mass of 13% and 52%, respectively; and a significant increase in HDL₂ of 90%. Changes in apolipoprotein A-1 and apolipoprotein B were furthermore noted (Superko *et al.*, 2009:389).

– ***Ezetimibe plus bile acid sequestrants***

The combination of ezetimibe with resins provides additive effects on LDL-cholesterol reduction. Ezetimibe inhibits cholesterol absorption; whereas bile resins enhance cholesterol excretion *via* enhanced conversion to bile acids (refer to “bile acid sequestrants” and “cholesterol absorption inhibitors”). This combination is therefore valuable for patients intolerant to statins at any dose, or for whom statins are contraindicated (Hou & Goldberg, 2009:90).

Bays and co-workers (2006:2198) showed a 32% reduction of LDL-cholesterol from baseline by combination therapy of colestevlam with ezetimibe (10 mg), compared with a 21% reduction achieved with ezetimibe monotherapy.

– ***Other therapeutic agents and combinations***

The combination of three or more lipid-lowering agents can be useful in high-risk patients who have very high levels of LDL-cholesterol, e.g. patients diagnosed with familial hypercholesterolaemia and baseline LDL-cholesterol levels larger than 250 mg/dL (Hou & Goldberg, 2009:90). In a 1990-study by Kane and colleagues (1990:3009), a combination of lovastatin, niacin and colestipol showed regression of atherosclerotic lesions compared with evidence of progression in a diet-only group. More recently, Guyton *et al.* (2008:1567) evaluated the safety and lipid-altering efficacy of the combination of ezetimibe (10 mg), simvastatin (20 mg) and extended-release niacin. Results of the study by Guyton *et al.* showed a reduction of 58% in LDL-cholesterol and 42% in triglycerides from baseline, as well as a 30% increase in HDL-cholesterol. A combination of fenofibrate (160 mg), pravastatin (40 mg) and ezetimibe (10 mg) therapy has also been shown to improve the global atherogenic lipid profile in type 2 diabetic patients with mixed hyperlipidaemia (Farnier *et al.*, 2012).

Orlistat, a gastric lipase inhibitor (refer to paragraph 2.9.1.5.2), has also been proved a useful adjunct to conventional therapies in the treatment of severe hypertriglyceridaemia, as it reduces intestinal chylomicron synthesis in response to fatty acids. According to Wierzbicki *et al.* (2002:231), the addition of orlistat to fibrate-statin combination therapy resulted in a further 35%

reduction in triglycerides in patients with type V hyperlipidaemia.

2.9.2.6 Summary of (atherogenic) dyslipidaemia

Insulin-resistant states, such as type 2 diabetes and the metabolic syndrome, are associated with a distinctive atherogenic profile, characterised by a threefold entity of small, dense LDL-cholesterol particles, moderately raised (often high normal) triglycerides and low HDL-cholesterol and apolipoprotein A-1 levels (refer to paragraph 2.9.2.1). Each of these types of lipids is independent risk factors for the metabolic syndrome, diabetes and CVD, contributing significantly to cardiovascular morbidity and mortality in the industrialised world (refer to paragraph 2.9.2.3). This causes concern – especially with the majority of the world's population having elevated levels of total serum cholesterol (refer to paragraph 2.9.2.2).

Non-treatment of dyslipidaemia carries a high cost in terms of human life and health care expenditures (Tovar & Schering, 2006:63). Conversely, 2-3 years' treatments with lipid-modifying agents can lead to a substantial reduction in cardiovascular-related inpatient care, thus avoiding the utilisation of unnecessary, expensive health care resources such as hospitalisation or surgical procedures. Low serum cholesterol levels are furthermore associated with an increased longevity and a better quality of life. Improving these levels may ultimately reduce the use of scarce resources (refer to paragraph 2.9.2.4).

Current dyslipidaemia treatment guidelines deal with the role of lifestyle changes; the management of major cardiovascular risk factors and the use of prophylactic therapies in the deterrence of CVD (refer to paragraph 2.9.2.5). The collective effect of multiple therapeutic lifestyle changes may yield up to a 30% decrease in LDL-cholesterol and result in a significant increase in HDL-cholesterol (Hayden, 2006:170) and is considered more cost-effective than pharmacological therapies for the primary prevention of CVD in patients with dyslipidaemia (Prosser *et al.*, 2000:778).

Although the mainstream of patients will be able to manage their dyslipidaemia successfully with intensive dietary modification and exercise, most of them will fail to achieve LDL-cholesterol goal levels that decrease the risk for CVD (Gau & Wright, 2006:450). The majority of patients thus often require the addition of pharmacological therapies. There are currently several classes of lipid-modulating agents available for the treatment of abnormal lipoprotein levels. Of these, the statins are considered the agents of choice for patients with abnormal LDL-cholesterol levels, whereas niacin/nicotinic acid and the fibrates are considered the agents of choice for patients with high triglyceride and low HDL-cholesterol levels. Combining dietary therapy with different pharmacological therapies may also enhance the cost-effectiveness of

therapies.

2.9.3 Elevated blood pressure

Elevated blood pressure occurs frequently in individuals with insulin resistance; hypertension is therefore commonly listed among metabolic risk factors for the metabolic syndrome (Grundy & Brewer *et al.*, 2004:433). A discussion concerning the classification, prevalence and the risk for elevated diastolic and systolic blood pressure for metabolic syndrome, diabetes and CVD is provided here. Section 2.9.3 concludes with a discussion on the treatment of hypertension.

2.9.3.1 Definition and classification of elevated blood pressure levels

Levine and Levine (2006:263) define normal blood pressure as “*systolic pressure lower than 120 mmHg and diastolic pressure lower than 80 mmHg, although even lower systolic pressure down to 100 mmHg may be preferable*”. Prehypertension is then defined as systolic pressure in the range of 120-139 mmHg or diastolic pressure between 80-89 mmHg, whereas an elevated blood pressure is defined as the level that exceeds the threshold for either systolic or diastolic blood pressure (i.e. 130/85 mmHg) (Leibowitz & Grossman, 2009:S277). Giles *et al.* (2005:505) and Poulter (2010:11) define hypertension (high blood pressure) as a repeatedly elevated blood pressure exceeding 140- over 90 mmHg.

The South African hypertension guideline (Seedat *et al.*, 2006:341) – a joint guideline by the Southern African Hypertension Society (SAHS) and the South African National Department of Health - was based on the European Society of Hypertension/European Society of Cardiology guidelines (Mancia *et al.*, 2007:1105). According to these guidelines, high blood pressure in adults over the age of 18 years is divided into various stages, as depicted in Table 2.7.

Table 2.7: Current recommended blood pressure thresholds in adults (Seedat *et al.*, 2006:341)

Category	Recommended blood pressure threshold	
	Systolic blood pressure (SBP) mmHg	Diastolic blood pressure (DBP) mmHg
Optimal	<120	<80
Normal	120-129	80-84
High-normal	130-139	85-89
Borderline high	140-149	<90
Mild hypertension (Stage I)	140-159	90-99
Moderate hypertension (Stage 2)	160-179	100-109
Severe hypertension (Stage 3)	>180	>110
Isolated Systolic	≥140	<90

Normal blood pressure in children is defined as a blood pressure <90th percentile for gender, age and height. Hypertension in children is then defined as the systolic blood pressure and diastolic blood pressure $\geq$ 95th percentile for gender, age and height on three or more occasions. Blood pressure levels between the 90th and 95th percentile are regarded as “high normal” and denoted as “prehypertension in children”. Adolescents with blood pressure levels $\geq$ 120/80 mmHg should also be considered prehypertensive. Stage 1 hypertension in children and adolescent is then defined as a systolic blood pressure and diastolic blood pressure at the 95th to 99th percentile plus 5 mmHg, and stage 2 hypertension as a systolic blood pressure and diastolic blood pressure >99th percentile plus 5 mmHg (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004:555-560). Based on the findings from an analysis in Han adolescents, Lu and co-workers (2010:5) furthermore advocate the use of the “blood pressure-to-height” ratio, measured as 75 over 48 mmHg for males and 78 over 51 mmHg for females as optimal thresholds for stages 1 and 2 hypertension in children.

2.9.3.2 Prevalence and epidemiology of elevated blood pressure

A pooled analysis by Kearney *et al.* (2005:220) showed that approximately 1 billion of the world’s adult population (26.6% of men vs. 26.1% of women) had hypertension in the year 2000. About one-third of these individuals were in economically developed countries (the residual two-thirds lived in economically developing countries), with the highest prevalence in Eastern Europe and the Latin American/Caribbean region (Kearney *et al.*, 2005:219). The lowest prevalence of hypertension was in Korea, Thailand/Taiwan (at rates between 19.8% and 30.5% for men and 19.4 to 21.4% for women, respectively) and sub-Saharan Africa (at rates of 15% in Cameroon and 33.1% in Zimbabwe). Addo *et al.* (2007:1015) furthermore showed a higher hypertension prevalence in urban than rural areas of sub-Saharan African countries. Data from the 2005-2006 NHANES indicated an overall prevalence of 29% for hypertension and 28% for prehypertension (Lloyd-Jones *et al.*, 2010:e115) in the US population. Din-Dzietham and co-workers (2007:1493) estimates the general prevalence of hypertension and prehypertension in children and adolescents at approximately 4% and 10%, respectively.

The most comprehensive estimates of the prevalence of hypertension in South Africa were provided by the 1998-Demographic and Health Survey (SADHS). Data from this survey showed that an estimated 29% of all people aged 15 years and older in South Africa had hypertension in 1998. Approximately 3.3 million South Africans therefore had a blood pressure equal or above 160/95 mmHg and 6.1 million had a blood pressure equal or above 140/90 mmHg, of whom 13% were male and 16% female (Department of Health, 2002). Data from the 2003-SADHS showed a decrease in prevalence to a rate of 27.6% (8.8% male vs.

18.8% female) (Department of Health, 2007).

The patterns of blood pressure (systolic and diastolic) (and therefore prevalence) vary by patients' age and gender, beginning in adolescence and maintained throughout adulthood. Data from the Framingham Heart Study (Franklin *et al.*, 1997:313) established a linear rise, independent of gender, in systolic blood pressure from age 30 through 84 years and concurrent increases in diastolic blood pressure and mean arterial pressure. After age 50-60 years, the decline in diastolic blood pressure is consistent (Franklin *et al.*, 1997:313). Data from the Framingham Study furthermore showed a more remarkable ascend in systolic pressure in older females than in their male counterparts (Kannel, 1995:185), for example among patients aged 69-80 years, systolic hypertension represents 8% and 69% of all hypertension diagnosed in men and women, respectively. Elevated systolic hypertension predominates in patients aged 65-89 years, regardless of gender (Bakris, 2007:S4). Tu and co-workers (2008:1432) recently confirmed previous research findings that the prevalence of hypertension is higher in younger male patients, compared with their female counterparts, also adding that the opposite was true in patients aged 50 years and older from their study. According to Vasan *et al.* (2002:1006), the lifetime risk for becoming hypertensive among adults 50 years and older, is 90%.

In an estimate of high blood pressure burden in South Africa in 2000, Norman and Gaziano *et al.* (2007:694) determined that mean systolic blood pressure increased with age and was higher in males than females across all ages, except for those aged 70-79 years and those older than 80 years, where the opposite was true. The population-attributable fraction of disease burden from the study was therefore higher in males under the age of 70 years and higher in females older than 70 years.

2.9.3.3 Elevated blood pressure as risk factor

Elevated blood pressure is a common and powerful predisposing factor for stroke, coronary disease, cardiac failure and peripheral artery disease, imposing a 2- to 3-fold increased risk for one or more of this atherosclerotic sequela (Kannel, 2009:556; Tocci *et al.*, 2008:1477). Data from the World Health Organization Global Burden of Disease Study (Lawes *et al.*, 2008:1515) showed that approximately 54% of stroke, 47% of ischemic heart disease, 75% of hypertensive disease and 25% of other cardiovascular diseases globally in 2001, were caused by high blood pressure. Although global WHO data from 2004 showed a decline in cardiovascular risk attributable to high blood pressure, according to Mathers *et al.* (2009), 51% of stroke (cerebrovascular disease) and 45% of ischemic heart disease deaths were still attributable to high systolic blood pressure in 2004. Norman and Gaziano *et al.* (2007:694-695) estimated that high blood pressure caused 46 888 (95% CI: 44 878 - 48 566), or approximately 9% of all

deaths and 390 860 or 2.4% of all DALYs (95% CI: 377 955 - 402 256) in South Africa in 2000. Similar to the data from the WHO, approximately 50% of stroke, 42% of ischemic heart disease, 72% of hypertensive disease and 22% of other cardiovascular burden in South African adults older than 30 years were attributable to a systolic blood pressure ≥ 115 mmHg in 2000.

Diastolic blood pressure is a more potent cardiovascular risk factor than systolic blood pressure until age 50 years; thereafter systolic blood pressure plays a more important role (Franklin *et al.*, 2001:872). According to Lewington *et al.* (2002:1909) each difference of 20 mmHg systolic blood pressure increase or 10 mmHg diastolic blood pressure increase over 115/75 mmHg at ages 40-69 years, was associated with more than a 2-fold increase in mortality associated with coronary artery disease and stroke. The absolute differences in risk per year were larger in old age, although the proportional differences in vascular mortality were about half as severe at ages 80-89 years as at ages 40-49 years. The age-specific associations in the study by Lewington and colleagues were comparable for men and women (Lewington *et al.*, 2002:1910).

The presence of metabolically linked risk factors and already existent cardiovascular conditions furthermore enhance the likelihood of the development of cardiovascular disease in the hypertensive patient considerably (Alba & Delgado, 2009:147). The occurrence of these co-morbidities is more pronounced among women; Ong (2008:1146) estimate that women with hypertension are significantly more likely to have three or more cardiovascular disease risk factors. Patients with hypertension commonly present with concomitant diabetes mellitus and dyslipidaemia (Wong *et al.*, 2007:2431). For example, hypertension is 2- to 3-times more common in patients with type 2 diabetes mellitus than in non-diabetic subjects (Bretzel, 2007:S36) and is frequent in patients with type 1 diabetes as well (Maahs *et al.*, 2005:302). The time course and natural history of hypertension, however, differ markedly between type 1 and 2 diabetes. In type 1 diabetes, blood pressure levels are usually normal for the first 5-10 years, where after it rises shortly after the onset of micro-albuminuria, increasing further at the stage of proteinuria and with end-stage renal disease (Weidmann *et al.*, 1993:1510). Hypertension is subsequently present in about one-third to half of patients with type 1 diabetes (Motala, 1996:70), in particular men, those with micro-angiopathy, overweight or obesity and older age (Chillarón *et al.*, 2011:234) and longer diabetes duration i.e. of greater than 30-year duration (Motala, 1996:70). By contrast, hypertension occurs in ~40% of patients with type 2 diabetes (Jarret, 1990:556) and may be discovered before or at the time of diagnosis or may develop during nephropathy (Weidmann *et al.*, 1993:1510). Data from the Multiple Risk Factor Intervention Trial (Brancati *et al.*, 1997:2072; Stamler *et al.*, 1993:443) and the PROCAM Study (Assmann *et al.*, 2002:314) furthermore showed that diabetes and hypertension are additive risk factors for atherosclerosis and CVD and that hypertension enhances the risk for such disease more in patients with diabetes than in normoglycaemic hypertensive subjects.

Hypertension also increases the risk for micro-and macrovascular complications in patients with type 2 diabetes (Nazimek-Siewniak *et al.*, 2002:273). Moreover, elevated blood pressure is strongly correlated with body weight, for example, data from the Framingham study suggests that approximately 78% of hypertension in men and 65% in women are directly attributable to adiposity (Garrison *et al.*, 1987:249). Doll *et al.* (2002:52) and Das *et al.* (2005:76) confirmed these statements respectively measuring a higher prevalence of hypertension among study participants with greater BMIs and waist-to-hip ratios. According to Lloyd-Jones *et al.* (2005:470) and Ong *et al.* (2008:1146), this effect is more pronounced in women up to age 60 years.

Hypertension may affect from 33% up to 85% of patients with metabolic syndrome (Franklin *et al.*, 2006:2014; Leoncini *et al.*, 2005:458), whereas patients with metabolic syndrome have a 2-fold risk for new hypertension, compared with those without the syndrome (Franklin, 2006:296). The prevalence of metabolic syndrome among those with hypertension varies with age and gender – being higher in older individuals (Addo *et al.*, 2007:1015; Redon *et al.*, 2009:255). Young women with the metabolic syndrome rarely have a 10-year, 20% risk for cardiovascular events, compared with 20% of their male counterparts with metabolic syndrome who are at this risk level (Wong *et al.*, 2003:1424). This situation changes considerably in middle age, where after there is a gender-related reversal whereby more women than men develop hypertension due to hormonal changes, predominantly isolated systolic hypertension (Clara *et al.*, 2007:16; Franklin *et al.*, 2001:872).

Small reductions in blood pressure may have a significant preventive beneficial effect on cardiovascular events. For example, Van den Hoogen *et al.* (2000:4) showed that sustained differences of 10 mmHg in systolic blood pressure and of 5 mmHg in diastolic blood pressure were each associated with a 28% difference in the risk of death from coronary heart disease.

2.9.3.4 Elevated blood pressure disease burden

Hypertension is one of the leading risk factors for cardiovascular disease (refer to paragraph 2.9.3.3) and represents a major progressive economic and health burden (Duvnjak *et al.*, 2008:84). Based on a global analysis by Gaziano *et al.* (2009:1477), elevated blood pressure is likely to cost nearly US\$ 500 billion a year in direct health care related expenditure. In the presence of indirect costs, this amount could be approximately 20 times that. Lawes *et al.* (2008:1515) furthermore showed that non-optimal blood pressure (i.e. systolic blood pressure >115 mmHg) was responsible for 7.6 million deaths per year (i.e. ~14% of the global total), as well as a loss of 92 million disability-adjusted life years worldwide (i.e. ~6% of the global total in 2001). Based on calculations by Norman, Bradshaw and Schneider *et al.*

(2007:638) high levels of blood pressure accounted for 2.4% of the 16.2 million DALYs in South Africa for the year 2000.

The burden of hypertensive disease is more pronounced (>50-80%) in low-income and middle-income regions, as well as in younger patients (Lawes *et al.*, 2008:1515-1516). In high-income countries, only 7% of deaths caused by high blood pressure occur in individuals under the age of 60 years, compared with 25% in the African Region (Mathers *et al.*, 2009). Compared with normotensive individuals, those with hypertension furthermore report more bodily pain, poorer general health, more limitations in social activities and lower scores on emotional scales (e.g. vitality and mental health) (Erickson *et al.*, 2001:542; Liang *et al.*, 2006:228; Ogunlana *et al.*, 2009). Presenteeism resulting from hypertension was also associated with substantial cost, accounting for up to US\$ 279.5 billion in the US for 2003 (DeVol *et al.*, 2007).

Data from the 2006-US National Ambulatory Medical Care Survey showed that management of hypertension accounts for approximately 30% of ambulatory care office visits for people aged 45-64 years, compared with more than 40% of visits for people aged 60-74 years and those older than 75 years (Cherry *et al.*, 2008:25). The direct and indirect costs of hypertension are also significant, for example, hypertension is the second most costly cardiovascular related disorder in the US, at total costs of US\$69.4 billion in 2008, \$73.4 billion in 2009 and \$76.6 billion in 2010 (Lloyd-Jones *et al.*, 2010:e92,e118).

Recent research confirmed the cost-effectiveness of hypertension guidelines *inter alia* in countries such as Finland (Booth *et al.*, 2007), Germany (Gandjour & Stock, 2007:260), England (Richardson *et al.* 2004:769) and Argentina (Perman *et al.*, 2011). According to Cutler and co-workers (2007:100), antihypertensive treatment has generated a benefit-to-cost ratio of at least 6:1. However, up to two-thirds of patients with hypertension are not treated successfully, that is, achieve blood pressure control with treatment (Alderman, 2007:347). Failure by patients to use medication as prescribed (poor compliance and persistence) and poor adherence are major reasons for poor blood pressure control (Bramlage & Hasford, 2009), adverse health outcomes (Halpern *et al.*, 2006:1046), substantial health care costs (Brunenberg *et al.*, 2007:240; Gaziano *et al.*, 2009:1472) and higher health care resource utilisation such as use of hospital and emergency department services, office visits and other medical resources (Lynch *et al.*, 2009:875,879; Sokol *et al.*, 2005:527). Likewise, days absent from work are associated with substantial cost. In 1996, employees with hypertension lost nearly US\$12 billion in wages due to missed workdays (Druss *et al.*, 2001:237). Based on a report by the American Hospital Association (2007), 4.5 weeks of work were lost for every 1 000 US workers in 2006, due to episodes of hypertension.

2.9.3.5 Treatment of elevated blood pressure

The 2006-Hypertension Guidelines of South Africa based on the 5th and 7th Report of the Joint National Commission (JNC) for the Management of Blood Pressure, states that hypertensive adults should be managed according to associated cardiovascular disease risk (Greeff, 2006:18). The guidelines warrant dietary treatment for six months to achieve targeted blood pressure control. Pharmacological treatment is advocated in individuals with a low added CVD risk (despite a 6-12 month period of lifestyle modification and observation), for those with moderate added risk despite lifestyle modification and those with high or very high added risk (Seedat *et al.*, 2006:340). Targets for blood pressure on lifestyle modification and medicine treatment are <140/90 mmHg for all stages of hypertension (Zhang *et al.*, 2011:1506) and <130/80 mmHg for high-risk patients (i.e. those with diabetes, renal disease and congestive heart failure) (Chobanian *et al.*, 2003a:2560; Greeff, 2006:18). The use of lifestyle treatment is furthermore advocated for those with prehypertension (Chobanian *et al.*, 2003a:2560; Pimenta & Oparil, 2010:28).

Similar to adults, lifestyle changes (i.e. exercise and diet with weight reduction where appropriate) should be initiated in children and adolescents with blood pressure in the high-normal range (systolic or diastolic blood pressure >90th percentile for age, sex and height) or blood pressure >120/80 mmHg (Lurbe *et al.*, 2009:1721). For those children not reaching the goal after 3-6 months or for those with secondary hypertension, monotherapy with antihypertensives should be initiated (Salanitro & Roumie, 2010:112). Targets for blood pressure in children and adolescents with compelling indications (e.g. diabetes), are to reduce blood pressure to lower than the 90th percentile (NIH, 2005).

Lifestyle modification of hypertension is briefly discussed in the following section. A discussion on the pharmacotherapy of elevated blood pressure levels ensues in paragraph 2.9.3.5.2.

2.9.3.5.1 Lifestyle modification of elevated blood pressure

In addition to the promotion of smoking cessation, the South African Hypertension guidelines (Seedat *et al.*, 2006:340), similar to the JNC-7, specify five therapeutic lifestyle changes for the prevention and treatment of hypertension (Bond Brill, 2011:357; NIH, 2004). These changes (discussed briefly below) include a loss of excess weight (goal BMI <25 kg/m²), an increase in exercise/physical activity, reducing alcohol consumption, following a heart-healthy diet and reducing daily sodium intake to less than 100 mEq/L (i.e. <2.4 g sodium or 6 g sodium chloride)].

- **Weight loss**

The relationship between obesity and blood pressure appears to be linear in all ages (Tesfaye *et al.*, 2007:32). The strength of this association varies among different racial and ethnic groups (Doll *et al.*, 2002:55; Davy & Hall, 2004:R812). Risk estimates from the Framingham Heart Study suggested that approximately 78% of hypertension cases in men and 65% in women, respectively, were directly attributable to overweight or obesity (Garrison *et al.*, 1987:234). Similar findings were reported more recently by Kotsis *et al.* (2005:605), Pitsavos *et al.* (2008:101) and Jordan and Grassi (2010:1131), suggesting that excess weight gain is a consistent predictor for subsequent development of essential hypertension. Weight loss is therefore considered the most effective non-pharmacological therapy for the treatment of hypertension in obese hypertensive patients (Bhatt *et al.*, 2007:617; Stevens *et al.*, 2001:10).

A 5-10 kg reduction in body weight, on average, culminate in a fall of 6-10 mmHg systolic- and 3-7 mmHg diastolic blood pressure (Dickinson *et al.*, 2006:230). A systematic review by Aucott and colleagues (2009:760) however determined that the initial effects of weight loss on blood pressure might be short lived, as blood pressure tends to revert to initial levels after a period of ≥ 2 years. This therefore suggests that although weight loss is important, other aspects of lifestyle difference (such as increased physical activity, or improved diet) may also be critical for hypertension treatment. A lower body weight (in association with other dietary measures and increased physical activity) may furthermore limit the incidence of hypertension for up to 10 years by reducing the progression of prehypertension to hypertension (The Trials of Hypertension Prevention Collaborative Research Group, 1997:665).

- **Increasing exercise/physical activity**

The prevalence of hypertension is inversely related to physical activity (Bacon *et al.*, 2004:309). Physically inactive individuals also have a higher relative risk for developing hypertension compared with high fitness individuals. In addition, individuals with weight increases despite being physically active have an odds ratio 1.68 (95% CI: 1.45 - 1.94) for becoming hypertensive if male and 1.42 (95% CI: 1.05 - 1.92) if female (Williams, P.T., 2008:2542). Individuals with increased habitual levels of physical activity, have on average a 5 mmHg lower systolic blood pressure as compared with matched individuals who are not physically active or are less fit (Kokkinos *et al.*, 2001:515). Regular physical activity is therefore recommended for individuals with elevated blood pressure.

The effects of exercise on blood pressure vary to some extent, with reductions up to 3 mmHg (95% CI: 2.6 - 4.7) in systolic blood pressure and 2 mmHg (95% CI: 1.8 - 3.1) in diastolic blood

pressure in normotensive individuals. Individuals with hypertension generally experience larger reductions in blood pressure because of exercise, e.g. 6-10 mmHg in systolic- and 2.4-7.6 mmHg in diastolic blood pressure (Bronas & Leon, 2009:429).

There is some controversy on the specific form of exercise, such as aerobic vs. resistance training, as well as the intensity, duration and training intervals of the specific form of exercise to follow for blood pressure reduction. For example, according to Fagard and Cornelissen (2007:16), the reduction in blood pressure with regular physical activity appears to be independent of baseline adiposity level, age, gender and level of training intensity. Hagberg and colleagues (2000:195) on the other hand, reported that middle-aged adults experienced greater reductions in blood pressure following exercise training than young adults do. The effects were also more pronounced in women compared with their male counterparts (Hagberg *et al.*, 2000:196). In addition, findings from a recent animal study of hypertension showed excessive long-term exercise to enhance cardiac fibrosis and to have deleterious effects on cardiac remodelling (Schultz *et al.*, 2007:410). Exercise, as non-pharmacological treatment in hypertension, should therefore be moderate (Schulze, 2009:601).

- **Reducing alcohol consumption**

Results from a meta-analysis of 15 randomised controlled trials indicated that a 67% reduction in consumption of alcohol might decrease systolic and diastolic blood pressure by 3.3 and 2.0 mmHg, respectively (Xin *et al.*, 2001:1114). Foerster and co-workers (2009:366) showed similar results in a more recent analysis, thereby establishing this dose-responsive relationship between alcohol consumption and blood pressure. This elevating effect of alcohol consumption on blood pressure is also more prominent among older patients (Wakabayashi & Araki, 2010:S54).

Moderation of alcohol intake among those who drink may therefore be an effective approach to lower blood pressure. Moderate alcohol consumption has also been associated with lower coronary artery disease risk (Brügger-Andersen *et al.*, 2009:231; Suzuki *et al.*, 2009). The relationship between alcohol intake and the relative risk for developing CHD is a J- or U-shaped dose-response, where the risk is lower when alcohol consumption is light-to-moderate and is high when alcohol consumption is higher or absent altogether (Brügger-Andersen *et al.*, 2009:231; Hines & Rimm, 2001:750).

The mechanism underlying the cardioprotective effects of moderate alcohol consumption may involve prevention of atherogenesis through beneficial alcohol-induced changes in serum lipids, blood clotting proteins, platelets, inflammatory cytokines and insulin resistance (Foerster *et al.*,

2009:367; Hines & Rimm, 2001:747). An increased alcohol intake seems to cause resistance to antihypertensive therapy (Franco *et al.*, 2004:3081).

- **Heart-healthy diets/ Healthful dietary patterns**

Dietary factors play important (and likely leading) roles in elevating blood pressure (Appel, 2010:79; Sacks & Campos, 2010:2106). Dietary modification is often considered the first step in the treatment of stage-1 hypertension and is initiated before treatment with blood pressure medication commences. Based on the JNC-7 guidelines, lifestyle changes should also be initiated in individuals with blood pressure in the range of prehypertension. Among those who are already taking medication, dietary modification (with specific targets of reducing sodium intake; increasing potassium, calcium and magnesium intake, and whole dietary patterns), can further lower blood pressure and support step-down of pharmacological therapy (Appel, 2010:80).

Present dietary recommendations for the prevention of hypertension advocate a lowering in alcohol and sodium intake whilst increasing potassium intake and following dietary patterns rich in fruits, vegetables and low-fat dairy products, reduced in total and saturated fats, such as the DASH (Dietary Approaches to Stop Hypertension) diet and variants of the DASH and Mediterranean diets (Appel, 2010:80). Table 2.8 summarises some of the effects of different dietary changes on blood pressure levels.

Table 2.8: Effect of dietary modification on blood pressure levels

Dietary Intervention	Blood pressure (BP) reduction
DASH diet	Average 5.5 mmHg (SBP)/3 mmHg (DBP) (Appel <i>et al.</i> , 1997:1123) 11.4 mmHg (SBP)/5.5 mmHg (DBP) in hypertensive patients; 3.5 mmHg (SBP)/2.2 mmHg (DBP) in prehypertensive patients
Soluble fibre (11.5-14 g per day)	1.1 - 1.6 mmHg (SBP)/ 1.3 - 2.0 mmHg (DBP) (Streppel <i>et al.</i> , 2005:154; Whelton <i>et al.</i> , 2005:478).
Reduced salt intake (30-60% reduction)	2.1 - 6.7 mmHg (SBP) /1.1 – 3.5 mmHg (DBP) (Sacks <i>et al.</i> , 2001:7)
Calcium (>1 000 g/day)	1.4 mmHg (SBP) /0.8 mmHg (DBP) (Griffith <i>et al.</i> , 1999:90)
Magnesium	0.6 mmHg (SBP) /0.8 mmHg (DBP) (Jee <i>et al.</i> , 2002:691)
Monosaturated fat	2.4 - 4.8 mmHg (SBP) /2.1 - 4.8 mmHg (DBP) (Rasmussen <i>et al.</i> , 2006:224)
Long-chain omega-3 polyunsaturated fatty acid (≥3 g/d)	2.3 - 4.0 mmHg (SBP) /2.2 - 2.5 mmHg (DBP) (Dickinson <i>et al.</i> , 2006:231)
High potassium intake (1.8-1.9 g/day)	4.4 mmHg (SBP)/2.5 mmHg (DBP) in hypertensive patients 1.8 mmHg (SBP) /1.0 mmHg (DBP) in normotensive patients (Whelton <i>et al.</i> , 1997:1630).

SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

Several mechanisms are proposed whereby these dietary modifications lower blood pressure, *inter alia*:

- Resetting of the pressure-natriuresis curve (lower pressure suffices to excrete sodium and reduce blood volume) (Akita *et al.*, 2003:9).
- Reduction of aortic stiffness (Al-Solaiman *et al.*, 2009:826).
- Improvement of vasodilatation in small resistance vessels (Rallidis *et al.*, 2009:263).

2.9.3.5.2 Pharmacotherapy of elevated blood pressure

Antihypertensives are generally categorised into three groups, namely diuretics, adrenergic inhibitors (that act centrally, peripherally or as receptor blockers) and vasodilators (that act directly *via* calcium channel blockade, angiotensin-converting enzyme inhibition or angiotensin receptor blockade) (Khatib & El-Guindy, 2005:55).

The 2006-South African Hypertension guideline advocates a 3-step approach to the management of hypertension in adults without compelling indications (i.e. target-organ damage and/or associated clinical conditions) (Seedat *et al.*, 2006:344), namely:

- Step one: diuretics (low dose thiazide or thiazide-like diuretic).
- Steps two and three: allow for considerations based on the cost of the various pharmacological classes and other patient-related factors such as the presence of major risk factors, associated clinical conditions and target organ damage. One of the following medicine classes is recommended as second- or third-line therapy in the absence of other compelling indications, from: (1) angiotensin converting enzyme (ACE) inhibitors [in ACE inhibitor intolerance use angiotensin II receptor blockers (ARBs)] and (2) calcium channel blockers (CCBs) (long-acting dihydropyridines or non-dihydropyridines).

In 2003, the South African Department of Health published an algorithm for the treatment and management of hypertension as part of the Chronic Disease List (CDL) [as amendment to the regulations of the Medical Schemes Act, 1998 (Act 131/1998)] (refer to Annexure A.3 for algorithm). This algorithm specifies the use of other antihypertensives as initial therapy in compelling indications as indicated in Table 2.9.

Table 2.9: Compelling indications for the use of other antihypertensives as initial therapy (Department of Health, 2003b)

Drug class	Compelling indication
β-blocker	Angina Prior myocardial infarct (MI) or coronary artery disease Post MI Heart failure
calcium channel blockers	Angina Isolated systolic hypertension (elderly) (long-acting CCB)
ACE inhibitor	Prior myocardial infarct (MI) or coronary artery disease Post MI (in patients with systolic dysfunction) Heart failure Left ventricular hypertrophy Stroke Type 1 diabetes with proteinuria (usually in combination with diuretic) Type 2 diabetes with micro-albuminuria Type 2 diabetes without proteinuria (usually in combination with diuretic) Type 2 diabetes with proteinuria (usually in combination with diuretic)
Diuretics	Heart failure (treat with furosemide or spironolactone)
Low dose diuretic	Stroke Isolated systolic hypertension (elderly) (low dose thiazides)
ARB	Type 2 diabetes with micro-albuminuria (usually in combination with diuretic) Type 2 diabetes with proteinuria (usually in combination with diuretic)
α-blocker	Prostatism: (this should not be used as monotherapy)

A diastolic blood pressure less than 90 mmHg at the end of the titration period or maintenance of a diastolic blood pressure less than 95 mmHg for one year without tolerance is considered an optimal response to treatment of hypertension in adults (Meka *et al.*, 2010:63). According to Lasserson and colleagues (2011:1773), the time to reach 50% of the maximum estimated blood pressure lowering effect with any antihypertensive medicine is one week (systolic blood pressure 0.91 weeks, 95% CI: 0.74 - 1.10; diastolic blood pressure 0.95 weeks, 95% CI: 0.75 - 1.15). Titration increases both the predicted maximum effect and the time taken to reach 50% of the maximum estimated blood pressure lowering effect (systolic blood pressure 1.2 vs. 0.7 weeks; diastolic blood pressure 1.4 vs. 0.7 weeks). Dose titration is subsequently generally limited to a single step with a given antihypertensive (Kaplan & Rose, 2010). Pharmacological management of hypertension in paediatric patients is reserved for those who do not respond to a change in lifestyle (Pacifico *et al.*, 2011:458), with a target goal of reducing blood pressure to lower than the 90th percentile (NIH, 2005). Several pharmacological classes can be used for the treatment of high blood pressure in children, including the ACE inhibitors, angiotensin-receptor inhibitors, calcium channel antagonists, diuretics (aldosterone receptor antagonists), α- and β-blocking agents and α-agonists (Lande & Flynn, 2009:1942).

Based on a review of 354 trials of blood pressure-lowering agents, Law and co-workers (2003:1429) concluded that the major categories of antihypertensives (i.e. thiazides, β -blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and calcium channel blockers) “gave similar blood pressure reductions.” The mean placebo-adjusted reduction in this analysis by Law *et al.* was 9.1 mmHg (95% CI: 8.8 - 9.3) systolic and 5.5 mmHg (95% CI: 5.4 - 5.7) diastolic at standard/usual maintenance doses. Given in half the standard dose, blood pressure was only 20% lower. It is therefore recommended that in case of inadequate response with initial monotherapy doses are up-titrated (until adequate response is achieved or adverse events are intolerable), products are substituted (sequential monotherapy until the right agent is found), or combination therapy by the addition of a second, third or even fourth agent (either as multiple individual agents or as fixed-dose combinations) until blood pressure control is achieved (Ker, 2005:40; Stanton & Reid, 2002:75).

A discussion on each of the three antihypertensives groups that may be used in the treatment of hypertension (i.e. diuretics, adrenergic inhibitors and vasodilators) follows in subsequent sections.

- **Diuretics**

Diuretics have been used successfully during the past 40 years to treat hypertensive patients, forming the basis of therapy (monotherapy or in combination with other antihypertensives) (Shah *et al.* 2004:271). Diuretics may further enhance the antihypertensive efficacy of multidrug regimens, can be useful in achieving blood pressure control, have acceptable adverse effects profile, have a counteractive effect on salt and fluid retention caused by other antihypertensives and are more affordable compared with other antihypertensive agents (Chobanian *et al.*, 2003a:2564; Vidt, 2003:263). Chrysant and Oparil (2001:768) are further of the opinion that diuretics are “virtually unsurpassed” in preventing the cardiovascular complications of hypertension (coronary heart disease, stroke, heart failure and peripheral arterial disease) in individuals with metabolic syndrome.

Diuretics used for the treatment of hypertension may be divided in 3 major groups based on their primary site of action within the renal tubule, starting in the proximal portion and moving towards the collecting duct, namely the loop diuretics, thiazides and related sulphonamide compounds and potassium sparing agents (kidney epithelial sodium channel inhibitors and aldosterone receptor antagonists) (Opie & Gersh, 2001:84). The loop of Henle agents are the most powerful based on diuretic potency, causing the flux of 20-25% of filtered sodium load. The thiazide group and metolazone are moderately potent, resulting in the flux of 5-8% of filtered sodium, whereas the potassium-sparing agents are only mildly potent, causing the flux

of only 2-3% of filtered sodium (Brown, 2003:687; Hunt *et al.*, 2009:e24).

– **Loop diuretics**

Furosemide is the prototype loop diuretic; the class also includes bumetanide, ethacrynic acid, piretanide and torasemide. Loop diuretics, as a class, are less effective as antihypertensives although more potent as natriuretics than thiazides (Shah *et al.*, 2004:275). At best, these agents lower systolic blood pressure by 7.9 mmHg (95% CI: -10.5 to -5.4) and diastolic blood pressure by 4.4 mmHg (95% CI: -5.6 to -2.8) (Musini *et al.*, 2009:CD003825). The major use of these diuretics is in patients with renal insufficiency (GFR <50% of normal) and those with congestive heart failure (Guthrie, 2010:21). Loop diuretics can also benefit patients with hepatic, intestinal and ankle oedema coupled with right-sided heart failure or with ascites (Min & White, 2009:131). The loop diuretics are furthermore fundamental for treatment in children with advanced chronic renal failure or with heart failure (Lurbe *et al.*, 2009:1733). Ethacrynic acid is less widely used because of its side-effect profile and relative insolubility that makes it very difficult to administer intravenously. Ethacrynic acid is therefore primarily used for the treatment of patients who are allergic to sulphonamide derivatives such as furosemide, bumetanide and the thiazides (Molnar & Somberg, 2009:86).

Loop diuretics act primarily on the thick ascending limb of the loop of Henle, inhibiting the transport of sodium chloride out of the tubule into the interstitial tissue by inhibiting the sodium-potassium-chloride co-transporter on the apical membrane (Girvin & Johnston, 2009:17). [Furosemide, torasemide and bumetanide act directly on the chloride-binding site thereby inhibiting the carrier (Chen, 1996:343), whereas ethacrynic acid forms a complex with cysteine (Materson, 1983:189)]. Reabsorption of sodium chloride is reduced and the lumen-positive potential is reduced due to potassium recycling. Together these result in a diuresis, a secondary kaliuresis and loss of magnesium and calcium (Shankar & Brater, 2003:F12). Loop diuretics may also increase renal prostaglandin synthesis, accounting for the acute vasodilator effects on the renal arterioles and systemic veins (Girvin & Johnston, 2009:18). The loop diuretics thus lower blood pressure acutely because of its potent natriuretic effect and consequent fall in circulating blood volume.

The rate at which all loop diuretics is delivered to its site of action is dose-dependent and determines the efficacy thereof (Rose *et al.*, 2010). In normal individuals, an intravenous dose of furosemide (40 mg) results in a maximal response. Going above this maximum will produce no further diuresis but may increase the risk for adverse effects. The loop diuretics are similar in potency when given at equipotent doses (Min & White, 2009:132), i.e. a dose of furosemide (40 mg) is equivalent to bumetanide (1 mg) administered intravenously and torasemide

(15-20 mg) either oral or intravenous in patients with preserved renal function. In patients with severe renal insufficiency, furosemide (20 mg) is equivalent to bumetanide (1 mg) and torasemide (10 mg) (Min & White, 2009:132).

Because of its more favourable cost profile, furosemide has been the most commonly prescribed agent in the group of loop diuretics up to date (Gattis Stough *et al.*, 2006:510). Stroupe and colleagues (2000:429) however showed that torasemide had an even more favourable profile compared with furosemide for the treatment of heart failure. For example, patients treated with torasemide had fewer hospital admissions than those treated with furosemide, as well as a lower expected annual hospital cost per patient. The total direct costs were US\$ 2,124 lower with torasemide than with furosemide despite a higher acquisition cost, but this difference failed to reach statistical significance (Stroupe *et al.*, 2000:438). A pharmacoeconomic study by Noe and co-workers (1999:583) comparing torasemide and furosemide for treatment of heart failure furthermore indicated that a patients on torasemide had a mean of 1.6 days less hospital stay compared with those receiving furosemide. Patients receiving torasemide also had significantly better quality-of-life scores at 4 months. A recent comparison between torasemide and furosemide by the authors Wargo and Banta (2009:1845), showed torasemide as potentially cost saving compared with furosemide.

Loop diuretics are ineffective monotherapeutic agents for essential hypertension in the absence of a renal insufficiency rate. These agents should therefore only be added when therapeutic end-points cannot be achieved by life-saving alternative modalities (Min & White, 2009:132). Frequently reported adverse effects with the loop diuretics include dermatological sensitivities, gastro-intestinal irritabilities and haematological disturbances (Krakoff, 2005:e128). Loop-active diuretics may further cause hypokalaemic and hypomagnesaemia (Aronson, 2009:205), leading to life-threatening ventricular arrhythmias (Min & White, 2009:132). Chronic loop diuretic therapies (except with bumetanide) furthermore reduce tubular uric acid elimination – use is therefore discouraged in patients with a history of gout attack or near-baseline hyperuricaemia (Terkeltaub *et al.*, 2009:445; Pascual & Perdiguero, 2006:981). Loop diuretics (especially ethacrynic acid) may also cause ototoxicity, resulting in temporary or permanent deafness (Molnar & Somberg, 2009:91).

– **Thiazide and thiazide-like diuretics**

Thiazides and the thiazide-like diuretics has been the cornerstone in the long-term management of hypertension for more than half a century since their introduction in the late 1950's (Moser & Feig, 2009:1851). They bring about a decrease in the systolic and diastolic blood pressures of 10-15 mmHg and 5-10 mmHg respectively, and are considered the agents of choice in the

elderly, patients from African descent and patients with characteristics associated with high cardiac output (e.g. obesity) (Cutler & Davis, 2008:2703). Thiazides also revise the hypertension and electrolyte abnormalities associated with Gordon's syndrome (Ernst & Moser, 2009:2156) and potentiate other antihypertensive agents when used in combination, often producing an additive decrease in blood pressure (Palmer & Naderi, 2007:381). Moreover, pooled results from meta-analysis and systematic reviews report that thiazide-based therapy, as compared with placebo, reduces relative rates of heart failure (by 41-49%), stroke (by 29-38%), coronary heart disease (by 14-21%), and death from any cause (by 10-11%) (Law *et al.*, 2009; Psaty *et al.*, 2003:2542; Wright & Musini, 2009:CD001841). Despite the less favourable metabolic profile associated with thiazide diuretics (refer to adverse effects below), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that treatment with a thiazide-type diuretic in patients with diabetes as well as the metabolic syndrome resulted in superior cardiovascular outcomes compared with treatment with calcium channel blockers, α -blockers, and ACE inhibitors (Black *et al.*, 2008:357; Wright *et al.*, 2008:215).

Thiazides and thiazide-like diuretics exert similar actions in the distal convoluted tubule by inhibiting the electroneutral sodium-chloride symporter, so-doing interfering with sodium reabsorption (Ernst & Moser, 2009:2153). This results in a decrease in plasma and extracellular volume. This sodium depletion results in activation of the renin-angiotensin-aldosterone system, increasing renin release from the juxtaglomerular apparatus and the formation of angiotensin II (Atlas, 2007:S10). This in turn leads to vasoconstriction, sodium retention and activation of the sympathetic nervous system (Sood *et al.*, 2010:886).

Hydrochlorothiazide and chlorthalidone are the two most frequently used diuretics in major clinical trials (Ernst & Moser, 2009:2158). Chlorthalidone is approximately 1.5-2.0 times (i.e. 50-75%) more potent than hydrochlorothiazide on a milligram-to-milligram basis (Neff & Nawarskas, 2010:52). The two agents are considered interchangeable, although most fixed-dose combination products incorporate hydrochlorothiazide (Carter *et al.*, 2004:4; Psaty *et al.*, 2004:43). Chlorthalidone also has a much longer duration of action (Carter *et al.*, 2004:5) and was shown to be superior to both amlodipine and lisinopril in its effects on the primary end point of coronary heart disease and mortality as first-line therapy in a step-up treatment regimen (The ALLHAT Officers and Coordinating for the ALLHAT Collaborative Research Group, 2002:2995).

Pooled data from a recent systematic review (Chen & Zhou *et al.*, 2010:CD003654) showed that 12.5 mg and 25 mg hydrochlorothiazide (monotherapy) decreased systolic blood pressure and diastolic blood pressure by 5.7/3.9 mmHg and 8.5/4.7 mmHg, respectively. Indapamide shows little advantage over other thiazide and thiazide-like diuretics (Shah *et al.*, 2004:274). The

sustained release form, though, showed decreases in fatal stroke of 39%, heart failure of 64% and death of 21% in patients older than 80 years of age (Beckett *et al.*, 2008:1887). Metolazone is rarely used to treat hypertension but because it remains an effective diuretic in patients with impaired renal function, it is used in combination with a loop diuretic to treat refractory oedema in congestive cardiac failure (Shah *et al.*, 2004:275).

Liew *et al.* (2004:S148) proved thiazide diuretics as the most cost-effective agents for the primary prevention of cardiovascular disease at an incremental cost-effectiveness ratio of US\$929 per DALY according to a $\geq 15\%$, 5-year risk (compared with β -blockers, calcium channel blockers and renin angiotensin system antagonists). Fretheim and co-workers (2003:18) found similar results, furthermore showing the cost of “many non-thiazide drugs” (i.e. α -blockers, β -blockers, calcium channel blockers, ACE inhibitors and angiotensin II receptor blockers) to be 10-fold that of thiazides. According to these authors, thiazides were by far the lowest priced antihypertensive agents in the majority of countries in the early 20th century (e.g. Canada, the US, the UK, Germany, France and Norway) (Fretheim *et al.*, 2002:963).

There remains some controversy as to whether thiazides should be the initial treatment for all hypertensive patients, because of the number of associated metabolic complications. These include hypokalaemia, metabolic alkalosis, hypomagnesaemia, hyperuricaemia and decreased urinary calcium excretion (Duarte & Cooper-DeHoff, 2010:793; Krakoff, 2005:e128; Salvetti & Ghiadoni, 2006:S26). Thiazides may also affect lipid metabolism, causing increases of approximately 4% in total cholesterol levels and 10% in LDL-cholesterol levels (Neutel, 1996:80S). A more recent study by Martins and co-workers (2008:572) showed similar findings, suggesting that treatment with diuretic monotherapy might even promote an atherogenic lipid profile. Type 2 diabetes and glucose intolerance might also develop during the course of thiazide-type diuretic treatment (Kostis *et al.*, 2005:34; Siegel & Swislocki, 2010:96). Caution is therefore advised in using thiazide diuretics in patients with an increased risk for the development of type 2 diabetes, i.e. those with the metabolic syndrome, fasting glucose intolerance and/or obesity. Salvetti and Ghiadoni (2006:S26) recommended the close monitoring of metabolic parameters in these patients, with thiazides treatment at the lowest active dose and possibly in combination with renin angiotensin system (RAAS) antagonists.

– **Potassium sparing agents**

There are two classes of potassium-sparing diuretics: competitive antagonists of aldosterone (e.g. spironolactone and eplerenone) and kidney epithelial sodium transport channel (ENaC) inhibitors (e.g. triamterene and amiloride) (Opie & Gersh, 2001:84). Potassium-sparing agents induce only minimal natriuresis and are relatively ineffective in lowering blood pressure. Their

usefulness therefore resides in their ability to reduce the loss of potassium and hydrogen cations, especially in states of hyperaldosteronism when more proximal acting diuretics increase distal delivery and severe heart disease (Sica, 2007:73; Warrilow, 2009:562). Potassium-sparing diuretics also prevent the urinary loss of magnesium and are therefore used in combination with thiazide or loop diuretics to prevent hypokalaemia (Shah *et al.*, 2004: 275).

The potassium-sparing diuretics have their major sites of activity in the late reaches of the distal convoluted and in the collecting duct (Shah *et al.*, 2004:272). The mechanism of the action of potassium-sparing diuretics involves the aldosterone-responsive segments of the distal nephron, the controlling site for potassium homeostasis. Aldosterone increases the reabsorption of sodium ions whereby a negative potential is set up in the lumen, leading to the release and secretion of potassium and hydrogen ions into the lumen. The agents reduce sodium reabsorption by either competitively inhibiting aldosterone (spironolactone or eplerenone) or blocking sodium channels on a 1:1 basis (amiloride or triamterene). This causes the transepithelial electrical potential to fall, thereby reducing the driving force for potassium secretion (Neal, 2009:35).

Both eplerenone and spironolactone are regarded as efficacious and safe in the treatment of hypertension and heart failure, although eplerenone is approximately 50-75% as potent as spironolactone (Weinberger *et al.*, 2002:711). In the late 1960's Wolf and co-workers (1966:1147) demonstrated a reduction in blood pressure of around 10 over 5 to 20 over 10 mmHg with spironolactone (25- to 100 mg). More recently, Batterink *et al.* (2010:CD008169) showed a mean reduction in systolic blood pressure of 20.1 mmHg (95% CI: 16.58 - 23.06) and 6.8 mmHg (95% CI: 4.8 - 8.69) in diastolic blood pressure, at a median dose of 25 mg spironolactone (interquartile range: 25-50 mg). Patients with chronic, stable heart failure may furthermore benefit from a 30% reduction in relative death risk attributable to treatment with spironolactone (26 mg) treatment (Pitt *et al.*, 1999:709).

A recent review of the blood pressure lowering efficacy of amiloride and triamterene for primary hypertension showed no reduction in blood pressure and ruled out a blood pressure lowering effect of $>3/2$ mmHg (Heran *et al.*, 2010:CD008167). As second antihypertensive to hydrochlorothiazide and chlorthalidone, amiloride and triamterene also do not significantly reduce blood pressure further as compared with monotherapy (Heran *et al.*, 2010:CD008167).

Use of potassium-sparing diuretics may result in hyperkalaemia, especially in patients with chronic kidney disease or diabetes and in patients receiving concurrent treatment with an ACE inhibitor, angiotensin receptor blocker, non-steroidal anti-inflammatory agent, or potassium supplement (Krakoff, 2005:e129; McManus & Connell, 2009:1126). Spironolactone may

furthermore cause gynaecomastia in up to 10% of patients because of its anti-androgen effect (Barnes & Howard, 2006:74). Treatment with spironolactone may also result in menstrual irregularities in premenopausal women and incidences of male impotence (Karagiannis *et al.*, 2007:293). These effects occur seldom with the use of eplerenone (McManus & Connell, 2009:1126; Abuannadi & O'Keefe, 2010:323). Eplerenone is, however, approximately 6-7 times more expensive than spironolactone for the treatment of hypertension (Craft, 2004:220). Triamterene may result in a folic acid deficiency (Cassis, 2004:209).

- **Adrenergic receptor inhibitors**

Adrenergic receptors are defined by their response to stimulation by catecholamines, for example, the α -adrenergic receptor sites react predominantly to epinephrine and norepinephrine and less so, to isoproterenol, whereas β -adrenergic receptors respond primarily to isoproterenol and less so, to epinephrine and norepinephrine.

Antihypertensives that exert their action on adrenergic receptors include the selective α_1 -adrenoreceptor blockers, central α_2 -agonists, peripheral antagonists, β -adrenergic blockers and combined α - and β -adrenergic receptor blockers. From these agents, the central α_2 -agonists and peripheral adrenergic antagonists have a negative adverse effect profile – they are therefore not well suited for initial monotherapy as antihypertensive agents (Khatib & El-Guindy, 2005:57). A brief discussion of these latter two groups follows under “other antihypertensives”.

- **α -adrenergic receptor blockers**

α -Adrenergic receptors are subdivided into two distinct types based on their anatomical location: α_1 (most of which are located postjunctionally on vascular smooth muscle cells) and α_2 (located prejunctionally on sympathetic nerve endings as well as on vascular smooth muscle), with further sub-classification into α_{1A} , α_{1B} , α_{1D} , α_{2A} , α_{2B} and α_{2C} (Fine & Ginsberg, 2008:334; Kamibayashi & Maze, 2000:1345; Kanagy, 2005:433). The α_1 -adrenoreceptor has an important function in regulating vascular tone, whereas the α_2 -adrenoreceptors are concerned with the central and peripheral regulation of blood pressure (Tan & Liew, 2007:168).

The α_1 -adrenergic receptor blockers/antagonists can be further subdivided into selective (e.g. prazosin, terazosin and doxazosin) and non-selective (e.g. phenoxybenzamine, tolazoline, and phentolamine) agents (Hieble, 2000:163; Schwinn & Roehrbom, 2008:193). These agents reduce blood pressure by 8-10% in patients in the upright position, and reduce blood pressure incrementally when combined with most other antihypertensives (Sica, 2005b:757). The role of the α_1 -adrenergic receptor blocker in the treatment of hypertension has, however, become

somewhat controversial after the doxazosin arm of the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) was terminated early due to a doubling of the incidence of congestive heart failure (The ALLHAT Officers and Coordinating for the ALLHAT Collaborative Research Group, 2000:1973). The α_1 -adrenergic receptor blockers are therefore not regarded as first line therapy in patients with essential hypertension (Stump *et al.*, 2006:799), but retained for the treatment of resistant hypertension (Neal, 2009:37; Chapman *et al.*, 2010:1800). The selective α_1 -adrenoreceptor blockers are furthermore used as alternative agents for unique situations, such as men with benign prostatic hyperplasia with symptoms of lower urinary tract outlet obstruction (Taylor & Pool, 2005:221). The α_1 -antagonists are, in addition, essentially without adverse effects on glucose tolerance, uric acid and potassium levels (Lithell, 1996:150S). Some of the agents in the class (i.e. prazosin and doxazosin) also have favourable effects on lipids, reducing total cholesterol (approximately equivalent to 10 mg lovastatin) and triglycerides while increasing HDL-cholesterol by approximately 5% (Hirano *et al.*, 2001:911; Kinoshita *et al.*, 2001:269). This effect is dose-dependent and variable (Remaley, 2007:117). The non-selective α -adrenoreceptor blockers (phenoxybenzamine and phentolamine) are mainly used for the medical management of pheochromocytoma, male erectile dysfunction and Raynaud's syndrome (Tighe *et al.*, 2010:1).

Blocking of α_1 -adrenoceptors inhibit the binding of norepinephrine to the smooth muscle receptors, thereby reducing the sympathetic tone of blood vessels, resulting in a decrease of peripheral vascular resistance and vasodilation and thus a lowering of blood pressure (Tighe *et al.*, 2010:1). Prazosin, terazosin and doxazosin have equal affinity for all α_1 -receptor subtypes (Schwinn & Roehrbom, 2008:193) and are comparable in efficacy (Fine & Ginsberg, 2008:334). Phenoxybenzamine binds irreversibly and covalently to α -receptors, thereby blocking the binding of norepinephrine to the smooth muscle receptors. In addition, it also inhibits the re-uptake of released norepinephrine by presynaptic adrenergic nerve terminals, attenuating catecholamine-induced vasoconstriction, resulting in a decrease of peripheral vascular resistance thereby lowering blood pressure. Phentolamine competitively blocks both α_1 and α_2 receptors, causing a reduction in peripheral resistance (Tighe *et al.*, 2010:1). Tolazoline is an obsolete agent similar to phentolamine.

In 2004, Ohsfeldt and co-workers conducted a cost-effectiveness analysis of tamsulosin, doxazosin and terazosin in the treatment of benign prostatic hyperplasia. Results from this study showed that although tamsulosin was the most expensive of the three agents, it was more effective than generic terazosin or doxazosin, with an incremental cost of about US\$ 203 per year over a three-year period. Terazosin was the least expensive of the three agents (Ohsfeldt *et al.*, 2004:418).

A potentially severe adverse effect of the selective α_1 -adrenoreceptor antagonists is a first-dose phenomenon characterised by orthostatic hypotension accompanied by transient dizziness or faintness, palpitations and even syncope (Sica, 2005b:760; Aronson, 2009:7). These agents should be used with caution in older patients because of their diminished autonomic system compensatory responses to hypotensive stimuli (Saseen & Carter, 2008:209). Sodium and water retention also can occur with chronic administration; these agents are therefore most effective when given in combination with a diuretic to maintain antihypertensive efficacy and minimise potential oedema (Bryson & Psaty, 2002). α_1 -Antagonists may also cause priapism, fatigue, vivid dreams, weight gain and depression (Bryson & Psaty, 2002; Saseen & Carter, 2008:209). Blocking of the α_2 -prejunctional adrenoceptors in the heart by non-selective antagonists can lead to increases in heart rate and contractility due to the enhanced release of norepinephrine that binds to β_1 -adrenoceptors (Bryant & Knights, 2011:470).

– **Beta(β)-blockers**

The β -adrenergic receptors can be subdivided based on potency into subtypes β_1 (responsible for cardiostimulation and lipolysis), β_2 (responsible for bronchodilation and vasodepression), β_3 (stimulate thermogenesis) and possibly β_4 (Kanagy, 2005:433; Vansal, 2004:5).

β -blockers were traditionally used as first line agents in the treatment of uncomplicated hypertension. Recent trials and meta-analysis, however, questioned the use of these products as ideal agents (De Caterina & Leone, 2010:1435; Lavie & Messerli *et al.*, 2009:1163; McGill, 2010:365; Panjra & Messerli, 2006:84; Tsaltas *et al.*, 2008:42), arguing that the β -blockers are “less effective” and have “numerous adverse effects” compared with other antihypertensive agents currently available. In addition, β -blockers do not result in any significant risk reduction for the end-points of all-cause mortality, cardiovascular mortality and non-fatal myocardial infarction - even when compared with placebo (Bradley *et al.*, 2006:2139; Khan & McAlister, 2006:1740). They are associated with a 19-20% reduction in the risk for stroke (Lindholm *et al.*, 2005:1549; Wiysonge *et al.*, 2007:CD002003); albeit, this reduction is inferior to that produced by other antihypertensives (Warmack *et al.*, 2009:2039). On the other hand, Ram (2010:1821) argues that much of the unfavourable data were compiled from studies involving the traditional, non-vasodilating type β -blockers.

The South African Hypertension guidelines advocate that β -blockers should be retained for use in patients with angina pectoris, post-myocardial infarction, congestive heart failure and tachyarrhythmias (Seedat *et al.*, 2006:346). Aronow (2010:S5) and Ram (2010:1822-1824) add diabetes mellitus, acute coronary syndromes, after coronary artery bypass graft surgery and patients who are pregnant, have thyrotoxicosis, glaucoma, migraine, essential tremor,

perioperative hypertension, or an excessive blood pressure response after exercise, to this list of uses for β -blockers.

β -blockers can be sub-classified into three (possibly four) categories depending on their properties/potency (Schwinghammer, 2009:117):

- First-generation compounds (i.e. nadolol, pindolol, propranolol and timolol) are non-selective in their blockade of beta-adrenergic receptors.
- Second-generation compounds (i.e. metoprolol, atenolol, betaxolol, esmolol and bisoprolol) have no ancillary vasodilating effects and can be considered “cardioselective” as they have much greater affinity for β_1 than β_2 receptors at low doses. This selectivity is lost at high doses. Acebutolol, carteolol, penbutolol and pindolol possess intrinsic sympathomimetic activity or partial β -receptor agonist activity. The density of β -receptors changes with disease, for example in heart failure β_1 -receptors are down-regulated (Hefland *et al.*, 2007).
- The third-generation compounds carvedilol, bucindolol and labetalol lack intrinsic activity, but have both non-selective β -blocking and α_1 -blocking properties (Opie & Yusuf, 2005:29; Schwinghammer, 2009:117). The ratio of α - to β - blockade for carvedilol is 1:4. For labetalol, α - to β - blockade ratio is 1:10 (Frishman, 2008:569). Nebivolol is a selective β_1 -blocker; this agent has the highest selectivity for β_1 -receptors among third-generation compounds (Pedersen & Cockcroft, 2006:279).

The mechanism by which β -blockers exert their antihypertensive effect has not yet been determined. Several mechanisms have been proposed recently, *inter alia*:

- Mediation of reduced cardiac output by means of the inhibition of cardiac adrenoceptors (Schwinghammer, 2009:121). When β_1 -receptors are stimulated by catecholamines in the heart, both myocardial contractility and heart rate increase (Mansoor & Kaul, 2009:7). Therefore, when β_1 -receptors are blocked, heart rate and myocardial contractility reduce, lowering the arterial blood pressure and cardiac output (Che *et al.*, 2009:534).
- Emotional stress may lead to hypertension by enhancing sympathetic activity. An enhanced sympathetic activity induces a presynaptic blockade, leading to an attenuated release of catecholamines (Che *et al.*, 2009:534).
- β -blockers may inhibit the release of the enzyme renin by the juxtaglomerular cells of the kidneys. Renin secretion caused by the renal nerves is partially mediated by β_1 -adrenoceptors in the kidney. The decrease in renin concentration by β -blockers leads to a decrease in angiotensin II and aldosterone, and subsequent renal loss of sodium and water, resulting in a reduced arterial pressure (Bangalore & Messerli, 2008:118).

Various other mechanisms have also been put forward, such as resetting of baroreceptor levels and reduction of plasma volume, the generation of nitric oxide (by nebivolol and carvedilol) (Kalinowski *et al.*, 2003:2751), the reduction of vasomotor and/or vascular tone and the improvement of vascular compliance (Bangalore & Messerli, 2008:118).

Although β -blockers reduce peripheral blood pressure, they are less effective in reducing aortic blood pressure (i.e. the pseudo-antihypertensive effect) (De Caterina & Leone, 2010:1435). The blood pressure lowering efficacy of β -blockers is similar to other antihypertensive agents in younger patients (RR, 0.97; 95% CI: 0.88 - 1.07), but sub-optimal in older patients (RR, 1.06; 95% CI: 1.01 - 1.30) (Che *et al.*, 2009:539; Wiysonge *et al.*, 2007:CD002003). There is furthermore no difference in clinical antihypertensive efficacy of the β -blockers, with the exception of the newer agents (i.e. carvedilol and labetalol) which seem to have a better efficacy and safety profile (Bangalore & Messerli, 2008:121; Schwinghammer, 2009:121). Carvedilol has even been shown to improve insulin sensitivity and to facilitate vasodilation; it may therefore be used in diabetic patients (Bell, 2004:50B). In general, because of their questionable clinical significance, β -blockers should not be used as a first-line antihypertensive treatment, except in cases in which there are compelling indications, mainly for patients with coronary heart disease (Williams, B., 2008:1813; Wiysonge *et al.*, 2007:CD002003). Given as second-line treatment, the addition of a β -blocker to diuretics or calcium-channel blockers reduces blood pressure by 6/4 mmHg at 1 times the starting dose and by 8/6 mmHg at 2 times the starting dose (Chen & Heran *et al.*, 2010:CD007185). Chen and Heran *et al.* (2010:CD007185) furthermore established that second-line β -blockers reduce systolic blood pressure to the same extent as second-line thiazide diuretics, although with a greater degree of diastolic blood pressure reduction.

Based on an analysis by the American National Institute for Health and Clinical Excellence (National Collaborating Centre for Chronic Conditions, 2006), β -blockers were the least cost-effective agent compared with other antihypertensives for 65-year-old men and women with an annual cardiovascular disease risk for 2%, heart failure risk for 1% and diabetes risk for 1.1%. They ascribed their conclusion to the metabolic adverse effects of β -blockers, its direct and indirect costs and the direct and indirect costs of increased stroke risk in the elderly.

Adverse effects from non-selective β -blockers include drowsiness, lethargy, sleep disturbance, visual hallucinations, depression, blurring of vision, nightmares, decreased exercise tolerance, weight gain, bradycardia, increased airway resistance in asthmatics and erectile dysfunction (De Caterina & Leone, 2010:1436; Messerli *et al.*, 2008:2711-2712; Sontheimer *et al.*, 2007:313). β_2 -receptor blockade in arteriolar smooth muscle may cause cold extremities and exacerbate Raynaud's phenomenon because of reduced peripheral blood flow (Frishman,

1998:1761; López-Sendó *et al.*, 2004:1345). β -blockers have also been shown to increase insulin resistance and predispose patients to a 22% increased diabetes risk (Bangalore *et al.*, 2007:1260). Chronic administration of β -blockers may furthermore increase triglyceride levels by 20-50% and decrease HDL-cholesterol by 10-15% (Weir & Moser, 2000:180).

Carvedilol and labetalol seem to have a neutral effect on lipoprotein lipase activity and levels of triglycerides and HDL-cholesterol (Schwinghammer, 2009:121; Sharp *et al.*, 2008:569). The Carvedilol or Metoprolol European Trail (COMET) furthermore showed that the risk for new-onset diabetes was 22% lower in patients receiving carvedilol than in those receiving metoprolol (Poole-Wilson *et al.*, 2003:7). According to De Caterina and Leone (2010:1437), McGill (2009:37) and Siegel and Swislocki (2010:97), in the class of β -blockers, the newer beta-blockers (i.e. carvedilol, labetalol and nebivolol) should be the preferential compound in patients with the metabolic syndrome, impaired glucose tolerance and type 2 diabetes.

- **Calcium channel antagonists**

Calcium channel antagonists (CCBs) or calcium entry blockers have been used as cardiovascular medicine for more than two decades (Balijepalli *et al.*, 2004:337; Eisenberg *et al.*, 2004:35). There was some controversy around the safety and cardiovascular effects of the CCBs during the last decade and a half. For example in the early 1990s, some researchers reported “an increased incidence of myocardial infarction” in patients receiving CCBs compared with those receiving diuretics, β -blockers and ACE inhibitors (Psaty *et al.*, 1995:623; Pahor *et al.*, 1995:1191). Currently, several researchers are of the opinion that the cardiovascular protection provided by the CCBs is at least as effective as that obtained with most other antihypertensives (Black *et al.*, 2003:2073; Dahlöf *et al.*, 2005:903; Julius *et al.*, 2004:2022), with superiority over β -blockers (Chen & Zhou *et al.*, 2010: CD003654). As such, the World Health Organization and International Society of Hypertension (WHO/ISH, 2003:1988-1989) and the European Society of Hypertension and the European Society of Cardiology (Mancia *et al.*, 2007:1105) all recommended CCBs as first-line antihypertensives and emphasized their capacity to be used with most of the other antihypertensive medicine classes, including thiazides, to better achieve blood pressure goals. Calcium channel blockers are furthermore particularly recommended for elderly patients with systolic hypertension and for patients from African descent (Simon & Levenson, 2003:103).

Calcium channel blockers exert their action by inhibiting the entry of calcium in smooth muscle of vasoconstrictor arterioles. The entry of calcium is regulated by transmembrane L-type voltage-gated ion channels (Triggle, 2007:1). Cellular calcium concentration is thereby lowered, lowering peripheral resistance and reducing vascular smooth muscle contraction. Hereby a

reduction in both mean arterial pressure and total renal vascular resistance is achieved, and an increased renal flow and glomerular filtration rate (Treadway, 2009:199). Furthermore, calcium channel blockers decrease cardiac contractility by decreasing the conduction through the sinoatrial- and atrioventricular nodes (negative inotropic effect). Increased myocardial oxygen supply is facilitated by dilation of the coronary arteries (Goroll & Mulley, 2009:254).

There are currently two subclasses of calcium channel blockers based on chemical structure, namely the dihydropyridines and the non-dihydropyridines (i.e. the phenylalkylamines and benzothiazepines) (Kaplan & Rose, 2010). The CCBs are similar in their antihypertensive effectiveness, but are pharmacologically very dissimilar. The different classes are distinguished by their binding site within the L-channel and by their relative clinical effects on myocardial conducting system and vascular functions. For example, the dihydropyridines are potent vasodilators that have little or no negative effect upon cardiac contractility or conduction (Girvin & Johnston, 2007:32; Sica, 2006:54). They can be further divided into three categories based upon half-life and effect on contractility, namely first generation (short-acting, e.g. nifedipine), second generation [longer-acting formulations with little cardiac depressant activity, e.g. felodipine, isradipine, nicardipine, nifedipine gastro-intestinal therapeutic system (GITS), nifedipine coat core (CC) and nisoldipine] and third generation (long-acting agents with no cardiac depressant activity, e.g. amlodipine and lacidipine). These agents are particularly effective in older patients with isolated systolic hypertension (Saseen & Carter, 2008:208). The non-dihydropyridines reduce vascular permeability and affect cardiac contractility and conduction, allowing for their use in the treatment of atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardia (Taylor & Pool, 2005:219).

Calcium channel blockers rank low compared with other antihypertensives from a cost-effectiveness perspective. According to Goroll and Mulley (2009:255), even generic sustained release formulations are as much as 5 times the cost of generic β -blockers; brand name formulations may be as high as 10-25 times more expensive. An analysis by Furberg and co-workers (1996:1145) demonstrated that the monthly wholesale cost of slow-release calcium antagonist formulations ranged from US\$38 to \$65, compared with the cost of generic thiazide diuretics, which was approximately US\$ 1 per month. Based on The Hypertension Detection and Follow-up Program Cooperative Group (1979:2562), 76 patients needed to be treated for 5 years to prevent 1 death, or 380 person-years to prevent one death with slow-release calcium channel blockers. The product cost per death prevented in this study deciphered to roughly US\$ 4,500 for the generic diuretic and from \$173,000 to almost \$300,000 for slow-release calcium antagonists, suggesting that these products were not cost-effective.

The adverse effects of the calcium channel blockers depend on the particular agent used. The

potent vasodilators (i.e. the dihydropyridines) can lead to headache, dizziness or light-headedness, flushing and peripheral oedema, in 10-20% of patients (Aronson, 2009:100; Auer, 2004:242). Nifedipine may increase the frequency, intensity and duration of angina in association with acute hypotension; this rare affect can be avoided by using sustained-release formulations of nifedipine (Girvin & Johnston, 2007:37). Other adverse effects with dihydropyridines include gingival hyperplasia, mood changes and various gastro-intestinal complaints (Reese *et al.*, 2006:236). Diltiazem and verapamil can cause cardiac conduction abnormalities such as bradycardia or atrioventricular block in high doses (Zeltser *et al.*, 2004:106). These problems occur at increased frequency in those with pre-existing abnormalities in the cardiac conduction system. Both agents may cause anorexia, nausea, peripheral oedema and hypotension (Auer, 2004:242). Verapamil furthermore causes constipation in between 25-40% of patients. This adverse effect also occurs with diltiazem, but to a lesser extent (Eisenberg *et al.*, 2004:35; Girvin & Johnston, 2007:37).

- **Angiotensin-converting enzyme (ACE) inhibitors**

ACE inhibitors have been used for more than a decade to treat high blood pressure and were cited in a recent survey of primary care supervisors as “the treatment most often recommended by guidelines and favoured over other antihypertensives as first-line agents” (Eastman, 2008:969). Angiotensin-converting-enzyme inhibitors have also been shown to decrease mortality and morbidity in congestive heart failure after recent and remote myocardial infarction, blunt the decline in glomerular filtration rate, reduce incidence of stroke, produce greater regression of left ventricular hypertrophy than non-renin-angiotensin-aldosterone system blocking therapies, reduce albuminuria, delay the onset of new diabetes and improve endothelial function (Cushman, 2003:20; London *et al.*, 2002:1720). Based on this effect *inter alia*, Putnam and colleagues (2012:H1228) regard the RAS blockers as an effective management strategy in patients with the metabolic syndrome, to control impaired glucose and insulin tolerance and dyslipidaemia. These antihypertensives can also be used for the treatment of heart failure and diabetic nephropathy in children, as well as for children with severe bilateral renal artery stenosis (or severe stenosis of the artery supplying a single functioning kidney) (Costello, 2011).

The renin-angiotensin system plays an important role in the genesis of hypertension because of its integral role in the pathogenesis of cardiovascular disease (Catanzaro & Frishman, 2010:669). According to Dzau (2001:1047), angiotensin II (a potent vasoconstrictor agent that also stimulates aldosterone secretion) causes direct vasoconstriction, salt and water retention and sympathetic nerve stimulation, all of which increase blood pressure (Dzau, 2001:1047). This reduction in blood pressure is caused by the angiotensin-converting enzyme (ACE)

inhibitors competitively blocking the conversion of angiotensin I to angiotensin II (Carretero, 2005:H1796). As a result, circulating and local levels of angiotensin-II are lowered with a subsequent inhibition of angiotensin II-mediated vasoconstriction and aldosterone secretion (Laight, 2009:753). In addition, ACE inhibitors may also inhibit kininase II and increase bradykinin levels, which in turn stimulates the β_2 -receptors leading to the release of nitric oxide (NO) and vasoactive prostaglandins (prostacyclin and prostaglandin E_2) (Kaplan & Weber, 2010:37). Angiotensin-converting enzyme inhibitors furthermore decrease systemic vascular resistance without increasing heart rate and cardiac output.

ACE inhibitors are classified in three categories based on the group that binds the zinc atom of the angiotensin converting enzyme-molecule into those containing a sulphydryl group (e.g. benazepril, captopril, zofenopril), a carboxyl group (e.g. cilazapril, enalapril, lisinopril, perindopril, quinapril, ramipril, spirapril, trandolapril) or a phosphoryl group (e.g. fosinopril) as zinc ligand (Jackson, 2001:809). Findings from a Cochrane review of the blood pressure lowering efficacy of ACE inhibitors for primary hypertension (Heran *et al.*, 2008:CD003823), showed that these agents render a mean reduction in systolic blood pressure of 6-9 mmHg and in diastolic pressure from 4-5 mmHg. At half of the maximum recommended dose, or less, ACE inhibitors achieved most of their potential in reducing blood pressure equating to almost 90% of the efficacy (Bronson, 2009:49). ACE inhibitors are furthermore more effective in younger and Caucasian patients (Mpe, 2007:27). Patients from African descent should receive higher doses, or combinations of ACE inhibitors with diuretics (Burnier, 2001:906) or combinations of angiotensin II receptor blockers and calcium channel blockers (e.g. valsartan and amlodipine) (Plosker & Robinson, 2008:373).

ACE inhibitors as first-line antihypertensive treatment are unfavourable in terms of cost-effectiveness compared with conventional antihypertensive therapy with β -blockers or diuretics (Nordmann *et al.*, 2003:581). Campbell and co-workers (2007:1104,1108) showed that the prescribing of an ACE inhibitor to every newly diagnosed patient with type 2 diabetes in the US, could avert 68 314 cardiovascular events, 46 410 lives could be saved and 48 patients would be prevented from needing dialysis over 8 years, suggesting that treatment with ACE inhibitors could be cost-saving.

ACE inhibitors are well tolerated although several adverse reactions related to their pharmacological actions may occur (Taylor & Pool, 2005:220). Unwanted effects include hyperkalaemia (Saseen *et al.*, 2003:157) and renal insufficiency (particularly older patients with congestive heart failure), proteinuria, pronounced first-dose symptomatic hypotension particularly in patients with high plasma renin activity, dry cough (5-15% of patients) (Chase & Peterson, 2006:246) and angioedema (particularly in patients from African descent and

smokers) (Saseen & Carter, 2008:205). Skin rashes and taste disturbances are uncommon, but may be more likely with sulphhydryl-containing products, particularly captopril (Aronson, 2009:13). ACE inhibitors can also cause foetal abnormalities (i.e. oligohydramnios, pulmonary hypoplasia, foetal growth retardation, renal dysgenesis, neonatal anuria and neonatal death) when administered during the second or third trimester of pregnancy (Kaplan & Weber, 2010:37).

- **Angiotensin II receptor blockers**

Angiotensin II receptor antagonists or blockers, also called A₂RA or ARBs, were developed to overcome some of the mechanistic barriers associated with the ACE inhibitors. For example, bradykinin or substance P levels are not influenced by ARBs; the risk for cough and angioedema is thus significantly less compared with ACE inhibitor therapy (Barreras & Gurk-Turner, 2005:124). Furthermore, the ARBs act at the final step of the RAAS cascade and block A₂-receptors, whether produced by systemic ACE- or by local ACE-dependent pathways in tissue such as myocardial chymase (Schwinghammer, 2009:119). The current South African Hypertension Guidelines (Seedat *et al.*, 2006:346) and others, i.e. the JNC-7 (Chobanian *et al.*, 2003a:2560), the European Society of Hypertension and European Society of Cardiology (Mancia *et al.*, 2007:1105), the British Hypertension Society (Williams *et al.*, 2004:634) and the Canadian Hypertension Education Programme (Campbell *et al.*, 2009) recommend ARBs for those who should receive an ACE inhibitor but are intolerant to it. These guidelines, together with several others (i.e. Armario & De la Sierra, 2009:202; Catanzaro & Frishman, 2010:671) also advocate the use of ARBs in the treatment of patients with concurrent heart failure, left ventricular hypertrophy, chronic kidney disease, metabolic syndrome and type 2 diabetes. Losartan has a uricosuric effect; this agent may therefore be a good option in hypertensive patients with elevated levels of serum uric acid or as an addition to low-dose thiazides for the treatment of hypertension (Hamada *et al.*, 2010:73; Khan *et al.*, 2008:166). Olmesartan was also shown to delay the onset and reduce the incidence of micro-albuminuria in patients with type 2 diabetes and normo-albuminuria at a dose of 40 mg once daily (Haller *et al.*, 2011:915). Telmisartan has further been identified possessing additional partial ligand activity at the PPAR γ receptors (Benson *et al.*, 2004:994; Schupp *et al.*, 2004:2055), suggesting a potential role for this agent in lipid and glucose metabolism. Fuke and colleagues (2010:396) support this suggestion, demonstrating significantly improved insulin resistance, fasting plasma glucose, immunoreactive insulin and adiponectin, with telmisartan in dosages of 20-80 mg/day in patients with diabetes, chronic kidney disease and hypertension.

There are currently eight ARBs marketed for the treatment of hypertension, namely candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan (Catanzaro

& Frishman, 2010:670) and the latest development, azilsartan medoxomil (FDA, 2011b). All ARBs share similar mechanisms of action, including indirect arterial vasodilation by the angiotensin II type 1 receptor blockade (AT₁R) (losartan, valsartan and eprosartan showed competitive receptor binding, whereas olmesartan, irbesartan, candesartan, telmisartan and azilsartan exhibit non-competitive binding), vasodilatory response from AT₂R stimulation, decreased sympathetic nervous system activity, possibly lowered concentrations of aldosterone, decrease in vasoconstrictors such as endothelin and/or improvement in endothelial dysfunction and a mild natriuretic response (Taylor & Pool, 2005:221; Sica, 2009:S16; Song *et al.*, 2010:347). Unlike ACE inhibitors, ARBs do not inhibit the breakdown of bradykinin. Therefore, some of the beneficial effects of bradykinin such as vasodilation (which can enhance blood pressure lowering), regression of myocyte hypertrophy and fibrosis and increased levels of tissue plasminogen activator are not present with ARB therapy (Aronson, 2009:30; Barreras & Gurk-Turner, 2003:123).

All ARBs have similar antihypertensive efficacy [with the exception of azilsartan that has been shown to be more effective compared with valsartan and olmesartan (FDA, 2011b)] and fairly flat dose-response curves (Schwinghammer, 2009:120). They also yield comparable reductions in blood pressure to ACE inhibitors and other antihypertensive agents (Aronson, 2009:30; Catanzaro & Frishman, 2010:670). ARBs furthermore produce similar blood pressure reductions in both gender groups, as well as all age categories. Similar to ACE inhibitors, the ARBs appear less effective in patients from African descent, unless co-administered with diuretics or calcium channel blockers (Burnier, 2001:906; Plosker & Robinson, 2008:373). ARBs are also generally well tolerated; according to Bourgault *et al.* (2005:607), Chen *et al.* (2005:795) and Elliott *et al.* (2007:72), ARBs have higher persistence/compliance rates at one year compared with ACE inhibitors, CCBs, diuretics or β -blockers.

A retrospective analysis of overall medical and pharmacy costs in a longitudinal pharmacy database (Thaker *et al.*, 2005:A222) demonstrated considerable annual cost-savings among patients initiating ARB therapy (US\$2,780). Savings in this study was attributable to the better compliance, tolerability and dosing simplicity of the ARBs. Data from the studies by Palmer and Rodby (2004:S119); Smith *et al.* (2004:26), Theodoratou *et al.* (2009:113-114) and Herman *et al.* (2003:683) also established cost-effectiveness and potential cost-savings among ARBs (in particular irbesartan, valsartan and losartan) vs. other antihypertensives in individuals with hypertension, type 2 diabetes mellitus and micro-albuminuria. In combination with hydrochlorothiazide, however, irbesartan was a dominant strategy when compared with losartan (50 mg) plus hydrochlorothiazide (12.5 mg) and valsartan (80 mg) plus hydrochlorothiazide (12.5 mg). Irbesartan was also cost-effective compared with losartan in moderate-to-severe hypertension, whereas the results compared with candesartan were mixed (Ekman *et al.*,

2008:853). Boersma and co-workers (2010:52) recently demonstrated that olmesartan was more cost-effective compared with losartan, valsartan and irbesartan in the Netherlands. The conclusions from this study, however, were based on incomparable blood pressure controls and excluded hard endpoints.

Apart from for hypotension, virtually no dose-related adverse effects have been reported with the ARBs (Aronson, 2009:31; Barreras & Gurk-Turner, 2003:124). Common adverse effects with the ARBs include headache, dizziness, weakness, fatigue, gastro-intestinal symptoms (i.e. diarrhoea, dyspepsia and abdominal pain), arthralgia and musculoskeletal pain and respiratory symptoms (e.g. upper respiratory tract infections, sinusitis and viral infections) (Barreras & Gurk-Turner, 2003:125). Other adverse effects include hyperkalaemia (especially in patients receiving concurrent treatment with potassium-sparing diuretics, significant renal insufficiency, renovascular hypertension, diabetes mellitus, or hypo-aldosterones) and oliguria/progressive azotemia in patients with severe heart failure whose renal function depends on the renin-angiotensin-aldosterone system (Aronson, 2009:40-41). Several cases of cough and angioedema have been reported, but less commonly than with ACE inhibitors (Kaplan & Weber, 2010:40; Matchar *et al.*, 2008:22-23).

Recent concerns have surfaced about possible links between ARBs and increased risks of myocardial infarction (Julius *et al.*, 2004:2029) and cancer (Bangalore *et al.*, 2011:80; Goldstein *et al.*, 2010:817; Huang *et al.*, 2011:1030). An evaluation of these and other studies, however, found the results inconsistent, therefore necessitating further research (Siragy, 2011:311). ARBs, like ACE inhibitors, should furthermore not be taken during pregnancy because of an increased risk for fetopathy (Taylor & Pool, 2005:221).

- **Other antihypertensives**

Certain agents with central sympatholytic action, arteriolar dilators and peripheral sympathetic inhibitors such as methyldopa, guanfacine, guanabenz, rilmenidine, moxonidine, clonidine, minoxidil, hydralazine, guanethidine, guanadrel and reserpine, are not well suited for initial monotherapy in the treatment of hypertension (Khatib & El-Guindy, 2005:57). A brief overview of these agents is provided here. Other pharmacological medicine classes useful in lowering blood pressure and agents under investigation are also described.

- ***Agents with central sympatholytic action***

Central agonists stimulate either the α_2 -adrenoreceptors (e.g. methyldopa, guanfacine, guanabenz), the I_1 -imidazoline receptors (e.g. rilmenidine, moxonidine) or both (e.g. clonidine)

(Khatib & El-Guindy, 2005:57). Methyldopa, guanfacine, guanabenz and clonidine lower blood pressure by stimulating presynaptic α_2 -adrenergic receptors in the central nervous system, thereby inhibiting noradrenalin release. This reduces sympathetic outflow to the heart thereby attenuating cardiac output by decreasing heart rate and contractility. Reduced sympathetic output to the vasculature decreases sympathetic vascular tone, which causes vasodilation and reduced systemic vascular resistance. This decreases arterial pressure, plasma renin activity and baroreceptor reflexes (Small, 2006:300; Wenzel *et al.*, 2000:S44). Moxonidine and rilmenidine – a new generation of centrally acting antihypertensives with less adverse effects – lower sympathetic tone by stimulation of hypothetical imidazoline-receptors in the rostral ventrolateral medulla and by inducing peripheral sympatho-inhibition *via* the inhibition of transmitter release from postganglionic sympathetic neurons (Szabo, 2002:20).

Central α_2 -agonists are effective as single therapy in some patients, but are usually employed as second- or third-line agents in cases of refractory hypertension (Taylor & Pool, 2005:222) because of the high frequency of intolerance, including sedation, fatigue, dry mouth, postural hypotension and impotence (Aronson, 2009:133). Guanfacine and guanabenz are used rarely in clinical practice, whereas clonidine is often used in resistant hypertension (Biaggioni & Robertson, 2009:127). Methyldopa is retained as a first-line agent for hypertension in pregnancy, although its side-effect profile includes that it may cause hepatitis or haemolytic anaemia (Schwinghammer, 2009:122). Moxonidine and rilmenidine display a favourable hemodynamic profile and show a lower incidence of adverse reactions, such as sedation and dry mouth, compared with classic centrally acting α -adrenoreceptor agonists (Van Zwieten, 2001:324). They are also efficient in reducing sympathetic activity (Esler *et al.*, 2004:1530) and may diminish insulin resistance – these agents may therefore prove useful in the treatment of the metabolic syndrome (Sharma *et al.*, 2004:670).

– **Direct arteriolar dilators**

Minoxidil and hydralazine are the two most commonly used oral vasodilators for the treatment of hypertension (Ram & Fenves, 2003:438). Both agents have pronounced effects on the resistance vessels and wield little to no venous vasodilation (Saseen & Carter, 2008:210). Because of their predominant effect on arterioles, these agents also reduce impedance to myocardial contractility, provoking the baroreceptor reflex that includes tachycardia, vasoconstriction and the release of renin. For this reason, they are usually employed as third agents in multidrug treatment of severe hypertension, usually in combination with β -blockers and diuretics (Schwinghammer, 2009:123). Hydralazine is retained for patients with heart failure, severe chronic kidney disease and kidney failure in combination with isosorbide dinitrate (Saseen & Carter, 2008:210) and for hypertensive disorders during pregnancy (Magee *et al.*,

2003:958). Minoxidil is more potent and longer acting than hydralazine (Westfall, 2004:229) and is regarded as a mainstay in the therapy in children and young adult patients with renal disease and refractory hypertension, when multidrug regimens have failed to achieve blood pressure control (Halling *et al.*, 2010:553). Minoxidil therapy is further used for patients requiring hydralazine that experience drug-induced adverse effects (Schwinghammer, 2009:124).

Hydralazine causes a dose-dependent drug induced lupus-like syndrome (Rubin, 2005:136). Other side effects of hydralazine include dermatitis, drug fever, peripheral neuropathy, hepatitis and vascular headaches, limiting its usefulness in the treatment of hypertension (Arce *et al.*, 2006).

– ***Peripheral adrenergic inhibitors***

Peripheral sympatholytic agents (i.e. reserpine, guanethidine and guanadrel) lower blood pressure by decreasing the activity of the sympathetic nervous system *via* depletion of catecholamines at sympathetic nerves (Armstrong *et al.*, 2008:445; Wilcox, 2009:226). As a class, these agents bind to receptors on the postganglionic axon. Reserpine depletes catecholamine stores from central and peripheral sympathetic neurons, blocking transport of norepinephrine into storage sites. Lowering of norepinephrine content in storage sites enhances its synthesis and thus its turnover, reducing sympathetic tone, decreasing peripheral vascular resistance and thus blood pressure (DeQuattro & Li, 2002:S118; O’Conner *et al.*, 2002:126). Guanethidine and guanadrel deplete norepinephrine from postganglionic sympathetic nerve terminals and inhibit the release thereof in response to sympathetic nerve stimulation, resulting in reduced cardiac output and peripheral vascular resistance (Schwinghammer, 2009:124).

Because of much higher rates of adverse effects, which include severe depression (reserpine), orthostatic hypotension and erectile dysfunction (guanethidine), these agents are rarely used to treat contemporary hypertension (Armstrong *et al.*, 2008:445; Schwinghammer, 2009:124) but may be combined with other antihypertensives in the treatment of refractory hypertension (Saseen & Carter, 2008:209).

– ***Therapeutic agents under investigation***

Aliskiren is the first agent in a new class of antihypertensives known as renin inhibitors (Van Tassell & Munger, 2007:456). Aliskiren blocks the renin-angiotensin-aldosterone system at its point of activation, which results in reduced plasma renin activity and thus a reduction in the

conversion of angiotensinogen to angiotensin I (with subsequent reduction in angiotensin II levels) (Cheng, 2008:33). Aliskiren thus decreases plasma renin activity and systemic vascular resistance thereby lowering systemic blood pressure (Parmar & Jadav, 2007:100). Aliskiren provides blood pressure reductions comparable to ACE inhibitors, ARBs or CCBs (Gao *et al.*, 2011:619), and has additive antihypertensive effects when used in combination with thiazides (Cheng, 2008:41). Based on this review by Cheng, the acquisition cost of aliskiren is much more than that of many alternative antihypertensives. Many of the cautions and adverse effects seen with ACE inhibitors and ARBs also apply to aliskiren, for example orthostasis, fatigue or weakness, gastro-intestinal disorders, headache and dizziness (Cheng, 2008:40; Van Tassell & Munger, 2007:461). Barrios and Escobar (2010:357) recommend that aliskiren should (at least for now) be used only as an alternative therapy because of the lack of long-term studies evaluating cardiovascular event reduction.

One side effect of the PPAR γ agonists (thiazolidinediones) is a lowering of blood pressure (refer to paragraphs 2.9.2.5.2 and 2.9.4.5.2). According to Raji and co-workers (2003:175), the thiazolidinediones are able to lower blood pressure by approximately 4-5 mmHg. Possible mechanisms postulated for the action of the PPAR γ agents on blood pressure regulation in animal studies suggest *inter alia* that PPAR γ may regulate the β_2 -adrenoreceptor expression with a concomitant change in β -adrenergic agonist sensitivity (Chang *et al.*, 2009:2169). Wang and co-workers (2009:21) also suggested that PPAR γ might lower blood pressure *via* regulation of endothelial muscle functions, whereas Yang and Soodvilai (2008) suggested an increase in vascular permeability *via* a variety of proposed mechanisms including vascular endothelial growth factor, nitric oxide and protein kinase C. From a renal perspective, however, the PPAR γ agents induce fluid retention, which results in plasma volume expansion and peripheral oedema. This fluid retention is resistant to diuretics (Karalliedde & Buckingham, 2007:741). Based on a recent review by Sutliff and co-workers (2010:153), the PPAR γ agonists may have potential as therapeutic targets for the treatment of pulmonary hypertension.

A wide range of other agents is also under investigation for use as antihypertensives. These include the vasopeptidase inhibitors, dopamine-2-receptor agonists, potassium channel openers, endothelin receptor antagonists (e.g. darusentan), transcription modulating agents, novel progestin's (e.g. drospirinone) and hypertension vaccines (Wu & Gerstenblith, 2010:265). Siebenhofer and colleagues (2009:CD007654) also showed potential for orlistat as blood pressure lowering agent, reducing systolic blood pressure for (SBP): weighted mean difference (WMD): -2.5 mmHg; (95% CI: -4.0 to -0.9) and for diastolic blood pressure (DBP): WMD - 1.9 mmHg; (95% CI: -3.0 to -0.9). Hydrophilic and lipophilic statins have also been shown to reduce systolic- and diastolic blood pressure. For example, in an intention-to-treat analysis, Golomb and co-workers (2008:724) showed that both simvastatin and pravastatin

reduced blood pressure relative to placebo, by 2.2 mmHg for systolic blood pressure and 2.4 mmHg for diastolic blood pressure.

- **Combination therapy with antihypertensives**

Approximately 19-54% of hypertensive patients worldwide achieve target blood pressure with antihypertensive monotherapy (Taylor, 2004:421). In South Africa, this rate is approximately 40% using a blood pressure goal of <140/90 mmHg and even less for a goal of <130/80 mmHg required by diabetic and other high-risk patients (Rayner, 2007:30). Most patients therefore need combination therapy with two or more antihypertensive agents to reach blood pressure goal (Kalra *et al.*, 2010; Rubio-Guerra *et al.*, 2009:55). For example, results from the ALLHAT trial showed that the majority of patients need up to four agents to attain target blood pressure levels (The ALLHAT Officers and Coordinating for the ALLHAT Collaborative Research Group, 2002:2984). Other indications for combination therapy include

- patient experience adverse effects on a single agent that may be improved by the addition of a second;
- systolic blood pressure ≥ 20 mmHg or diastolic blood pressure ≥ 10 mmHg above goal; and
- compelling indications present, that may benefit from different mechanisms of action of multiple antihypertensives (Chobanian *et al.*, 2003b:1206; Erdine, 2010:40; Erdine *et al.*, 2006:331).

Targeting multiple mechanisms provide advantages in the control of hypertension, for example, agents with different and multiple mechanisms may be combined to provide additive or synergistic effects, whilst allowing for the use of lower dosages (Rayner, 2007:34). Wald and co-workers (2009:299) demonstrated this principle in a meta-analysis of 42 trials, showing that combination therapy provided an additive effect that was approximately 5 times greater than resulted with the doubling of either agents (i.e. thiazides, β -blockers, ACE inhibitors and calcium channel blockers) alone. Combination therapy may also decrease the frequency of harmful metabolic effects of individual agents and decrease adverse events, whereas tolerability may be improved (Gradman *et al.*, 2010:43-44; Rayner, 2007:30; Rubio-Guerra *et al.*, 2009:56).

The recommended combinations for antihypertensives include low dose diuretics plus ACE inhibitors or ARBs and CCBs plus ACE inhibitors or ARBs (Mancia *et al.*, 2007:1105; Rayner, 2007:32; Schultz, 2009:26). Other combinations that are useful in difficult to control hypertensive patients include two CCBs from different classes, two diuretics (mostly thiazides plus potassium-sparing agents), ACE inhibitor/direct renin inhibitors plus ARBs (dual RAAS blocker-based combinations), β -blockers plus α -blockers, as well as adding a nitrate to any of

the antihypertensives (Crawford, 2009:1; Sica, 2005a:129). Some of these combinations are already available in fixed-dose combination, offering potential advantages in terms of higher efficiency, lower health care cost and improved patient compliance and persistence through the use of single, daily medication administration (Chrysant, 2008:713; Roberts & Epstein, 2009:385), reduced adverse event frequency and shorter time to attain blood pressure control (Neutel, 2006:1472; Smith, 2007:413).

Combinations not generally recommended because their combination produces little additional blood pressure reduction or they have more adverse effects in combination than with individual agents, include β -blockers plus RAAS inhibitors, β -blockers plus centrally acting agents (Gradman *et al.*, 2010:45-46), β -blockers plus non-dihydropyridine CCBs, thiazides plus CCBs (Schultz, 2009:26; Stanton & Reid, 2002:77), β -blockers plus diuretics (Schultz, 2009:26), dihydropyridine CCBs plus α -blockers or hydralazine (Rayner, 2007:32), and the combination of a direct renin inhibitor (e.g. aliskiren) plus an ACE inhibitor (or ARB) (Novartis, 2011).

The pharmacological rationale for combining some of the different antihypertensive agents is summarised in the following section.

– ***Diuretics plus RAAS blockers***

By causing volume and sodium depletion, thiazide diuretics stimulate the release of renin and subsequent production of angiotensin II, which leads to vasoconstriction, sodium retention and activation of the sympathetic nervous system – thus counteracting some of the diuretic's antihypertensive effects (Gehr *et al.*, 2003:159; Reboldi *et al.*, 2009:412). The addition of a RAAS inhibitor (e.g. ACE inhibitor, ARB, or direct renin inhibitor) counteracts the diuretic-induced activation of the renin-angiotensin system and its effects by interfering with the conversion of angiotensin I to angiotensin II (ARBs specifically block angiotensin II subtype 1, thereby selectively inhibiting the vasoactive properties of angiotensin II, whereas direct renin inhibitors block the renin-angiotensin-aldosterone system at its point of activation), leading to decreased sodium retention along with decreased angiotensin-mediated vasoconstriction and thus an enhanced antihypertensive effect (Sood *et al.*, 2010:886). This synergism is in particular prominent and effective in the elderly or patients from African descent in whom ACE inhibitor/ARB monotherapy has been shown to be less effective because of low plasma renin levels (Rao *et al.*, 2007:150; Rayner, 2007:32). RAAS inhibitors also decrease the occurrence of metabolic effects and electrolyte imbalances linked with diuretic monotherapy, such as hypokalaemia and new onset diabetes (Gillespie *et al.*, 2005:2261; Schultz, 2009:26).

An ARB/diuretic combination may be favoured over an ACE inhibitor/diuretic combination in

some patients as it has the advantage of better blockade of the renin-angiotensin system and is less associated with ACE inhibitor adverse effects such as cough and angioedema (Egras & Ram, 2010:132; Schultz, 2009:26).

– ***Calcium channel blockers plus RAAS blockers***

In addition to being potent vasodilators, calcium channel blockers also have diuretic and natriuretic properties (Haller, 2008:787), inducing the reflex activation of the sympathetic nervous system and/or the renin-angiotensin-aldosterone system, ultimately increasing plasma renin activity and thus angiotensin II production (Stanton & Reid, 2002:78). ACE inhibitors inhibit the central sympathetic stimulation that may result from calcium antagonist associated vasodilatation, furthermore buffering the CCB-induced activation of the renin-angiotensin-aldosterone axis (Kalra *et al.*, 2010). In addition, both inhibitors of RAAS and CCBs may counteract the hypertensive effects of endothelin-1 (Puddu *et al.*, 2004:555; Sood *et al.*, 2010:888). Calcium antagonists and ACE inhibitors may also work together to favourably influence target-organ disease independent of their effect on blood pressure, for example, Verdecchia and co-workers (2005:387,390) showed that ACE inhibitors appeared superior to CCBs for the prevention of coronary heart disease, whereas CCBs appeared superior to ACE inhibitors for stroke prevention. The combination of these two agents could, therefore, offer all-purpose cardiovascular and cerebrovascular prevention.

The combination of these 2 active substances furthermore results in fewer or milder adverse effects than with each agent alone (Schultz, 2009:26). The combination of a dihydropyridine calcium antagonist with a RAAS inhibitor significantly reduces the incidence of peripheral oedema and reflex tachycardia (Sica, 2006:56; Weir, 2003:330). Neither class of medications has prominent metabolic adverse effects, an advantage in patients with type 2 diabetes and renal disease (Rubio-Guerra *et al.*, 2009:59-60).

– ***Potassium-sparing and thiazide diuretics***

Potassium-sparing diuretics are occasionally used in combination with thiazide diuretics to counteract the potassium-wasting effect of the thiazides (Bhattacharya & Alper, 2008:360). Potassium sparing diuretics or potassium supplements are further also used in combination with thiazide diuretics to attenuate the risk for adverse metabolic effects, for example thiazide-induced hypokalaemia that can lead to cardiac arrhythmias and sudden death (Bhattacharya & Alper, 2008:360). This combination is particularly beneficial in obese patients, in whom aldosterone blockade plays an important role in helping achieve blood pressure goals (Calhoun, 2006:182), as well as in people with relatively well-preserved kidney function (i.e. estimated

glomerular filtration rate >50 mL/min per 1.73 m² body surface area) (Khosla *et al.*, 2009:418).

– **Dual RAAS-blocker based combinations**

The currently available agents that block the renin-angiotensin-aldosterone system include the ACE inhibitors, the ARBs and the direct renin inhibitors.

The combination of ACE inhibitors and ARBs may (theoretically) provide the advantage of a more complete RAAS-blockade (Reboldi *et al.*, 2009:421). ARBs will reduce the ACE inhibitor escape phenomenon, whereas the angiotensin II generated by the ACE-independent pathways will be blocked by the ARBs (Kalra *et al.*, 2010). Additionally, the ACE inhibitors itself inhibit bradykinin degradation (Azizi & Ménard, 2004:2492). Clinical trials have, however, shown that ACE/ARB combinations produce little additional blood pressure reduction compared with monotherapy with either agent; for example, the recent Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) study showed no reduction in primary outcomes when an ACE inhibitor/ARB combination was compared with an ACE inhibitor alone, despite a 2.4/1.4 mmHg lower blood pressure in the former group (Yusuf *et al.*, 2008:1547). The combination also resulted in more adverse effects than with individual agents. Although useful for proteinuria reduction and in the treatment of symptomatic patients with heart failure, the combination may be regarded as less effective in the reduction of blood pressure (Gradman *et al.*, 2010:45-46).

2.9.3.6 Summary of elevated blood pressure

Hypertension is one of the most prevalent risk factors for cardiovascular disease (refer to paragraph 2.9.3.3) and represents a major progressive economic and health burden (refer to paragraph 2.9.3.4). Much of the associated morbidity and mortality is potentially avoidable, providing that these patients are identified and treated appropriately.

Several national and international guidelines exist for the management of hypertension. The present South African guidelines (refer to paragraph 2.9.3.5.2) emphasise a treatment goal of <140/90 mmHg for all stages of hypertension and <130/80 mmHg for high-risk patients (i.e. those with diabetes, renal disease and congestive heart failure) (refer to paragraph 2.9.3.5), through a 3-stepped approach – the initial target of which is to reduce systolic blood pressure. Lowering blood pressure too aggressively can cause harm. For example, Protogerou *et al.* (2007:178) showed that a diastolic blood pressure of less than 60 mmHg was associated with increased mortality in the elderly. Furthermore, among patients with coronary artery disease, the risk for myocardial infarction was increased when diastolic blood pressure was less than

70 mmHg (Messerli *et al.*, 2006:890). Bavry and co-workers (2010:50) also demonstrated a J-shaped relationship between outcome and systolic blood pressure among patients with peripheral-artery disease, with an increased risk when the systolic blood pressure was less than 120 mmHg.

Currently, pharmacotherapy serves as the core intervention for the treatment of hypertension, although treatment may also include lifestyle modification, antihypertensives, or a combination of both as lifestyle changes further enhance the efficacy of antihypertensive pharmacotherapy (Bronas & Leon, 2009:426) (refer to paragraph 2.9.3.5). Lifestyle modification alone is appropriate therapy for patients with prehypertension. Patients diagnosed with stage 1 or 2 hypertension should be placed on lifestyle modifications and pharmacological therapy concurrently (Schwinghammer, 2009:113). More than often treatment with two or more agents from different pharmacologic classes will be necessary to achieve adequate blood pressure control (refer to paragraph 2.9.3.5.2). In these cases, fixed-dose combinations may offer potential advantages in terms of higher efficiency and lower health care cost, whilst improving patient compliance and persistence in treatment.

An analysis of hypertension-guidelines in the UK, by the National Institute for Health and Clinical Excellence (NICE, 2006) showed that the CCBs and RAAS-blockers were the two most cost-effective pharmacological classes for the treatment of hypertension. Cost-effective analyses are, however, site-specific (i.e. depending on cost of medicine and charging policy). The choice of antihypertensive should therefore be determined by the ability to reduce cardiovascular risk without compromising quality of life, co-morbidities and to a lesser extent by age and race (Karuparthi *et al.*, 2007:128; Mpe, 2007:27). For example, younger Caucasian patients respond better to monotherapy with β -blockers and ACE inhibitors (and probably ARBs), whereas African and older patients respond better to monotherapy with diuretics (thiazides) and CCBs (in particular diltiazem) (Flack *et al.*, 2010:788; Kato *et al.*, 2011:333; Mpe, 2007:27; Schachter, 2006:28). Most medications used for the treatment of adult hypertension may be used in children and adolescents – treatment should, however, be individualised based on the child's age, cause of hypertension, concomitant medicine intake and degree of blood pressure elevation required (Falkner, 2005:611). According to Sondheimer and co-workers (2007:590), β -blockers and ACE inhibitors are the standard first-line medical treatment for essential hypertension in children. Other conditions that require specialised hypertensive care include pregnancy, isolated systolic hypertension, renal disease, diabetes and accelerated hypertension (Ram & Fenves, 2003:438). In these high-risk patients, Reboldi and co-workers (2009:423) and Tocci *et al.* (2011:588) advocate the use of the combination of an ACE inhibitor or ARB and a CCB, as this combination provides both reno- and cardioprotection.

2.9.4 Elevated plasma glucose (hyperglycaemia)

Elevated plasma glucose (hyperglycaemia) is considered the “hallmark of metabolic abnormality associated with type 2 diabetes” (Nathan *et al.*, 2009:193) and a major component of the metabolic syndrome as defined by the various organisations (refer to Table 2.1). A discussion concerning the classification, prevalence and the risk hyperglycaemia conveys for metabolic syndrome, diabetes and CVD is provided here. The treatment of hyperglycaemia ensues in paragraph 2.9.4.5.

2.9.4.1 Definition, measurement and classification of hyperglycaemia

Hyperglycaemia refers to an abnormal (elevated) blood glucose concentration, caused by abnormalities in glucose metabolism (i.e. a lack of insulin resulting in a decreased peripheral utilisation of glucose, or increased hepatic output of glucose into circulation), which signifies uncontrolled diabetes mellitus (both types 1 and 2) clinically (Goel, 2007:45; Khurana, 2006:801).

Although there is no consensus on the most accurate screening test for the detection of diabetes, hyperglycaemia is most commonly measured with threshold criteria for fasting plasma glucose (FPG) or an oral glucose tolerance test (OGTT) (i.e. a 2-hour plasma glucose test measured after a 75 gram oral glucose load) (Santaguida *et al.*, 2005:3; Williamson & Narayan, 2009:213). An alternative screening/diagnostic test, the glycated haemoglobin test (haemoglobin A_{1c} or HbA_{1c}), represents a 2- to 3-month average of blood glucose concentrations and is regarded as a valuable tool for monitoring glycaemia during treatment (Dailey, 2006:153; Giugliano *et al.*, 2008a:218S). The correlation between HbA_{1c} values and mean plasma glucose (MPG) levels measurements as described by the American Diabetes Association is given in Table 2.10.

Table 2.10: Correlation between glycosylated haemoglobin (HbA_{1c}) and mean plasma glucose (MPG) levels (ADA, 2009:S19)

HbA _{1c} (%)	Mean plasma glucose (MPG) level	
	(mmol/L)	(mg/dL)
5	5.6	100
6	7.0	126
7	8.6	154
8	10.2	183
9	11.8	212
10	13.4	240
11	14.9	269
12	16.5	298

According to Garber *et al.* (2008:936) and Cobble and Peters (2009:S8) there is a continuous spectrum of glucose levels between that which is considered “normal”, “post-challenge” and that which is considered diagnostic for diabetes. A normal fasting plasma glucose level is defined as a FPG level less than 100 mg/dL (5.6 mmol/L), whereas an elevated fasting plasma glucose or fasting hyperglycaemia⁹ is divided (depending on the degree of abnormality) into intermediate states, i.e. impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), or type 2 diabetes (Alexander *et al.*, 2006:982; Santaguida *et al.*, 2005:2).

Impaired fasting plasma glucose (IFG) levels include plasma glucose levels in the range of 100-125 mg/dL (5.6-6.9 mmol/L) (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003:3161). Values greater than or equal to 126 mg/dL (7.0 mmol/L), or 2-hour plasma glucose >11.1 mmol/L during an oral glucose tolerance test, indicates diabetes (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003:3161). The diagnostic category of impaired glucose tolerance is retained to describe individuals whose FPG is less than 126 mg/dL (<7.0 mmol/L) (therefore lower than that required for the diagnosis of diabetes) but whose 2-hour plasma glucose is between 140 and 199 mg/dL (7.8 - 11.0 mmol/L) after the start of the OGTT (Nathan *et al.*, 2007:753) (refer to Table 2.10). Both IFG and IGT or a combination of both, represent a “prediabetic” state (Nathan *et al.*, 2007:753), or the transitional state between normal glucose metabolism and overt diabetes (Aroda & Ratner, 2008:3259). Hyperglycaemia that does not meet the criteria for diabetes is therefore considered prediabetes (O'Mara, 2008).

Diabetes mellitus is defined as a group of chronic disorders that is characterised by, *inter alia*, persistent elevated glucose levels (chronic hyperglycaemia) due to lack of or decrease in insulin secretion and/or insulin resistance in both the liver and peripheral tissue (Horton, 2009:S21; WHO, 1999:17). Diabetes mellitus includes different etiological types and different clinical stages of hyperglycaemia. For example, according to Deeg (2005:37E), “early diabetes may manifest itself as post-prandial hyperglycaemia, while fasting glucose measurements and HbA_{1c} may be normal or slightly elevated”. The two main etiological categories have been identified as diabetes types 1 and 2. In addition to these two main types, the World Health Organization identifies a number of other etiological types, e.g. other specific types, genetic defects of islet β -cells function, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drug or chemical-induced diabetes, uncommon forms of immune-mediated diabetes, other genetic syndromes associated with diabetes and gestational diabetes mellitus (GDM) (WHO, 1999:17; WHO, 2006:29).

⁹ Fasting hyperglycaemia is defined as the glucose concentration after an overnight fast, reflecting abnormal hepatic glucose output and normal insulin resistance in the periphery and the liver (Petersen & McGuire, 2005:10, Vasan, 2008:47). Post-load hyperglycaemia reflects an acute increase in blood glucose level after a glucose load and is associated with decreased insulin secretion, normal to slightly reduced hepatic insulin resistance and increased insulin resistance in the periphery (especially in the skeletal muscle) (Færch *et al.*, 2008:854).

2.9.4.2 Prevalence and epidemiology of hyperglycaemia

Research show prediabetes as a common disorder in the majority of populations, *inter alia*, the US (Cowie *et al.*, 2009:292); Australia (Dunstan *et al.*, 2002:829), Korea (Song *et al.*, 2007:378), Mauritius, Fiji and Nauru (Shaw *et al.*, 1999:399) and India (Zargar *et al.*, 2006:329). The reported prevalence of prediabetes, however, fluctuates according to the ethnic background of the study population, the demographic profile and definition used (Pratley & Matfin, 2007:121; Zhang & Dall *et al.*, 2009:159).

Impaired glucose tolerance (IGT) is more prevalent than impaired fasting glucose (IFG) in most populations, with some degree of overlap between the categories. The International Diabetes Federation (2009) estimated that as from 2010, 344 million adults between the ages of 20 and 79 years worldwide would have IGT. Both IFG and IGT increase in prevalence with age (Meigs *et al.*, 2003:1481); impaired glucose tolerance increases linearly, peaking in those aged ≥ 75 years, whereas impaired fasting glucose doubles between ages 20-39 and 40-59 years and tends to plateau in those ≥ 60 years (Cowie *et al.*, 2009:290; Pratley & Matfin, 2007:121). Data from the DECODE and DECODA studies furthermore showed IFG to be more frequent in men than women in virtually all age groups, typically being 1.5-3 times higher, but up to seven or eight times higher in Europeans aged 50-70 years. The prevalence of IGT, conversely, was higher in women than in men in all age groups except in Asian populations over the age of 60 years and in the Europeans over the age of 80 years (The DECODE Study Group, 1998:373; The DECODA study group, 2003:1774). Similar observations were made in populations in Denmark, Australia and the US (Abdul-Ghani & Jenkinson *et al.*, 2006:1433; Cowie *et al.*, 2006:1266; Shaw *et al.*, 1999:399; Weyer *et al.*, 1999:2197).

In the early 1990s, Omar and co-workers (1993:642) found higher prevalence rates of impaired glucose tolerance in South African men (11.5%) compared with females (5.5%). More recently, Motala *et al.* (2008:1785) found similar results in a group of rural African study participants based on the 1985-WHO criteria for a 75 g oral glucose tolerance test. Using the 1998-WHO criteria, the prevalence was similar for both gender groups for diabetes and IGT, with predominance for IFG. The prevalence of diabetes escalated with increase in age; peak prevalence was in age group 55 to 64 years. Impaired glucose tolerance prevalence also increased, peaking in those older than 65 years (Motala *et al.*, 2008:1785).

Findings from the US Diabetes Prevention Program (DPP) (Knowler *et al.*, 2002:397) showed no overall gender difference in incident diabetes, though; gender difference in manner of diagnosis was observed. For example, more women than men progressed to diabetes based on 2-hour glucose criteria, whereas more men than women progressed based on the

combination of fasting and 2-hour glucose criteria.

According to the International Diabetes Federation (2009), approximately 246 million adults worldwide had diabetes in 2007. This included an estimated 17.2 million Americans (i.e. 7.7% of the adult American population) in 2007 (Lloyd-Jones *et al.*, 2010:e47) and a further 10.4 million people or 3.1% of the adult population in the African Region (IDF, 2009). Based on their estimates, the ethnic Indian population of Tanzania and the South African population respectively, had the highest prevalence rates among the different communities in sub-Saharan Africa for 2007. Current estimates by the IDF (2009) furthermore predict a 54% increase in prevalence to give a global prevalence of 438.4 million by 2030. Based on the 2003-SADHS, the burden of diabetes in South Africa was measured as 390 people per 100 000 in 2003 (Department of Health, 2007).

The incidence of type 1 diabetes mellitus peaks at ages 4-6 years and 10-14 years (Haller *et al.*, 2005:1554), with the pubertal peak of incidence in females preceding that in males by 1-2 years (Gale & Gillespie, 2001:4). About half of all type 1 diabetics, though, present as adults older than the age of 43 years, with a male predominance (Wild *et al.*, 2004:1050). Type 2 diabetes is the most frequent form of diabetes, representing roughly 80-95% of cases in developed countries and even higher levels in developing countries (Ahmed *et al.*, 2010:147; Weber *et al.*, 2010). The prevalence, however, varies considerably throughout the world, ranging from less than 1% in certain populations of developing countries to over 50% in the Pima Indians of Arizona (Zimmet, 1982:409). Type 2 diabetes mellitus is commonly diagnosed in individuals older than 40 years (onset from 25-64 years), with incidence increasing to peak in those 60-65 years and prevalence up to 10% in those older than 70 years (Donovan, 2002:109). Furthermore, there is a 3:2 male predominance for patients with type 2 diabetes mellitus (Williams, 2005:326). The prevalence of diabetes is therefore in general higher amongst men, but because prevalence increases with age and women live longer, there are more females with diabetes than males (Wild *et al.*, 2004:1050). In accordance, data from the 2003-SADHS showed that the self-reported prevalence rates of diabetes in South Africa were higher in females than for males, at 3.9% vs. 2.6% respectively (Department of Health, 2007).

2.9.4.3 Hyperglycaemia as risk factor

Hyperglycaemia is associated with many CVD risk factors (Glümer *et al.*, 2003:2336) and has been reported to increase CVD risk both in diabetic (Fuller *et al.*, 2001:S55) and non-diabetic individuals (Levitan *et al.*, 2004:2149; Meisinger & Wölke *et al.*, 2006:536). Patients with hyperglycaemia *per se* are furthermore at increased risk for developing type 2 diabetes (IDF, 2009; Menaka *et al.*, 2007:34; Santaguida *et al.*, 2005:8), as well as diabetes complications.

Landmark studies such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) showed that by reducing hyperglycaemia, both the incident risk and progression of diabetic complications were reduced, with no threshold level of HbA_{1c} beneath which further prognostic advantage could not be achieved (DCCT Research Group, 1996:1296; UKPDS, 1998b:851). Data from the UKPDS, for example, suggest that for every 1% reduction in HbA_{1c} there will be a 21% reduction in diabetes-related death, a 14% reduction in incidence of myocardial infarction, a 37% reduction in microvascular complications and a 43% reduction in peripheral vascular disease.

The pathogenesis of prediabetes (similar to that of type 2 diabetes), is linked to relative insulin deficiency and tissue insulin resistance, causing abnormal blood glucose levels despite secondary hyperinsulinaemia (Abdul-Ghani & Tripathy *et al.*, 2006:1130). Impaired fasting glucose is associated with hepatic insulin resistance, resulting in hyperglycaemia, whereas impaired glucose tolerance is primarily associated with skeletal insulin resistance (Pratley & Matfin, 2007:122). The underlying mechanisms linking elevated plasma glucose levels and insulin resistance to the development of the metabolic syndrome were described in section 2.8. Following is a brief description of the influences of IFG, IGT and prediabetes on the risk for cardiovascular disease and diabetes.

About 6-10% of patients with IGT progress yearly to diabetes and for patients with both IFG and IGT, the cumulative incidence of diabetes by 6 years may be as high as 65% (compared with 5% for those with normal glucose levels) (De Vegt *et al.*, 2001:2110; Garber *et al.*, 2008:940). Similar findings were reported by Twigg and co-workers (2007:461-462), estimating the annual progression risk to diabetes for a patient with both IGT and IFG at 3-10% - i.e. approximately six times that of an individual with a normal glucose tolerance. In general, approximately 25% of individuals with IFG/IGT progress to type 2 diabetes in 5 years, whereas about 50% remain prediabetic and 25% revert to normal (Larson *et al.*, 2000:1226). According to Unger and Parkin (2009:145), this rate of progression varies according to the degree of initial hyperglycaemia, racial and ethnic backgrounds and the influences from the environment.

Based on data from The DECODE Study Group (2001:397), impaired glucose tolerance (IGT) is more frequently associated with an increase in cardiovascular-related, as well as all-cause mortality than impaired fasting glucose (IFG). Nathan *et al.* (2007:757) and Santaguida *et al.* (2005:8) estimated this risk of nonfatal CV events per 100 patients with IGT or IFG at 11.6 to 12.4 and 0.63 to 9.70, respectively. IGT is also more strongly associated with the development of diabetes than IFG (D'Agostino *et al.*, 2004:2238; Lorenzo *et al.*, 2003:3157).

Once impaired glucose tolerance evolves into diabetes-level hyperglycaemia, elevated glucose

levels constitute an independent key risk factor for CVD (Alexander *et al.*, 2006:984; Grundy & Brewer *et al.*, 2004:434). Diabetes mellitus in itself remains a key risk factor for CVD and is associated with a 3- to 4-fold higher risk for cardiovascular disease events (Grundy, 2006c:1248; Meeuwisse-Pasterkamp *et al.*, 2008:330), as well as a 2- to 4-fold increasing risk for mortality from complications of cardiovascular events (Buse *et al.*, 2007:169; Deshpande *et al.*, 2008:1257). The effect of post-prandial hyperglycaemia is also greater than the effect of fasting hyperglycaemia on cardiovascular risk (Milicevic *et al.*, 2008:S155). This risk for mortality translates to about 80% of those with diabetes (Triplitt & Alvarez, 2008:177). Despite the fact that women face a lower risk of cardiovascular morbidity and mortality than men do before menopause, they have the same (or a higher risk) if they develop diabetes. For example, the Framingham Heart study further showed that this risk for cardiovascular mortality was 2-fold higher in men and 5-fold higher in women with diabetes (Preis *et al.*, 2009:1730, 1732). The risk for cardiovascular mortality is furthermore higher in younger patients (age's ≤ 65 years) with diabetes, compared with those without diabetes (Gottdiener *et al.*, 2000:B1635).

There is a major overlap between the presence of the metabolic syndrome and fasting hyperglycaemia, for example, according to Alexander *et al.* (2006:983), 80% from all individuals with fasting hyperglycaemia (impaired fasting glucose and diabetes) have the metabolic syndrome, whilst only about half of all individuals with the metabolic syndrome, have impaired fasting glucose. The risk for diabetes furthermore varies based on abnormalities present, for example, individuals with the metabolic syndrome (but without impaired glucose tolerance) have a 12%, 7-year risk for diabetes, compared with those with impaired glucose tolerance (without metabolic syndrome) who have a 25% risk and those with both IGT and IFG who have a 55% risk (Haffner *et al.*, 1990:2896). The metabolic syndrome *per se*, may also present a prediabetic state that have an immediate heightened risk for coronary heart disease (Garber *et al.*, 2008:936).

2.9.4.4 Hyperglycaemia disease burden

Patients with hyperglycaemia are generally poorer in health compared with those with normoglycaemia; they also carry excess medical costs. This excess medical cost is significantly higher for IGT and combined IFG/IGT (relative to normoglycaemia and IFG) (Nichols *et al.*, 2008:795). Adults with prediabetes furthermore have, on average, 1.1 times the annual number of physician office visits compared with those with normoglycaemia (Dall *et al.*, 2010:300). These additional visits translate into approximately 10% of additional hospital outpatient visits per year and 2.7 additional prescriptions per year (Zhang & Dall *et al.*, 2009:160).

The annual direct health care cost of diabetes worldwide for individuals aged 20-79 years, is

estimated to at least 153 billion international dollars (IDF, 2006). Based on 2005 statistics, the IDF predicted the total direct health care expenditure on diabetes worldwide in 2025, to between 213 billion and 396 billion international dollars (translating to a 7-13% in the world's health care budget being spent on diabetes care in 2025) (WHO, 2005:78). The medical expenditure in individuals with diabetes is further on average about 2.3 times higher compared with that of patients without diabetes, alongside higher use of hospital/inpatient care, outpatient and physician office visits, emergency visits, nursing facility stays, home health visits, visits with other health professionals and prescription products and medical supply use (ADA, 2008:608; Anon., 2010a:1513; Dall *et al.*, 2010:300; Gulliford *et al.*, 2008:36). Based on an earlier estimate by Jacobs and colleagues (1991:S27), late complications of diabetes also resulted in a significant cost burden, accounting for approximately 7 million hospital days costing in excess of US\$5 billion dollars annually.

Diabetes furthermore has a negative effect on patients' quality of life, life expectancy and economic productivity due to early retirement, disability and mortality (Colagiuri & Davies, 2009:98; Kamarul *et al.*, 2010:159; Tunceli *et al.*, 2005:2662), and cardiovascular disease risk (Homko *et al.*, 2010:487). In addition, diabetics have a 0.8% higher health-related absenteeism rate (equivalent to 1.9 workdays per worker, per year) compared with individuals without diabetes (Goetzel *et al.*, 2004:405). The American Diabetes Association (2008:603) further estimated a decline in productivity rate of 6.6% (14 days per worker, per year) because of the disease. These affects of diabetes on work-loss days and loss of life-years are more pronounced among females. For example, Narayan *et al.* (2003:1887) calculated a loss of approximately 11.6 life-years for males at age 40 years compared with 14.3 life-years for females of similar age.

Compared with patients with type 2 diabetes, those with type 1 diabetes, have a (relative) higher *per capita* use of health care services. For example, Dall *et al.* (2009:107) determined that approximately 6% of people in the United States had type 1 diabetes in 2007, whilst carrying about 9% of the economic burden of diagnosed diabetes, whereas the ratio of economic burden per case for type 2 diabetes was 1.03:1. This economic burden amplified with age, at a faster rate for those with type 1 diabetes compared with those with type 2 diabetes (Dall *et al.*, 2009:109). Complications associated with chronic hyperglycaemia typically found in patients with diabetes (both types 1 and 2), i.e. microvascular complications (retinopathy, neuropathy and nephropathy) and macrovascular complications (Ahmed *et al.*, 2010:152), exert a huge additional social and economic burden, as was shown by Fu and co-workers (2009:2189). Based on their study, diabetic patients with macrovascular co-morbid conditions have a statistically significant higher annual health care costs (US\$ 5,120), more missed work days (13.03 days), and more bed days (7.60 days) per patient compared with those without co-

morbid conditions.

According to Idemyor (2010:650), the diabetic population in sub-Saharan Africa, consists mainly of the economically productive age group of 30 to 45 years. This is opposing to developed countries where the mainstream of individuals diagnosed with diabetes is 60 years of age. The late diagnosis of diabetes in this region, coupled with inequalities in access to care, leads to early presentations of diabetic complications in the sub-Saharan Africa region. The disease in Sub-Saharan Africa is further coupled by an enormous economic burden as shown by Kirigia and colleagues (2009). Based on their analysis, the region's resulting economic loss was US\$25.51 billion in purchasing power parity as recorded by countries of the African region in 2000. According to Norman, Bradshaw and Schneider *et al.* (2007:638), diabetes furthermore accounted for 1.6% of the 16.2 million DALYs in South Africa for the year 2000.

The additional cost for patients who ultimately develop diabetes begin at least five (Gulliford *et al.*, 2005:47) to eight (Nichols *et al.*, 2000:1656) years before the actual diagnosis thereof. Delaying the onset and slowing down the progression from hyperglycaemia to diabetes may therefore have tremendous potential in improving associated clinical and economic consequences for individuals, families, health systems and countries.

2.9.4.5 Treatment of hyperglycaemia

Glycaemic control is a cornerstone for reducing end-organ disease and therefore crucial to the successful treatment of patients with diabetes mellitus (Spellman, 2009:8). The treatment goals in the consensus guidelines from the American Diabetes Association (2009:S13) and the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE, 2010:155) refer to glycosylated haemoglobin (HbA_{1c}) levels as the determinant of optimal glycaemic control.

The American Association of Clinical Endocrinologists (AACE) (Jellinger *et al.*, 2007:260) and the European Association for the Study Of Diabetes (EASD) (Rydén *et al.*, 2007:124) currently recommend a target HbA_{1c} level of $\leq 6.5\%$, whereas the American Diabetes Association (ADA, 2009:S13) and subsequently the Society for Endocrinology, Metabolism and Diabetes of South Africa (Levitt *et al.*, 2009:55) advocate an HbA_{1c} level $\leq 7\%$ in most individuals, or as close to normal as possible ($<6\%$) without significant hypoglycaemia in selected individuals. An HbA_{1c} level of $\geq 7\%$ should therefore serve as a point at which to initiate or change therapy (Distiller, 2009:128; Nathan *et al.*, 2009:194). ISPAD (the International Society for Pediatric and Adolescent Diabetes) furthermore advocates a target HbA_{1c} of $<7.5\%$ for all children and adolescents (Rewers *et al.*, 2009:77).

The management of prediabetes is based on lifestyle management; there are currently no pharmacological therapies approved for the prevention of diabetes in individuals (Aroda & Ratner, 2008:3262; Lavernia, 2010:eS14). Pharmacological therapy may however be required as prediabetes progresses towards hyperglycaemia. The approach to treating adult hyperglycaemia depends on the degree of hyperglycaemia – in mild to moderate hyperglycaemia ($\text{HbA}_{1\text{C}} < 9\%$), lifestyle therapy (followed by monotherapy) may be adequate to achieve glycaemic control, whereas in those with more severe hyperglycaemia (i.e. $\text{HbA}_{1\text{C}} \geq 9\%$), pharmacological measures (most likely combination therapy) should commence immediately. In cases with marked hyperglycaemia (i.e. $\text{HbA}_{1\text{C}} \geq 11\%$), insulin therapy should be initiated (Deeg, 2005:39E). All forms of glucose abnormalities in children and adolescents should be treated with lifestyle modification (including dietary changes) and increased physical activity. Pharmacological treatment should be retained for obese children with the highest fasting concentrations of glucose and insulin (Pacifico *et al.*, 2011:457).

The lifestyle modification of hyperglycaemia is briefly discussed in the following section. A discussion on the pharmacotherapy thereof ensues in paragraph 2.9.4.5.2.

2.9.4.5.1 Lifestyle modification of hyperglycaemia

The goal of lifestyle modification in patients with hyperglycaemia is to decrease insulin resistance and to prevent or delay the development of prediabetes and progression to type 2 diabetes in high-risk populations (Hinnen *et al.*, 2006:612; Weber *et al.*, 2010). Implementation of a healthier lifestyle with increase in physical activity and reduction of body weight, based on the regulation of calories and fat intake, forms the basis of this approach.

Statistical analysis of the Diabetes Prevention Program (DPP) Study (Diabetes Prevention Program Research Group, 2003:2520), the Diabetes Prevention study (DPS) (Lindgren *et al.*, 2007:180) and the Indian Diabetes Prevention Programme (Ramachandran *et al.*, 2007:2550) has projected the lifestyle intervention in each programme to be cost-effective. For example, in the DPP, the cost of lifestyle intervention from a health system's perspective was US\$15,655 per case of diabetes prevented and US\$ 31,338 per case of diabetes prevented with metformin, compared with placebo (Diabetes Prevention Program Research Group, 2003:2520).

- **Weight loss and dietary management**

Excess weight and obesity are strongly related to the risk for type 2 diabetes (Avenell *et al.*, 2004:77), with lifetime diabetes risk escalating with increase in BMI. For example, in the late 1990s, Ford and co-workers (1997:218) determined that for each unit of BMI increase above the

normal weight-range, the risk for diabetes increased by 12%. Meisinger and Döring *et al.* (2006:485) and Narayan *et al.* (2007:1564) demonstrated similar findings, furthermore adding that the highest risk was associated with the largest waist circumference and waist-to-hip ratio. Weight loss is therefore the primary goal of lifestyle modification in those at risk for developing diabetes (Deeg, 2005:38E; Kyrou & Kumar, 2010:282).

Already in the 1970s, Hadden and co-workers (1975:277) showed that a weight loss of 2.25 - 4.5 kg was associated with a reduction in plasma glucose. Moderate weight loss (i.e. 5% of body weight) may further improve insulin action, thereby reducing the need for diabetes medication (Williams & Kelly, 2000:128) and improve the health-related quality of life significantly, especially for those with the poorest quality of life at baseline (Williamson *et al.*, 2009:170). According to the American Diabetes Association, the North American Association for the study of Obesity and the American Society for Clinical Nutrition (2005:130) an even better outcome for long-term weight reduction occurs when increased physical activity and behaviour therapy are combined with dietary management.

Intensive dietary management can provide adequate control of fasting plasma glucose without pharmacologic therapy in those with diagnosed type 2 diabetes (Hadden *et al.*, 1975:277) and reduce the use of hypoglycaemic medications while improving glycaemic control (Pi-Sunyer *et al.*, 2007:1380). Dietary change should typically include a limitation of calorie intake to approximately 1 500 kcal per day, restriction of fat intake to 30-35% of total daily energy uptake (reservation of 10% for monounsaturated fatty acids), avoidance of trans-fats, increased fibre uptake to 30 g per day and the avoidance of liquid mono- and disaccharides (Tuomilehto *et al.*, 2001:1348; Wolfram & Ismail-Beigi, 2010:20).

Weight loss alone may reverse the course of insulin resistance and normalise blood glucose concentrations, but is associated with high attrition rates, complicating weight loss sustainment (Bazzano *et al.*, 2005:315). Lifestyle change should therefore also focus on increasing physical activity, which improves insulin sensitivity independent of the effect on BMI (refer to paragraph 2.9.1.5.1). The combination of weight loss and physical activity renders the best results, for example, data from the DPP-trial demonstrated that weight loss (7% of weight loss in the first year) and increased physical activity (150 minutes of brisk walking per week), reduced the 4-year incidence of type 2 diabetes by 58% in individuals with impaired glucose tolerance (Knowler *et al.*, 2002:400).

- **Increasing exercise/physical activity**

Physical activity is an important component of any weight management programme. Although

energy restriction by dieting is largely responsible for initial weight loss, regular physical activity helps to maintain weight loss and prevent regain (Wing & Hill, 2001:340) (refer to paragraph 2.9.1.5.1).

Regular physical activity furthermore leads to various favourable physiological changes that influence muscle and liver insulin sensitivity, muscle glucose uptake and utilisation and overall glycaemic control positively (Goodpaster & Brown, 2005:153; Sigal *et al.*, 2006:1436). Consistently performed activity can also improve lipid profile, decrease body weight and percentage of body fat, lower blood pressure and positively influence thromboembolic state and thus reduce overall cardiovascular disease risk (Haskell *et al.*, 2007:1085). This reduction in cardiovascular disease risk is of primary importance for individuals with diabetes who are 3-4 times as likely to experience serious cardiovascular disease events (refer to paragraph 2.9.4.3). Implementation and maintenance of an active lifestyle can lessen this risk by approximately 38-55% (Orchard *et al.*, 2005:619; Petrella *et al.*, 2005:699). Additionally, physical activity can add to the prevention or delay in development of other long-term diabetes complications, such as neuropathy, retinopathy and nephropathy and may slow progression of existing complications (Boule *et al.*, 2001:1226).

The American Diabetes Association (ADA, 2009:S26; Sigal *et al.*, 2006:1436) and the American Heart Association (Marwick *et al.*, 2009:3254) recommend that all type 2 diabetes patients should get at least 150 minutes per week of moderate-intensity exercise or 90 minutes/week of vigorous-intensity exercise, or some combination of the two to improve cardiovascular risk. Gill and Cooper (2008:821-822) furthermore suggested that patients should be defined as “high” or “low” risk for developing diabetes according to BMI or waist threshold. Based on their suggestion, those with a low risk should aim to achieve current physical activity (as stated above), whereas those at high risk (i.e. those with IGT, individuals who were small and thin at birth and those with a first-degree relative with type 2 diabetes) should increase their physical activity beyond this level (i.e. ~300 minutes per week of moderate-intensity exercise or 120-150 minutes/week of vigorous-intensity exercise).

Exercise is not generally considered part of the treatment of type 1 diabetes, as hypoglycaemia and hyperglycaemia often develop during light to moderate exercise (unless the insulin dose is reduced or extra carbohydrates consumed) and during and after brief, maximal-intensity exercise (due to a higher rate of glucose production compared with glucose disposal), respectively (Bastaki, 2005:113; Kordi & Rabbani, 2007:53). The American Diabetes Association and American College of Sports Medicine (ADA, 2003:S73) published new guidelines for regulating the glycaemic response to physical activity for type 1 diabetics in 2003. Based on these guidelines, patients should achieve metabolic control before physical activity,

monitoring blood glucose levels before and after physical activity and control their food intake. Patients with good metabolic control can participate in most activities.

In summary, lifestyle therapy (decreasing weight and increasing physical activity) renders an expected decrease in HbA_{1c} levels of about 1-2%. A major disadvantage of this type of therapy, however, is that it is insufficient for most within the first year of therapy – limiting the role of lifestyle intervention as an effective means of controlling glycaemia on the long run (Nathan *et al.*, 2009:195). Based on a review by Ahmad and Crandall (2010:54), the weight loss technique with the highest success rate is bariatric surgery. Sjöström *et al.* (2004:2690) for example, showed that the risk for diabetes was reduced by 86% at 2 years and 75% at ten years follow-up in patients who underwent surgical procedures (mostly vertical banded gastroplasty). Bariatric surgery also induces remission of existing diabetes (Dixon *et al.*, 2008:320). Surgery is expensive and associated with a high mortality rate; it should be reserved only for morbidly obese patients (refer to paragraph 2.9.1.5.2). The large majority of patients therefore still require the addition of medicine over the course of their diabetes (Horton, 2009:S24).

2.9.4.5.2 Pharmacotherapy of hyperglycaemia

Antihyperglycaemics generally used for lowering plasma glucose include the insulins (i.e. short- and rapid-acting, intermediate-acting, long-acting and premixed products), amylin analogues, insulin secretagogues [i.e. sulphonylureas, meglitinides (glinides), glucagon-like peptide-1 agonists and dipeptidyl peptidase-4 inhibitors], insulin sensitizers (i.e. biguanides, the glitazones and dual PPAR α / γ agonists) and α -glucosidase inhibitors (Deeg, 2005:38E).

Based on results of a study by Standl and Füchtenbusch (2003:M34), the Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD) suggests that the stage of disease and the related predominant metabolic phenotype be taken into account when tailoring therapy to a patients' individual needs (Rydén *et al.*, 2007:115). These suggestions are depicted in Table 2.11.

Table 2.11: Suggested policy for the selection of glucose-lowering therapy (Standl & Füchtenbusch, 2003:M34)

Glucometabolic situation	Glucose-lowering therapy
Post-prandial hyperglycaemia	Alpha-glucosidase inhibitors, short-acting sulphonylureas, glinides, short-acting regular insulin, or insulin analogues
Fasting hyperglycaemia	Biguanides, long-acting sulphonylureas, glitazones, long-acting insulin, or insulin analogues
Insulin resistance	Biguanides, glitazones, alpha-glucosidase inhibitors
Insulin deficiency	Sulphonylureas, glinides, insulin

The primary goal of early glucose-directed therapies is to normalise glucose levels, to avert or delay progression to diabetes and to prevent microvascular complications, without any hypoglycaemic episodes (Garber *et al.*, 2008:939; Hall & Nicholson, 2009:1727; Motala *et al.*, 2006:81). In normalising glucose levels, the American Diabetes Association advocates taking the “ambient level of glycaemic control” into consideration in selecting a class of pharmacological agents, or a specific medication within a class, for initiating or changing therapy. For example, in patients with glycaemic levels nearer to the target levels (e.g. HbA_{1c} <7.5%), medications with lesser potential to lower glycaemia and/or a slower onset of action may be considered. Pharmacological classes with superior and more rapid glucose-lowering effectiveness, or potentially earlier initiation of combination therapy should be considered for patients with high levels of glycaemia (e.g. HbA_{1c} >8.5%) (Nathan *et al.*, 2009:196).

The 2009-ADA/European Association for the Study of Diabetes (EASD) consensus treatment algorithm for the management of hyperglycaemia in patients with type 2 diabetes (Nathan *et al.*, 2009:200) (refer to Annexure A.4 for algorithm), consists of a 2-tier system, taking into account information on the safety, cost and efficacy of agents for which there is considerable clinical experience (tier 1) and the availability of relatively new agents (tier 2) that act through other, complementary mechanisms. The South African algorithm for the management of hyperglycaemia in type 2 diabetics in South Africa (Levitt *et al.*, 2009:58), as illustrated in Figure 2.3, was based on this approach.

STEP 1	AT DIAGNOSIS: LIFESTYLE MODIFICATION + METFORMIN				
Initiate metformin at diagnosis and titrate dose up to 2 550 mg per day over 1-2 months					
↓ HbA_{1c}>7% after >3 months or if metformin is contraindicated					
STEP 2a	ADD SULPHONYLUREA Especially if HbA _{1c} <8.5% Use glibenclamide (glyburide) only if serum creatine is normal Titrate to maximum tolerated dose over 3 months	OR	ADD BASAL INSULIN Especially if HbA _{1c} >8.5% Start 10u at bedtime Titrate by 2u/week until fasting glucose <7.0mmol/L	OR	ADD PIOGLITAZONE Not preferred except under special circumstances
↓ HbA_{1c}>7% after >3 months					
STEP 2b (optional)	ADD A 3rd AGENT FROM STEP 2 i.e. Choose a 3rd as yet unused agent from STEP2a				
↓ HbA_{1c}>7% after >3 months					
STEP 3	START BIPHASIC INSULIN ± METFORMIN When intensive insulin therapy is not feasible	OR	REFER FOR INTENSIVE INSULIN THERAPY i.e. Basal + prandial insulin therapy		

Figure 2.3: Management of glycaemia in type 2 diabetics (Levitt *et al.*, 2009:58)

Figure 2.3 show that metformin is the agent of choice for the majority of patients with hyperglycaemia. If treatment goals are not met with lifestyle changes and the use of the maximal tolerated dose of metformin, another medication (from insulin, a sulphonylurea or thiazolidinediones) should be added within two to three months of the initiation of therapy or at any time when the HbA_{1c} goal is not achieved. Patients with HbA_{1c} levels greater than 7% may furthermore require short- or rapid-acting insulin prior to meals in addition to basal insulin to control glycaemia (Levitt *et al.*, 2009:57-58). The South African Department of Health (2003b) also published an algorithm for the treatment and management of type 1 diabetes mellitus as part of the Chronic Disease List (CDL) (refer to Annexure A.5 for algorithm).

The modification of lifestyle in patients with hyperglycaemia was addressed in paragraph 2.9.4.5.1. A discussion on each of the pharmacological groups used in the treatment of elevated plasma glucose follows in subsequent sections.

- **Insulin secretagogues**

Insulin secretagogues correct hyperglycaemia by stimulating insulin secretion in the presence of functioning β -cells (Lebovitz, 2002:812). This class of medicine can be divided into those acting on the potassium sensitive-adenosine triphosphate channel, i.e. the sulphonylureas and non-sulphonylureas (meglitinides), and the incretin-based therapies, i.e. the dipeptidyl peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 (GLP-1) analogues (Deeg, 2005:38E).

- **Sulphonylureas**

The sulphonylureas are subdivided into first generation agents (i.e. acetohexamide, chlorpropamide, tolbutamide and tolazamide), second-generation agents (i.e. glipizide, glyburide or glibenclamide, gliclazide, gliquidone and glyclopyramide) and third generation agents (i.e. glimepiride), based on when they became available (Green & Feinglos, 2006:374; Koski, 2006:870). These agents (especially the second generation agents' glipizide and glyburide and third generation glimepiride) have been the mainstay of managing glycaemia in patients with type 2 diabetes for several decades (Deeg, 2005:38E; Gilbert, 2009). The Society for Endocrinology, Metabolism and Diabetes of South Africa (Levitt *et al.*, 2009:57), also regard the use of sulphonylureas as one of the agents in the "backbone" of diabetes management in South Africa. Findings from the UK Prospective Diabetes Study (UKPDS, 1998b:837) furthermore demonstrated that intensive glycaemic control with sulphonylureas resulted in significant reductions in microvascular complications. A subsequent analysis of the UKPDS data by Stratton and co-workers (2000:410) demonstrated a further reduction in macrovascular complications associated with improved glycaemic control, in contrast to increases in mortality

suggested by the findings of the older University Group Diabetes Program (Goldner *et al.*, 1971:1409). In addition, according to Sutherland and Hoehns (2004:381), the sulphonylureas are the least expensive of the oral agents available to treat type 2 diabetes. They may also be beneficial for diabetic patients with acute ischemic stroke (Kunte *et al.*, 2007:2529), obese (or of normal weight) patients older than 30 years and females who are not considering pregnancy (Goldfine & Maratos-Flier, 2001:1345).

The sulphonylureas have similar mechanisms of action (Nathan *et al.*, 2009:196), acting by binding to the transmembrane sulphonylurea receptor (SUR-1) subunit of potassium sensitive-adenosine triphosphate (ATP) channels on the cells of islet of Langerhans (β -cells), leading to closure of the potassium channel (Bastaki, 2005:120; Bösenberg & van Zyl, 2008:80). This in turn causes a reduction in cellular efflux of potassium, with subsequent membrane depolarisation, followed by the opening of voltage-dependent calcium channels with influx of calcium into the cell (Holstein *et al.*, 2011:13). Intracellular calcium then mobilises pre-formed insulin-containing granules with release of insulin to the exterior (Evans & Rushakoff, 2010; Green & Feinglos, 2006:374). According to Zhang and Katoh *et al.* (2009:607), the sulphonylureas may, potentially, also modify the activity of Epac2, a guanine nucleotide exchange factor for the small guanosine triphosphatase repressor activator protein 1 (Rap-1).

Most sulphonylureas result in equivalent reductions in glucose levels at equipotent doses, although the generations differ with regard to potency, pharmacokinetics and safety. For example, the second-generation agents are in general 20-50 times more potent and normally have better pharmacokinetic and safety profiles than the first generation agents (Koski, 2004:40; Mehanna, 2005). The overall efficacy relates to pre-treatment levels of fasting plasma glucose and HbA_{1c} – the higher the level, the greater the effect will be. On average, this medicine class reduces HbA_{1c} levels by 0.8-2% and fasting plasma glucose (FPG) concentrations by 60-70 mg/dL (3.3-3.9 mmol/L) (Evans & Rushakoff, 2010; Fonseca & Kulkarni, 2008:S30). The blood glucose effect starts plateauing after the half-maximal recommended dose is reached and eventually results in a loss of therapeutic effectiveness of 3-10% per year (Lebovitz, 2006:145). The efficacy of these agents therefore depends on adequate cell function, which subsequently reduces with disease progression (Desai & Tandon, 2007:193). Patients with inadequate levels of β -cells, i.e. those with type 1 diabetes, pancreoprivic diabetes or later stages of type 2 diabetes, therefore also do not respond to the sulphonylureas (Fowler, 2010a:133).

A potentially life threatening and major adverse effect seen with more potent and longer acting sulphonylureas is hypoglycaemia (annual incidence 1-2%) (Nathan *et al.*, 2009:196). According to Fowler (2010a:133), the risk for hypoglycaemia is higher in elderly patients, in particular more

with glyburide (glibenclamide) and chlorpropamide than with the other sulphonylureas. Recurrent cases of hypoglycaemia may also occur in patients with impaired renal function. In light of this, initiation of treatment should be at the lowest recommended dose. Another major adverse effect of sulphonylurea treatment is weight gain (typically 2-5 kg) (Lebovitz, 2001:920; Srinivasan *et al.*, 2008:524). Major adverse effects of first-generation agents include skin rash, alcohol-induced flushing and hypernatremia. This latter affect also limits their use (Bastaki, 2005:121; Cheng & Fantus, 2005:219). Glimepiride has been reported to be the most weight-neutral sulphonylurea (Weitgasser *et al.*, 2003:18). Sulphonylureas furthermore do not have a clinically significant effect on the lipid profile (Hanefeld, 2007:24).

– ***Non-sulphonylureas (meglitinides)***

The non-sulphonylureas (meglitinides or “glinides”) are a relatively new class of medications, currently represented by nateglinide (a d-phenylalanine derivative), repaglinide (a benzoic acid derivative) (Gilbert, 2009; Goldfine & Maratos-Flier, 2001:1344) and mitiglinide (a benzylsuccinic acid derivative) (Konya *et al.*, 2009:1905).

Similar to the sulphonylureas, repaglinide, nateglinide and mitiglinide stimulate β -cells to increase insulin secretion (Nathan *et al.*, 2009:196; Phillippe & Wargo, 2010:1617), though *via* a different, adjacent site on the sulphonylurea receptor (Cheng & Fantus, 2005:219; Malaisse, 2003:403). The meglitinides have somewhat different characteristics when compared with the sulphonylureas, for example, they have a very short onset of action and half-life; these agents are therefore best taken just before or with meals (Holstein *et al.*, 2011:14; Luna & Feinglos, 2001:1751). Repaglinide only enhances glucose-dependent insulin secretion in the first phase and early second phase of insulin secretion, whereas nateglinide and mitiglinide mainly enhance the glucose-dependent first phase (Desai & Tandon, 2007:194). The meglitinides are mainly used in post-prandial blood glucose control and are useful for those with renal impairment, those predisposed to hypoglycaemia such as patients with irregular eating patterns and the elderly (Desai & Tandon, 2007:194; Fowler, 2010a:133; Luna & Feinglos, 2001:1752). The lower risk for weight gain associated with these agents (see adverse effects below) also makes the meglitinides attractive alternatives to the sulphonylureas (Bösenberg & Van Zyl, 2008:82) and metformin (in cases where adverse effects of metformin are intolerable or where metformin is contraindicated) (Black *et al.*, 2007:CD004654).

Monotherapy with repaglinide lowers the HbA_{1c} level by 0.1-2.1%, whereas nateglinide appears somewhat less efficacious, lowering HbA_{1c} levels by only 0.2-0.6% compared with placebo (Black *et al.*, 2007:CD004654). Mitiglinide has been shown to decrease HbA_{1c} levels similar to that obtained by nateglinide (Kim *et al.*, 2007:173; Konya *et al.*, 2009:1906). These agents may

also provide additive effects in combinations with other hypoglycaemics (refer to “combination therapy with hypoglycaemics”).

Similar to sulphonylureas, the main adverse effects of the meglitinides are hypoglycaemia and weight gain (Srinivasan *et al.*, 2008:524). The risk for weight gain is similar to that of the sulphonylureas, but hypoglycaemia may be less frequent (Fonseca & Kulkarni, 2008:S30; Nathan *et al.*, 2009:196). These adverse effects are also more pronounced with repaglinide compared with nateglinide and mitiglinide (Evans & Rushakoff, 2010; Kim *et al.*, 2007:173). Other adverse effects commonly associated with repaglinide include upper respiratory tract infections, rhinitis, bronchitis and headaches (Culy & Jarvis, 2001:1627), whereas nateglinide is more frequently associated with nausea, diarrhoea, dizziness and light-headedness (Evans & Rushakoff, 2010). The safety and adverse effect profile of mitiglinide is similar to that of nateglinide (Phillippe & Wargo, 2010:1621).

Although the meglitinides have no significant effect on lipid profile, their cardiovascular safety is still uncertain (Fisman & Tenenbaum, 2009). They are furthermore relatively expensive compared with the sulphonylureas, a factor that may also be amplified by the frequent dosing interval required with these agents (Fowler, 2010a:134; Sutherland & Hoehns, 2004:382).

– ***Dipeptidyl peptidase-4 inhibitors***

Dipeptidyl peptidase-4 is a highly specific serine protease in the endothelium of different organs that acts by rapidly cleaving endogenous incretin hormones to render them inactive (Idris & Donnelly, 2007:154; Thornberry & Gallwitz, 2009:479). These incretin hormones, e.g. glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), are secreted by the L-cells of the distal ileum and colon and the K-cells of the duodenum and upper jejunum in response to ingestion of a meal - increasing post-prandial insulin levels (Chia & Egan, 2008:3703; Sena *et al.*, 2010:147). Incretin hormones are responsible for a multitude of hypoglycaemic effects, including the glucose-dependent stimulation of insulin secretion and the suppression of glucagon release, increasing neogenesis, reducing apoptosis of pancreatic islet β -cells and slowing of gastric emptying and increased satiety (Janosz *et al.*, 2009:387; Penfornis *et al.*, 2008:S80; Ross & Ekoé, 2010:640). Inhibition of the dipeptidyl peptidase-4 enzyme therefore increases the level of endogenous incretins, enhancing their activity (Campbell, 2007:52; Ng & Kong, 2007:33).

The dipeptidyl peptidase-4 (DPP-4) inhibitors (or so-called incretin enhancers or “gliptins”) are a novel class of oral agents available for the treatment of type 2 diabetes (Bohannon, 2009:1; Fowler, 2010a:135). Four gliptins have been approved for the treatment of type 2 diabetes, e.g.

sitagliptin and vildagliptin (Ross & Ekoé, 2010:639), saxagliptin (Ahrén, 2009:487) and linagliptin (FDA, 2011c). Several others, e.g. melogliptin, denagliptin and dutogliptin are currently in various stages of phase II and III clinical trials (Janosz *et al.*, 2009:389; Seshadri & Kirubha, 2009:612), whereas alogliptin is currently under review for approval in various countries (Deacon, 2008:402).

Sitagliptin and vildagliptin appear similar in efficacy, with sitagliptin reducing HbA_{1c} levels by 0.6%-1% from baseline (Ahrén, 2010:35), whereas vildagliptin is associated with mean reduction in HbA_{1c} levels ranging from 0.5% (Mikhail & Cope, 2010) to 1% (De *et al.*, 2011:100) compared with baseline. Compared with the former two gliptins, saxagliptin appears more effective, demonstrating dose-dependent reductions in HbA_{1c} of 0.6-1.7% when administered at a daily dose of 2.5- to 10 mg (Rosenstock, 2010:819). Alogliptin appears less effective, reducing HbA_{1c} levels by 0.56% and 0.59% (~0.6% from baseline in daily doses of 12.5 mg and 25 mg, respectively) (Andukuri *et al.*, 2009:120; DeFronzo *et al.*, 2008:2316). Linagliptin appears the least effective, reducing HbA_{1c} levels by 0.31% and 0.28% from baseline in daily doses of 2.5 mg and 10 mg, respectively (Forst *et al.*, 2011:548).

According to Waugh and co-workers (2010:xv) the gliptins are comparable to the glitazones in cost. Schwarz *et al.* (2008:53) however showed that compared with adding rosiglitazone or a sulphonylurea to metformin therapy in type 2 diabetics who were not at goal after treatment, the gliptins (in particular sitagliptin) were either cost-saving or cost-effective. These agents furthermore have relatively less adverse effects compared with the other oral antihyperglycaemics (including hypoglycaemia) (Bloomgarden & Dexler, 2008:308-309; Campbell, 2007:57). The gliptins are therefore the agents of choice in those in whom concerns about hypoglycaemia are greatest (thus precluding sulphonylurea therapy), the elderly and those who are intolerant to either metformin or thiazolidinediones (Pratley & Salsali, 2007:929; Smushkin & Vella, 2009:86-87). In addition, the gliptins are without treatment-limiting gastrointestinal adverse effects (Campbell, 2007:57; Williams-Herman *et al.*, 2010) and are weight-neutral (Amori *et al.*, 2007:204; Schweizer *et al.*, 2007:959; Taskinen *et al.*, 2011:72), providing advantage over current weight-promoting therapies, such as sulphonylureas, thiazolidinediones and insulin (Nadeau, 2010:11). Gliptins are also effective when combined with these agents (Bloomgarden & Dexler, 2008:309; Chia & Egan, 2008:3710, 3711). According to Richter and colleagues (2008:CD006739), the most common adverse effects associated with sitagliptin are infections (e.g. nasopharyngitis, upper respiratory tract infections and urinary tract infections) (RR, 1.5; 95% CI: 1.02 - 1.31). Similar findings were illustrated with vildagliptin (Chia & Egan, 2008:3711), saxagliptin (Lam & Saad, 2010:215) and linagliptin (Forst *et al.*, 2011:548). Headaches were also reported for sitagliptin and vildagliptin, although more common with the latter agent (Richter *et al.*, 2008:CD006739; Smushkin & Vella, 2009:87). According to

Davidson (2009:S34) the incidence of hypoglycaemia in patients receiving DPP-4 inhibitors is 2% or less.

– ***Glucagon-like peptide-1 (GLP-1) agonists***

Glucagon-like peptide-1 (GLP-1) agonists (or so-called incretin mimetics) imitate some effects of endogenous incretin hormones *via* a glucose-dependent mechanism when blood glucose levels are higher than normal, with subsequent hypoglycaemic actions (Campbell, 2007:52; Janosz *et al.*, 2009:389) (refer to effects of incretins under “dipeptidyl peptidase-4 inhibitors”). These agents can be administered as monotherapy or as add-on therapy in those who have not achieved adequate blood glucose control with either dual or triple therapy for the treatment of type 2 diabetes (Halimi, 2008:S94; Kyriacou & Ahmed, 2010:2556; Ryan & Hardy, 2010:11). Liraglutide (a human analogue GLP-1 receptor agonist) and exenatide (a synthetic derivate of exendin-4, a hormone found in the saliva of the Gila monster) have been approved for use in patients with type 2 diabetes (Unger & Parkin, 2009:148-149). Other incretin mimetics currently in various stages of development are taspoglutide and lixisenatide (human analogue GLP-1 receptor agonists) and albiglutide (a long-acting GLP-1 receptor agonist) (Davidson, 2009:S29; Janosz *et al.*, 2009:389; Werner *et al.*, 2010:58).

Overall, the GLP-1 agonists reduce HbA_{1c} with 0.8-1.7% (Vilsbøll *et al.*, 2007:1609; DeFronzo *et al.*, 2005:1098). These agents therefore reduce hyperglycaemia generally more than the DPP-4 inhibitors do (Halimi, 2008:S94). Within the class of GLP-inhibitors, liraglutide reduces mean HbA_{1c} levels significantly more than exenatide (1.12% vs. 0.79%; 95% CI: -0.47 to -0.18) (Buse *et al.*, 2009:42). Both agents, however, promote comparable weight losses (liraglutide 3.24 kg vs. exenatide 2.87 kg) and reductions in blood pressure (liraglutide 2.51 mmHg systolic, 1.05 mmHg diastolic vs. exenatide 2.00 mmHg systolic, 1.98 mmHg diastolic). Results of the study by Buse and colleagues (2009:44-45) additionally showed that liraglutide increased the HOMA index of β -cell function more than did exenatide, indicating more-sustained GLP-1 receptor activation with liraglutide than with exenatide. Liraglutide furthermore reduced triglycerides and free fatty acid values significantly more than did exenatide, whilst increases in VLDL-cholesterol were smaller with liraglutide.

Liraglutide is considerably more expensive than exenatide. According to The Regional Drug and Therapeutic Centre of the United Kingdom (2009), liraglutide 1.8 mg was double the price of exenatide 10 mcg in 2009. Compared with the sulphonylureas (in particular glimepiride), liraglutide is considered cost-effective at a cost-effectiveness ratio of £13,257 to £18,837 per quality-adjusted life year (NICE, 2010).

Both liraglutide and exenatide are generally well tolerated, with dose-dependent gastro-intestinal disorders (e.g. nausea, vomiting, dyspepsia and diarrhoea) as the most common adverse effect associated with liraglutide, occurring in 35-44% of recipients (Amori *et al.*, 2007:203). Exenatide is also associated with gastro-intestinal adverse effects, occurring in 30-45% of recipients (Buse *et al.*, 2004:2633; Kendall *et al.*, 2005:1089). These gastro-intestinal symptoms (both liraglutide and exenatide) tend to abate over time (Gadsby, 2010:142). Buse and co-workers (2009:44) further demonstrated that both liraglutide and exenatide showed small increases in heart rates; this increase was, though, significantly greater for liraglutide than for exenatide. Patients receiving exenatide furthermore experience lower rates of hypoglycaemia than those treated with either insulin glargine or aspart (Barnett *et al.*, 2007:2346). Liraglutide shows no major hypoglycaemic events (Davidson, 2009:S32), but presents potential risks for pancreatitis and thyroid C-cell tumours based on animal studies (FDA, 2011d).

- **Insulin sensitizers**

Insulin sensitizers improve hyperglycaemia by decreasing insulin resistance. Besides reducing the risk for cardiovascular complications, their unique contribution to the management of type 2 diabetic patients resides in that they alleviate many of the components of the metabolic syndrome (dyslipidaemia, procoagulant state, endothelial dysfunction and inflammatory responses) (Lebovitz, 2002:816). Pharmacological classes included in this category include the biguanides, the glitazones e.g. thiazolidinediones (PPAR γ agonists) and dual PPAR agonists.

- ***Biguanides***

The biguanides (e.g. metformin, phenformin and buformin) were introduced into clinical practice in the mid-1950s for the treatment of type 2 diabetes mellitus (Bailey, 1992:755). All but metformin were removed from the international market in the 1970s because of the associated high risk for lactic acidosis (refer to adverse effects) (Bailey & Turner, 1996:574).

A meta-analysis by Salpeter and colleagues (2008:154) showed that metformin reduced body mass index by 5.3% (95% CI: 4.0 – 6.7), fasting glucose by 4.5% (95% CI: 3.0 – 6.0), fasting insulin by 14.4% (95% CI: 8.9 – 19.9) and calculated insulin resistance by 22.6% (95% CI: 18.0 – 27.3). Metformin is therefore considered the agent of choice in obese type 2 diabetics (Bösenberg & Van Zyl, 2008:82; Fisman & Tenenbaum, 2009; Berne & Campbell, 2011:49). In addition, Salpeter and colleagues (2008:154) showed a 5.3% reduction in triglycerides (95% CI: 0.03 – 10.5), a 5.6% reduction in low-density lipoprotein cholesterol (95% CI: 3.0 – 8.3%) and an increase in high-density lipoprotein cholesterol of 5.0% (95%

CI: 1.6 - 8.3) with metformin compared with placebo or no treatment. Metformin furthermore has a very low risk for hypoglycaemia (Sena *et al.*, 2010:145). Data from the UKPDS (1998c:864) moreover showed a reduction in the relative risk for all-cause mortality by 36%, myocardial infarction by 39% and all macrovascular end-points by 30% with metformin. Similar findings were reported by Gulliford and Latinovic (2004:244), suggesting that besides the beneficial effect on lipid concentrations, metformin also shows cardiovascular benefit. At length, the American Diabetes Association (Nathan *et al.*, 2007:758) and International Diabetes Federation (Alberti *et al.*, 2007:463) regard metformin as the agent of choice in individuals with prediabetes, predominantly those with combined IFG and IGT.

Metformin has furthermore been approved for paediatric patients 10 years of age and older with type 2 diabetes (Costello, 2006:411) and is regarded as the oral hypoglycaemic of choice in children. In addition to its use in type 2 diabetes, metformin may be used as adjunctive therapy in adolescents with type 1 diabetes (Hamilton *et al.*, 2003:140). Metformin may also be used to produce weight loss or aid in weight control in normoglycaemic adolescents and adults (Kay *et al.*, 2001:1459) (refer to paragraph 2.9.1.5.2), or as adjunct therapy in patients receiving psychotropic medication known to cause significant weight gain (Morrison *et al.*, 2002:655). Metformin has also been used successfully in restoring normal menses in oligo-amenorrhoeic adolescent females with polycystic ovary syndrome (Diamanti-Kandarakis *et al.*, 2010:199).

The major actions of metformin in patients with diabetes are to reduce blood glucose levels and enhance insulin-stimulated peripheral glucose uptake by inhibiting hepatic glucose production, reducing insulin resistance (primarily in liver and muscle) and by decreasing intestinal absorption of glucose thus decreasing post-prandial hyperglycaemia (Hemmingsen *et al.*, 2009:3; Scarpello & Howlett, 2008:157; Sena *et al.*, 2010:145). The mechanisms by which metformin exerts these antihyperglycaemic effects are still unclear (Bösenberg & Van Zyl, 2008:82; Joshi, 2005:963; Schernthaner & Schernthaner, 2007:77). Several have been postulated, *inter alia* (1) the activation of hepatic and muscle adenosine monophosphate-activated protein kinase (AMPK) (resulting in the phosphorylation and inhibition of acetyl-coenzyme A carboxylase, catalysing the rate-limiting step of lipogenesis and promoting fatty acid oxidation) (Bosi, 2009:4; Desai & Tandon, 2007:194; Zhou *et al.*, 2001:1172); and (2) reducing the energy supply necessary to execute gluconeogenesis by disrupting coupled oxidative phosphorylation in the mitochondria (Kirpichnikov *et al.*, 2002:E27). Metformin has also been shown to stimulate glucagonlike-peptide-1 (GLP-1) production from the gastrointestinal tract, thereby suppressing pancreatic α -cell function and subsequently reducing serum glucagon and further reducing fasting hyperglycaemia (Sinha Roy *et al.*, 2007:S284).

Metformin lowers glucose levels in a dose-related manner across most of its dosage range in

those with type 2 diabetes (Fujioka *et al.*, 2005:37), lowering HbA_{1c} concentrations by about 1.5-2% and fasting glucose by 3-4 mmol/L (Desai & Tandon, 2007:194; Saenz *et al.*, 2005:CD002966). The efficacy of metformin monotherapy is thus in the same range as that observed with sulphonylurea monotherapy. The long-term glucose-lowering efficacy of metformin is furthermore similar to or more effective than other antihyperglycaemic agents, i.e. the thiazolidinediones (Pavo *et al.*, 2003:1643), the α -glucosidase inhibitors (Hoffmann & Spengler, 1997:488) and the dipeptidyl peptidase-4 inhibitors (Schweizer *et al.*, 2007:959).

An analysis by Herman and co-workers (2005:328) showed that although treatment with metformin was dominated by lifestyle intervention, it was relatively cost-effective, especially in individuals younger than 65 years. In patients 65 years of age or older, metformin treatment cost more than US\$100,000 per QALY per patient. Palmer *et al.* (2004:319) demonstrated that metformin also improved life expectancy versus control with mean improvements in non-discounted life expectancy of 0.11. Metformin also rendered cost savings vs. control in other countries, such as Australia, France, Germany and Switzerland (Palmer *et al.*, 2004:319).

The most frequently described adverse effect of metformin therapy (observed in 10-20% of patients, depending on the dose) (Cheng & Fantus, 2005:217; Desai & Tandon, 2007:194) is a transient, dose-dependent gastro-intestinal upset, signified by abdominal discomfort, anorexia, bloating, metallic taste in the mouth, nausea and diarrhoea (Fonseca & Kulkarni, 2008:S31; Fowler, 2010a:132). These adverse effects can be avoided by administering the agent with food, by slow dose titrations (Sheehan, 2003:192) or by using an extended release form of the product (Levy *et al.*, 2010). A potentially fatal, though very rare side effect of metformin therapy is lactic acidosis (Nathan *et al.*, 2009:196) [0.43 cases per 1 000 treated patients-years (Salpeter *et al.*, 2010:CD002967)]. The agent should therefore be avoided in patients with a high risk for lactic acidosis or drug accumulation, e.g. those with moderate to severe kidney, liver or cardiac dysfunction (Scarpello & Howlett, 2008:162).

– **Thiazolidinediones (Glitazones)**

Thiazolidinediones (refer to paragraph 2.9.2.5.2), act selectively on PPAR γ receptors in adipose tissue, altering gene transcription in adipocytes (Sheehan, 2003:193; Mudaliar & Henry, 2001:241). This results in changes in lipid metabolism and distribution (Holstein *et al.*, 2011:12), decreasing free fatty acid concentrations by approximately 20-40%, with subsequent enhancement of peripheral insulin-receptor signalling (Hall & Nicholson, 2009:1728). The thiazolidinediones therefore lower glycaemia by reducing insulin resistance and improving insulin sensitivity, resulting in a reduction of fasting plasma glucose and insulin (Holstein *et al.*, 2011:12). They may also provide additive effects in combinations with other hypoglycaemics

(refer to “combination therapy with hypoglycaemics”).

The hypoglycaemic efficacy of the thiazolidinediones in patients with type 2 diabetes is less than, to equal to that of the sulphonylureas and metformin (Sheehan, 2003:193; Sutherland & Hoehns, 2004:384). Rosiglitazone (refer to paragraph 2.9.2.5.2) reduces fasting plasma glucose by approximately 30-65 mg/dL and HbA_{1c} by 0.8-1.5% (Lebovitz *et al.*, 2001:286; Phillips *et al.*, 2001:313) compared with pioglitazone that lowers fasting plasma glucose by 39.1-65.3 mg/dL and HbA_{1c} by 1-1.6%, respectively from placebo (Chilcott *et al.*, 2001:1819; Lester & Fernandes, 2005:138). DeFronzo and colleagues (2011:1110-1111) also showed that pioglitazone reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes mellitus by 72% compared with placebo, in addition to lowering diastolic blood pressure by 2.0 mmHg. DeFronzo and colleagues furthermore determined that treatment of 18 patients with pioglitazone for one year would be necessary to prevent one case of diabetes. Rivoglitazone, a novel PPAR γ agonist, has been shown to reduce HbA_{1c} levels by 0.11% in doses of 0.5 mg, 0.22% with a 1 mg dose, and 0.17% with a 1.5 mg dose respectively, compared with placebo (Kong *et al.*, 2011:811).

The thiazolidinediones are expensive relative to other antihyperglycaemic agents (Sutherland & Hoehns, 2004:384). Addition of pioglitazone to existing therapy in the treatment of type 2 diabetic patients with a history of macrovascular disease, however, increases treatment cost-effectiveness because of the reduction in the long-term cumulative incidence of most diabetic complications and improvement of quality of life expectancy (Brändle *et al.*, 2009:177). Pioglitazone further appear more cost-effective than rosiglitazone in treating patients with dyslipidaemia and type 2 diabetes, as shown by Tunis and co-workers (2008:3090). Results of their study showed that pioglitazone was associated with a higher mean quality-adjusted life years (QALYs) (i.e. 7.48 ± 0.12) compared with 7.3 ± 0.13 for rosiglitazone. Pioglitazone was also found to have long-term treatment value, with an incremental cost ratio of US\$20,171/QALY respective to rosiglitazone.

– **Dual PPAR α / γ agonists**

Dual PPAR α / γ agonists (i.e. muraglitazar, naveglitazar, ragaglitazar and tesaglitazar) have an affinity for both PPAR α and γ receptors (Bishop-Bailey & Wray, 2003:5). None of these agents, however, has been approved for clinical use due to the serious safety concerns (refer to paragraph 2.9.2.5.2). The newest developed dual PPAR α / γ agonist, aleglitazar, designed to be a balanced agonist of both PPAR γ and PPAR α , shows a significant, dose-dependent reduction of 0.85% in HbA_{1c} (95% CI: 0.50 - 1.20) and a 2.16 mmol/L reduction in the concentration of fasting plasma glucose (95% CI: 1.35 - 2.98) compared with placebo (Henry *et al.*, 2009:133).

- **Alpha(α)-glucosidase inhibitors**

The α -glucosidase inhibitors were introduced in the early 1990s (Bösenberg & Van Zyl, 2008:86; Sheehan, 2003:193), exclusively to interrupt the absorption of complex carbohydrates in the small intestine which results primarily in a reduction in post-prandial plasma glucose levels, simulating the effect of a low glycaemic index/high fibre diet (Bastaki, 2005:125; Van de Laar, 2008:1190). These agents are thus useful as monotherapy in the elderly, as well as patients with predominant post-prandial hyperglycaemia (Luna & Feinglos, 2001:1754). The α -glucosidase inhibitors do not stimulate insulin release and therefore hypoglycaemia and weight gain do not occur (Nathan *et al.*, 2009:196); the agents are therefore also considered suitable for patients with mild to moderate hyperglycaemia, for those prone to hypoglycaemia and for those at risk for lactic acidosis (Evans & Rushakoff, 2010). In addition, results from the STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial (Chiasson *et al.*, 2002:2076) showed that α -glucosidase inhibitors could be utilised in the prevention of type 2 diabetes by delaying progression from an impaired fasting glucose state to overt diabetes.

A secondary analysis of the STOP-NIDDM data furthermore established the effectiveness of α -glucosidase inhibitors in the treatment of metabolic syndrome patients, with a number needed to treat (NNT) of 5.8 in this group compared with a NNT of 16.5 among those without the syndrome (Hanefeld *et al.*, 2009:34). Similar findings were also demonstrated with one of the newer analogues in this pharmacological class (voglibose) among high-risk individuals with impaired glucose tolerance (Kawamori *et al.*, 2009:1614). The α -glucosidase inhibitors additionally reduce triglyceride levels (Desai & Tandon, 2007:195; Krentz & Bailey, 2005:409), improve blood pressure levels and reduce the risk for myocardial infarction and other cardiovascular events in patients with type 2 diabetes (Hanefeld & Cagatay *et al.*, 2004:13,15).

There are four agents belonging to the class of α -glucosidase inhibitors, namely acarbose (an oligosaccharide of microbial origin), miglitol (a desoxynojirimycin derivative), voglibose and emiglitate (structural analogues) (Van de Laar, 2008:1190). Acarbose and miglitol are more effective than voglibose, but have more adverse effects (refer to adverse effects below) (Van de Laar *et al.*, 2005:CD003639). Compared with placebo, the α -glucosidase inhibitors demonstrate an average HbA_{1c} lowering effect of about 0.5-0.8% (Van de Laar *et al.*, 2005:CD003639). The hypoglycaemic efficacy of the α -glucosidase inhibitors in patients with type 2 diabetes is thus approximately less than 50% of either sulphonylureas (Sutherland & Hoehns, 2004:385), metformin (Saenz *et al.*, 2005:CD002966) or thiazolidinediones (Bolen *et al.*, 2007:2).

Competitive reversible inhibition of several enzymes of the alpha-glucosidase group (i.e. maltase, isomaltase, sucrase and gluco-amylase) forms the basis for the primary mechanism of

action displayed by α -glucosidase inhibitors (Fisman & Tenenbaum, 2009). These membrane bound enzymes are predominantly located in the brush border of the proximal half of the small intestine mucosa (Desai & Tandon, 2007:195), where they hydrolyse oligosaccharides and disaccharides to glucose (Sheehan, 2003:194). Inhibition of these enzymes thus delays digestion of carbohydrates and shifts their absorption to more distal parts of the small intestine and colon, with subsequent blunting in the post-prandial rise of plasma glucose without involving endogenous insulin secretion (Holstein *et al.*, 2011:11; Sutherland & Hoehns, 2001:385). α -Glucosidase inhibitors – in particular miglitol that is absorbed in the small intestine - may therefore be highly beneficial in combination with insulin for the treatment of type 1 diabetes mellitus (Kubo *et al.*, 2010:62).

The main adverse effects of the α -glucosidase inhibitors are related to gastro-intestinal disturbances occurring in approximately 25-30% of patients (Modi, 2007:42). These include predominantly bloating, abdominal discomfort, diarrhoea and flatulence (Aronson, 2009:361; Chiasson *et al.*, 2003:492), nausea and dyspepsia (Arungarinathan *et al.*, 2011:79). Dose-dependent hepatotoxicity may also occur (Fowler, 2010a:134), therefore contraindicating the use of these agents in patients with irritable bowel syndrome, cirrhosis or severe kidney or liver dysfunction (Fonseca & Kulkarni, 2008:S31; Joshi & Joshi, 2009:13).

- **Amylin agonists (pramlintide)**

Amylin, a neuroendocrine hormone, is co-stored and co-secreted with insulin from pancreatic β -cells in response to hyperglycaemia (Roth *et al.*, 2008:317). According to Kruger *et al.* (1999:395), amylin works with insulin to regulate plasma glucose concentrations in the bloodstream, suppressing the post-prandial secretion of glucagon and restraining the rate of gastric emptying. Individuals with diabetes have a deficiency in the secretion of amylin that parallels the deficiency in insulin secretion, resulting in an excessive inflow of glucose into the bloodstream during the post-prandial period (Nathan *et al.*, 2009:197). Amylin agonists therefore display beneficial effects similar to that of GLP-1, *inter alia* the inhibition of excessive glucagon secretion from pancreatic α -cells, delaying gastric emptying and increased satiety (Schmitz *et al.*, 2004:S234; Zdrojewicz & Belowska-Bień, 2006:170). In addition, amylin agonists do not increase the number of hypoglycaemic events nor cause weight gain, making these agents ideal for the treatment of the obese diabetic (Schmitz *et al.*, 2004:S237).

Pramlintide, a synthetic analogue of amylin, was approved in March 2005 as a subcutaneous injection for the adjunctive treatment of patients who have type 1 or 2 diabetes mellitus and have failed to achieve glycaemic control despite optimal therapy with insulin (Day, 2005:152; Jones, 2007:1832). This agent has been shown to exhibit beneficial effects similar to those of native

amylin (Want, 2008:15S), reducing HbA_{1c} levels by 0.5-0.7% in doses of 120 µg, whilst decreasing body weight by approximately 1-1.5 kg (Edelman *et al.*, 2008:378; Riddle *et al.*, 2007:2797). Pramlintide has also been shown to reduce total cholesterol levels (McQueen, 2005:2370).

The most common adverse effect associated with pramlintide is nausea, occurring in 28% of type 2 and 48% of type 1 diabetic patients receiving pramlintide in addition to insulin therapy (Day, 2005:154). The nausea occurs mostly at the beginning of treatment, gradually abating over the treatment period. Other gastro-intestinal disorders include anorexia, fatigue and vomiting (Nathan *et al.*, 2009:197). Pramlintide has also been associated with an increased risk for insulin-induced severe hypoglycaemia (Kleppinger & Eva, 2003:1087).

Based on an analysis by Jones (2007:1832), pramlintide (120 mcg, three times a day) is approximately double the price of exenatide (a GLP-1 agonist) (5 mcg, twice daily dosage) at US\$382 vs. US\$176.

- **Insulin**

Under normal circumstances, insulin secretion consists of discrete components: low basal levels secreted between meals, through the night and during fasting, and very high levels secreted post-prandially (i.e. bolus secretion) (Dave & Delport, 2006:30). Glucose entry into adipose tissues, muscles and the liver is facilitated by insulin, which stimulates several enzymatic reactions starting at the insulin receptors. An increase in membrane phosphorylation, caused by the stimulation of an intrinsic tyrosine kinase of the insulin receptor, consequently increases the membrane permeability to glucose through a complicated cascade of intracellular events (Greenstein & Wood, 2006:83). In patients with type 2 diabetes, progressive impairment of pancreatic β -cell function, however, results in a loss of normal patterns of glucose-stimulated insulin secretion, excess glucagon secretion and peripheral insulin resistance, leading to hyperglycaemia in both fasting and post-prandial states (Butler *et al.*, 2003:108).

Initially, about 30% (Roseblum & Kane, 2003:309) to 50% (Gambert & Pinkstaff, 2006:222) of patients with type 2 diabetes require the addition of insulin injections to manage their disease. However, almost all type 2 diabetics will eventually fail to respond adequately to oral antihyperglycaemic agents and therefore require insulin therapy (MacIsaac *et al.*, 2010:565; Van Avendonk & Rutten, 2009:415). In those with type 1 diabetes, hyperglycaemia (both fasting and post-prandial states) develops predominantly due to an insulin deficiency caused primarily by a cellular-mediated autoimmune destruction of pancreatic β -cells (De Boer *et al.*,

2008:1867; Fowler, 2010b:177). Insulin therapy, alone or in combination with oral agents, is therefore essential in controlling fasting and post-prandial glucose levels and to improve long-term glycaemic control in patients with diabetes (Dailey, 2006:152; Rendell, 2008:125).

There are a large number of insulin preparations available for type 1 and advanced type 2 diabetes, including human insulin and insulin analogues. Insulin preparations can be classified as rapid- or short-acting insulin (that are used for bolus therapy to control post-prandial hyperglycaemia), or intermediate- and long-acting basal insulin (that provide stable plasma insulin concentrations for up to 24 hours or longer) (Sena *et al.*, 2010:146). Various pre-mixed insulin preparations that combine long-acting and short-acting insulin are also available to control both fasting plasma glucose and post-prandial glucose levels. Table 2.12 summarises the main characteristics of the different insulin preparations.

Table 2.12: Main characteristics of insulin preparations (adapted from Neumiller *et al.*, 2009:86-87 and Valla, 2010)

Preparation	Onset	Peak	Duration
Short-acting insulin			
Regular soluble insulin	30-60 min	2-3 hrs.	5-8 hrs.
Intermediate-acting insulin			
Neutral protamine Hagedorn (NPH)	2-4 hrs.	4-10 hrs.	10-16 hrs.
Rapid-acting analogues			
Insulin Lispro	5-15 min	30-90 min	3-5 hrs.
Insulin Aspart	5-15 min	30-90 min	3-5 hrs.
Insulin Glulisine	5-15 min	30-90 min	3-5 hrs.
Long-acting analogues			
Insulin glargine	2-4 hrs.	No peak	20-24 hrs.
Insulin detemir	3-8 hrs.	6-8 hrs.	Dose-dependent 5.7-23.2 hrs.
Premixed products			
Regular/NPH 30/70	30-60 min	Dual	10-16 hrs.
Aspart protamine suspension/insulin aspart injection 70/30	5-15 min	Dual	10-16 hrs.
Lispro protamine suspension/insulin lispro injection 75/25			
Lispro protamine suspension/insulin lispro injection 50/50			

min = minutes; hrs. = hours

According to Dave and Delport (2006:30) and Horton (2009:S25), the aim of insulin therapy in patients with diabetes is to mimic the secretion pattern of insulin in order to provide adequate insulin throughout a 24-hour period to meet the basal requirements and to deliver higher boluses of insulin to meet the glycaemic effect of meals. There is, however, currently no consensus about the specific insulin regimen to choose. The American Diabetes Association and the European Association for the Study of Diabetes (Nathan *et al.*, 2009:197) recommend that initial treatment should be aimed at increasing basal insulin levels, usually with

intermediate- or long-acting insulin, although patients may also need prandial therapy with short- or rapid-acting insulin. In accordance, the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) algorithm for the management of hyperglycaemia in type 2 diabetics (refer to Figure 2.3), advocates the use of insulin as first-line therapy in patients with severely uncontrolled diabetes with catabolism, i.e. for patients with the following conditions (Levitt *et al.*, 2009:57):

- Fasting glucose levels >14 mmol/L, random glucose levels consistently >16.7 mmol/L, HbA_{1c} >10% or the presence of ketonuria, or
- Symptomatic diabetes with polyuria, polydipsia and significant weight loss.

The SEMDSA-guideline further advocates the addition of insulin to oral agents, as second- or third-line therapy, when glycaemic targets are unmet after three months of treatment with metformin and lifestyle management (refer to Figure 2.3). In these cases, basal insulin therapy with intermediate or long-acting agents should be initiated at bedtime, titrated until a fasting glucose target of 4-6 mmol/L is reached. If the HbA_{1c} level is still above 7% after another three months of treatment, biphasic insulin treatment or intensive insulin therapy (i.e. basal and prandial insulin therapy) should be initiated (Levitt *et al.*, 2009:58). According to Palumbo and Wert (2010:24), the early initiation of insulin treatment is essential, in particular patients with type 2 diabetes of more than 10 years duration.

The long-acting analogues (i.e. insulin glargine and detemir) and the intermediate-acting neutral protamine Hagedorn insulin (NPH) (refer to Table 2.12) are similar in lowering HbA_{1c} levels (Horvath *et al.*, 2007:CD005613). Glargine and detemir insulin are, however, associated with a lower incidence of hypoglycaemia compared with NPH insulin in both type 1 and type 2 diabetics (Alemzadeh *et al.*, 2005:1343; Porcellati *et al.*, 2004:1218) and are therefore preferred during the basal insulin strategy (Rendell, 2008:127). Fujii and co-workers (2010:1518) furthermore showed an improved quality of life in patients using insulin detemir, compared with those using NPH. Basal insulin treatment given as monotherapy unfortunately does not target post-prandial glucose and is not as effective at lowering HbA_{1c} when given alone as when it is used in combination with short-acting insulin; combination therapy with short-acting insulin is therefore necessary (Holman *et al.*, 2007:1728; Kazda *et al.*, 2006:150).

The rapid-acting insulin analogues are equal to, or superior, to regular human insulin in controlling post-prandial hyperglycaemia in patients with diabetes (Fowler, 2010b:177). Based on a systematic review by Siebenhofer and co-workers (2006:CD003287), the weighted mean difference of HbA_{1c} was estimated at -0.1% (95% CI: -0.2% to -0.1%) in support of the analogues (i.e. insulin lispro, aspart and glulisine) in patients with type 1 diabetes, whereas in patients with type 2 diabetes, the weighted mean difference of HbA_{1c} was estimated at 0% (95%

CI: -0.1% to 0.1%). The early onset of action of rapid-acting insulin analogues accounts for the improved post-prandial glucose control (Rendell, 2008:127). These agents are also indicated for the treatment of medical emergencies or when fast onset of action is required e.g. in very young children refusing food, when timing of injections in relation to meals is difficult, in children with pre-launch hypoglycaemia, those who eat late in the evening and those prone to nocturnal hypoglycaemia (Costello, 2011; Fowler, 2010b:178).

Pre-mixed insulin analogues combine rapid insulin analogues and its intermediate-acting protaminated form (Qayyum *et al.*, 2008:549) and were developed to provide more flexibility in treatment regimens (Kazda *et al.*, 2006:151; Monnier & Collette, 2006:10), as well as to provide better post-prandial glucose control due to the short-acting insulin component (Malone *et al.*, 2005:379; Raskin *et al.*, 2007:60). Pre-mixed analogues are comparable to premixed human insulin in decreasing fasting glucose and HbA_{1c} levels, but are more effective in decreasing post-prandial glucose levels. The pre-mixed insulin analogues are also more effective than long-acting insulin analogues and oral antihyperglycaemic agents in decreasing HbA_{1c} and post-prandial glucose levels (Lasserson *et al.*, 2009:1996; Qayyum *et al.*, 2008:555). In decreasing fasting glucose, the pre-mixed insulin analogues are, however, less efficient than long-acting insulin analogues.

According to Cameron and Bennett (2009:406), the cost-effectiveness of insulin analogues depends on the type of analogue and type of diabetes. Based on their review, only the rapid-acting insulin analogues as used in type 1 diabetes proved cost-effective compared with routine use, especially long-acting analogues in type 2 diabetes. For example, Cameron and Bennett showed that insulin aspart was more effective and less costly than regular human insulin for the treatment of type 1 diabetes, whereas insulin lispro was more effective, but also more costly. In the treatment of type 2 diabetes, both insulin apart and lispro proved more effective; both agents were, however, also more costly. The long-acting analogues, insulin glargine and detemir, were more effective than NPH insulin for the treatment of type 1 and type 2 diabetes but also more costly (Cameron & Bennett, 2009:403). Van Avendonk and Rutten (2009:426) reported similar findings in a systematic review of insulin therapy in type 2 diabetes. Cameron and Bennett (2009:405) furthermore showed that at a cost-effectiveness threshold of Canadian \$50,000 per QALY for the treatment of type 1 diabetes, the probability of insulin aspart being more cost-effective than conventional insulin was 86.8%, compared with 51.2% for insulin lispro, 42.5% for insulin glargine and 29.2% for insulin detemir. As for type 2 diabetes, the probabilities of being more cost-effective than conventional insulin were less than that obtained for type 1 diabetes, at 52.5% for insulin aspart, 46.3% for insulin lispro, 25.1% for insulin glargine and 10.8% for insulin detemir.

With the exception of hypoglycaemia, the incidence of adverse effects is similar between insulin analogues and conventional insulin (Singh *et al.*, 2009:393). The most commonly adverse reactions to insulin include weight gain (Russell-Jones & Khan, 2007:810), lipodystrophy (Harvey *et al.*, 2009:288), allergic reactions (Heinzerling *et al.*, 2008:148) and local site reactions (Setter *et al.*, 2006:1067). Hypoglycaemia - the most serious adverse effect associated with insulin therapy - occurs more with conventional insulin than with the insulin analogues (Siebenhofer *et al.*, 2006: CD003287; Singh *et al.*, 2009:394; Van Avendonk & Rutten, 2009:424). Lasserson and co-workers (2009:1997) furthermore showed that prandial (i.e. rapid- and short-acting) insulin cause more weight gain than basal insulin (i.e. intermediate- and long-acting) do.

- **Combination therapy with antihyperglycaemics**

Results from the United Kingdom Prospective Diabetes Study (UKPDS, 1998a:173) showed that insulin, sulphonylureas and metformin therapy each increased the proportion of patients who achieved blood glucose target, by 2- to 3-fold compared with diet alone. However, 3 years into the UKPDS study, only half of the patients treated with monotherapy achieved glycaemic goal and by 9 years, only 25% were able to do so (Turner *et al.*, 1999:2009). The UKPDS (1995:1256) also showed that patients with type 2 diabetes had only 60% of their predicted β -cell function in addition to insulin resistance, and that this function deteriorated to 25% after 6 years. This data thus suggest that the majority of diabetic patients may require the addition of a second or even third agent to reach treatment goal and that the objective of combining oral antihyperglycaemics should be to address both insulin resistance and insulin deficiency. The selected regimen should preferably exert a physiologically rapid prandial insulin response to maintain glycaemic control with the minimum number of adverse effects such as hypoglycaemia and weight gain (Yudkin *et al.*, 2010:2083). Insulin may further be added when target glucose levels are not attained by combinations of oral antihyperglycaemics, or if some, or all, of the antihyperglycaemics are contraindicated or cause adverse effects.

Examples of effective combinations include sulphonylureas with biguanides (metformin), sulphonylureas with α -glucosidase inhibitors, biguanides with α -glucosidase inhibitors, biguanides with meglitinides, biguanides with thiazolidinediones and sulphonylureas with thiazolidinediones (with or without metformin) (Loh & Leow, 2002:726). The combination of sulphonylureas and insulin is less efficacious and results in more weight gain than metformin and insulin (McCulloch *et al.*, 2010). The combination of sulphonylureas and non-sulphonylureas (meglitinides) is also not recommended as these agents have a similar mechanism of action (Koski, 2006:874). The pharmacological rationale for combining some of the different antihyperglycaemic agents is summarised in the following section.

– ***Biguanides plus sulphonylureas***

Biguanides (insulin sensitizers) have an additive glycaemic effect when combined with sulphonylureas (insulin secretagogues). For example, Lewin and co-workers (2007:853) showed that the addition of metformin (extended release form) to glyburide (glibenclamide) in adult patients with type 2 diabetes, significantly reduced HbA_{1c} levels by 0.74% (95% CI: 0.64% - 0.85%), compared with 0.08% (95% CI: 0.08% - 0.25%) in the sulphonylurea monotherapy group. Mean fasting plasma glucose was also reduced by 12.9 mg/dL (95% CI: 8.7 - 17.1) in the combination group compared with the sulphonylurea monotherapy group (FPG: 15.5 mg/dL; 95% CI: 8.2 - 22.8 mg/dL). In this particular study, there was a significant difference between treatment groups with regard to the prevalence of hypoglycaemia (11.6% in the combination therapy group vs. 4.2% for the sulphonylurea monotherapy group). The shorter acting sulphonylureas, such as glipizide, are less likely to cause hypoglycaemia than the older, long-acting sulphonylureas – these agents are therefore preferred, especially in older patients (McCulloch *et al.*, 2010).

A fixed-dose combination containing metformin and glibenclamide is available in South Africa marketed under the brand name Glucovance® (Trevorrow, 2003:288). An observational study by Fisman and colleagues (2001:156), however, indicated an all-cause increased crude mortality over a mean 7.7-year follow-up in diabetics with coronary disease on this combination. The combination consisting of metformin and glibenclamide should thus be avoided in the long-term treatment of type 2 diabetes mellitus in patients with proven coronary artery disease.

– ***Biguanides plus meglitinides (non-sulphonylureas)***

Similar to the sulphonylureas, the meglitinides may also be combined with the biguanides, resulting in superior glycaemic control compared with monotherapy with either agent. According to Raskin and co-workers (2003:2066) the combination of repaglinide and metformin is more effective than the combination of nateglinide and metformin; it is, unfortunately, also associated with more adverse effects. For example, this study showed that the mean reduction from baseline in HbA_{1c} was 1.3% with repaglinide and 0.7% with nateglinide when added to metformin. At study endpoint, 59% of patients receiving repaglinide and 47% of those receiving nateglinide achieved treatment target. The mean decrease in fasting plasma glucose was also significantly larger with repaglinide/metformin than with nateglinide/metformin (i.e. 39 mg/dL vs. 21 mg/dL). Hypoglycaemic episodes were reported by 7% of patients receiving repaglinide/metformin and by 2% of those receiving nateglinide/metformin (Raskin *et al.*, 2003:2067). In addition, Schatz *et al.* (2003:264) showed that adding nateglinide to metformin was also associated with significant improvement in both diastolic and systolic blood pressure

and resulted in a small but significant reduction in body weight of 1.5 kg.

– ***Biguanides plus incretin-based therapies***

Biguanides can also be given in combination with the incretin-based therapies. For example, Pratley and colleagues (2010:1450) showed that when added to metformin, 1.2 mg and 1.8 mg liraglutide once daily significantly improved blood glucose control (change in HbA_{1c} from baseline: 1.24%, 95% CI: 1.11 – 1.37 for 1.2 mg; 1.50% for 1.8 mg, 95% CI: 1.37 – 1.63) vs. sitagliptin (100 mg once daily) (0.90%, 95% CI: 0.77 – 1.03). Only minor hypoglycaemia was recorded in about 5% of participants in each treatment group. Similar findings were also recorded with exenatide twice daily (DeFronzo *et al.*, 2005:1097), exenatide (long-acting release) once weekly (Buse *et al.*, 2009:45) and the DPP-4 inhibitors vildagliptin (Ferrannini *et al.*, 2009:163) and saxagliptin (DeFronzo *et al.*, 2009:1652).

– ***Thiazolidinediones plus sulphonylureas***

Sulphonylureas and thiazolidinediones exert their glucose-lowering effect through differing mechanisms of action – the sulphonylureas by stimulating insulin secretion, whereas the thiazolidinediones act as insulin-sensitising agents and increase the peripheral action of insulin. The glycaemic efficacy of the thiazolidinediones in combination with a sulphonylurea is illustrated by, *inter alia*, the findings of the Quartet study, where the addition of pioglitazone to existing sulphonylurea therapy resulted in a 1.2% reduction in HbA_{1c} after 1 year therapy in patients with inadequately controlled type 2 diabetes (Hanefeld & Brunetti *et al.*, 2004:144). Derosa and co-workers (2005:9) also reported significant (1.3%) and sustained reductions in HbA_{1c} levels when either rosiglitazone or pioglitazone was added to failing glimepiride in patients with type 2 diabetes and the metabolic syndrome after 1 year.

– ***Thiazolidinediones plus non-sulphonylureas***

The meglitinides act synergistically in combination with the thiazolidinediones. Jovanovic and colleagues (2004:132) compared the efficacy of repaglinide plus pioglitazone to repaglinide or pioglitazone therapy in type 2 diabetic patients with inadequate response in previous sulphonylurea or metformin monotherapy. Findings of this study showed comparable baseline HbA_{1c} values (9.0% for repaglinide, 9.1% for pioglitazone and 9.3% for the combination). Mean changes in HbA_{1c} values at the end of treatment were a 1.76% reduction for the repaglinide/pioglitazone combination, compared with a reduction of 0.18% for repaglinide and increase of 0.32% for pioglitazone. Fasting plasma glucose reductions were 82 mg/dL for combination therapy, 34 mg/dL for repaglinide and 18 mg/dL for pioglitazone, respectively.

Minor hypoglycaemia occurred in 5% of patients for the combination, 8% for repaglinide and 3% for pioglitazone (Jovanovic *et al.*, 2004:129-130), suggesting that the combination might be a safer option for treatment in patients with type 2 diabetes.

– ***Biguanides plus thiazolidinediones***

According to Stolar (2009:289), metformin is effective in reducing hepatic and to a lesser extent muscle insulin resistance, but has only modest effects on long-term β -cell function. The thiazolidinediones, on the other hand, have mechanistically distinctive effects on hepatic, muscle and adipocyte insulin resistance, as well as having somewhat greater effects on β -cell function and durability of glycaemic control. The combination of the two agents therefore has some potential in lowering glycaemia, without the risk for hypoglycaemia associated with insulin secretagogues.

The glycaemic efficacy of the thiazolidinediones in combination with biguanides is illustrated by *inter alia* the CANOE (CANadian Normoglycaemia Outcomes Evaluation) trial, where patients with impaired glucose tolerance were randomly assigned to receive a combination rosiglitazone (2 mg) and metformin (500 mg) twice daily or matching placebo for a median of 3.9 years (Zinman *et al.*, 2010:109). In this study, the authors showed that the relative risk reduction was 66% (95% CI: 41 - 80) with the combination, yielding a number needed to treat of four (95% CI: 2.70 - 7.14). Furthermore, about 80% of patients in the treatment group regressed to normal glucose tolerance compared with 53% in the placebo group.

– ***Combinations with α -glucosidase inhibitors***

α -Glucosidase inhibitors specifically target post-prandial plasma glucose (Godbout & Chiasson, 2007:333). Administration of these agents in combination with other antihyperglycaemic agents may improve their adverse effect profiles, whilst effectively lowering glycaemia levels. For example, Chiasson and Naditch (2001:991) showed that compared with metformin alone, the combination of miglitol plus metformin resulted in a 21.8% reduction in mean placebo-subtracted HbA_{1c} compared with 21.3% with metformin alone. The combination of miglitol plus metformin also resulted in better metabolic control than metformin alone for fasting plasma glucose (244.8 vs. 220.4 mg/dL). Rosak *et al.* (2002:148) furthermore showed that by combining acarbose and glibenclamide, post-prandial blood glucose levels increased by 23.7 ± 17.3 mg/dL compared with placebo (101.6 ± 49.2 mg/dL).

The α -glucosidase inhibitors are poorly tolerated because of flatulence and other gastrointestinal adverse effects (McCulloch *et al.*, 2010). The combination of acarbose and

glibenclamide (Rosak *et al.*, 2002:148) furthermore showed a higher (10%) risk for hypoglycaemic episodes with the combination, compared with none with acarbose monotherapy.

– ***Biguanides plus insulin***

Several trials comparing insulin monotherapy with insulin plus metformin, suggest a synergistic effect of combined therapy. For example, Wulffelé and co-workers (2002:2139) determined that patients, randomised to metformin or placebo in addition to insulin, had mean HbA_{1c} levels of 6.9% at 16 weeks, compared with 7.6% in the insulin-only group. The insulin dose requirements were also reduced by about 8 units per day, with an associated weight loss of 0.4 kg compared with a mean weight gain of 1.2 kg in patients receiving insulin only. Ponssen and colleagues (2000:716) also showed a 0.7% reduction in HbA_{1c} levels favouring metformin plus insulin after 5 months of treatment. The study by Wulffelé *et al.* furthermore showed a 0.21 mmol/L decrease in LDL-cholesterol levels with the combination therapy regimen, compared with a 0.02 mmol/L decrease in the insulin-only group.

– ***Thiazolidinediones plus insulin***

Similar to the combination of metformin with insulin, the addition of thiazolidinediones to insulin provides better glycaemic control. Raskin *et al.* (2001:1230) demonstrated a reduction of 1.2% in HbA_{1c} with twice-daily insulin combined with rosiglitazone, compared with twice-daily insulin plus placebo. The required daily dose was further reduced by 12% compared with zero in the insulin plus placebo group. Rosenstock *et al.* (2002:255) showed similar findings with insulin plus pioglitazone, compared with insulin plus placebo; HbA_{1c} levels were reduced by 1.3% over a 16-week period. The combination of insulin and thiazolidinedione carries an excessive risk for severe oedema and coronary heart failure (Brietzke, 2007:6). The combination is consequently best avoided in patients with class III or IV heart failure.

• **Therapeutic agents under investigation**

Several other pharmacological medicine classes and/or medications have hypoglycaemic effects. Short descriptions of the effects of these pharmacological classes and/or agents are provided here.

– ***Anti-obesity agents***

The anti-obesity agents orlistat and sibutramine (refer to paragraph 2.9.1.5.2) show potential as

antihyperglycaemic agents. For example, the addition of orlistat for 1 year in overweight or obese patients (BMI 28-40 kg/m²) with diabetes treated with other oral antihyperglycaemic agents or insulin has been shown to decrease body weight by about 4-6.5% and improve HbA_{1c} concentrations by 0.3-0.9% (Hanefeld & Sachse, 2002:419; Kelly *et al.*, 2002:1039). In a study by Berne (2005:616), type 2 diabetic patients receiving orlistat concurrently with metformin or with sulphonylurea/metformin combination vs. placebo, achieved greater reduction in HbA_{1c} (1.1% vs. 0.2%). The reduction in HbA_{1c} was also accompanied by greater improvements in β -cell function and insulin resistance. Similar to orlistat, cetilistat (refer to paragraph 2.9.1.5.2) has shown to reduce HbA_{1c} levels by 0.8%, 1.0% and 0.9% in doses of 40 mg, 80 mg and 120 mg, respectively (Kopelman *et al.*, 2010:110).

Sibutramine has also been shown to reduce HbA_{1c} levels by 0.6% (Lloret-Linares *et al.*, 2008:1148), in addition to reducing insulin resistance and CRP-levels (Derosa *et al.*, 2010:382). Anti-obesity agents therefore show potential as add-on therapy to other antihyperglycaemic agents in treating obese diabetic patients.

– ***Cholesterol lowering agents***

The bile acid sequestrant, colesevelam (refer to paragraph 2.9.2.5.2), reduces glucose levels by a variety of mechanisms, *inter alia* the alteration of GLP-1 levels and/or alteration of nuclear receptors such as the farnesoid X receptor, liver X receptor and fibroblast growth factor-19 (Bays & Cohen, 2007:1673), TGR5-mediated effects on intestinal glucose absorption and/or hepatic glucose metabolism thereby reducing post-prandial glucose excursions (Garg & Grundy, 1994:420), and influences on peripheral insulin sensitivity, incretin effects and energy homeostasis (Fonseca *et al.*, 2010:390). When added to metformin (Bays *et al.*, 2008:1981), insulin (Goldberg *et al.*, 2008:1538), or sulphonylurea-based treatment (Fonseca *et al.*, 2008:1482) in those with inadequately controlled type 2 diabetes, colesevelam reduced HbA_{1c} levels by 0.54%, 0.50% and 0.54%, respectively.

In the West of Scotland Coronary Prevention Study (WOSCOPS) (Freeman *et al.*, 2001:359), pravastatin was shown to reduce the risk for developing diabetes by 30%. Yee and co-workers (2004:965) furthermore showed that statins might even delay the need for insulin therapy in patients with type 2 diabetes with up to 10 months. Statins are in particular beneficial for patients with diabetic dyslipidaemia, reducing the microvascular and macrovascular complications associated with diabetes (Nesto, 2008:10; Tuomilehto & Leiter, 2005:73).

Resins, ezetimibe, and niacin or combinations may also be used for treatment in diabetic patients with high LDL-cholesterol levels (Moon & Kashyap, 2004:1709). In those with high

triglyceride levels, fibrates should be the agents of choice. According to Elkeles (2011:5,8) fibrates (in particular bezafibrate) are useful in the prevention of type 2 diabetes by correcting high triglyceride levels and low HDL-cholesterol levels, therefore improving insulin resistance and delaying the onset of type 2 diabetes.

– ***Antihypertensives***

Antihypertensive agents with RAAS modifying characteristics may reduce the incidence of type 2 diabetes by either altering insulin sensitivity, or by improving β -cell function (Jandeleit-Dahm *et al.*, 2005:464; MacFarlane *et al.*, 2008:535). For example, Scheen (2004:494) found a 22% relative risk reduction of new type 2 diabetes (95% CI: 18 - 26) with ACE inhibitors and ARBs. In this study by Scheen, the number needed to be treated to prevent one new case of diabetes over a 4- to 5-year period was 45. ACE inhibitors and ARBs may further improve pancreatic flow, whereas angiotensin II may affect basal, pulsatile and glucose-stimulated insulin secretion, thereby inhibiting the first phase of insulin secretion (Fliser *et al.*, 1997:1159). The vasodilatory properties of the CCBs could improve insulin resistance in a similar fashion to the ACE inhibitors and ARBs, *via* an increase in blood supply to the peripheries (MacFarlane *et al.*, 2008:538).

– ***Dopamine-2 agonists***

The central acting dopamine-2 agonist, bromocriptine, is the first medication approved to target dopamine activity to improve glycaemic control in patients with type 2 diabetes (Via *et al.*, 2010:47). Bromocriptine reduces mean plasma glucose levels by enhancing suppression of endogenous glucose production and/or by increasing splanchnic glucose uptake after glucose ingestion (Pijl *et al.*, 2000:1155), lowering HbA_{1c} levels by 0.4% (Aminorroaya *et al.*, 2004:57) to 0.6% (Pijl *et al.*, 2000:1159) in dosages of 2.5 mg to 4.8 mg daily respectively, compared with placebo. Bromocriptine also causes mild decreases of 3-7 mmHg in systolic blood pressure (Colao *et al.*, 2006:209).

– ***Novel agents***

Several other novel agents show potential as hypoglycaemics. These include *inter alia* the oligonucleotides (Liu, 2004:335), G-protein-coupled receptor 119 agonists, interleukin-1- β -inhibitors, recombinant hyaluronidase enzymes, sodium-dependent glucose co-transporter-2 inhibitors (e.g. dapagliflozin, remogliflozin and sergliflozin), zinc finger protein activators, 11- β -hydroxysteroid dehydrogenase type 1 inhibitors, fibroblast growth factor-21, glucokinase activators, gluconeogenesis inhibitors, oral insulin, insulin mimetics, gene-based

therapies (Sena *et al.*, 2010:151-155; Tahrani *et al.*, 2011:182) and a low dose phentermine/topiramate combination (i.e. Qnexa) (Gadde *et al.*, 2011:1349).

2.9.4.6 Summary of hyperglycaemia

The progression from normal glucose tolerance to diabetes is characterised by twofold defects that include insulin resistance (characterised by decreased tissue sensitivity to insulin and marked compensatory hyperinsulinaemia) and an insulin secretory defect caused by β -cell dysfunction (Brody, 2003:13-14; Phillips & Rhee, 2006:29). As the disease advances, there is a decline in β -cell secretory capacity, with subsequent decreased first phase insulin secretion and increased post-prandial glucose levels. Further decline in β -cell function gradually leads to the elevation of fasting glucose levels and eventually, persistent elevated glucose levels or chronic hyperglycaemia (Lavernia, 2010:eS14; Rao *et al.*, 2004:1964).

Hyperglycaemia is associated with reduced life expectancy and significant morbidity due to specific diabetes related microvascular complications, and increased risk for macrovascular complications (refer to paragraph 2.9.4.3). This represents a large burden to health care resources, incurring significant costs for associated care and treatment (refer to paragraph 2.9.4.4). Early detection of those at risk for the development of diabetes and early intervention strategies can prevent the progression of diabetes and its associated complications.

There are multiple treatment options available for patients with various stages of elevated blood glucose. Dietary modifications and daily exercise can provide adequate benefit in some patients with impaired insulin sensitivity and diabetes (refer to paragraph 2.9.4.5.1). The majority of patients, however, will require the initiation of hypoglycaemic therapies. Medications available for the treatment of hyperglycaemia all have different mechanisms and efficacy (refer to paragraph 2.9.4.5.2). Currently, no pharmacological agents are advocated for the treatment of prediabetes (IGT, IFG or both); however, metformin, acarbose, orlistat, pramlintide, the incretin mimics and enhancers and the thiazolidinediones show potential (Gerich, 2006:316; Lavernia, 2010:eS16).

The choice of hypoglycaemic agent in patients with type 2 diabetes is determined by both patient- and product-specific characteristics, although metformin is generally accepted as the agent of choice in both adults and children (refer to Figure 2.3). If adequate blood glucose control is not attained using a single oral agent, a combination of agents with different mechanisms of action or insulin treatment may have additive therapeutic effects and result in better glycaemic control (refer to paragraph 2.9.4.5.2, under “combination therapy with antihyperglycaemics”). According to Pratley (2009:10S) and Nauck and Vardarli (2010:32) the

incretin-based medications and α -glucosidase inhibitors are the best “options” for combination-therapy with metformin. Goudswaard *et al.* (2004:CD003418) also demonstrated that basal insulin combined with oral glucose-lowering agents provides the same degree of blood glucose control as insulin monotherapy and is associated with a reduction in insulin requirements of approximately 46%. Gastric bypass surgery also show potential for the treatment of type 2 diabetes, achieving remission in 93% (n = 60) of patients after a 12-month period (Lee *et al.*, 2011:146). Study participants in the trial conducted by Lee and co-workers furthermore also lost more weight, achieved a lower waist circumference and had lower glucose, HbA_{1c} and blood lipid levels, coupled with no serious complications.

Early recognition and treatment of the causes of hyperglycaemia can make a major difference in the costs associated with diabetes mellitus while also improving outcome, reducing morbidity and improving the quality and quantity of life for many millions of individuals.

2.9.5 Prothrombotic and pro-inflammatory state

Most individuals with the metabolic syndrome show signs of a prothrombotic state (Durina & Remkova, 2007:279; Van Zwieten & Mancina, 2006:208), characterised by elevations of plasminogen activator inhibitor-1 and fibrinogen (Alberti, 2005:D5; Alessi & Juhan-Vague, 2006:2201) and a pro-inflammatory state, characterised by elevations of C-reactive protein (Alberti, 2005:D5). The prothrombotic and pro-inflammatory states are not included in the proposed criteria for diagnosis of the metabolic syndrome (refer to section 2.4) due to the conviction that these states are not risk factors *per se*, but consequences of other risk factors (Walsh *et al.*, 2009:HS12). These states, however, have the tendency to aggregate with the diagnostic criteria (Grundy & Hansen *et al.*, 2004:551).

Although there are no specific therapies available to treat these abnormalities, the American Heart Association/ National Heart, Lung and Blood Institute advocated the use of low-dose aspirin (80 to 100 mg daily) for the treatment of the prothrombotic state in patients with the metabolic syndrome with a risk of 10% or more for developing a coronary event within a period of 10 years (Grundy & Cleeman *et al.*, 2005:2750), those with overt type 2 diabetes mellitus (Butalia *et al.*, 2011) or ASCVD, or others in the high-risk category (Grundy, 2007:401). Clopidogrel may also be used in patients with ASCVD in whom aspirin is contraindicated (Grundy & Cleeman *et al.*, 2005:2750).

Some of the agents used for the treatment of the other metabolic risk factors (i.e. statins, nicotinic acid, fibrates, ACE inhibitors and thiazolidinediones) will also reduce C-reactive protein levels typically found in the pro-inflammatory state (Grundy & Cleeman *et al.*, 2005:2750); Heart

Protection Study Collaborative Group, 2011:473; Ridker *et al.*, 2004:2822).

2.10 TREATMENT OF THE METABOLIC SYNDROME

According to Blaha *et al.* (2008:935), the first step in the treatment of metabolic syndrome is the recognition thereof. The concept of the metabolic syndrome is, however, controversial but continues to gain acceptance because it places “a growing burden on limited health care resources” (Giugliano *et al.*, 2008:8).

The definitions for the metabolic syndrome vary to some extent, but generally include a certain set of risk factors from atherogenic dyslipidaemia, elevated blood pressure, elevated glucose, a prothrombotic state and a pro-inflammatory state (Grundy & Cleeman *et al.*, 2005:2735) (refer to sections 2.3 and 2.4). In essence, the term “metabolic syndrome” identifies a person at increased lifetime risk for atherosclerotic cardiovascular disease (ASCVD) and/or type 2 diabetes mellitus (Grundy & Cleeman *et al.*, 2005:2737).

The main purpose in the management of the metabolic syndrome is therefore to reduce this risk for ASCVD and type 2 diabetes in those patients who do not yet manifest clinical diabetes (Grundy & Cleeman *et al.*, 2005:2739). There are, however, no established guidelines for the treatment of the metabolic syndrome in total, and furthermore, there are no therapeutic agents approved specifically for the treatment of the metabolic syndrome independent of those most appropriate for specific abnormal risk factors (FDA, 2008; Hadley, 2010; Heal *et al.*, 2009:873). The American Heart Association and the National Heart, Lung and Blood Institute (Grundy & Hansen *et al.*, 2004:553) therefore advocate two goals in addition to smoking cessation for the treatment of the metabolic syndrome:

- The first is to address its modifiable underlying causes, namely obesity, lack of physical activity and atherogenic diet through changes in lifestyle (i.e. weight loss in obese individuals, increased physical activity and an anti-atherogenic diet).
- The second goal is to treat (guided by short- and long-term risk assessment) all the clinical risk factors in the metabolic syndrome patient with therapeutic agents as they occur. The current recommendations for the management of the risk factors of the metabolic syndrome encompass the following steps:
 - Risk assessment (Step 1).
 - Management of underlying risk factors (Step 2).
 - Management of major risk factors (Steps 3-5).
 - Management of the prothrombotic and pro-inflammatory state (optional) (Step 6).

These steps are addressed in subsequent paragraphs. A summary of the goals and specific

recommendations follows in Table 2.13.

- **Risk assessment**

According to a systematic review by Matheny *et al.* (2011:11), there are approximately 102 risk models available for the assessment of cardiovascular disease risk, of which only 17 are externally validated. In their review, the most commonly externally validated risk models were the 1991 Framingham model for CVD (Anderson *et al.*, 1991:293), the 1998-Framingham study model for total coronary heart disease (CHD) (Wilson *et al.*, 1998:1843), the FRS Adult Treatment Panel III (ATP III) model that calculates the 10-year risk of coronary events based on an adaptation of the original Framingham function (D'Agostino *et al.*, 2008:743), the Prospective Cardiovascular Münster (PROCAM) model for hard CHD (Assmann *et al.*, 2002:312), and the Systematic Coronary Risk Evaluation (SCORE) model that measures the absolute risk of cardiovascular mortality in the next 10 years (Conroy *et al.*, 2003:987).

Other validated risk prediction algorithms, such as QRISK2 cardiovascular risk score that incorporates ethnicity, deprivation, and other clinical conditions are used to identify patients at high risk defined by a 10 year cardiovascular disease threshold of $\geq 20\%$ in the UK (Hippisley-Cox *et al.*, 2008:1475). The Reynolds risk score (a risk assessment technique that measures global cardiovascular risk in women by including conventional CVD risk factors in addition to family history and CRP-levels) may also be used to assess risk (Ridker *et al.*, 2007:612). The metabolic syndrome *per se* can furthermore be used as a prediction score of coronary heart disease, stroke and type 2 diabetes (Wannamethee *et al.*, 2005:2648).

The 2006-South African lipid guidelines (refer to paragraph 2.9.2.5) recommended that the assessment of risk for coronary heart disease risk in South Africa be based on the Framingham Heart Study, with a 10-year risk of non-fatal and fatal coronary heart disease of $\geq 20\%$ as a cut-point for intervention. Figure A.7 (Annexure A) depicts the Framingham Risk Score system.

- **Management of underlying risk factors (lifestyle modification)**

Lifestyle changes in the obese, hypertensive, hypercholesterolaemic and hyperglycaemic patient have been addressed in paragraphs 2.9.1.5.1, 2.9.2.5.1, 2.9.3.5.1 and 2.9.4.5.1. Findings from these foregoing discussions show that an increase in physical activity levels and/or a decrease in calorie intake are associated with an improvement in abdominal obesity, glucose metabolism, dyslipidaemia and blood pressure. Several reviews have indicated that lifestyle modification (by change in behaviour and diet and exercise) may result in significant improvements in the major components of the metabolic syndrome in both adults and children,

in addition to lowering the prevalence of the syndrome (Esposito *et al.*, 2008:1526; Harralson *et al.*, 2010:71; Lien *et al.*, 2007:615; McMurray & Andersen, 2010:183; Stone & Saxon, 2005:18E). For example, Esposito and colleagues (2008:1526) showed that intensive lifestyle changes might reduce the prevalence of the metabolic syndrome by up to 20-48%. Ilanne-Parikka *et al.* (2008:807) furthermore showed that lifestyle intervention might reduce risk for cardiovascular disease in patients with metabolic syndrome. According to Hu and co-workers (2006:280), a structured lifestyle intervention in the metabolic syndrome should include the following:

- A regular exercise regimen (to improve cardiorespiratory fitness and maintain weight loss).
- Strict goals for calorie restriction to ensure a healthy diet and gradual weight loss.
- Comprehensive patient education.
- Regular follow-up and counselling to monitor progress (refer to Table 2.13).

About 50% of people with the metabolic syndrome however, do not reach treatment goals with lifestyle interventions only and thus require concomitant pharmacological intervention (Hanefeld & Schaper, 2005:390).

- **Management of major risk factors**

The following sections summarises the recommended approaches to the management of each of the major risk factors (i.e. steps 3 to 5, refer to Table 2.13) of the metabolic syndrome (as identified by the AHA/NHLBI definition).

- ***Atherogenic dyslipidaemia***

Dyslipidaemia in patients with the metabolic syndrome is characterised by an atherogenic profile, consisting of low HDL-cholesterol levels, moderately raised triglycerides, raised apolipoprotein levels and small, dense LDL-cholesterol particles (refer to paragraph 2.9.2.1). This atherogenic dyslipidaemia associated with the metabolic syndrome is an important cardiovascular risk factor and requires treatment with lifestyle changes (with emphasis on weight loss) and pharmacological agents if necessary (refer to paragraph 2.9.2.5).

First-line dyslipidaemic therapy with pharmacological agents in individuals with metabolic syndrome should always be directed towards LDL-cholesterol and non-HDL-cholesterol (Nakajima, 2010:133). Statins improve lipid profiles principally by lowering LDL-cholesterol and may exert anti-inflammatory and anti-atherothrombogenic effects (Sadowitz *et al.*, 2010:244-245), which ameliorate the fundamental pathophysiology of metabolic syndrome. Second- and

third-line treatments are then directed towards high triglyceride levels and low HDL-cholesterol levels, typically with agents such as fibrates and niacin (refer to paragraph 2.9.2.5.2). Fibrates also have pleiotropic effects that improve cardiometabolic risk factors, including insulin resistance (Hiserote & Clearfield, 2010:eS9; Wierzbicki, 2009:375). Niacin should be used with caution as it may exacerbate insulin resistance and worsen glycaemic control (refer to paragraph 2.9.2.5.2), whereas the concurrent use of fibrates and statins may increase the risk for myopathy and/or rhabdomyolysis (Rovira, 2002:164).

Other agents including ezetimibe, the bile acid sequestrants and omega-3 fatty acids may also provide benefit for patients with atherogenic dyslipidaemia in the metabolic syndrome (Goumas, 2009:96; Tan, 2007:105).

– ***Elevated blood pressure***

More than half of the hypertensive population have metabolic syndrome (refer to paragraph 2.9.3.3). The therapeutic approach to patients with hypertension and the metabolic syndrome should therefore include both non-pharmacological and pharmacological treatment in order to modify an unhealthy lifestyle that may exacerbate the underlying pathology (Duvnjak *et al.*, 2008:87). Hypertensive patients with the metabolic syndrome are at increased risk for associated conditions (e.g., target organ damage or cardiovascular disease). When either diabetes or chronic renal disease is present, blood pressure target should be reduced to <130/80 mmHg (refer to Table 2.13). In these circumstances, patients should be treated with antihypertensive agents that have the least adverse metabolic effects (Siegel & Swislocki, 2010:96), directed towards preventing new-onset diabetes (Franklin, 2006:293).

Some international hypertension treatment guidelines (the South African guideline included) recommend diuretics as the first-step therapy for hypertensive patients without a compelling indication. High doses of diuretics and, probably, β -blockers have been shown to increase the risk of new-onset diabetes. These agents should therefore preferably be avoided as first line treatment in patients with the metabolic syndrome without known cardiovascular disease (Blaha *et al.*, 2008:936; Mayor, 2006:8). Conversely, calcium channel blockers (Franklin, 2006:295) and RAAS-blockers (ACE inhibitors and angiotensin II receptor blockers) decrease the risk of new-onset diabetes (Abuissa *et al.*, 2005:821; Siegel & Swislocki, 2010:99).

Other agents that exert additional beneficial benefits, e.g. central sympatholytic agents (particularly the I₁-imidazoline agents such as rilmenidine and moxonidine) (Duvnjak *et al.*, 2008:87) can also be used for the treatment of hypertension in metabolic syndrome patients. Franklin (2006:295) adds that low-dose diuretics may be suitable as add-on second and third

choice agents for patients with diabetes and the metabolic syndrome, with or without concurrent chronic kidney disease.

– ***Hyperglycaemia***

The metabolic syndrome is characterised by an abnormal fasting level of serum glucose, or sometimes impaired glucose tolerance (refer to paragraphs 2.4 and 2.9.4.3). At present, no pharmacological treatment is recommended for use in patients with impaired fasting glucose levels or prediabetes (refer to paragraph 2.9.4.5.2). These patients should be treated with lifestyle changes such as weight reduction and increased physical activity. Therapeutic agents may, however, be necessary once diabetes develops. The therapeutic approach to patients with hyperglycaemia and the metabolic syndrome should therefore include both non-pharmacological and pharmacological treatment, directed towards preventing progression to diabetes, its complications and cardiovascular risk factors (Gerich, 2006:317). Among pharmaceutical agents, particular emphasis is placed on weight-loss promoting agents (i.e. orlistat), exenatide, metformin, pioglitazone, α -glucosidase inhibitors, nateglinide, the DPP-4 inhibitors and insulin (Derosa *et al.*, 2004:749; Gerich, 2006:318-323; Lavernia, 2010:eS17).

– ***Management of the prothrombotic and pro-inflammatory state (optional)***

Most individuals with the metabolic syndrome show signs of a prothrombotic- and pro-inflammatory state (refer to paragraph 2.9.5). Aspirin or clopidogrel may decrease platelet aggregation and effectively reduce the risk of initial thrombotic events. Other agents that may show potential in the treatment of the pro-inflammatory state include statins and renin-angiotensin system inhibitors.

• **The “polypill” concept**

The concept of the “polypill” for the metabolic syndrome, which contains more than one agent, would potentially address more than one cardiometabolic risk factor simultaneously (Matfin, 2010:92). These polypills may result in improved compliance (due to reduction in the polypharmacy which is the norm for many patients with the syndrome) and decrease human and societal costs. For example, several studies have shown the value of multifactorial cardiovascular risk targeting in high-risk patients, *inter alia*, the STENO-2 study, which showed that simultaneously addressing glycaemic control, renin blockade and using antilipid and antiplatelet agents in patients with type 2 diabetes, reduced death from cardiovascular disease (HR, 0.43; 95% CI: 0.19 - 0.94) and cardiovascular events (HR, 0.41; 95% CI: 0.25 - 0.67) (Gæde *et al.*, 2008:589). Several “polypills” are currently in development (Matfin, 2010:93).

In conclusion, although there are several areas of uncertainty with respect to the definition, usefulness and pathogenesis of metabolic syndrome, it serves as a simple clinical tool to identify individuals associated with an increased long-term risk for both ASCVD and type 2 diabetes. Lifestyle interventions (including weight control, increased physical activity and an atherogenic diet) therefore deserve prime consideration for risk reduction. Concomitant therapy with pharmacological agents of both major and metabolic risk factors can furthermore contribute to the risk reduction in metabolic syndrome patients with relatively high 10-year ASCVD risks (Grundy & Cleeman *et al.*, 2005:2751).

Table 2.13: Therapeutic goals and recommendations for the clinical assessment and management of metabolic syndrome (adapted from Gazi *et al.*, 2004:248-249; Grundy & Cleeman *et al.*, 2005:2741; Hu *et al.*, 2006:280 and Spinler, 2006:215S)

Step	Description	Cross-reference
Step 1: Assess risk	- For patients without atherosclerotic CVD, estimate 10-year risk for CHD using the Framingham Risk Score - High-risk patients have atherosclerotic CVD, or diabetes with other CHD risk factors: - High risk $\geq 20\%$ - Moderately high risk is 10-20% - Low-to-moderate risk is $\leq 10\%$	Par. 2.10
Step 2: Manage underlying risk factors	- Abdominal obesity - Calculate BMI (treatment goal = BMI $<25 \text{ kg/m}^2$) - For 7-10% weight loss in 6-12 months, decrease calories by 500-1000 kcal/day - Increase physical activity to 30 min 5 days/week - Consider use of weight-loss agents in certain patients (e.g. sibutramine or orlistat) - Consider bariatric surgery in certain patients - Physical inactivity - Advise ≥ 60 min of continuous or intermittent aerobic exercise per day - Atherogenic and diabetogenic diet - Consider exercise stress testing on high-risk individuals - Decrease total calories for weight control - Diet low in saturated fats, <i>trans</i>-fats, cholesterol, sodium and simple sugars - Recommend consumption of fruits, vegetables, whole grains and fish	Par. 2.9.1.5.1 Par. 2.9.1.5.1 Par. 2.9.1.5.2 Par. 2.9.1.5.1 (Par. 2.9.1.5.1; 2.9.2.5.1; 2.9.3.5.1; 2.9.4.5.1)
Step 3: Measure fasting plasma glucose, identify patients with diabetes and prediabetes Treat patients with prediabetes and diabetes	- Impaired fasting glucose = 100-125 mg/dL - Impaired glucose tolerance = 2-h glucose level ≥ 140 and <200 mg/dL - For prediabetes, delay or prevent onset of diabetes with lifestyle changes (e.g. weight reduction and increase in physical activity) - For type 2 diabetes, HbA_{1c} should be $\leq 7\%$. - Modify other risk factors and behaviour. - Consider pharmacotherapy with metformin or thiazolidinediones (pioglitazone).	Par. 2.9.4.1 Par. 2.9.4.5.1 Par. 2.9.4.1 Par. 2.9.4.5.2
Step 4: Measure fasting lipid panel, treat atherogenic dyslipidaemia	- LDL-cholesterol level primary target: - For CHD and CHD risk equivalents, goal is <100 mg/dL - For two or more risk factors, goal is <130 mg/dL - Treat with statins to achieve LDL goal - Consider intensifying LDL-treatment if not on goal - For non-HDL-cholesterol level, <130 mg/dL is secondary target - Add fibrates (preferable fenofibrate) or nicotinic acid - Triglycerides: - For no or one risk factor, <150 mg/dL is the goal - Treat regardless of LDL-cholesterol level if >500 mg/dL - add fibrates (preferable fenofibrate) or nicotinic acid - HDL-cholesterol level: - Maximise lifestyle treatment - Consider adding fibrate or nicotinic acid	Par. 2.9.2.5.1 Par. 2.9.2.5.2 Par. 2.9.2.5.2 Par. 2.9.2.5.2

Table 2.13: Therapeutic goals and recommendations for the clinical assessment and management of metabolic syndrome (*continued*)

Step	Description	Cross-reference
Step 5: Measure and treat elevated blood pressure	- Target: <140/90 mmHg (<130/80 mmHg for patients with diabetes, chronic renal disease) - For blood pressure $\geq$ 120/80 mmHg, initiate or maintain lifestyle modification in all patients with metabolic syndrome (e.g. weight control, increase activity, alcohol moderation, reduced sodium intake, heart-healthy diet) For blood pressure $\geq$140/90 mmHg, treat as tolerated, add antihypertensives to achieve goal (preferable an ACE inhibitor, angiotensin II receptor inhibitor or calcium channel blocker)	Par. 2.9.3.1 Par. 2.9.3.5.1 Par. 2.9.3.5.2; 2.9.3.6
Step 6: Consider aspirin therapy	- To reduce the prothrombotic state: 81-325 mg/day for established atherosclerotic CVD 81 mg/day for a Framingham Risk Score $\geq$10% 75-162 mg/day for patients with diabetes type 1 or 2 who are >40 years, or those >20 years with other CVD risk factors	Par. 2.9.5
Optional: Measure C-reactive protein (CRP) level	- Emerging target for assessment and treatment: - If level is >3 mg/dL, consider lifestyle modification	Par. 2.9.5

2.11 CHAPTER SUMMARY

This chapter provided an overview of the concept of metabolic syndrome. Topics addressed were the history of the development of the metabolic syndrome including the origin and nomenclature, the defining criteria for diagnosis, the prevalence and epidemiology, the pathophysiology and aetiology, and the composing risk factors of the metabolic syndrome. The impact of metabolic syndrome and its components on the utilisation and cost of health care services were furthermore addressed. The chapter concluded with a summary on the goals and recommendations for the treatment of the metabolic syndrome. Potential developments were pointed out. Hereby the specific objectives of literature review have been answered.

Chapter 3 will focus on the research methodology followed during the empirical investigation phase of the study.

CHAPTER 3

Empirical Investigation

This study consisted of two phases (refer to paragraph 1.4). Phase one (literature review) was documented in Chapter 2 and focused on conceptualising the metabolic syndrome. Phase two of the study consisted of an empirical investigation – in particular, a retrospective drug utilisation review. This was done by quantitatively analysing medicine claims data obtained from a South African pharmaceutical benefit management company. The present chapter provides a short overview of aspects of the drug utilisation review and the instruments used for the empirical investigation.

3.1 DRUG UTILISATION REVIEW

In the late 1970s the World Health Organization (1977) defined drug utilisation as “*The marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences*”. From this original definition it is evident that “drug utilisation” not only entails the process whereby a drug or medication becomes available for its use by individuals, but also the outcomes thereof. Drug utilisation may also be regarded as a strategy that evaluates, examines and clarifies rates or costs and reviews the suitability of drug usage to determine inappropriate use and avert adverse drug interactions, whilst enhancing correct use (Wolters Kluwer Health, 2005). “Drug utilisation research” is then described as “*An eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes*” (Wettermark et al., 2008:159).

According to Ervin (1991:596), “retrospective drug utilisation reviews” are “*Approved, systematic processes that capture, review, analyse and interpret aggregate archival medication use data within specific health care environments*”. This type of review therefore analyses drug utilisation after the prescription has been dispensed, and often occurs after the patient has completed therapy (Fulda et al., 2004:433). Alternatively, drug utilisation review criteria may be implemented retrospectively to pharmacy claims data to identify inappropriate prescribing and dispensing practices (Radloff & Jones, 2007:34). The value of retrospective drug utilisation

reviews therefore lies in identification of patterns of prescribing or medicine use that may lead to future preventable drug-related morbidity, mortality and unnecessary costs.

There are different types of (retrospective) drug utilisation studies that can be conducted, *inter alia*, qualitative studies and quantitative studies such as those of prescriptions and prescribing behaviour, studies of patient compliance and/or adherence, studies on drug effects, studies on patients' knowledge about drugs, the determinants of drug utilisation, consumption studies, impact of drug use and *ad hoc* studies (Capellà, 1993:66-72; Lyle *et al.*, 2001:78). Quantitative studies (as implemented in this study) are valuable in comparing trends in the use of certain medications in different countries or areas, in evaluating the effects of regulatory measures and information campaigns and in undertaking benefit-risk analyses (Capellà, 1993:68-69). According to Gama (2008:70) quantitative drug utilisation review studies can furthermore be used to plan medicine importation, production and distribution, and to estimate medicine expenditures, to monitor the utilisation of medications from therapeutic categories where particular problems can be expected and to determine crude estimates of disease prevalence. These studies can therefore create a sound socio-medical and health economic basis for health care decision-making.

3.2 STUDY DESIGN

The approach of the research design followed in this study can be classified as quantitative and exploratory-descriptive. Descriptive research represents or provides accurate characterisation or information on groups or the phenomenon under investigation (Fink, 1998:93), whereas exploratory research is a preliminary examination of data undertaken in order to ascertain whether there are any patterns in the data that warrant a more detailed examination (Birley & Moreland, 1998:68). This research can also be classified as *ex post facto* according to the time sequence regarding the collection of data.

3.3 DATA SOURCE

The data employed in the study consisted of convenience datasets sourced from the central medicine claims database of a South African Pharmaceutical Benefit Management (PBM) company. Medicine claims databases are ideal for research with regard to drug utilisation, physician prescribing, adverse drug effects and risk management, beneficial drug effects and health policies (Schneeweiss & Avorn, 2005:324-325). These claims databases are usually administrative databases created by payers from bills generated by providers seeking payment for services rendered (Schwartz *et al.*, 1999:291-292). Within the context of South Africa, claims data is defined as "*Clinical information collected through claims submitted by health care*

providers to medical schemes for access to benefits and reimbursement; claims usually contain clinical, financial and administrative information” (Matshidze & Hanmer, 2007:92).

The Pharmaceutical Benefit Management (PBM) company providing the data for the study is a privately owned South African managed care organisation (identity may not be disclosed due to a confidentiality agreement), has been in business for 22 years, and currently provides real-time electronic pharmaceutical claims processing services to approximately 39 medical schemes in South Africa, or more than 1.6 million medical scheme beneficiaries. Data for a 4-year period, starting January 1, 2005 through December 31, 2008 were obtained as individual data files.

3.4 STUDY POPULATION

This section entails a discussion of the rationale for the selection of the study population, as well as the processes followed in selecting these patients.

3.4.1 Rationale for the selection of the study population

To identify patients with metabolic syndrome, either a definite diagnosis thereof, e.g. an ICD code (refer to paragraph 2.4.3) is required, or detailed clinical data, including information on waist circumference, waist-to-hip ratio and/or BMI, fasting plasma glucose levels, systolic and diastolic blood pressure, serum triglycerides, and high-density lipoprotein levels are required. In addition, certain defining criteria used for the diagnosis of the syndrome may require information on patient’s clinical history, his/her family history and/or ethnicity (refer to paragraph 2.4). The database employed in this study, however, lacked clinical data. The implementation of the ICD-10 coding system for diseases was furthermore only formally introduced in July 2005 in the private health care sector of South Africa (Matshidze & Hanmer, 2007:95). The ICD-10 code did not provide for metabolic syndrome, *inter alia*. Because of this and other limitations (refer to paragraph 2.4.3), a standardised version of the ICD-10 classification system was developed and implemented during the course of 2007. The use of and the contents of the classification system were therefore in a state of flux over this period (i.e. 2005-2007) in the private South African health care sector. The standardised ICD-10 code implemented in 2007 provided for the metabolic syndrome, designated by the code “I10/E78.5/E66.9/E11.9” (CMS, 2007a) (refer to paragraph 2.4.3). However, no cases of metabolic syndrome could be identified based on the “I10/E78.5/E66.9/E11.9”-code provided by the standardised ICD-10 coding system on the dataset for 2007 or 2008.

The literature study showed that from the 7 definitions that currently exist for the diagnosis of the metabolic syndrome in adult populations (refer to paragraph 2.4.1) the European Group for

Study of Insulin Resistance (EGIR), International Diabetes Federation (IDF), American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) and the new joint interim statement (JIS) (refer to paragraph 2.4) consider pharmacological treatment as equivalent to abnormal measured levels of risk factors. From these four definitions, both the EGIR and IDF have compulsory components that require the presence of clinical data for example fasting insulin concentration (EGIR) or central obesity (based on ethnic specific waist hip ratios) (IDF) (refer to Table 2.1). The basis of the AHA/NHLBI definition and the JIS definition, however, is similar in that obesity is not a prerequisite for diagnosis, but one of five criteria, so that any three of five risk factors – of which four can be measured based on pharmacological treatment for hypertension, raised triglycerides, low HDL-cholesterol and elevated fasting plasma glucose constitute a diagnosis (refer to paragraph 2.4.1). The discussions in paragraphs 2.9.2.5.2, 2.9.3.5.2 and 2.9.4.5.2, show that the treatment for these aforementioned conditions mainly reside within the pharmacological medicine classes of antidiabetics, antihypertensives (including diuretics) and hipolipidaemic agents. Claims for medicine items/active substances within the aforementioned medicine classes were therefore used as a proxy for diagnosis, recognising that these medications and/or pharmacological drug classes might also be used for the treatment of other conditions. For the purpose of this study, the conceptual importance lies in the chance that they are prescribed to a particular patient concurrently. The limitations of using this approach are addressed in Section 3.9.

“Metabolic syndrome” was subsequently defined as *“An individual on the medicine claims database with a claim for at least one medicine item(s) per year from each of the pharmacological drug classes of antihypertensives (including diuretics) (based on the MIMS® classification 7.3 and 16.1), hipolipidaemics (MIMS® classification 7.7) and antidiabetics (MIMS® classification system for medicines 19.1)”*. Patients receiving one or more medicine items (monotherapy or in combination) per year (but not concurrent with all three pharmacological drug classes) were classified as “at risk” for the development of metabolic syndrome, based on the discussions in paragraphs 2.9.2.3, 2.9.3.3 and 2.9.4.3. These identification criteria were applied across the 4-year study period to assure consistency in the study population selection process for each study period.

3.4.2 Selection process for the study population

The process followed from obtaining the data to the selection of the study population (i.e. metabolic syndrome patients) is depicted in Figure 3.2. The steps followed in this process were:

- Step 1: Data (refer to Table 3.1) were obtained from PMB’s central database.
- Step 2: Data were cleaned by application of exclusion criteria (refer to Table 3.2) to

obtain individual datasets for 2005, 2006, 2007 and 2008, respectively.

- Step 3: Application of inclusion criteria (Table 3.3) to obtain individual data subsets for 2005, 2006, 2007 and 2008, respectively.
- Step 4: Categorisation of patients from each data subset into 6 “at risk” categories and study population (*alias* metabolic syndrome category).

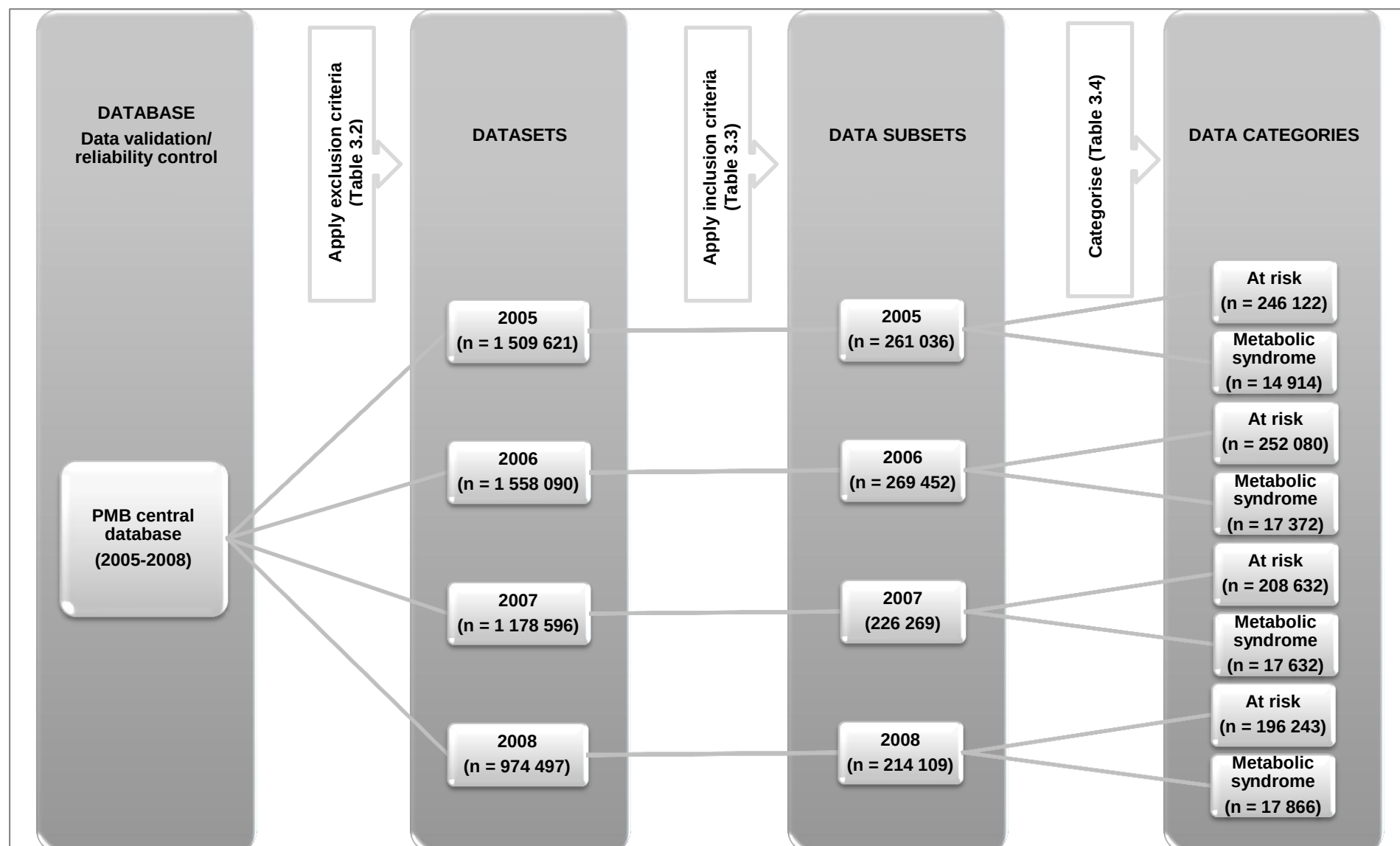


Figure 3.1: Selection process of the study population

- **Step 1: Obtaining data from the PMB's central database**

The data elements available from the PBM's central database selected for research are shown in Table 3.1. A data field was added to the database at this stage, containing the Monthly Index of Medical Specialities (MIMS®) classification code for each active ingredient that appeared on the specific dataset, based on the NAPPI®^h codes of these products.

Table 3.1: Data elements included in the PBM's database selected for research

Type of data	Selected data element
Membership	Date of birth Gender Anonymous membership identifier Anonymous member dependant identifier
Medicine claims	Anonymous prescriber type identifier Anonymous provider identifier National Pharmaceutical Product Interface (NAPPI®)-code Drug trade name Quantity dispensed Days' supply Date filled Amount paid by medical aid scheme Amount paid by patient Diagnosis code ⁱ

A discussion of the variables analysed during the study derived or computed from the available elements from the database (Table 3.1) follows in section 3.5.

- **Step 2: Cleaning of data by application of exclusion criteria**

Data were cleaned by application of exclusion criteria (refer to Table 3.2) to obtain individual datasets for 2005, 2006, 2007 and 2008, respectively.

Table 3.2: Exclusion criteria for selection of the datasets

Study period	Criteria
2005 -2008	• Unpaid claims • Non-medicine items (e.g. medical equipment and or medicine items not classified by the MIMS®)

Data (refer to Table 3.1) for 1 509 621 patients from 2005 were obtained, compared with 1 558 090 from 2006, 1 178 596 from 2007, and 974 497 from 2008. In 2005 these patients represented 22.1% of all beneficiaries covered by medical aid schemes registered in terms of the Medical Schemes Act (Act 131/1998) in South Africa (N = 6 835 621) (CMS, 2006:47), compared

^h The NAPPI-code is a unique nine digit number implemented with electronic transactions in mind in South Africa; incorporating the product name, pack size, strength and manufacturer plus exclusions of the dispensed product. This code is a Trademark of MediKredit Integrated Healthcare Solutions (Pty) Ltd.

ⁱ A code assigned to each claim by the BPM, based on pre-authorisation by the PBM or patient's medical aid scheme.

with 21.9% (N = 7 127 343) in 2006 (CMS, 2007b:49), 15.8% in 2007 (N = 7 478 040) (CMS, 2008:62) and 12.4% in 2008 (N = 7 874 826) (CMS, 2009:123). The age distribution of patients from the respective datasets (i.e. 2005 to 2008) is shown in Figure 3.2.

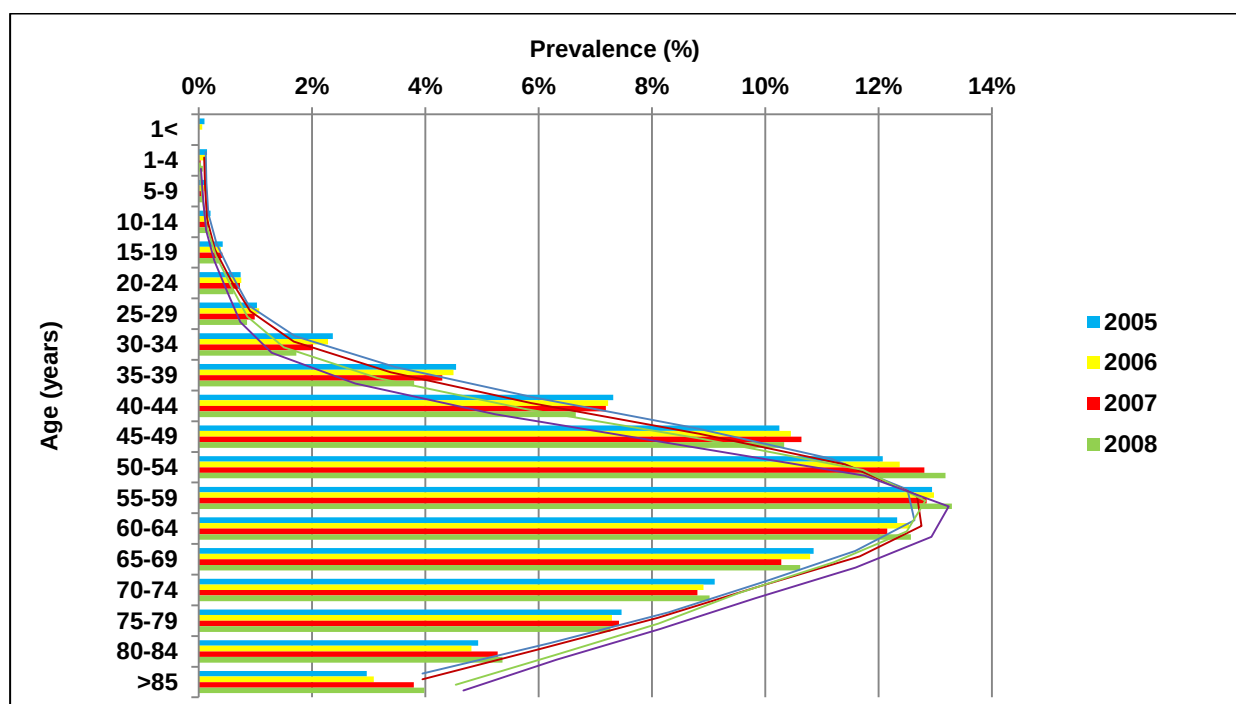


Figure 3.2: Percentage distribution of patients from the respective datasets by age group

Based on the annual reports from the Council for Medical Schemes the percentage age distribution of the total number of all beneficiaries covered by medical aid schemes registered in South Africa from 2005 to 2008 emulated a bimodal distribution with coverage in the 20-29 year age group lower, compared with the age groups on either side (CMS, 2006:48; CMS, 2007b:50; CMS, 2008:63; CMS, 2009:123). In comparison, Figure 3.2 shows that the patient distribution on the database emulates a left-skewed distribution, indicating that the PBM most likely provided fewer services to medical aid schemes members below the age of 25 years, with the majority of patients in the 40-80 years age bracket across the 4-year study period.

- **Step 3: Application of inclusion criteria to obtain data subsets**

The data subsets were obtained by the application of inclusion criteria (refer to Table 3.3).

Table 3.3: Inclusion criteria for the selection of the data subsets

Study period	Criteria
2005-2008	• All patients receiving ≥ 1 medicine item(s) at any given time during a specific study period (year) from any (but at least ≥ 1) of the following pharmacological medicine classes (based on the MIMS® classification): antidiabetics, antihypertensives (including diuretics) and hipolipidaemics (refer to Table B.1, Annexure B).

The data subsets therefore consisted of all patients with at least one prescription for an antihypertensive [(MIMS® classification 7.3.1-7.3.10, and 16.1.3 (diuretics)], hipolipidaemic (MIMS® classification 7.7.1-3) and/or antidiabetic (MIMS® classification 19.1.1-2) during the period January 1, 2005 to December 31, 2008.

The data subset for 2005 consisted of the information for a total of 261 036 patients, i.e. 17.3% of patients from the corresponding dataset in 2005 ($n = 1\,509\,621$), compared with 269 452 (17.3%, $n = 1\,558\,090$) from 2006, 226 264 (19.2%, $n = 1\,178\,596$) from 2007 and 214 109 (22.0%, $n = 974\,497$) from 2008. An index date was set as the date of the first prescription for a particular medicine item (refer to Table B.1, Annexure B) for each year of study (i.e. 2005, 2006, 2007 or 2008). Patients therefore may have received such medicine before/after the inception period (i.e. before January 1, 2005 and after December 31, 2008). This period prevalence estimate therefore combines prevalent and incident cases.

- **Step 4: Categorisation of patients from each data subset**

The patients from each data subset were categorised into 6 “at risk” categories and a “metabolic syndrome” category as depicted by Table 3.4 (refer also to paragraph 3.4.1).

Table 3.4: Categorisation of patients from the data subsets

Category	Designation	Description	MIMS® classification
At risk	Antidiabetic category	Patients receiving only antidiabetics	19.1.1-19.1.2
	Antihypertensive category	Patients receiving only antihypertensives	7.3.1-7.3.10; 16.1.3
	Hipolipidaemic category	Patients receiving only hipolipidaemic agents	7.7.1-7.7.3
	Antidiabetic/ antihypertensive category	Patients receiving both antidiabetics and antihypertensives	19.1.1-19.1.2; 7.3.1-7.3.10; 16.1.3
	Antihypertensive/ hipolipidaemic category	Patients receiving both antihypertensives and hipolipidaemic agents	7.3.1-7.3.10; 16.1.3; 7.7.1-7.7.3
	Antidiabetic/ hipolipidaemic category	Patients receiving both antidiabetics and hipolipidaemic agents	19.1.1-19.1.2 7.7.1-7.7.3
Metabolic syndrome	Metabolic syndrome category	A patient with a claim for at least one medicine item(s) per year from each of the therapeutic drug classes of antihypertensives (including diuretics), hipolipidaemics and antidiabetics on the medicine claims database	19.1.1-19.1.2; 7.3.1-7.3.10; 16.1.3 7.7.1-7.7.3

3.5 STUDY VARIABLES

The discussion in this section entails a description of the various dependent and independent variables (derived or computed from the available elements from the database as shown in Table 3.1) analysed during the study.

3.5.1 Age

In this study “age” was calculated by computing the age of the patient on his/her treatment date, in relation to his/her date of birth, using January 1 of the following year, as index date for each study year. For example, a patient with a date of birth of June 10, 1950, would be considered 58 years old on a treatment date of August 10, 2008. For the assignment of age group, patients were stratified into 6 age groups:

- Age group 1: Children and pre-adolescents ($>0, \leq 15$ years).
- Age group 2: Adolescents, late adolescents and young adults ($>15, \leq 30$ years).
- Age group 3: Young adulthood ($>30, \leq 45$ years).
- Age group 4: Middle adulthood ($>45, \leq 60$ years).
- Age group 5: Elderly patients ($>60, \leq 75$ years).
- Age group 6: Mature patients older than 75 years.

The motivation for the assignment of age groups stems from the lack of a universally accepted definition of the metabolic syndrome in children and adolescents (refer to paragraph 2.4.2). The International Diabetes Federation (2007) published the first definition of metabolic syndrome in children and adolescents in 2007, based on percentile definitions that were standard across age ranges, i.e. children aged $6 < 10$ years, $10 < 16$ years and ≥ 16 years. This definition provides for the identification and treatment of dyslipidaemia (i.e. high triglyceride levels and low HDL-cholesterol levels) and abnormal blood pressure in those ≥ 16 years, based on pharmacological treatment. Because the selection of the study population (refer to paragraph 3.4.1) depended on the use of medicine use as proxy measure for identification of patients, age group assignments were done accordingly.

3.5.2 Gender

For the assignment of gender, only patients whose gender group (i.e. male or female) was known, were included. There was a third gender group in the total database that includes all patients whose gender was unknown to the PBM. This could be the result of a medical aid scheme not supplying the gender of the patient to the PBM.

3.5.3 The number of prescriptions and medicine items

The Oxford English Dictionary (2011) defines a prescription as “*An instruction written by a medical practitioner that authorizes a patient to be issued with a medicine or treatment*”. A prescription can contain more than one medicine item in South Africa. “Medicine” is defined as “*Any substance or mixture of substances used or purporting to be suitable for use or manufactured or*

sold for use in the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man” in terms of the Medicines and Related Substances Control Act (Act 101/1965). For the purpose of this study, “medicine” therefore refer to any product (substance, active ingredient or mixture) prescribed to, or claimed by a patient, recorded on the medicine claims database.

NAPPI® -codes (refer to Table 3.1) of each active substance claimed, were furthermore linked to the MIMS® classification system. The presence of any of the listed active substances in Table B.1 (Annexure B) constitutes a prescription/claim for a medicine item from antihypertensives (including diuretics), antidiabetics and hipolipidaemics or a combination of thereof, respectively.

3.5.4 Medicine cost

According to the National Institute of Health (2011), direct cost is defined as “*those costs borne by the healthcare system, community and patients’ families in addressing the illness*”. For the purpose of this study, the direct cost of medicine treatment per patient on the database was calculated by summing the total amount reimbursed by medical aid schemes and the patient co-payment levied per medicine item.

3.5.5 Diagnosis codes

A count of the International Classification of Diseases, 9th Revision (ICD-9), medical diagnoses codes has been used previously as measure of comorbidity in patients (Schneeweiss & Maclur, 2000; Baldwin *et al.*, 2006; Chu *et al.*, 2010; Thygesen *et al.*, 2011). Based on this method each patient is assigned a comorbidity status or chronic disease score (depending on the outcomes of the study) by summing the number of conditions associated with each patient. Feinstein (1970:455) described “comorbidity” as additional diseases beyond the condition under study. More recently Valderas and colleagues (2009:357) defined comorbidity as a term used to indicate a medical condition in a patient that causes, is caused by, or is otherwise related to another condition in the same patient. These comorbidities can be chronic diseases or acute illnesses and increase a patient’s total disease burden. Comorbidity in general is associated with poor health outcomes, generally requiring more complex clinical management and increased health care costs (Vogeli *et al.*, 2007:393), even more so in patients with diabetes and cardiovascular disease (Davis *et al.*, 2011:211).

The Amendments to the Regulations of the Medical Schemes Act (Act 131/1998), published in November 2002 mandated the full payment for the diagnosis, treatment and medication for 27 chronic conditions (defined as the Chronic Disease List or CDL), *inter alia*, to be implemented

from January 1, 2004, as part of the prescribed minimum benefit (PMB) package for all South African medical aid schemes (Council for Medical Schemes, 2005:2). The medication or medicine classes proposed for the treatment of each of these chronic conditions was stipulated in treatment algorithms published in 2003 (CMS, 2003). In order for a patient to access these chronic medications, the prescribing or treating doctor must register the patient's chronic condition with his/her medical aid scheme. A valid ICD-10 code (in accordance to the codes specified for the 27 chronic conditions by the Council for Medical Schemes, refer to Table B.3, Annexure B) and report of severity status (with appending proof) are required for registration. Claims for medicine items for any of the 27 Chronic Disease List conditions are therefore firstly verified against eligibility by registration and medicine approved for the particular condition, before reimbursement. Medicine claims data therefore normally contain relative accurate claims data for these CDL conditions.

With each claim for the treatment of any of these 27 chronic disease list conditions, the PBM (or medical aid scheme) assigns a "diagnosis code" to the specific medicine items claimed, based on the ICD-10 code for the relevant condition as specified by the Council for Medical Schemes. For the purpose of this study these diagnosis codes were used to determine the prevalence of chronic diseases appearing on the Chronic Disease List, co-occurring in patients from the 2008 metabolic syndrome category. The chronic conditions hypertension, hyperlipidaemia and diabetes mellitus types 1 and 2 were omitted as these were used for identification of the patient. The number of diagnosis codes per metabolic syndrome patient was furthermore counted to attain a "chronic disease count" per patient [refer to paragraphs 3.5.5 and 3.8 (specific empirical objective #12)].

3.6 MEASURES OF CONSUMPTION/UTILISATION

The discussion in this section entails a description of the various measures of medication consumption and/or health care service utilisation employed during the data analysis.

3.6.1 Prescribing volume (prescriptions and medicine items)

The number (frequency and/or percentage) of prescriptions and medicine items claimed was used as measure of prescribing volume. Prescribing volume, based on the number of medicine items was furthermore used as a proxy for condition or disease prevalence, for example individuals with claims for antihypertensive medication were classified as having high blood pressure whereas individuals currently taking insulin or an oral hypoglycaemic medication were classified as having diabetes. In similar fashion individuals with claims for hipolipidaemics were classified as having dyslipidaemia.

Individuals with a claim for at least one prescription for an antihypertensive [(MIMS® classification 7.3.1-7.3.10 and 16.1.3 (diuretics)], lipolipidaemic (MIMS® classification 7.7.1-3) and/or antidiabetic (MIMS® classification 19.1.1-2) during the period January 1, 2005 to December 31, 2008 (but not from all three classes concurrently), were defined as those “at risk” for the development of the metabolic syndrome. Individuals with a claim for at least one medicine item(s) per year from *each* of the pharmacological drug classes of antihypertensives, including diuretics (based on the MIMS® classification 7.3 and 16.1), lipolipidaemics (MIMS® classification 7.7) and antidiabetics (MIMS® classification system for medicines 19.1) were defined as “metabolic syndrome” (refer to paragraph 3.4.1).

The limitations of using prescribing volume of medicine item claimed as proxy measure are addressed in section 3.9.2.

3.6.2 Beers Criteria

The Beers Criteria (or Beers List) is a list of explicitly defined criteria to identify inappropriate use of medications in patients over the age of 65 years (Beers *et al.*, 1991:1825). This list, originally developed in 1991, currently consists of 68 medications or medication classes (refer to Table B.2, Annexure B).

For the purpose of this study the Beers Criteria was used to estimate the prevalence and severity of potentially inappropriate medications prescribed in metabolic syndrome patients older than 60 years^l.

3.6.3 Chronic disease count

Diagnosis codes (refer to paragraph 3.5.5) were used to determine the prevalence of chronic diseases appearing on the Chronic Disease List, co-occurring in patients from the 2008 metabolic syndrome category. The number of diagnosis codes per metabolic syndrome patient was counted to attain a “chronic disease count” per patient (refer to paragraphs 3.5.5 and 3.8).

3.6.4 Direct medicine treatment cost

The direct cost of medicine treatment (refer to paragraph 3.5.4) was used to estimate the average and total annual resource consumption per patient, from the respective datasets, data subsets and data categories. The total health care costs represent the costs incurred by the medical aid scheme and the member’s co-payment.

^l The age of ≥ 61 years was chosen to conform to the assignment of age groups for analysis (refer to paragraph 3.5.1).

3.6.5 Cost-prevalence index (CPI)

The cost-prevalence index (CPI) developed by Serfontein (1989:180) is the relationship between the number of medicine items prescribed or claimed and the total cost associated with these items (refer to paragraph 3.7.8). The CPI can be used as an indicator of the relative expensiveness of chronic medicine items and therefore as a measure of health care resource consumption (refer to paragraph 3.7.8). Medicine items with a CPI value >1 were regarded as cost drivers within the private health care sector from South Africa.

3.7 DATA ANALYSIS

The data were analysed by using the Statistical Analysis System® SAS 9.1® programme (SAS institute Inc., 2003) in consultation with the Statistical Consultation Services of the North-West University. Microsoft® Office Excel 2010 was used for general computations. All study variables were analysed descriptively. A summary of these statistics is provided here, followed by a summary of the statistical tests/analysis conducted to attain each specific objective of the empirical investigation phase (refer to Table 3.5).

3.7.1 Frequency and prevalence

The Oxford English Dictionary (2011) describes frequency as “*the rate at which something occurs over a particular period of time or in a given sample*”, whereas prevalence is described as “*the count of cases (new and old) at a point in time in a population size defined by characteristics (i.e. age and gender), and place*” (Bhopal, 2002:317). McKenzie and co-workers (2011:67) further describe a prevalence rate as the number of people with the condition divided by the number of people at risk. Denominators for frequency and prevalence calculations therefore included all patients in the particular dataset or data subset, stratified by age and gender, as necessary.

3.7.2 Average (arithmetic mean)

The average (or arithmetic mean) is defined as the “*quotient of the sum of several quantities and their number*” (OED, 2011), and is used to provide a measure of central location for the data (Anderson *et al.*, 2009:83; Ott & Longnecker, 2010:81). The following quotation (Anderson *et al.*, 2009:83) was used for the calculation of the sample average:

$$\bar{x} = \frac{\sum xi}{n}$$

where:

$\bar{x}$ = average

$\sum xi$ = sum of all given x values

n = number of observations in the sample

3.7.3 Weighted average

Petrie and Sabin (2005:16) describe the weighted average as similar to an arithmetic mean, where instead of each of the data points contributing equally to the final average, certain values of the variable of interest, $\bar{x}$, are more important or larger than others. The weighted average was calculated using Microsoft® Office Excel 2010. The following formula (Microsoft®, 2011a) was used:

$$\text{Weighted average} = \text{SUMPRODUCT}(X_i:X_n, Y_i:Y_n) / \text{SUM}(Y_i:Y_n)$$

where:

X_i = average of first observation

X_n = average of the last observation

Y_i = frequency of the first observation

Y_n = frequency of the last observation

3.7.4 Standard deviation

According to the Oxford English Dictionary (2011) the standard deviation is defined as “a quantity expressing by how much the members of a group differ from the mean value for the group”. Ott and Longnecker (2010:93) described the standard deviation as the positive square root of the variance. The sample standard deviation (Anderson *et al.*, 2009:95) was calculated as follows:

$$s = \frac{\sqrt{\sum(x - \bar{x})^2}}{n - 1}$$

where:

s = standard deviation

x = any value in the dataset

$\bar{x}$ = average (arithmetic mean)

n = number of observations

A small standard deviation is indicative of clustering of observations around the average, whereas a large standard deviation indicates a spread of data around the average (Banerjee, 2003:5).

3.7.5 Weighted standard deviation

Similar to the standard deviation the weighted standard deviation is calculated as the positive square root of the variance, though, employing the weighted variance of the weighted average (Kozak *et al.*, 2008:27). The weighted standard deviation was calculated using Microsoft® Office Excel 2010 with the formula (Microsoft®, 2011b):

$$\text{Weighted standard deviation} = \text{SQRT}(\text{SUMPRODUCT}((X_i - Z)^2, Y_i) / (\text{SUM}(Y_i) - 1))$$

where:

X_i = average of first observation

X_n = average of the last observation

Y_i = frequency of the first observation

Y_n = frequency of the last observation

Z = weighted average

3.7.6 Median

The median as measure of central tendency is the middle value when measurements are arranged from lowest to highest (Ott & Longnecker, 2010:79). According to Delucchi and Bostrom (2004:1161) the median may be more appropriate in describing skew data than the average, as is typically the case with the distribution of cost data. This is caused by the presence of a relatively small number of patients with high treatment costs and the absence of negative costs (Barber & Thompson, 1998:1196).

3.7.7 Effect sizes (Cohen's *d*-values)

Marczyk and co-workers (2005:92) describe effect size as the extent of the differences between group averages or other test statistics. Steyn (2009) calculated effect size by using the following formula:

$$d \equiv \delta = \frac{\bar{x}_1 - \bar{x}_2}{s_{max}}$$

where:

$d \equiv \delta$ = effect size

$\bar{x}_1$ = average medicine treatment cost of a

$\bar{x}_2$ = average medicine treatment cost of b

s_{max} = maximum standard deviation between a and b

The following guidelines are used to evaluate the value of d (Cohen, 1988:25):

$|\delta| = 0.2$: small effect size

$|\delta| = 0.5$: medium effect size

$|\delta| = 0.8$: large effect size

Effect sizes ≥ 0.8 were deemed practically significant (Steyn, 2009).

3.7.8 Cost-prevalence index

The cost-prevalence index (CPI) developed by Serfontein (1989:180) is the relationship between the number of medicine items prescribed or claimed and the total cost associated with these items. The following equation is used by Serfontein to calculate the cost-prevalence index:

$$CPI = \frac{\text{Cost (\%)}}{\text{Prevalence (\%)}}$$

The CPI can be used as an indicator of the relative expensiveness of chronic medicine items and is interpreted as follows:

- If cost-prevalence index < 1 the medicine item is considered relatively inexpensive.
- If cost-prevalence index $= 1$ there is equilibrium between the cost and prevalence of the medicine item.
- If cost-prevalence index > 1 the medicine item is considered relatively expensive.

3.8 APPLICATION OF STATISTICAL TESTS /MEASURES

This section entails a summary (depicted in Table 3.5) of the statistical tests/measures conducted for each objective of the empirical investigation phase of the study (refer to paragraph 1.5.2).

Specific empirical objectives #1-3 relate to the **datasets** as obtained from the central database of the South African pharmaceutical benefit management (PBM) company. This analysis was conducted to position the database used for analysis with regard to the South African private health care sector, and to establish a baseline for comparison with regard to medicine claims patterns (prescriptions and medicine items) and associated direct treatment cost for all patients.

Specific empirical objectives #4-6 relate to the group of patients receiving ≥ 1 medicine item(s) at any given time during a specific study period (year) from any (but at least ≥ 1) of the following pharmacological medicine classes (based on the MIMS® classification): antidiabetics, antihypertensives (including diuretics) and hipolipidaemics (refer to Table B.1, Annexure B) or

so-called **data subsets**.

The patients from each data subset were categorised into 6 “at risk categories for the development metabolic syndrome” and a “metabolic syndrome” category as depicted by Table 3.4 (refer also to paragraph 3.4.1). The analysis with regard to the “at risk” categories was conducted to position patients with one or more risk factors for the development of metabolic syndrome [as defined by the definitions of the American Heart Association/National Heart, Lung and Blood Institute, and the joint interim statement (refer to paragraph 3.4.1)] with regard to all patients from the respective datasets. The analysis was further conducted to establish baseline utilisation information with regard to medicine claims patterns (prescriptions and medicine items) and associated direct treatment cost for these “at risk” patients.

Specific empirical objectives #7-11 relate to the **study population**, i.e. metabolic syndrome patients. The analysis to attain specific empirical objectives #7-10 was conducted on the data across all 4-study periods (i.e January 1, 2005 – December 31, 2008). Specific empirical objective #11-12 was attained by analysing data from January 1, 2008 to December 31, 2008.

Table 3.5: Application of statistical tests/measures to specific objectives

Objective number	Description	Statistical test/measure	Variables/Applications
1, 4 & 7	Objectives relating to determining patients' prevalence and demographic profile	Frequency	– Demographic profile of patients (age and gender distribution) per dataset, data subset, “at risk” category and study population from 2005-2008.
		Averages & standard deviation	– Average prevalent age of patients on date of claim per dataset, data subset, “at risk” category and study population from 2005-2008.
		Effect sizes (Cohen's <i>d</i>)	– Difference in average age of patients (age and gender) per dataset, data subset, “at risk” category and study population from 2005-2008.
2, 5 & 8	Objectives relating to the prescribing patterns in patients	Frequencies/percentages	– Number of prescriptions and medicine items claimed, stratified by age and gender, per dataset, data subset, “at risk” category and study population from 2005-2008. – Specific active substances claimed for patients from the study population for 2005-2008. – Relative change in percentage claims for age and gender groups from the study population for 2005-2008.
		Averages, medians & standard deviations	– Average and median number of prescriptions and medicine items claimed per patient, stratified by age and gender, dataset, data subsets, “at risk” category and study population from 2005-2008. – Average pill-burden for patients from the study population (average number of tablets received per patient, per year, divided by the number of prescriptions claimed for 2005-2008.
		Ranges	– Minimum and maximum number of medicine items claimed per prescription per year, for patients from the data subsets and study population for 2005-2008.
		Effect sizes	– Differences between gender and age groups in terms of average number of prescriptions and items claimed, per dataset, data subset, “at risk” category and study population from 2005-2008.
3, 6 & 9	Objectives relating to the direct medicine treatment cost of medicine item claims	Frequencies	– Total direct medicine treatment cost, stratified by age and gender, for datasets, data subsets, “at risk” categories and study population from 2005-2008. – Total contribution by medical aid scheme vs. patient contribution per dataset, data subset, “at risk” category and study population from 2005-2008.
		Averages, medians & standard deviations	– Average and median medical aid scheme contribution vs. average and median patient contribution per dataset, data subset, “at risk” category and study population from 2005-2008. – Average annual direct medicine treatment cost per patient from datasets, data subsets, “at risk” categories and study population.
		CPI values	– Relative expensiveness of medicine in relation to age and gender groups.
		Effect sizes	– Difference in average cost per medicine item between gender/age group per dataset, data subset, “at risk” category and study population from 2005-2008. – Average amount reimbursed by medical aid schemes and the patient co-payment levied per claim per dataset, data subset, “at risk” category and study population from 2005-2008.

Table 3.5: Application of statistical tests/measures to specific objectives (*continued*)

Objective number	Description	Statistical test/measure	Variable
10	Determine a prescribing index for metabolic syndrome patients, based on prescribing volume and cost from the central database of a South African PBM from the period January 1, 2005 to December 31, 2008.	Frequencies & percentages	– Prescribing volume of medicine items (active substances) claimed.
		Averages, medians & standard deviations	– Average and median cost per active substance claimed.
		CPI values	– Indicator for relative expensiveness of active substances.
11	Determine the prescribing volume, nature and direct cost of the most claimed treatment regimens used for metabolic syndrome patients from the central database of a South African PBM from the period January 1, 2008 to December 31, 2008.	Frequencies	– Prescribing prevalence of different treatment regimen groups. – Determine the top 20 foremost treatment regimens.
		Weighted average & weighted standard deviations	– Average cost per treatment regimen and treatment regimen group.
		CPI values	– Relative expensiveness of treatment regimen.
		Effect sizes	– Differences between weighted average costs per treatment regimen group.
12	Determine the prevalence of chronic conditions co-occurring in metabolic syndrome patients from the central database of a South African PBM from the period January 1, 2008 to December 31, 2008.	Frequencies, averages & standard deviations	– Average chronic disease count per patient. – Determine the foremost chronic diseases co-occurring per patient.

3.9 EMPIRICAL INVESTIGATION: RELIABILITY AND VALIDITY

Because medicine claims data are not created for research purposes, there are two major potential problems that could arise in the use of these databases to provide reliable information, i.e. the quality of the data contained within the database and the ability of the analyses of observational (i.e. non-experimental) data to provide valid results (Motheral & Fairman, 1997:350; Tannen *et al.*, 2009). These two problems that may occur, and the action taken in this study to prevent these, are addressed in subsequent paragraphs.

3.9.1 Data quality

According to De Coster *et al.* (2006) errors in data can be caused by inaccurate or missing information in the patient record, failure to abstract relevant data or from incorrect coding of the abstracted data.

The PBM providing the data for the study has the following validation processes in place to ensure the validity and reliability of data: gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit management (refer to Table B.5, Annexure B for the complete list of data validation techniques). These validation processes ensure that claiming standards are met, for example, in the case of a missing or invalid product or member number, such a claim would be rejected. The PBM also conducts supplementary services such as integrated pre-authorisation services (including exception management), management of medicines for the Chronic Disease List (CDL), Prescribed Minimum Benefits (PMBs) and other conditions, and medicine management in capitation environments.

Data were additionally cleaned by deleting all non-paid claims and claims for non-medicine items (refer to paragraph 3.4.1 and 3.4.2.). The datasets were verified after each cleaning process by performing random data checks.

3.9.2 Measures taken to assure validity of the results

Utilising claims data for retrospective research *per se*, has some advantages, for example, claims database research is nonintrusive in general (i.e. patients and providers are not contacted for data collection purposes), implying that research activities do not affect the study outcome whilst recall bias is limited (Ghandi *et al.*, 1999:218). It is furthermore generally free of non-response and drop-out (Baron & Weiderpass, 2000:200) in addition to normally being of a higher quality because it is subject to audit and assessment. Moreover, these databases are

usually population-based and therefore generally large enough to enable identification of sufficient numbers of patients with the condition under investigation (Johantgen, 2010:242). These positive characteristics of claims data all held true for the database employed in this empirical investigation (refer to paragraphs 3.3 and 3.4, and Table 3.6).

Unfortunately, employing claims data for research purposes poses several threats to internal^k and external^l validity. For example, Burton and Jesilow (2011:26), Motheral and Fairman (1997:350) and Zaitzow and Fields (2006:329) list the following factors as threats to internal validity:

- Diagnostic information such as the use of the International Classification of Diseases (ICD) codes in database research may not always be reliable or valid, because of study bias caused by under- and over-coding.
- The presence of confounding variables on the database, such as severity of illness, smoking status, and family history of illness, alcohol use, drug use and use of over-the-counter drugs is not always recorded on research databases – and hence, cannot be controlled for.

Possible threats to external validity include the characteristics of the data, plan design of medical aid scheme benefits, geographic variations and differences in cost across time and place, patient's privacy and confidentiality issues and changes in enrolment to medical aid schemes during the study period (Motheral & Fairman, 1997:350). This data was not available for research purposes and could therefore not be verified (refer to Table 3.7). Missing data also present a threat to external validity. This was a particular cause of concern in this empirical investigation because of a lack of clinical data and incomplete ICD-10 coding fields on the database for the period 2005-2007. The study population was therefore identified by using surrogate criteria for elevated blood pressure, hyperglycaemia and dyslipidaemia (refer to paragraph 3.4.1).

Although the AHA/NHLBI definition and the JIS definition provide for the identification of patients based on the pharmacological treatment for hypertension, raised triglycerides, low HDL-cholesterol and elevated fasting plasma glucose (refer to paragraphs 2.4.1 and 3.4.2), the use of medicine treatment as a proxy for the presence of a medical condition can be misleading and therefore also limits internal validity. For example some active substances have multiple uses and thus complicate determining disease state (e.g. diuretics or clonidine for the identification of hypertension). In addition, the off-label use of substances could lead to the risk of misidentifying patients with a medical condition that they might not have (e.g. indapamide for

^k Internal validity refers to the plausibility and nature of a causal relation (Mellenberg, 1999:325).

^l External validity refers to the applicability or generalisability of the results of a study to other "populations, settings, treatment variables and measurement variables" (Jüni *et al.*, 2001:93).

the treatment of diabetes insipidus). Likewise, patients with the medical condition of interest might not be included since not all diagnosed individuals receive treatment (e.g. patients with prediabetes; refer to paragraph 2.9.4.5). The data obtained for the empirical investigation furthermore included only prescriptions that were filled. This in turn could be influenced by various other factors, such as the perceived benefit of the medication, ease of filling the prescription, patient characteristics and the direct cost to the patient (Boslaugh, 2007:4). The presence of a prescription claim furthermore, does not reflect those patients who may have received medication without the presence of a prescription claim. This approach further assumes that beneficiaries/patients, for whom claims data were not reported, had no utilisation of medicine during the study period – the approach therefore underestimates utilisation. Hivert *et al.* (2009), however, recently conducted an electronic health record (EHR) analysis to identify metabolic syndrome patients at risk for future diabetes and cardiovascular disease. In their analysis, medication use was used as surrogate estimates for missing data. Validation of this EHR-defined metabolic syndrome approach had 73% sensitivity and 91% specificity for the condition as directly measured, confirming that electronic health care records could be reliably used to identify individuals with the syndrome.

Motheral and colleagues (2003:90-96) recommend using a checklist compiled by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR), to ensure reliable^m results when conducting retrospective database studies. Table 3.6 provides a summary of this list and the approaches followed in this study to achieve each checklist objective where applicable. The Edmonton Quality Assessment Tool for Drug Utilization Reviews (EQUATDUR-2) (Spooner *et al.*, 2000:958) was further used to evaluate the present study for potential researcher bias. A self-rated score of 8 was attained (refer to the evaluation form in Table B.4, Annexure B).

^m Reliability refers to the stability, dependability and predictability of the research method (Herbert, 1990:21) or as according to Birley and Moreland (1998:43) the “extent to which a test would give consistent results if applied more than once to a sample people under standard conditions”.

Table 3.6: Checklist for retrospective database studies to assess quality (adapted from Motheral *et al.*, 2003:90-96)

Considerations	Aspect	Checklist item	Approach followed/Cross-reference
Data source	Relevance	Have the data attributes been described in sufficient detail for decision makers to determine whether there was a good rationale for using the data source? Has the overall generalisability of the data source been described?	The following key attributes were described: health care profile of the population and available services (refer to paragraph 3.3).
	Reliability and validity	Were the reliability and validity described? Were data checked for quality? Were the data cleaned?	The datasets were verified by performing random data checks. The datasets were furthermore cleaned by deleting non-paid claims and non-medicine items. In addition, the PBM providing the data for the study had certain validation processes in place to insure the validity and reliability of data (refer to paragraph 3.9.1, and Table B.5, Annexure B).
	Data linkages	Have the necessary linkages among data sources and/or different and/or care sites been carried out appropriately?	The patient claims data were received in comma separator value (.csv) -format, and imported into the SAS® for Windows 9.1 analytical programme. As patient medicine claims appeared as line items, data needed to be transposed for individual patients. This process was conducted by complex data programming. The datasets were verified by performing random data checks after transposing.
	Eligibility	Was the type of data used to determine member eligibility been described?	Data on patients' health plans were not available for research due to a patient confidentiality agreement. Eligibility could therefore not be assessed. This is seen as a study limitation.
Methods	Research design	Was a data analysis plan, including study hypothesis developed <i>a priori</i> ?	Not applicable.
	Design selection	Was a rationale for the particular research design provided?	Refer to paragraphs 3.2, 3.4 and 3.9.
	Research design limitations	Has design as potential limitations of the study been identified and addressed?	
	Treatment effect	Were a comparison group specified for studies that were trying to make inferences about the effects of interventions?	Not applicable.
Study population and variable definitions	Sample selection	Were the inclusion and exclusion criteria described? Were the steps used to derive the final sample from the initial population described?	Refer to paragraphs 3.4.1 and 3.4.2.
	Eligibility	Are subjects eligible for the time period over which measurement is occurring?	Data on patients' health plans were not available for research due to a patient confidentiality agreement. Eligibility could therefore not be assessed. The PBM providing the data for the study, however, had a number of validation and eligibility checks in place (refer to Table B.5, Annexure B).
	Censoring	Were inclusion/exclusion or eligibility criteria used to address censoring and was the impact on study findings discussed?	

Table 3.6: Checklist for retrospective database studies to assess quality (*continued*)

Considerations	Aspect	Checklist item	Approach followed/Cross-reference
Study population and variable definitions (<i>continued</i>)	Definition validity	Was a rationale and/or supporting literature for the definitions and criteria used? Was sensitivity analysis performed for definitions or criteria that are controversial, uncertain, or novel?	Refer to paragraphs 3.4.1 and 3.4.2
	Timing of outcome	Is there a clear temporal (sequential) relationship between the exposure and outcome?	Not applicable.
	Event capture	Are the data, as collected, able to identify the intervention and outcomes if they actually occurred?	The database only includes data for medicine items claimed. Out-of-pocket expenditure could therefore not be assessed.
	Disease history	Is there a link between the natural history of the disease being studied and the period for analysis?	Four years' data were used in the analysis. An index date was set as the date of the first prescription for a particular medicine item (refer to Table B.1, Annexure B) for each year of study (i.e. 2005, 2006, 2007 or 2008) (refer to paragraph 3.4). Patients therefore may have received such medicine before/after the inception period (i.e. before January 1, 2005 and after December 31, 2008). This period prevalence estimate therefore combines prevalent and incident cases. The disease history could not be assessed because of the lack of reliable diagnostic codes (refer to paragraphs 3.4.1 and 3.4.2).
	Resource valuation	Was an exhaustive list of resources affected by the intervention defined and measured? Were resource prices adjusted to yield a consistent valuation that reflected the opportunity cost of the resource?	The study was conducted from an economic perspective. However, only direct medicine treatment cost was analysed, consisting of the medical aid scheme contribution and patient co-payment. The cost of medicine items only regarded the final price of the product (i.e. the sum of the dispensing fee and single exit price of a product). The influence of possible inflation factors was not taken into consideration during evaluation of the change in cost over the study period. Each year of study was analysed independently.
Statistics	Influential cases	Was the sensitivity of the results to influential cases examined?	The datasets were verified by performing random data checks. Only paid claims were included in the analysis. The datasets were furthermore cleaned by deleting non-paid claims and non-medicine items.
	Relevant variables	Were all variables identified hypothesized to influence the outcome of interest? Were all available variables included in the model?	Not applicable
	Statistical models	Was the rationale for the model/statistical method used, explained?	The data in the study was described descriptively. Medians were used alongside averages and standard deviations to describe costs. Refer to paragraph 3.6.
	Statistical assumptions	Was the validity of the statistical assumptions underlying analysis, investigated?	Not applicable.

Table 3.6: Checklist for retrospective database studies to assess quality (*continued*)

Considerations	Aspect	Checklist item	Approach followed/Cross-reference
Statistics (<i>continued</i>)	Multiple tests	If analysis of multiple groups is carried out, are the statistical tests adjusted to reflect this?	Not applicable.
	Model prediction	If multivariate statistical techniques are used, discuss how well the model predicts what it is intended to predict?	Not applicable.
	Control variables	Was a method employed to control for other variables that may affect outcome in studies that examine treatment effects?	The study examined medicine use and associated treatment cost. Clinical outcomes (e.g. effects of treatment) were not assessed. For the calculation of chronic disease count (refer to paragraph 3.6.3), inadequate clinical information present in the database limited the adjustments for severity of illness. The literature study established that the prevalence of the syndrome is highly age-dependent and affects more males, and occurs more frequently in the general adult population of developed countries, or urban areas of developing countries where lifestyle changes towards a western urbanised pattern (refer to paragraph 2.5.1). Moreover, the prevalence of chronic diseases increases with age (4.3.2.2). The study population originated from the central database of a PBM situated in the private health care sector of South Africa where the majority of patients live in "first world" conditions with a relative higher income. A potential for confounding therefore existed between certain variables, e.g. age, gender, co-morbidity, economic status and the prevalence of metabolic syndrome. These confounding factors could also have influenced the direct cost associated with the treatment of patients from this patient category. According to Wild and Byrne (2011:11), however, whether or not adjustment is applied, a potential for residual confounding will remain. Patients' genetic background, ethnicity, lifestyle factors such as diet, levels of physical activity, obesity, use of alcohol and smoking status, levels of over- and under-nutrition, birth weight, social status, level of education, place of residence and medical aid scheme choice were missing from the database - hence they cannot be controlled for.
Discussions/ Conclusions	Theoretical basis	Was a theory provided for the findings and have they ruled out other plausible alternative explanations for the findings?	Refer to chapter 4.
	Practical vs. statistical significance:	Have the statistical findings been interpreted in terms of their clinical or economic relevance?	Practical significance was assessed. Refer to paragraph 3.7.7.
	Generalisability	Have populations and settings to which the results can be generalised, been discussed?	Refer to paragraphs 3.3 and 3.4.

3.10 ETHICAL CONSIDERATIONS

Permission to conduct the study was obtained from the board of directors of the PBM, as well as the Ethical Committee of the North-West University (NWU-00005-07-A5) (refer to Annexure B, Annex B.6).

Data privacy and confidentiality were maintained at all times. Therefore, no patient or medical scheme/administrator could be traced and it was also not possible to determine which prescribers or providers (i.e. name of the prescriber/provider) were involved in the prescribing/dispensing of the medicine items. The PBM providing the data for the study is furthermore nowhere identified in the thesis. The researcher, study promoter and co-promoter further signed confidentiality agreements.

Funding for conducting the study was obtained from MUSA (Medicine Usage in South Africa, the research niche area from the Faculty of Health Sciences, North-West University) and the Medical Research Council (MRC). The research was therefore not sponsored by the private pharmaceutical sector or the PBM providing the data, minimising the potential for any bias in the study. Views expressed in this study are those of the researcher and do not necessarily reflect the official policy or position of the MRC or MUSA.

3.11 CHAPTER SUMMARY

In this chapter the research methodology followed during the empirical investigation phase of the study was outlined, which included the research method, study design, the data source and composition of the study population, the study variables and measures, and the procedure for analysis of data. Lastly, the application of the statistical tests and measures were described followed by a discussion of the validity and reliability of the data and the handling of ethical considerations.

This study is described as a descriptive-exploratory, retrospective drug utilisation review which makes use of quantitative information to research the prevalence and the cost of treatment associated with the metabolic syndrome and its components in the private health care sector of South Africa. The following chapter will focus on the results obtained in the empirical investigation.

CHAPTER 4

Results and Discussion

This chapter provides the results and discussion of the empirical investigation phase of the study consisting of a quantitative drug utilisation review, described in Chapter 3. The results of this review are presented in three main parts. The first part details the results of an analysis of the datasets (from 2005, 2006, 2007 and 2008, respectively), the second part details the results of an analysis concerning patients “at risk” for the development of metabolic syndrome, whereas the third details the results of an analysis regarding metabolic syndrome patients. The data will be reported by averages of frequency and descriptive tables. Graphs will also be used where applicable to illustrate findings.

4.1 ANNOTATIONS CONCERNING THE DATA ANALYSIS/RESULTS

The following notes and definitions pertain to the data analysis and/or reporting of results in this chapter through to Chapter 5:

- The term “database” refers to all medicine claims data from the respective study periods (i.e. 2005, 2006, 2007 or 2008) as supplied by the Pharmaceutical Benefit Management (PBM) (refer to paragraph 3.3, Table 3.1). “Datasets” then refers to the individual sets of data for 2005, 2006, 2007 and 2008, respectively obtained after the application of exclusion criteria (refer to Table 3.2). “Data subsets” refers to the collective name for individual subsets of data for 2005, 2006, 2007 and 2008, respectively obtained after the application of inclusion criteria (refer to Table 3.3). Patients from the data subset were categorised into 6 “at risk” categories and a “metabolic syndrome” category (refer to Table 3.4).
- “At risk” patients are those patients on the medicine claims database with a claim for at least one medicine item(s) per year from one or more of the pharmacological drug classes of antihypertensives (including diuretics) (based on the MIMS® classification 7.3 and 16.1), hipolipidaemics (MIMS® classification 7.7) and antidiabetics (MIMS® classification system for medicines 19.1) (but not concurrently from all three pharmacological drug classes). As such, there were 6 “at risk” categories (refer to Table 3.4).
- “Patients receiving ‘only’ antidiabetics”, imply that patients received antidiabetics in the absence of medicine items from the two other medication classes, i.e. antihypertensives

and hipolipidaemic agents. The corresponding is true for “patients receiving ‘only’ antihypertensives” and “patients receiving ‘only’ hipolipidaemic agents”.

- “Metabolic syndrome” is defined as *“An individual on the medicine claims database with a claim for at least one medicine item(s) per year from each of the pharmacological drug classes of antihypertensives (including diuretics) (based on the MIMS® classification 7.3 and 16.1), hipolipidaemics (MIMS® classification 7.7) and antidiabetics (MIMS® classification 19.1)”*.
- The terms “prescribed” and “dispensed” are used interchangeably when referring to “claims for medicine items” or “claims for prescriptions” as recorded on the datasets/data subsets/categories. This was done due to a lack of captured primary prescription data on the different datasets/subsets. For example, a specific medicine item dispensed by the provider may not necessarily be that originally prescribed due to generic substitution, availability, patient’s medical aid scheme benefits and/or patient choice.
- Within the context of this study, “beneficiaries” are principal members and their dependants registered as members of medical aid schemes in South Africa in terms of the Medical Schemes Act (Act 131/1998) for the period Jan. 1, 2005 to Dec. 31, 2008 (without any reference to utilisation of health care services). A “patient” is then regarded a person whom has received a prescription/medicine item, recorded as a “claim” on the medicine claims database.
- The prescribing index is defined as *“a list of 20 most commonly prescribed medications for patients from the metabolic syndrome category, based on prescribing volume and/or direct medicine item cost”*.
- “Treatment regimens” are defined as *“the active ingredients claimed simultaneously per prescription during a specific study period”*, whereas a “treatment regimen groups” are defined as *“the number of active ingredients claimed simultaneously per prescription during a specific study period”*.
- For the purpose of this study, “chronic diseases” are defined as *“the specific Chronic Disease List (CDL) condition(s) identified per patient from the metabolic syndrome category for the period January 1, 2008 to December 31, 2008”*. The Chronic Disease Count is defined as the *“number of Chronic Disease List conditions identified based on ICD-10 codes per patient”*.
- Average prevalent age is defined as the average age of the patient on the date of treatment.
- Average pill-burden is defined as the average number of tablets received per patient, per year, divided by the number of prescriptions claimed over the study period.
- Percentages in the data have been rounded to the nearest decimal; the cumulative sum will therefore not necessarily add up to 100%.
- The cost of medicine is limited to direct medicine treatment costs and does not include

expenses such as medical accessories or other treatment costs.

- The cost of medicine items only regards the final price of the product (i.e. the sum of the dispensing fee and single exit price of a product). Each year of study was analysed independently. The influence of possible inflation factors was not taken into consideration during evaluation of the change in cost over the study period.

4.2 OUTLINE FOR THE PRESENTATION OF RESULTS

Figure 4.1 portrays the composition of the datasets, data subsets and study population, and depicts the order in which the results of the empirical investigation phase will be presented.

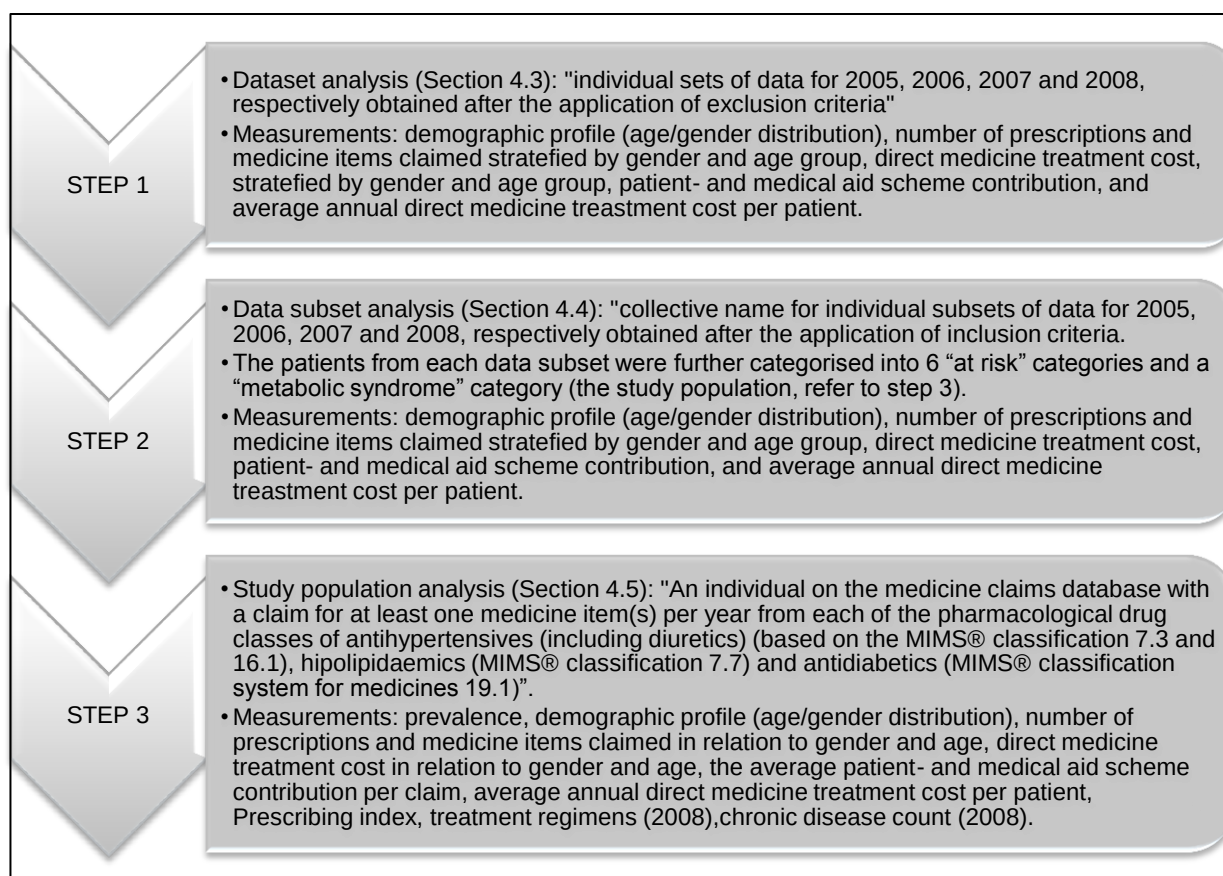


Figure 4.1: Flow diagram illustrating the order in which the results are presented

The first section of the results (i.e. Section 4.3) provides a general overview of the different datasets. These datasets, obtained after the application of exclusion criteria (refer to paragraph 3.4.2), comprise medicine claims data from four study periods (i.e. 2005, 2006, 2007 and 2008, respectively). The discussion in Section 4.3 focuses on the prevalence and demographic profile of patients from the datasets in comparison with the total number of beneficiaries covered by medical aid schemes registered in terms of the Medical Schemes Act, (Act 131/1998), in South Africa from 2005 to 2008. Utilisation trends for prescriptions and medicine items claimed per

dataset, in relation to gender and age, with age being split into 6 sub-groups (refer to paragraph 3.5.1), as well as the direct medicine treatment cost corresponding therewith will be established. The following statistics will be used in the presentation of the results and findings in this section, i.e.: frequencies, percentages, ratios, averages, standard deviations (SDs), medians and *d*-values (refer to Table 3.5).

Section 4.4 focuses on the different data subsets. The data subsets consist of all patients on the medicine claims database with at least one prescription for an antihypertensive [(MIMS® classification 7.3.1-7.3.10, and 16.1.3 (diuretics)], hipolipidaemic (MIMS® classification 7.7.1-3) and/or antidiabetic (MIMS® classification 19.1.1-2) during the period January 1, 2005 to December 31, 2008. The data subsets were obtained after the application of inclusion criteria (refer to paragraph 3.4.2). The discussion in this section focuses on the prevalence and demographic profile of patients from the data subset in comparison with the total number of patients from the datasets, general utilisation trends for prescriptions and medicine items claimed per dataset, as well as the direct medicine treatment cost corresponding therewith (with reference to the contributions made by the medical aid scheme vs. the patient co-payment). The following statistics will be used in the presentation of the results and findings in this section: i.e.: frequencies, percentages, averages, standard deviations (SDs), medians and *d*-values (refer to Table 3.5).

The patients from the respective data subsets were furthermore categorised into 6 “at risk” categories (i.e. a group with patients receiving only antidiabetics, those that received only antihypertensives, those that received only hipolipidaemic agents, those that received antidiabetics and antihypertensives, those that received antidiabetics and hipolipidaemic agents and those that received antihypertensives and hipolipidaemic agents concurrently) and a “metabolic syndrome” category as depicted in Table 3.4 (refer also to paragraph 3.4.1 and 3.4.2). For each of the 6 “at risk” categories, an overview of the prevalence and demographic profile of patients were provided, along with general utilisation trends for prescriptions and medicine items claimed in relation to age and gender, as well as the direct medicine treatment cost corresponding therewith. Statistics used in the presentation of these results and findings included frequencies, percentages, ratios, averages, standard deviations, medians, ranges and *d*-values (refer to Table 3.5).

Section 4.5 entails the analysis of the study population (i.e. patients categorised as metabolic syndrome) (refer to paragraph 3.4.1 and 3.4.2). The discussion in this section focuses on the prevalence and demographic profile of patients, general utilisation trends for prescriptions and medicine items claimed per study period in relation to age and gender, as well as the specific medicine items prescribed, and the direct medicine treatment cost corresponding therewith (with

reference to the contributions made by the medical aid scheme vs. the patient co-payment). The 20 foremost medicine items claimed (a prescribing index based on prescribing volume and cost) over the study period were determined. Treatment regimens prescribed for the treatment of patients (and associated direct treatment cost) during 2008 were calculated. Finally, a chronic disease count (based on the specified 27-Chronic Disease List conditions, refer to Table B.3, Annexure B) per metabolic syndrome patient from 2008 was determined (refer to Table 3.5).

4.3 GENERAL OVERVIEW OF THE DATASETS

This section entails an overview of the respective datasets obtained from the central database of the PBM from the period January 1, 2005 to December 31, 2008 (Figure 4.1, Step 1), based on the following specific objectives set for analysis:

- Review the prevalence and demographic profile of patients on the respective datasets.
- Review claims patterns (prescriptions and medicine items) for patients from the datasets, stratified by age and gender.
- Review cost associated with prescriptions and medicine claims claimed for patients from the datasets, stratified by age and gender.

The discussions in this section are based on the frequency values in Table 4.1; this includes a demographic overview of the total number of patients (paragraph 4.3.1) and the utilisation trends for prescriptions and medicine items claimed (paragraph 4.3.2), stratified by gender and age group (paragraphs 4.3.2.1-4.3.2.2). A discussion on the direct medicine treatment cost corresponding with these medicine items (in relation to study period, patients' age and gender) ensues in paragraph 4.3.3.

Table 4.1: General characteristics of the respective datasets (2005-2008)

	2005	2006	2007	2008
Total number of patients (n)	1 509 621	1 558 090	1 178 596	974 497
Female	842 386	868 891	654 348	538 254
Male	665 505	688 091	523 841	436 243
Unknown gender	1 730	1 108	407	0
Age group 1 (>0, ≤15 years)	301 254	299 627	230 310	162 675
Age group 2 (>15, ≤30 years)	262 236	274 825	215 778	169 124
Age group 3 (>30, ≤45 years)	392 727	403 309	283 524	223 077
Age group 4 (>45, ≤60 years)	330 605	351 478	270 911	249 185
Age group 5 (>60, ≤75 years)	157 443	162 882	123 688	118 947
Age group 6 (>75 years)	65 356	65 969	54 385	51 489
Total number of prescriptions (n)	8 391 836	8 906 344	7 911 072	6 775 863
Female	5 036 494	5 336 202	4 754 911	4 062 386
Male	3 348 219	3 565 328	3 154 343	2 713 477
Unknown gender	7 123	4 814	1 818	0

Table 4.1: General characteristics of the respective datasets (2005-2008) (*continued*)

	2005	2006	2007	2008
Age group 1 (>0, ≤15 years)	931 772	964 999	802 761	553 426
Age group 2 (>15, ≤30 years)	897 520	964 109	840 179	663 844
Age group 3 (>30, ≤45 years)	1 951 246	2 048 687	1 709 936	1 341 318
Age group 4 (>45, ≤60 years)	2 271 293	2 459 363	2 232 011	2 023 821
Age group 5 (>60, ≤75 years)	1 551 264	1 637 946	1 505 331	1 418 908
Age group 6 (>75 years)	788 741	831 240	820 854	774 546
Total number of medicine items (n)	19 500 774	21 113 422	19 075 724	16 439 253
Female	11 750 190	12 699 707	11 509 346	9 893 928
Male	7 734 461	8 403 158	7 562 466	6 545 325
Unknown gender	16 123	10 557	912	0
Age group 1 (>0, ≤15 years)	2 295 273	2 411 180	2 004 886	1 354 121
Age group 2 (>15, ≤30 years)	1 953 967	2 141 694	1 880 311	1 461 257
Age group 3 (>30, ≤45 years)	4 402 613	4 697 181	3 979 774	3 100 135
Age group 4 (>45, ≤60 years)	5 151 760	5 722 219	5 314 328	4 874 843
Age group 5 (>60, ≤75 years)	3 742 464	4 037 738	3 778 869	3 623 107
Age group 6 (>75 years)	1 954 697	2 103 410	2 117 556	2 025 790

4.3.1 Demographic overview of the datasets

Medicine claims data for approximately 1.5 million patients from both 2005 and 2006, 1.2 million in 2007 and 1 million in 2008 (Table 4.1) were included in the study. In 2005, these patients represented 22.1% of all beneficiaries covered by medical aid schemes registered in terms of the Medical Schemes Act, (Act 131/1998), in South Africa (N = 6 835 621) (CMS, 2006:47). A marginal decrease to 21.9% (N = 7 127 343) was observed in 2006 (CMS, 2007b:49), followed by a steep decline to 15.8% in 2007 (N = 7 478 040) (CMS, 2008:62) and 12.4% in 2008 (N = 7 874 826) (CMS, 2009:123). Table 4.1 therefore shows a ~10% decrease in percentage of patients that claimed for pharmaceutical benefits from 2005 to 2008 on the PBMs database. There may be various reasons for this decrease in market share over the study period as illustrated, *inter alia*; patients could have changed to medical aid schemes not administered by the PBM. Another possibility is that the number of medical aid schemes and beneficiaries administered by the PBM providing the data for the analysis may have decreased because of the decrease in the number of registered medical schemes in South Africa from 131 in 2005 to 119 in 2008 (CMS, 2006:49; CMS, 2008:123). This decrease, in turn, was caused by the conversion of bargaining councils into restricted schemes (2000 onwards) and the introduction of GEMS (Government Employees Medical Scheme) in 2006 (CMS, 2006:47; CMS, 2007b:62; CMS, 2009:123).

The demographic data showed that there were fewer male than female patients in the respective datasets (refer to Table 4.1), at a prevalence ratio of 1:1.3 for male vs. female. These trends reflect the demographic profile of beneficiaries covered by medical aid schemes

registered in South Africa in terms of the Medical Schemes Act (Act 131/1998) from 2005 to 2008 (CMS, 2006:48; CMS, 2007b:50; CMS, 2008:63; CMS, 2009:123). The percentage of males however shows a marginal but constant upward trend from 44.1% ($n = 1\,509\,621$) in 2005 to 44.8% ($n = 974\,497$) in 2008, whilst that of females correspondingly decreases from 55.8% ($n = 1\,509\,621$) to 55.2% ($n = 974\,497$) over the 4 years. Female patients were furthermore slightly older than their male counterparts, similar to all beneficiaries covered by medical aid schemes registered in South Africa from 2005 to 2008, at average (+SD) ages of:

- 37.9 ± 21.1 years for females and 35.8 ± 21.6 years for males in 2005 [vs. 32.8 years for all female and 31.4 years for all male beneficiaries in South Africa in 2005 (CMS, 2006:48)].
- 38.1 ± 20.9 years for females and 36.2 ± 21.5 years for males in 2006 [vs. 31.6 years for all female and 30.9 years for all male beneficiaries in South Africa in 2006 (CMS, 2007b:50)].
- 38.3 ± 21.3 years for females and 36.1 ± 21.6 years for males in 2007 [vs. 32.1 years for all female and 30.7 years for all male beneficiaries in South Africa in 2007 (CMS, 2008:63)].
- 40.5 ± 21.3 years for females and 38.5 ± 21.5 years for males in 2008 [vs. 32.1 years for all female and 30.9 years for all male beneficiaries in South Africa in 2008 (CMS, 2009:125)].

Figure 4.2 shows the distribution of the percentage of patients from the respective datasets by age group [Figure 4.2(a)] and over the 4-year study period [Figure 4.2(b)].

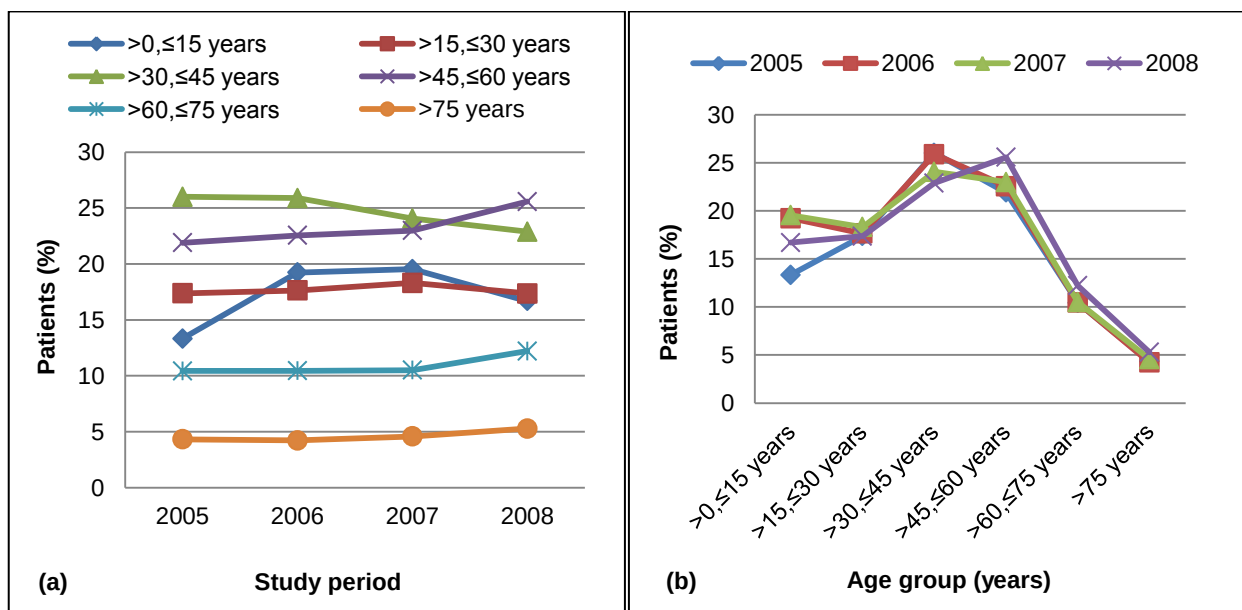


Figure 4.2: Distribution of patients from the datasets in relation to study period and age group (years) (2005-2008)

Based on Figure 4.2(a) the percentage patients aged 0-15 years, 46-60 years, 61-75 years and those older than 75 years, increased by 3.4%, 3.7%, 1.8% and 1.0%, respectively from 2005 to 2008, whilst those aged 31-45 years decreased by 3.1%. The percentage patients aged 16-30 years remained relatively constant over the 4 year period, at approximately 18% of the number of patients from each of the respective datasets. The largest percentage of patients from the datasets over all 4 study periods was in age groups 3 and 4, i.e. adult patients 31-45 years [22.9% (2005) - 26.0% (2008)] and those 46-60 years of age [21.9% (2005) - 25.6% (2008)] [Figure 4.2(b)]. Patients older than 60 years represented approximately 15% to 18% of all patients in 2005 ($n = 1\,509\,621$) and 2008 ($n = 974\,497$), respectively.

4.3.2 General prescribing patterns pertaining to the datasets

Approximately 8.4 million prescriptions were claimed in 2005, increasing by 6.1% to 8.9 million in 2006. An 11.2% decline from 2006 to 7.9 million in 2007 was observed, followed by a further 14.4% decline from 2007 to 6.8 million prescriptions in 2008, resulting in a relative decrease of 19% over the study period. The number of medicine items likewise decreased by 18% from 19.5 million in 2005 to 16 million in 2008, after an initial 7% increase to 21 million in 2006 (refer to Table 4.1).

A median of three prescriptions was claimed per patient during 2005 (average per patient prescription claim rate: 5.6 ± 6.75) and 2006 (average 5.7 ± 6.96), compared with four during 2007 (average 6.7 ± 7.55) and 2008 (average 7.0 ± 7.85). A median of two medicine items was claimed per prescription over the 4 year study period (average 2.3 ± 1.52 in 2005, 2.4 ± 1.55 in 2006, 2.4 ± 1.59 in 2007 and 2.4 ± 1.64 in 2008). Table 4.2 shows the effect sizes calculated for the difference in the average number of prescriptions and medicine items claimed per study period.

Table 4.2: Effect sizes: average number of prescriptions and medicine items claimed in the respective datasets (2005-2008)

	Average number of prescriptions claimed			Average number of medicine items claimed		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.02	-	-	0.03	-	-
2007	0.15	0.13	-	0.06	0	-
2008	0.18	0.16	0.03	0.07	0	0

Table 4.2 shows small effect sizes ($0 \geq d \leq 0.18$), indicating that there were no practically significant differences between the respective study periods with regard to the average number of prescriptions claimed yearly per patient, or the number of medicine items claimed annually per

prescription.

4.3.2.1 Average number of prescriptions and medicine items, in relation to gender

The majority of claims (prescriptions and medicine items) on the datasets over the four year period were for female patients, at approximately 60% compared with the 40% of males (refer to Table 4.1). This is in accordance with the larger percentage of females on the respective datasets.

Prescription claim rates per patient are normally higher for females than for males (Achat *et al.*, 2010:135; Daban *et al.*, 2010). According to Verbrugge (1982:420), sex differentials and attitudes about symptoms, medical care, medicines and self-care are responsible for this higher claim rate among females in developed countries; for example, women are more frequently ill than men, but with relatively milder problems. These frequent symptoms lead to activity that is more restricted and subsequently to more physician and dentist visits and medication use by women. By contrast, men feel ill less often, but their illnesses and injuries are more serious, leading to more permanent limitations and hospitalisation. Males may also be socialised to ignore physical discomforts; thus, they are unaware of symptoms that females feel ardently. In addition, men may be less willing and able to seek medical care for perceived symptoms - when diagnosis and treatment are finally obtained; men's conditions are probably more advanced and less amenable to control. In developing countries, however, women tend to underutilise health services because of various reasons, for example, services factors (e.g. accessibility, affordability and appropriateness including friendliness of the health infrastructure for meeting women's needs), user factors (e.g. social constraints, marital status, family roles and work conditions) and institutional factors (e.g. men's decision-making power and control of health budgets and facilities) (Buvinić *et al.*, 2006:197).

In accordance with general prescribing patterns found in developed countries (and subsequent contrast to the findings by Buvinić and co-workers), the demographic data from this empirical investigation indicates that the average number of prescriptions claimed per patient was marginally higher for females than for males over the study period, at an average claim rate of 6.0 ± 7.16 for females in 2005 (males 5.0 ± 6.15), 6.1 ± 7.37 in 2006 (males 5.2 ± 6.35), 7.3 ± 7.99 in 2007 (males 6.0 ± 6.90) and 7.6 ± 8.32 in 2008 (males 6.2 ± 7.15). (A median of three prescriptions per female patient was claimed from 2005-2006 and a median of four from 2007-2008 vs. a median of three claimed for males over the 4-year study). This utilisation trend can possibly be explained by the nature of beneficiaries and dependants covered by medical aid schemes registered in terms of the Medical Schemes Act, (Act 131/1998), in South Africa. The majority of beneficiaries registered are female (CMS, 2006:48; CMS, 2007b:49; CMS, 2008:62;

CMS, 2009:123). Furthermore, the typical medical aid scheme member in South Africa represents more or less individuals from a relative higher income bracket living in “first world” conditions (The World Bank, 2009); third world conditions (i.e. that typically found in developing countries as described by Buvinić and colleagues) do not necessarily apply.

An equal number of medicine items (median two) was claimed per prescription for both gender groups, at an average of 2.3 ± 1.54 items for females in 2005 (males 2.3 ± 1.47), 2.4 ± 1.58 in 2006 (males 2.4 ± 1.50), 2.4 ± 1.62 in 2007 (males 2.4 ± 1.55) and 2.4 ± 1.67 in 2008 (males 2.4 ± 1.59). Table 4.3 shows the calculated *d*-values for the differences between the average number of prescriptions and medicine items claimed by gender group, over the study period.

Table 4.3: Effect sizes: average number of prescriptions and medicine items claimed by gender (2005-2008)

	Average number of prescriptions claimed (Females)			Average number of medicine items claimed per prescription (Females)		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.01	-	-	0.06	-	-
2007	0.16	0.15	-	0.06	0	-
2008	0.19	0.18	0.04	0.06	0	0
	Average number of prescriptions claimed (Males)			Average number of medicine items claimed per prescription (Males)		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.03	-	-	0.07	-	-
2007	0.14	0.12	-	0.06	0	-
2008	0.17	0.14	0.03	0.06	0	0

Despite the difference in the average number of prescriptions claimed between male and female patients, calculated *d*-values (Table 4.3) show small effect sizes (Cohen’s $d < 0.19$), indicating no practically significant differences between patients (both sexes) from the respective study periods with regard to the average number of prescriptions claimed yearly per patient. The *d*-values calculated for the difference in the number of medicine items claimed yearly between males and females per prescription were zero.

4.3.2.2 Average number of prescriptions and medicine items, in relation to age

The distribution of the percentage prescriptions and medicine items claimed for the different age groups from the respective datasets is depicted in Figure 4.3.

Figure 4.3 shows that in accordance with the higher number of patients in age groups 3 and 4 [refer to Figure 4.2(b)], the majority of prescriptions and medicine items claimed on the

respective datasets were for patients aged 31-60 years and to a lesser degree for patients aged 61-75 years. The lowest percentage of prescription and medicine item claims was for children aged ≤ 15 years, young adults (16-30 years) and those older than 75 years.

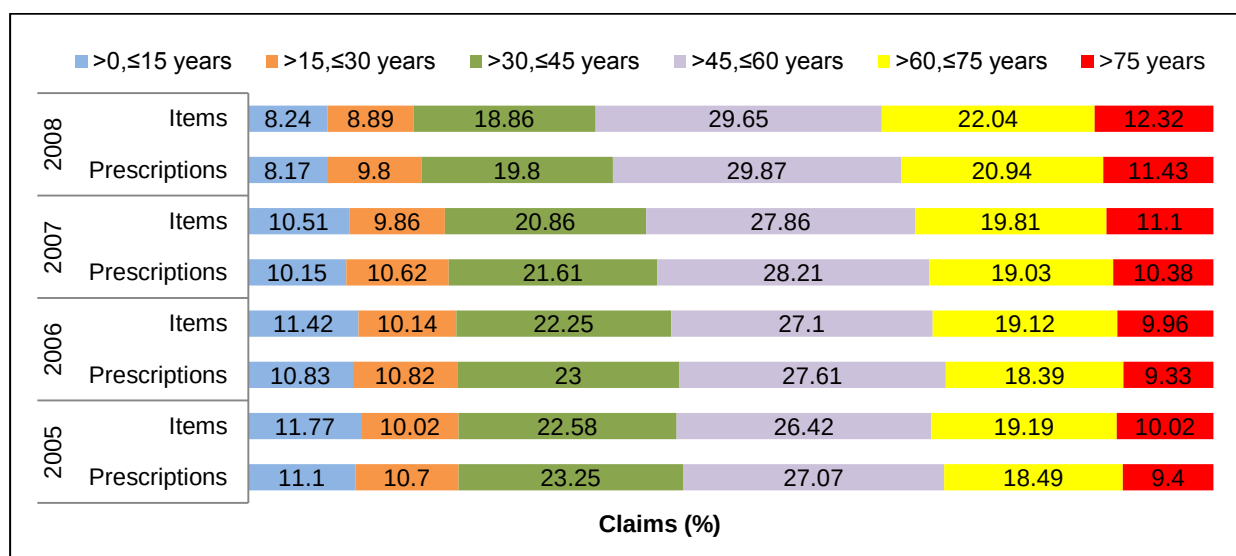


Figure 4.3: Distribution of the percentage prescriptions and medicine items claimed (%) by study period and age group (years) (2005-2008)

With regard to the percentage prescriptions and medicine items claimed per prescription by age group, the following utilisation trends were observed:

- Children and pre-adolescents up to the age of 15 years (age group 1): a median of two prescriptions per year (containing a median of 2 items per prescription) was claimed annually. An average number of prescriptions claimed per patient per year: 3.1 ± 3.14 in 2005, 3.2 ± 3.27 in 2006, 3.5 ± 3.50 in 2007 and 3.4 ± 3.52 in 2008. An average of 2.5 ± 1.35 medicine items was claimed per prescription in 2005, compared with 2.5 ± 1.38 in 2006, 2.5 ± 1.39 in 2007 and 2.5 ± 1.39 in 2008.
- Adolescents, late adolescents and young adults 16-30 years (age group 2): similar to age group one, a median of two prescriptions was claimed per patient per year. The average number of prescriptions claimed per patient per year slightly increased from age group 1 to 3.4 ± 3.87 in patients aged 16-30 years in 2005, compared with 3.5 ± 3.99 in 2006, 3.9 ± 4.25 in 2007 and 3.9 ± 4.39 in 2008. A median of two medicine items was also claimed per prescription over the study period at an average 2.2 ± 1.32 in 2005, compared with 2.3 ± 1.35 in 2006, 2.3 ± 1.36 in 2007 and 2.2 ± 1.36 in 2008. This was a slight decrease compared with patients from age group 1.
- Young adults aged 31-45 years (age group 3): These patients received almost double the number of prescriptions per patients as compared with those aged 16-30 years, at an average of 5.0 ± 5.55 (median 3) per patient in 2005, compared with 5.1 ± 5.75 (median 3) in 2006, 6.0 ± 6.27 (median 4) in 2007 and 6.0 ± 6.38 (median 4) in 2008. Similar to

patients from age group 2, a median of two medicine items was claimed per prescription over the 4 year study period (average 2.3 ± 1.40 items per prescription in 2005, compared with 2.3 ± 1.42 in 2006, 2.4 ± 1.45 in 2007 and 2.4 ± 1.45 in 2008).

- Middle adulthood patients 46-60 years (age group 4): the average number of prescriptions claimed per patient per year in 2005 was 6.9 ± 7.50 (median 4), compared with 7.0 ± 7.64 (median 4) in 2006, 8.2 ± 8.07 (median 5) in 2007 and 8.1 ± 8.07 (median 5) in 2008. Again, a median of two medicine items was claimed per prescription over the 4 year study period; an average of 2.3 ± 1.5 items per prescription in 2005, compared with 2.4 ± 1.55 in 2006, 2.4 ± 1.59 in 2007 and 2.4 ± 1.62 in 2008.
- Elderly adults 61-75 year (age group 5): The average number of prescriptions claimed per patient per year increased almost one and a half times from patients aged 46-60 years, at 9.9 ± 9.45 in 2005, compared with 10.1 ± 9.75 in 2006, 12.1 ± 9.97 in 2007 and 11.9 ± 10.03 in 2008. A median of two medicine items was claimed per prescription over the 4 year study period; an average of 2.4 ± 1.76 items per prescription in 2005, compared with 2.5 ± 1.80 in 2006, 2.5 ± 1.84 in 2007 and 2.6 ± 1.88 in 2008.
- The average number of prescriptions claimed per patient per year in 2005 for mature patients >75 years (age group 6) was 12.1 ± 10.84 , compared with 12.6 ± 11.25 in 2006, 15.1 ± 11.32 in 2007 and 15.0 ± 11.64 in 2008. The average number of prescriptions claimed was therefore 4-5 times more than those received for children and pre-adolescents, to 1.3 times that received by patients aged 61-75 years. Similar to patients from age groups 1 to 5, a median of two medicine items was claimed per prescription over the 4 year study period; an average of 2.5 ± 1.87 items per prescription in 2005, compared with 2.5 ± 1.91 in 2006, 2.6 ± 1.95 in 2007 and 2.6 ± 1.99 in 2008.

Older people generally carry a higher disease/illness burden for which medications are indicated (Cobbs *et al.*, 2002:40; Hilmer *et al.*, 2007:786) and are subsequently utilising health care services at greater rates (Nie *et al.*, 2008:1044). For example, Wolff and co-workers (2002:2275) suggested that approximately 32% of the population in the age group 65-69 years suffered from three or more chronic conditions, whereas in the age group 80-84 years, the prevalence of multimorbidity increased to 52%. In addition, older adults were more likely to have multiple prescribers and multiple health care transitions (e.g. admissions, discharges and changes in pharmacy and formularies) than younger people (Molony, 2009:70) that could aggravate the risk of polypharmacy, as was shown by Wilson *et al.* (2007:10). In their study, Wilson and colleagues showed that 40% of older adults took five or more prescription medications a day. Vegda and co-workers (2009) further showed that patients older than 65 years had *inter alia*:

- An average of 4.4 physician service visits per person per year. Patients 85 years and older made 46% more visits than patients aged 65-69 years. Women made 11% more visits than men.

- An average specialist visits rate of 2.4 visits per year, with the highest rates of utilisation occurring in the 75-84 year age groups. Men made 17% more visits than women.
- An average of 7.7 chronic health conditions per patient. Patients 85 years and older had 37% more chronic health conditions than patients aged 65-69 years (6.5 ± 3.7). Women had 6% more chronic health conditions than men.
- An average of 8.2 prescriptions and non-prescription medications over a two year study period. Patients 85 years and older had 37% more different medications recorded in their charts than patients aged 65-69 years (6.9 ± 4.6). Women used an 8% greater number of medications than men.

Table C.1 (Annexure C) details effect sizes calculated for the per patient prescription claim rate and per prescription medicine item claim rate over the 4-year period. Table C.1 shows very small effect sizes for patients up to the age of 60 years ($d \leq 0.2$) and effect sizes approaching a medium level (i.e. $d = \sim 0.3$) in those older than 60 years. Based on a cut-off point of 0.8, however, these d -values indicate that the increase in the average number of prescriptions and medicine items claimed per prescription over the 4-year period was of no practical significance.

Tables C.2 and C.3 (Annexure C) show the calculated effect sizes between the different age groups with regard to the average number of prescriptions claimed and items prescribed. In accordance to general utilisation trends for the elderly, the average yearly prescription claim rate per patient for mature patients older than 75 years was relatively large (and practically significantly higher based on Cohen's d -value than that of patients in age groups one and two (patients up to the age of 30 years) (refer to Table C.2, Annexure C). This was a consistent finding in all four study periods.

4.3.3 Direct medicine treatment cost pertaining to the datasets

Only direct medicine cost was considered in this study. The cumulative drug cost per patient was determined by summing the medical scheme contribution and the patient co-payment levied per medicine item for all prescription fills/claims during the study.

Table 4.4 provides a breakdown of these costs (values are frequencies). This table is discussed in subsequent paragraphs. The total direct cost of medicine items and/or prescriptions claimed in 2005 summed to R1.82 billion, increased to R1.96 billion in 2006, and was followed by a decline to R1.92 billion in 2007 and R1.79 billion in 2008 (Table 4.4). These costs represented approximately 25% of benefits paid for medicines dispensed by pharmacists and providers other than hospitals in the private health care industry in South Africa during 2005 ($N = R7.2$ billion) (CMS, 2006:49), decreasing to 23% ($N = R8.7$ billion) of benefits paid in 2006 (CMS, 2007b:51),

20% (N = R9.4 billion) in 2007 (CMS, 2008:64) and 16% (N = R11.2 billion) in 2008 (CMS, 2009:126). This decrease in direct treatment associated costs may be ascribed to the decrease in percentage medicine items claimed over the study period (refer to paragraph 4.3.2).

Table 4.4: Direct medicine treatment cost corresponding with the respective datasets (2005-2008)

	2005	2006	2007	2008
Medicine treatment cost (R)	1 819 865 251.64	1 959 738 734.13	1 918 284 176.64	1 785 871 013.83
Patient co-payments	217 417 602.22	261 028 782.73	303 277 143.74	307 322 784.93
Scheme contribution	1 602 447 649.42	1 698 709 951.40	1 615 007 032.90	1 478 548 228.90
Female	1 084 626 865.30	1 162 254 536.33	1 138 188 990.84	1 057 274 453.61
Male	733 769 633.85	796 360 401.04	779 508 488.81	728 596 560.22
Unknown gender	1 468 752.49	1 123 796.76	586 696.99	0.00
Age group 1 (>0, ≤15 years)	134 261 603.65	140 528 793.96	122 858 761.13	91 420 354.23
Age group 2 (>15, ≤30 years)	151 141 512.45	161 554 194.74	148 763 475.15	126 928 585.34
Age group 3 (>30, ≤45 years)	349 293 642.75	368 624 262.33	336 835 406.42	285 144 460.78
Age group 4 (>45, ≤60 years)	510 810 642.22	560 546 255.53	555 671 549.32	538 362 081.83
Age group 5 (>60, ≤75 years)	444 749 542.72	483 378 456.81	488 758 797.41	483 850 628.91
Age group 6 (>75 years)	229 608 307.85	245 106 770.76	265 396 187.21	260 164 902.74

Private insurers/medical aid schemes contributed 88.1% (n = R1 819 865 251.64) towards the direct medicine treatment cost of patients in 2005, decreasing to 86.7% (n = R1 959 738 734.13) during 2006, 84.2% (n = R1 918 284 176.70) in 2007 and 82.8% (n = R1 785 871 013.83) in 2008 - a relative decrease of approximately 6% over the study period. Patients therefore paid an excess 12.0% out-of-pocket for co-payments levied on medicine items in 2005 (n = R1 819 865 251.64), compared with 13.3% (n = R1 959 738 734.13) in 2006, 15.8% in 2007 (n = R1 918 284 176.70) and 17.2% (n = R1 959 738 734.13) in 2008. This translates to an average patient co-payment of R11.15 ± 42.24 (median R0.00) per item per year for 2005, compared with R29.31 ± 88.47 (median R0.03) during 2006, R38.34 ± 171.45 (median R7.87) in 2007 and R45.36 ± 181.31 (median R11.79) (n = R1 785 871 013.83) in 2008. Although the average co-payments increased by nearly 307% from 2005 to 2008, *d*-values calculated for this period approached a small level ($0.01 \leq d \leq 0.21$), indicating no practical significance in this difference (Table 4.5).

Table 4.5: Effect sizes: average yearly medical aid scheme and patient contribution per medicine item claimed from the respective datasets (2005-2008)

	Average scheme contribution			Average patient co-payment		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.01	-	-	0.21	-	-
2007	0.01	0.01	-	0.16	0.05	-
2008	0.02	0.02	0.01	0.19	0.09	0.04

It should however be noted that the largest difference in the average patient co-payment emerge from 2005 to 2006, where after the differences seem to level out. A possible reason for this trend may be the changes to the pricing structure and control that was implemented by the South African Department of Health in 2004 (Department of Health, 2004). Interestingly, there were no practically significant differences in the average contribution paid by medical aid schemes towards medicine items claims per prescriptions over the 4-year period. Cohen's d ($d \leq 0.02$) was much smaller than that measured in the average patient co-payment ($d \leq 0.21$) over the 4-year study period – implying that the excess costs were absorbed by patients.

The average annual direct cost of medicine treatment for a patient from the 2005-dataset summed to R1 205.51 $\pm$ 3 044.30 (median R333.13), increasing to R1 257.78 $\pm$ 3 512.29 (median R316.46) in 2006, R1 627.60 $\pm$ 5 082.02 (median R415.45) in 2007 and R1 832.61 $\pm$ 6 668.66 (median R432.23) in 2008 – a relative increase in total annual patient cost of 52.0% over the 4-year study period. Median costs increased by approximately 30% from 2005 to 2008.

4.3.3.1 Average cost per prescription and medicine item

The average cost per prescription increased marginally from R216.86 $\pm$ 342.30 (median R135.40) in 2005, to R220.04 $\pm$ 395.22 (median R133.74) in 2006. A steep increase of 10.2% to R242.48 $\pm$ 600.31 (median R143.64) was observed in 2007, followed by a further 9.0% increase to R263.56 $\pm$ 789.01 (median R151.56) in 2008.

The average cost per medicine item initially decreased from R93.32 $\pm$ 166.36 (median R52.57) in 2005 to R92.82 $\pm$ 196.42 (median R51.22) in 2006, followed by an 8.3% increase to R100.56 $\pm$ 324.11 (median R54.54) in 2007. Between 2007 and 2008, the average cost per medicine item increased a further 8.0% to R108.63 $\pm$ 436.75 (median R59.30). Although this cost increase was not investigated further, it appears much higher than the 4.3% change in the general inflation rate from 2007 to 2008 (Statistics South Africa, 2011).

The utilisation trends displayed with this distribution may also reflect the uncertainty in the pricing structure experienced by the private health care sector from 2004 to 2006. The effect of the changes in the average cost of medicine items and prescriptions claimed over the 4-year study period was, however, very small ($d \leq 0.06$) and thus of no practical significance (Table 4.6).

Table 4.6: Effect sizes: average cost per prescriptions and medicine items claimed from the respective datasets

	Average cost per prescription			Average cost per medicine item		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.01	-	-	0	-	-
2007	0.04	0.04	-	0.02	0.02	-
2008	0.06	0.06	0.03	0.04	0.04	0.02

4.3.3.2 Average cost per prescription and medicine item, in relation to gender

The total direct treatment cost associated with claimed medicine items was highest for female patients across the 4-year study period, at approximately 60% compared with the 40% of males (refer to Table 4.4). These statistics correlate with the higher percentage female patients from the respective study periods, as well as the larger percentage of prescriptions and medicine items claimed per prescription for this group.

Female patients are generally more likely to fill a prescription or use medicine compared with their male counterparts (Cylus, 2011:154; Daban *et al.*, 2010; Fernández-Liz *et al.*, 2008:415), albeit, at a lower average cost (Roe *et al.*, 2002:37). In agreement with these studies, findings from this empirical investigation show that although the median cost per medicine item per year was marginally higher for female patients, the average cost per medicine item claimed yearly per prescription was slightly lower compared with their male counterparts, for example:

- R92.31 ± 158.69 (median R53.96) for females vs. R94.87 ± 176.88 (median R51.22) for males in 2005 ($d = 0.01$).
- R91.52 ± 188.12 (median R52.26) for females vs. R94.77 ± 208.10 (median R49.73) for males in 2006 ($d = 0.02$).
- R98.89 ± 300.67 (median R55.73) for females vs. R103.08 ± 356.74 (median R52.85) for males in 2007 ($d = 0.01$).
- R106.86 ± 416.84 (median R60.86) for females vs. R111.32 ± 465.21 (median R57.56) for males in 2008 ($d = 0.01$).

Calculated d -values depicted in Table 4.7 and the preceding paragraph, show very small effect size levels and therefore no practical significance in differences between the average cost per medicine item claimed per year between males and females (and for females or males) over the 4-year study period.

Table 4.7: Effect sizes: average cost per medicine item claimed per patient by gender (2005-2008)

	Average cost per medicine item (Females)			Average cost per medicine item (Males)		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.00	-	-	0.00	-	-
2007	0.02	0.02	-	0.02	0.02	-
2008	0.02	0.04	0.02	0.04	0.04	0.02

4.3.3.3 Average cost per prescription and medicine item, in relation to age

Figure 4.4 illustrates the distribution of cost corresponding with medicine items claimed yearly per prescription in relation to age groups (as percentage) over the study period.

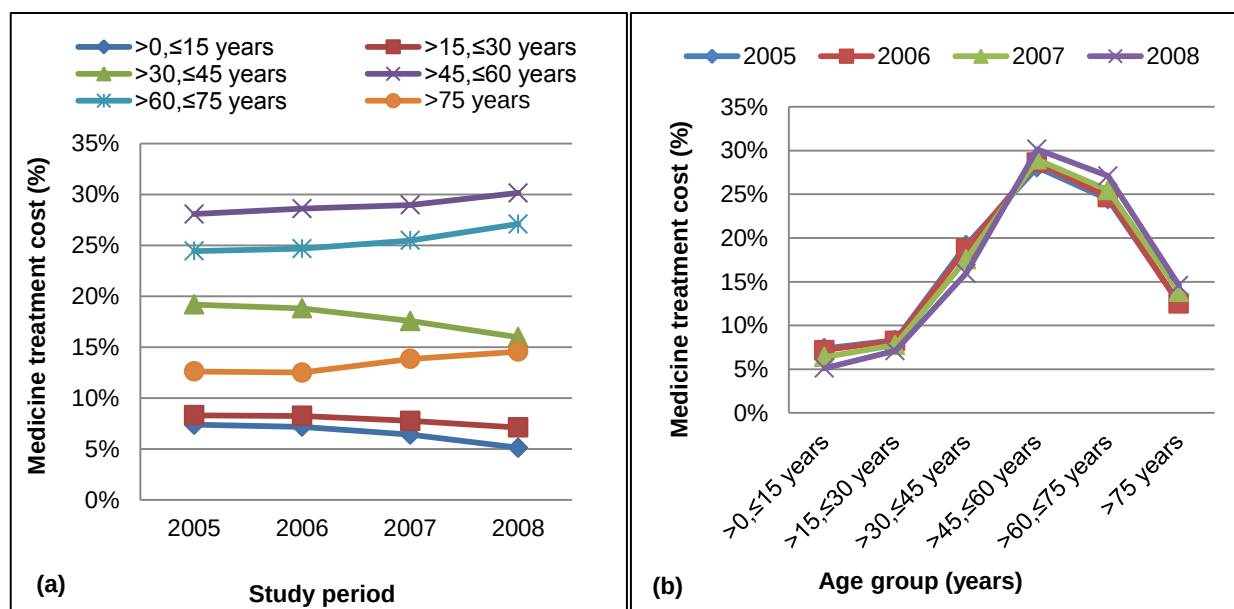


Figure 4.4: Distribution of direct medicine treatment cost (%) of medicine items by study period and age group (years) (2005-2008)

In agreement with the larger percentage medicine items claimed for patients aged 31-75 years (refer to paragraph 4.3.2.2), the total direct medicine treatment cost was highest for patients aged 46-60 years and 61-75 years and to a lesser degree, adult patients aged 31-45 years [Figure 4.4(b)]. Figure 4.4(a) also shows that the direct medicine treatment cost of items claimed for patients younger than and equal to 45 years, marginally decreased from 2005 to 2008, by 3.2%, 1.2% and 2.3%, respectively, whilst that of patients older than 45 years increased by 2.7%, 2.1% and 2.4%, respectively.

Elderly patients are generally more susceptible to all medical injuries, partly due to the aging process – causing not only deterioration in their health, but also an increase in cost required for

hospitalisation and medical interventions (Safilios-Rothschild, 2009:60). Based on “The State of Aging and Health in America 2007” report (CDC/Merck, 2007) a much higher proportion of the elderly than the non-elderly had expensive chronic conditions; the cost of caring for the elderly was therefore three to five times greater than the cost of caring for younger adults in American and OECD (Organization for Economic Cooperation and Development) countries. In this empirical investigation, the direct medicine treatment cost associated with patients ≥ 46 years of age was four times that associated with patients ≤ 30 years, whereas the direct medicine treatment cost associated with patients ≥ 61 years was approximately two and a half times that for patients ≤ 30 years (Table 4.4). The ratio of cost to prevalence percentage (Cost-Prevalence Index or CPI) (Serfontein, 1989:180) furthermore indicated that medicine items on the dataset claimed for patients up to the age of 45 years were relatively inexpensive (CPIs < 1), compared with items claimed for patients older than 45 years that were relatively expensive (refer to Tables 4.1 and 4.4).

Based on Table C.4 (Annexure C) effect sizes between the average cost per medicine item claimed were small (i.e. $d \leq 0.07$), thus indicating no practically significant increases in the average cost of medicine items over the 4-year study period. Table C.5 shows that the calculated effect sizes between the age groups with regard to the average cost of medicine items claimed approached a medium level of 0.3 in patients older than 60 years. This trend only emerged during 2005 and 2006. A flattening of the increase in average medicine item costs was observed in 2007 and 2008, with d -values below the level of 0.2. Based on Cohen’s guidelines for importance, these increases in average cost were practically insignificant.

4.3.4 Dataset summary

This section established a baseline of prescribing patterns for patients from the different datasets, and positioned the database used for analysis with regard to the South African private health care sector. Medicine claim patterns and associated direct medicine treatment costs were compared with general prescribing patterns as found in recent literature. The key findings of this analysis are summarised in paragraph 5.3.2 (Chapter 5) under the heading “conclusions derived from the empirical investigation”.

The following section focuses on reviewing the data subsets for 2005, 2006, 2007 and 2008, respectively obtained after the application of inclusion criteria (refer to Table 3.3).

4.4 GENERAL OVERVIEW OF THE DATA SUBSETS

The data subsets consisted of all patients on the medicine claims database receiving ≥ 1 medicine

item(s) at any given time during a specific study period (year) from any (but at least ≥ 1) of the following pharmacological medicine classes (based on the MIMS® classification): antidiabetics, antihypertensives (including diuretics) and hipolipidaemics, for the period of January, 1, 2005 through December, 31, 2008 (refer to Table 3.3). The patients from each data subset were further categorised into 6 “at risk” categories (depicted by Table 3.4) and a “metabolic syndrome” category (refer to Section 4.5).

The discussion in this section entails an overview of the respective data subsets from the period January 1, 2005 to December 31, 2008 (Figure 4.1, Step 2), based on the specific objectives set for analysis, namely to:

- Review the prevalence and demographic profile of patients considered “at risk” for the development of metabolic syndrome, stratified by age and gender.
- Review claims patterns (prescriptions and medicine items) for patients considered “at risk” for the metabolic syndrome, stratified by age and gender.
- Review the associated cost of medicine claims for patients considered “at risk” for the development of the metabolic syndrome, stratified by age and gender.

Table 4.8 details the basic demographic characteristics of the data subsets, as well as the total number of prescriptions and medicine items claimed and the total direct medicine treatment costs corresponding therewith.

Table 4.8: General characteristics of the respective data subsets (2005-2008)

	2005	2006	2007	2008
Number of patients (n)	261 036	269 452	226 264	214 109
Females	146 605	149 841	127 081	118 422
Males	114 282	119 491	99 163	95 687
Unknown gender	149	120	20	0
Age group 1 (>0, ≤15 years)	1 739	1 521	794	823
Age group 2 (>15, ≤30 years)	6 271	6 449	5 367	4 365
Age group 3 (>30, ≤45 years)	42 325	42 473	33 197	28 316
Age group 4 (>45, ≤60 years)	95 100	99 571	83 285	80 131
Age group 5 (>60, ≤75 years)	77 892	80 662	68 209	66 754
Age group 6 (>75 years)	37 709	38 776	35 412	33 720
Number of prescriptions (n)	1 911 296	2 081 849	1 943 498	1 848 474
Number of medicine items (n)	3 081 832	3 458 538	3 304 273	3 214 534
Medicine treatment cost (R)	394 586 482.52	432 361 357.98	424 665 162.64	400 155 046.30
Patient co-payments	41 945 356.26	50 868 153.54	55 325 366.53	64 806 715.26
Scheme contribution	352 641 126.26	381 493 204.44	369 339 796.11	335 348 331.04

The discussion in this section includes an overview of the total number of patients (paragraph 4.4.1) and the general utilisation trends for prescriptions and medicine items claimed (paragraph 4.4.2). A discussion on the total direct cost of medicine treatment associated with these patients

ensues in paragraph 4.4.3.

4.4.1 Demographic overview of the data subsets

The number of patients from the 2005 and 2006 data subsets represented 17.3% of all patients from the respective datasets of 2005 ($n = 1\,509\,621$) and 2006 ($n = 1\,558\,090$). A subsequent increase to 19.2% ($n = 1\,178\,596$) in 2007 and to 22.0% ($n = 974\,497$) in 2008 was observed (a relative increase of approximately 5% over the study period) (refer to Tables 4.1 and 4.8). About 56% of the patients from the total data subsets were female [56.2% ($n = 261\,036$) from 2005, vs. 55.6% ($n = 126\,022$) from 2006, 56.2% ($n = 226\,264$) from 2007 and 55.3% ($n = 214\,109$) from 2008], reflecting the demographic profile of patients from the respective datasets (refer to paragraph 4.3.1).

Men in general use chronic medication [in particular cardiovascular medications (with the exception of diuretics)] at an earlier stage than women (Roe *et al.*, 2002:33). In accordance to these findings by Roe and co-workers, male patients in the respective data subsets were marginally younger than their female counterparts (i.e. ~57-59 years for males vs. ~59-61 years for females). Based on Cohen *d*-values, these age differences were, however, very small and therefore practically insignificant (i.e. $d = 0.13$ for both 2005 and 2006, compared with 0.14 for both 2007 and 2008). Patients from the data subsets were furthermore, on average, approximately 20 years older than patients from the respective datasets (refer to paragraph 4.3.1), e.g.:

- 58.0 ± 15.20 years (median 57.83 years) vs. 36.4 ± 21.58 years for those from the dataset in 2005.
- 58.1 ± 15.03 years (median 57.83) vs. 36.9 ± 21.48 years for those from the dataset in 2006.
- 58.7 ± 15.0 years (median 58.35) vs. 36.8 ± 21.85 years for those from the dataset in 2007.
- 59.3 ± 14.72 years (median 58.81) vs. 39.0 ± 21.76 years for those from the dataset in 2008.

This finding was expected as the use of medications for chronic conditions in general increases with older age categories for both genders (Roe *et al.*, 2002:33), alongside the data subsets consisting of patients receiving medication mainly indicated for the treatment of chronic conditions, e.g. high blood pressure, high glucose levels and hyperlipidaemia. Accordingly, stratification by age [Figure 4.5(b)] shows the largest number of patients from the data subsets across all study periods in age groups 4 and 5, i.e. patients aged 46-75 years; representing 66.3% ($n = 261\,036$) for 2005, compared with 66.9% ($n = 269\,452$) in 2006, 67.0% ($n = 226\,264$)

in 2007 and 68.6% ($n = 214\ 109$) in 2008 – i.e. almost double the number of patients in the respective dataset-populations (refer to Figure 4.2).

Figure 4.5(a) furthermore shows that the number of patients in the data subsets remained relatively idem over the 4-year study period, with only minor decreases in the number of patients younger or equal to 45 years and marginal increases in those older than 45 years. The largest crude difference in prevalence (i.e. a decrease of 2.6%) emerged in patients aged 31-45 years – a trend that could be explained by the corresponding 3.1% decrease in the number of patients in this particular age group from the datasets over the 4-year period (refer to Figure 4.2).

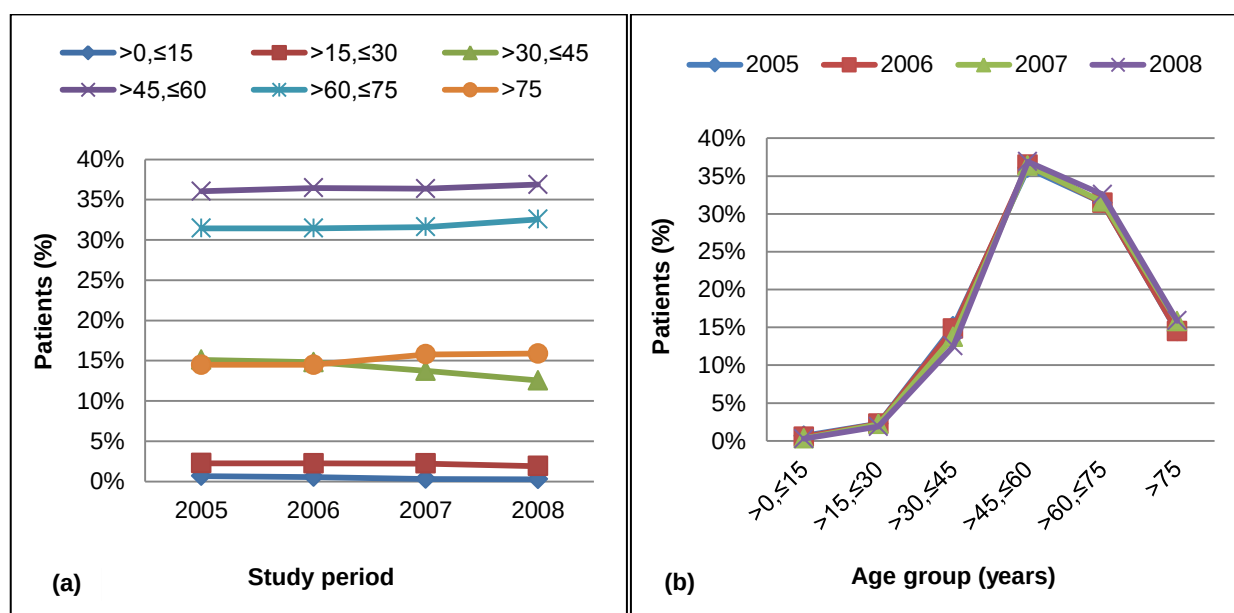


Figure 4.5: Distribution of patients from the data subsets in relation to study period and age group (years) (2005-2008)

4.4.2 General prescribing patterns pertaining to the data subsets

The 2005-data subset contained approximately 1.91 million prescriptions, increasing by 8.9% to about 2 million in 2006 (Table 4.8). A 6.7% decrease in this number was then observed to 1.94 million in 2007 and a further 5.0% decline to 1.84 million prescriptions in 2008 [a relative decrease of 3% vs. the 19% decrease observed in the datasets (refer to paragraph 4.3.2)]. Prescriptions from the 2005-data subset furthermore represented 22.8% ($n = 8\ 391\ 836$) of the number of prescriptions from the dataset in 2005, thereafter increasing to 23.4% ($n = 8\ 906\ 344$) in 2006, 24.6% ($n = 7\ 911\ 072$) in 2007, and 27.3% ($n = 6\ 775\ 863$) in 2008.

The number of medicine items claimed on the data subset increased from 15.8% ($n = 19\ 500\ 774$) of all items claimed from the dataset in 2005, to 16.4% ($n = 21\ 113\ 422$) in 2006, 17.3% ($n = 19\ 075\ 724$) in 2007 and 19.6% ($n = 16\ 439\ 253$) in 2008 (refer to Tables 4.1 and 4.8). In

contrast to the decreasing trend observed in medicine items claimed from the respective datasets, the number of medicine items from the data subsets increased by an overall 4.3% from 3.0 million in 2005 to 3.2 million in 2008, after an initial steep 12% increase to 3.4 million in 2006 and subsequent 4.5% decrease to 3.3 million (Table 4.8). A median of one medicine item was claimed per prescription per year by patients from the data subsets (i.e. an average of 1.6 ± 0.92 in 2005, vs. 1.7 ± 0.97 in 2006, 1.7 ± 1.01 in 2007 and 1.7 ± 1.04 in 2008), compared with a median of two for patients from the datasets (refer to paragraph 4.3.2).

4.4.3 Direct medicine treatment costs pertaining to the data subsets

The total direct medicine item cost associated with the 2005-data subset was ~R3.9 million, increasing by 9.6% to ~R4.3 million in 2006, followed by a 1.8% decline to ~R4.2 million in 2007 and a further 5.8% decline to ~R4.0 million in 2008 (refer to Table 4.8). These costs represented 21.7% of the cost corresponding with the medicine treatment of all the patients from the dataset during 2005 ($n = R1\ 819\ 865\ 252.00$), compared with 22.1% in both 2006 ($n = R1\ 959\ 738\ 734.00$) and 2007 ($n = R1\ 918\ 284\ 177.00$) and 22.4% ($n = R1\ 785\ 871\ 014.00$) in 2008.

Medical aid schemes contributed 89.4% ($n = R394\ 586\ 482.52$) towards the direct medicine treatment cost of patients on the data subset of 2005, compared with 88.2% ($n = R432\ 361\ 357.98$) during 2006, 87.0% ($n = R424\ 665\ 162.64$) in 2007 and 82.8% ($n = R401\ 155\ 046.30$) in 2008. This translated into an average contribution of $R114.43 \pm 102.51$ (median $R99.18$) in 2005, compared with $R110.30 \pm 104.00$ (median $R93.02$) in 2006, $R111.78 \pm 107.30$ (median $R98.08$) in 2007 and $R104.32 \pm 107.99$ (median $R87.23$) in 2008. Patients paid the excess 10.6% out-of-pocket for co-payments on medicine items in 2005, compared with 11.8% in 2006, 13.0% in 2007 and 16.2% in 2008. Average patient co-payments levied for a patient from the data subset summed to $R13.61 \pm 29.65$ (median $R0.00$) per item per year for 2005, compared with $R14.71 \pm 32.48$ (median $R0.00$) during 2006, $R16.74 \pm 34.31$ (median $R0.01$) in 2007 and $R20.16 \pm 36.87$ (median $R3.53$) in 2008 – an overall increase of 48% from 2005 to 2008.

The median of co-payments by patients from the 2005 to 2007 data subsets was (almost) zero, indicating that more than half of all patients with claims for antihypertensives (diuretics included), antidiabetics and hipolipidaemics had no co-payment across this 3-year period. The lower median (compared with average) could also be an indication of positively skewed data (Barber & Thompson, 2000:3222). These cost trends could, however, not be verified in the absence of the patient's diagnosis, medical aid scheme information and/or service providers. Based on the literature review (refer to paragraphs 2.9.2.5.2, 2.9.3.5.2 and 2.9.4.5.2), it was shown that

antidiabetics, antihypertensives (diuretics included) and hipolipidaemic agents were generally utilised (although not limited to) in the treatment of diabetes mellitus (types 1 and 2), hypertension and dyslipidaemia. All three of these conditions are considered “Chronic Disease List” (CDLs) conditions provided as part of the prescribed minimum benefits package within the South African private health care sector. Medical aid schemes are therefore obliged to fund (*inter alia*) the cost of the medicine treatment of these diseases in full (i.e. medical aid schemes cannot impose co-payments for PMBs). The reimbursements of claims are, however, subject to the registration of a patient by his/her medical aid scheme for CDL benefit. Medical aid schemes may, however, appoint designated service providers (DSPs) and/or apply formularies and treatment protocols (chronic medicine lists), and only fund diagnostic, treatment and care cost that these formularies/protocols provide for, or that their tariff structure (e.g. application of reference pricing) provides for.

The reference price (the maximum price for which the scheme will be liable for specific medicine or classes of medicine listed on the relevant scheme's chronic medicine list). The reference price (RP) applied, varies per medical aid scheme and per medical aid scheme option. Where a medication is above the RP, co-payments apply (the RP indicator is based on a patient using/claiming the most commonly prescribed therapeutic dose of the medication and where a patient uses a higher quantity there may be a co-payment). Co-payments will also apply when medical scheme members voluntarily choose not to go to a designated service provider for a specific service and/or when beneficiaries voluntarily decide not to use their medical aid schemes' protocol or formulary medication or treatments. Medical aid schemes may also require pre-authorisation before they fully fund the diagnosis, treatment and care costs of the PMBs, to establish whether a condition is indeed a PMB or to establish/verify whether a DSP is indeed unavailable. Patients may also be liable for payment of some (or all) of the costs of procedures if pre-authorisation is not obtained (CMS, 2011).

Reimbursement for acute medicine, defined as “*medicine used for diseases or conditions that have a rapid onset, severe symptoms, and that require a short course of medicine treatment*” and/or “*medicines that have not been classified as chronic medicine by the relevant medical aid scheme*” (CMS, 2011), is normally based on whether the medicine item is provided for by the patient's medical aid scheme formulary or treatment protocol, up to a limited amount of prescriptions. The patient has to co-pay approximately the difference in price between the medicine of choice and the price of the formulary medicine item.

The *d*-values calculated for the difference in the contribution of patients and medical aid schemes over the study period approached a small level ($d \leq 0.18$), indicating no practical significance (Table 4.9).

Table 4.9: Effect sizes: average contributions per medicine item from the data subset (2005-2008)

	Average scheme contribution			Average patient co-payment		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.04	-	-	0.03	-	-
2007	0.02	0.01	-	0.09	0.06	-
2008	0.09	0.06	0.07	0.18	0.15	0.09

The patients from the respective data subsets were further categorised into 6 “at risk” categories as depicted by Table 3.4 (refer also to paragraph 3.4.2), namely:

- an antidiabetic category
- an antihypertensive category
- a hipolipidaemic category
- an antidiabetic/antihypertensive category
- an antihypertensive/hipolipidaemic category
- an antidiabetic/hipolipidaemic category.

In the following paragraphs, these respective “at risk” patient categories will be discussed with regard to the number of patients, their demographic profile, the number of prescriptions and medicine items claimed per category and corresponding direct medicine treatment cost (refer to Section 4.4 for specific objectives).

The total number of patients in the data subset (n) (refer to Table 4.8) was used as denominator for all calculations in this section, except where explicitly stated otherwise.

4.4.4 Antidiabetic category

In this section, a detailed overview of patients receiving antidiabetics only (i.e. patients receiving antidiabetics in the absence of antihypertensives and/or hipolipidaemic agents, refer to paragraph 4.1) is presented, based on the summary in Table 4.10. The discussion in this subsection focuses on the total number of patients in the category and the utilisation trends for prescriptions and medicine items claimed over the 4-year study period, stratified by age and gender. The total direct cost of treatment associated with the antidiabetic category (also in relation to age and gender) is presented in paragraph 4.4.4.3.

Antidiabetics may also be used for the treatment of other conditions (refer to paragraph 2.9.4.5.2). Therefore, because of the lack of diagnosis, no definitive conclusions can be drawn from Table 4.10.

Table 4.10: General characteristics of the antidiabetic category (2005-2008)

	2005	2006	2007	2008
Number of patients (n)	16 239	16 549	13 136	12 026
Females	8 244	8 475	6 872	6 172
Males	7 990	8 070	6 262	5 854
Unknown gender	5	4	2	0
Age group 1 (>0, ≤15 years)	386	339	285	263
Age group 2 (>15, ≤30 years)	1 766	1 828	1 584	1 262
Age group 3 (>30, ≤45 years)	5 348	5 490	4 283	3 695
Age group 4 (>45, ≤60 years)	6 074	6 218	5 020	4 911
Age group 5 (>60, ≤75 years)	2 062	2 067	1 507	1 494
Age group 6 (>75 years)	603	607	457	401
Number of prescriptions (n)	73 587	79 187	69 220	64 288
Number of medicine items (n)	100 564	109 664	95 836	89 800
Medicine treatment cost (R)	16 401 193.05	18 218 410.82	16 785 908.17	15 408 607.46
Scheme contribution (R)	15 476 426.89	17 143 278.02	15 618 215.87	14 278 500.46
Patient co-payment (R)	924 766.16	1 075 132.80	1 167 692.30	1 130 107.00

4.4.4.1 Demographic overview of the antidiabetic category

Patients from the antidiabetic category represented 6.2% (n = 261 036) of patients from the data subset in 2005, followed by a marginal decrease to 6.1% (n = 269 452) in 2006, 5.8% (n = 226 264) in 2007 and 5.6% (n = 214 109) in 2008. Overall, these patients represented 1.1% of the total number of patients from the respective dataset in 2005 (n = 1 509 621), compared with 1.0% (n = 1 558 090) in 2006, 1.1% (n = 1 178 596) in 2007 and 1.2% (n = 974 497) in 2008.

According to Knowler *et al.* (2002:397), men and women have an equal chance of developing diabetes. The prevalence of diabetes, however, is generally higher in males, but because prevalence increases with age and women live longer than men, there are more females with diabetes. Impaired glucose tolerance (IGT) also presents with a female predominance, whereas impaired fasting glucose (IFG) is usually higher in males, although South African studies showed the opposite to be true (refer to paragraph 2.9.4.2). The findings from this empirical investigation showed that slightly over half of the number of patients in the antidiabetic category were female, i.e. 50.7% (n = 16 239) in 2005, vs. 51.2% (n = 16 549) in 2006, 52.3% (n = 13 136) in 2007 and 51.3% (n = 12 026) in 2008, which could fit in with the typical profile of a South African patient with type 2 diabetes or impaired fasting glucose levels.

This empirical investigation furthermore showed that (in contrast to the demographic profile of all patients from the respective datasets where females were generally older than their male counterparts), the average prevalent age in the antidiabetic category appeared earlier in females

than in males by 6 years, at average (+SD) ages of:

- 49.2 ± 14.67 years for males viz. 43.4 ± 15.02 years for females in 2005 ($d = 0.39$).
- 49.4 ± 14.19 years for males viz. 43.3 ± 15.02 years for females in 2006 ($d = 0.41$).
- 49.0 ± 14.40 years for males viz. 42.9 ± 14.85 years for females in 2007 ($d = 0.41$).
- 49.7 ± 14.17 years for males viz. 43.7 ± 14.72 years for females in 2008 ($d = 0.41$).

The d -values calculated in the preceding paragraph for the difference in the average age between males and females from the antidiabetic category approached a medium level ($d = \sim 0.4$). Based on the 0.8 cut-off point for Cohen's d , this difference is of no practical significance. The d -values calculated for the difference per gender group over the 4-year study period were very small ($d < 0.05$) - thus also indicating no practically significant difference in average age of patients between the respective study periods.

Figure 4.6 illustrates the distribution of cost corresponding with antidiabetic medicine items claimed yearly per prescription in relation to study period and age groups (as percentage).

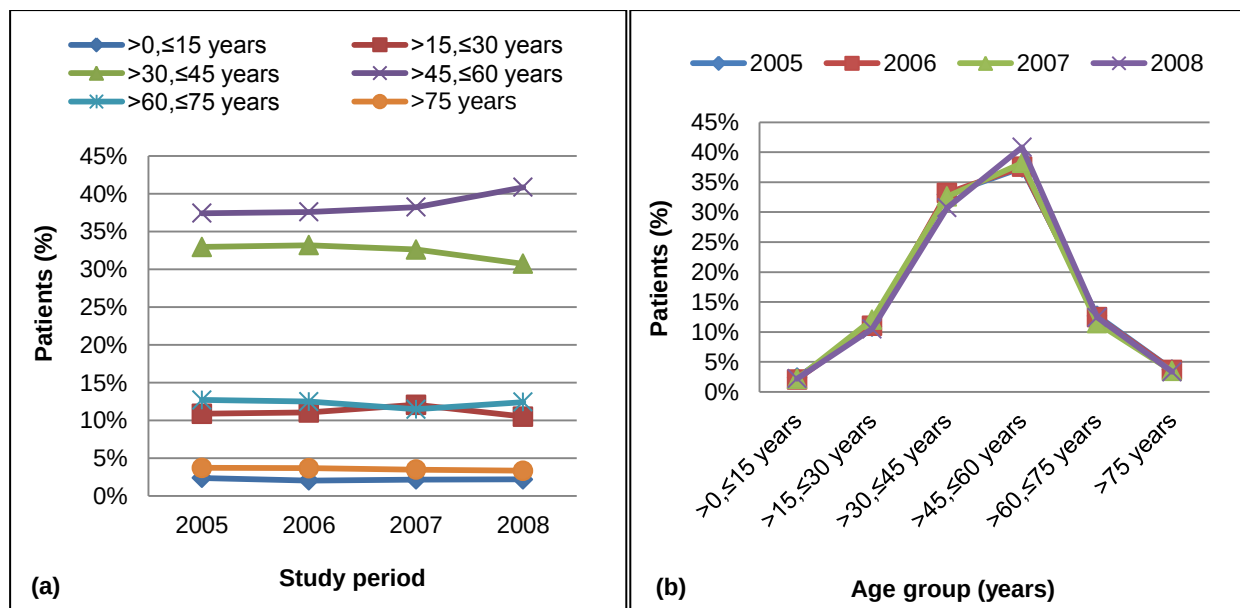


Figure 4.6: Distribution of patients from the antidiabetic category in relation to study period and age group (years)

Figure 4.6(a) shows that the number of patients in the antidiabetic category remained relatively constant over the 4-year study period, with only minor changes in the number of patients aged 31-45 years (where a 2.2% decrease in prevalence was observed) and in patients aged 46-60 years, where a more pronounced 3.4% increase was observed. This utilisation pattern was also observed within the population from the respective datasets [refer to Figure 4.2(a)].

Stratification of the antidiabetic category by age group [Figure 4.6(b)] showed a relatively low

“prevalence” in patients younger than, or equal to 30 years and in those aged 61-75 years, with prevalence rates peaking in those aged 31-45 and 46-60 years. Patients from age groups 3 and 4, that is those aged 30-60 years furthermore represented 70.3% ($n = 261\,036$) of all patients in the antidiabetic category for 2005, compared with 70.8% in both 2006 ($n = 269\,452$) and 2007 ($n = 226\,264$) and 71.6% ($n = 214\,109$) in 2008 - almost 5 times the prevalence in those patients ≤ 30 years of age. Both IFG, IGT and type 2 diabetes increase in prevalence with age; IGT increases linearly peaking in the elderly, whereas impaired fasting glucose doubles between ages 20-39 and 40-59 years and tends to plateau in those ≥ 60 years. The incidence of type 1 diabetes mellitus typically peaks at ages 4-6 years and 10-14 years, whereas type 2 diabetes mellitus is commonly diagnosed in individuals older than 40 years (onset from 25-64 years), with incidence increasing to peak in those of 60-65 years and prevalence up to 10% in those older than 70 years (refer to paragraph 2.9.4.2). The age distribution of patients from this data category therefore appears to reflect the epidemiology typically found in patients with type 2 diabetes or impaired fasting glucose levels. Differentiation between types 1 and 2 diabetes mellitus (or other types of glucose abnormalities) on the datasets/data subsets was however not possible because of a lack of diagnosis.

4.4.4.2 General prescribing patterns pertaining to the antidiabetic category

The antidiabetic category contained 73 587 prescriptions in 2005, increasing by 7.6% to 79 187 in 2006. A 12.6% decrease in this number was then observed to 69 220 in 2007 and a further 7.1% decline to 64 288 prescriptions in 2008 [an overall decrease of 12.6% vs. the 3% decrease observed in the total data subset (refer to section 4.4.2)]. The number of prescriptions furthermore represented 3.9% ($n = 1\,911\,296$) of the number of prescriptions from the total data subset in 2005, compared with 3.8% ($n = 2\,081\,849$) in 2006, 3.6% ($n = 1\,943\,498$) in 2007, and 3.5% ($n = 3\,214\,534$) in 2008 (refer to Tables 4.8 and 4.10).

The number of antidiabetic medicine items claimed decreased marginally over the study period, i.e. from 3.3% ($n = 3\,081\,832$) in 2005 to 3.2% ($n = 3\,458\,538$) in 2006, 2.9% ($n = 3\,304\,273$) in 2007 and 2.8% ($n = 3\,214\,534$) in 2008 (refer to Tables 4.8 and 4.10). This number of antidiabetic items therefore represented 0.5% of the total number of medicine items claimed from the datasets in 2005 ($n = 19\,500\,774$), 2006 ($n = 21\,113\,422$) and 2007 ($n = 19\,075\,724$), increasing to 0.6% ($n = 16\,439\,253$) in 2008 (refer to Table 4.1). An average of 1.4 ± 0.53 antidiabetics was claimed per prescription in 2005, vs. 1.4 ± 0.54 in 2006 and 1.4 ± 0.55 in both 2007 and 2008. The d -value calculated for the difference in the average antidiabetic item claim rate per prescription over the study period was zero.

Based on the treatment guidelines for a patient with hyperglycaemia (refer to paragraph 2.9.4.5),

metformin is the medication of choice for the majority of patients. If treatment goals are not met with lifestyle changes and the use of the maximal tolerated dose of metformin, other medication (from insulin, a sulphonylurea, or thiazolidinediones) should be added within two to three months of the initiation of therapy or at any time, followed with a third agent (again from insulin, a sulphonylurea, or thiazolidinediones). Patients with HbA_{1c} levels greater than 7% may furthermore require short- or rapid-acting insulin prior to meals in addition to basal insulin to control glycaemia (Levitt *et al.*, 2009:57-58). A patient with hyperglycaemia may therefore easily be treated with 5 or more antidiabetics. The empirical investigation showed that a maximum of 6 antidiabetics (items) (minimum 1) was claimed per prescription per year for patients from the antidiabetic category (i.e. 2005 – 2008), putting the findings well within the framework of the treatment protocol for patients with hyperglycaemia.

4.4.4.3 Direct medicine treatment cost associated with the antidiabetic category

The total direct medicine item cost from the antidiabetic category in 2005 was R1.64 million, increasing to R1.82 million in 2006, with a subsequent decline to R1.67 million in 2007 and R1.54 million in 2008 – an overall decrease in cost of 6.1%. These costs represent 4.2% of the cost associated with the medicine treatment from the data subset during 2005 ($n = R394\ 586\ 482.52$), compared with 4.2% in 2006 ($n = R432\ 361\ 357.98$), 4.0% in 2007 ($n = R1\ 918\ 284\ 177.00$) and 3.9% ($n = R400\ 155\ 046.30$) in 2008 (refer to Tables 4.8 and 4.10). Subsequently, the costs associated with the antidiabetic category represented 0.90% of the cost corresponding with the medicine treatment of all patients from the dataset during 2005 ($n = R1\ 819\ 865\ 252.00$), compared with 0.93% in 2006 ($n = R1\ 959\ 738\ 734.00$), 0.88% in 2007 ($n = R1\ 918\ 284\ 177.00$) and 0.86% ($n = R1\ 785\ 871\ 014.00$) in 2008 (refer to Tables 4.1 and 4.10). Based on Serfontein's CPI, antidiabetics claimed during the study period were relatively expensive (CPIs >1.5).

Medical aid schemes contributed 94.4% ($n = R394\ 586\ 482.52$) towards the direct medicine treatment cost of patients from the antidiabetic category of 2005, compared with 94.1% ($n = R432\ 361\ 357.98$) during 2006, 93.0% ($n = R424\ 665\ 162.64$) in 2007 and 92.7% ($n = R401\ 155\ 046.30$) in 2008 (Table 4.10). This translates to an average scheme contribution of $R153.90 \pm 196.96$ (median R52.71) in 2005, compared with $R156.33 \pm 202.33$ (median R52.45) in 2006, $R162.97 \pm 214.21$ (median R52.73) in 2007 and $R159.00 \pm 218.34$ (median R52.96) in 2008. Patients paid the excess 5-7% of costs out-of-pocket for co-payments on medicine items at an average $R9.20 \pm 38.53$ (median R0.00) per item per year for 2005, compared with $R9.80 \pm 40.46$ (median R0.00) during 2006, $R12.18 \pm 42.52$ (median R0.00) in 2007 and $R12.58 \pm 38.13$ (median R0.29) in 2008. The calculated *d*-values for the difference in the average contribution of patients and medical aid scheme's contribution

over the study period approached very small levels ($0.01 \leq d \leq 0.09$), indicating no practically significant difference over the 4-year period (Table 4.11).

Table 4.11: Effect sizes: average contributions per medicine item from the antidiabetic category (2005-2008)

	Average scheme contribution			Average patient co-payment		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.01	-	-	0.01	-	-
2007	0.04	0.03	-	0.07	0.06	-
2008	0.02	0.01	0.02	0.09	0.07	0.01

Patients with hyperglycaemia (in particular IGT, combined IFG/IGT and diabetes types 1 and 2) generally carry excess medical costs compared with normoglycaemic patients (refer to paragraph 2.9.4.4). The findings from this empirical investigation show that the average annual direct medicine treatment cost for a patient from the antidiabetic category summed to R1 009.99 $\pm$ 1 990.48 (median R239.25) in 2005; compared with R1 205.51 $\pm$ 3 044.30 (median R333.13) for all patients from the 2005-dataset (Cohen's $d = 0.06$; i.e. a practically insignificant difference between the costs) (refer to paragraph 4.3.3). Similar findings were reported in 2006, 2007 and 2008, with total costs per patient of R1 100.88 $\pm$ 2 149.40 (median R248.72), R1 277.86 $\pm$ 2 427.12 (median R269.90) and R1 281.27 $\pm$ 2 400.81 (median R298.11), respectively (Cohen's $d = 0.04$ for 2006, 0.07 for 2007 and 0.08 for 2008, refer to paragraph 4.3.3). These annual costs per patient, however, excluded other medication taken concurrently. The total cost per patient from the antidiabetic category will therefore undoubtedly be higher.

4.4.5 Antihypertensive category

In this section, a detailed overview of patients receiving antihypertensives only (i.e. patients receiving antihypertensives in the absence of antidiabetics and/or lipolipidaemic agents, refer to Section 4.1, is presented, based on the summary in Table 4.12.

The discussion in this section includes an overview of the total number of patients in the category and the utilisation trends for prescriptions and medicine items claimed over the 4-year study period, in relation to age and gender. A discussion on the direct medicine treatment cost associated with the antihypertensive category (also stratified by age and gender) ensues in paragraph 4.4.5.3.

Table 4.12: General characteristics of the antihypertensive category (2005-2008)

	2005	2006	2007	2008
Number of patients (n)	140 936	143 269	115 343	105 749
Females	88 506	88 508	72 657	65 104
Males	52 342	54 684	42 672	40 645
Unknown gender	88	77	14	0
Age group 1 (>0, ≤15 years)	580	600	412	308
Age group 2 (>15, ≤30 years)	3 132	3 271	2 721	2 068
Age group 3 (>30, ≤45 years)	24 895	25 075	19 038	15 607
Age group 4 (>45, ≤60 years)	51 190	53 437	42 911	40 609
Age group 5 (>60, ≤75 years)	37 703	37 846	30 215	28 859
Age group 6 (>75 years)	23 436	23 040	20 046	18 298
Number of prescriptions (n)	1 171 988	1 239 293	1 106 549	1 037 358
Number of medicine items (n)	895 581	936 203	832 331	770 532
Medicine treatment cost (R)	122 785 862.77	124 099 925.53	116 285 676.05	104 130 093.44
Medical aid scheme contribution (R)	107 834 053.94	107 175 687.30	98 062 495.67	83 155 537.85
Patient co-payment (R)	14 951 808.83	16 924 238.23	18 223 180.38	20 974 501.59

4.4.5.1 Demographic overview of the antihypertensive category

Patients from the antihypertensive category represented 54.0% (n = 261 036) of patients from the data subset in 2005, decreasing to 53.2% (n = 269 452) in 2006, 51.0% (n = 226 264) in 2007 and 49.4% (n = 214 109) in 2008 (refer to Tables 4.8 and 4.12). Overall, the number of patients from the antihypertensive category increased from 9.3% of the total number of patients from the dataset in 2005 (n = 1 509 621), to 9.5% in 2006 (n = 1 558 090) and 10.9% (n = 974 497) in 2008, after a substantial 19% decrease from 2006 to 7.4% in 2007 (n = 1 178 596) (refer to Tables 4.1 and 4.12).

Antihypertensives - defined as substances mainly used for the reduction of high blood pressure - are also prescribed for other cardiovascular diseases e.g.: heart failure, chronic renal disease, diabetes mellitus, high coronary disease risk, recurrent stroke prevention, peripheral arterial disease and post-myocardial infarction (Thompson *et al.*, 2011:920) (refer to paragraph 2.9.3.5.2). The incidence of cardiovascular disease is in general greater in men than in women; for example, in coronary heart disease women lag behind men in incidence by 10 to 15 years. This gap closes with advancing age and is nearly the same in men and women after the age of menopause (Fodor & Tzerovska, 2004:35). Blood pressure is likewise, in general, higher in male patients than in females up to the age of 60 years (refer to paragraph 2.9.3.2). After menopause (approximately at age 51.4 years), however, systolic blood pressure commence to increase in women such that the prevalence of hypertension in post-menopausal women is similar to, or higher than in men (Reckelhoff & Fortepiani, 2004:920). This empirical

investigation showed that more than 60% of the patients in the antihypertensive category were female, i.e. 62.8% ($n = 140\,936$) in 2005, compared with 61.8% ($n = 143\,269$) in 2006, 63.0% ($n = 115\,343$) in 2007 and 61.6% ($n = 105\,749$) in 2008.

The average prevalent ages of patients from the antihypertensive category were past the average age of menopause onset in females, furthermore appearing earlier than in males by 2 years, at average ($\pm$ SD) ages of:

- 58.8 ± 15.86 years for females *viz.* 57.2 ± 14.97 years for males in 2005 ($d = 0.10$).
- 58.7 ± 15.77 years for females *viz.* 56.8 ± 14.86 years for males in 2006 ($d = 0.12$).
- 59.2 ± 15.96 years for females *viz.* 57.3 ± 15.03 years for males in 2007 ($d = 0.12$).
- 60.0 ± 15.64 years for females *viz.* 57.6 ± 14.51 years for males in 2008 ($d = 0.15$).

Although no definitive conclusions can be drawn from Table 4.12, the utilisation patterns observed by patients from the antihypertensive category may well fit within the framework of an older hypertensive patient population. These usage patterns were also in agreement with the results from the 1998 South African Demographic Health Survey (Department of Health, 2002) that described a “self-reported antihypertensive agent utilisation prevalence rate” of 59.9% among women, compared to 50.9% for men. The antihypertensive category furthermore reflects the demographic of the overall dataset population (refer to paragraph 4.4.1). The d -values calculated in the preceding paragraph for the difference in the average age between males and females from the antihypertensive category, are small ($d < 0.2$) and therefore of no practical significance. The d -values calculated for the difference per gender group over the 4-year study period were also very small ($d < 0.05$) - thus also indicating no practically significant difference in average age of patients between the respective study periods. Figure 4.7 illustrates the distribution of cost corresponding with antihypertensive medicine items claimed yearly per prescription in relation to study period and age groups (as percentage).

Only minor changes occurred in the number of patients over the 4-year study period, with marginal decreases in the number of patients younger than 30 years (0.1% and 0.3%, respectively for patients aged ≤ 15 years and those aged 16-30 years) and increases in the number of patients older than 60 years (i.e. 0.5% for those aged 61-75 years and 0.7% for those older than 75 years) [Figure 4.7(a)]. More pronounced changes in prevalence were observed in patients aged 31-45 years (where a 2.9% decrease in prevalence was observed) and those aged 46-60 years, where a 2.1% increase was observed. Stratification of the antihypertensive category by age group shows a relatively low “prevalence” in patients ≤ 30 years, with prevalence rates increasing to peak in patients aged 46-60 years, reflecting the prevalence rates typically found in patients with, *inter alia*, hypertension (refer to paragraph 2.9.3.2). Patients from age groups 4 to 6 (i.e. patients ≥ 45 years) represented about 80% of all

patients in the antihypertensive category over the 4-year study period - almost 4 times the prevalence in those patients ≤ 30 years [refer to Figure 4.7(b)].

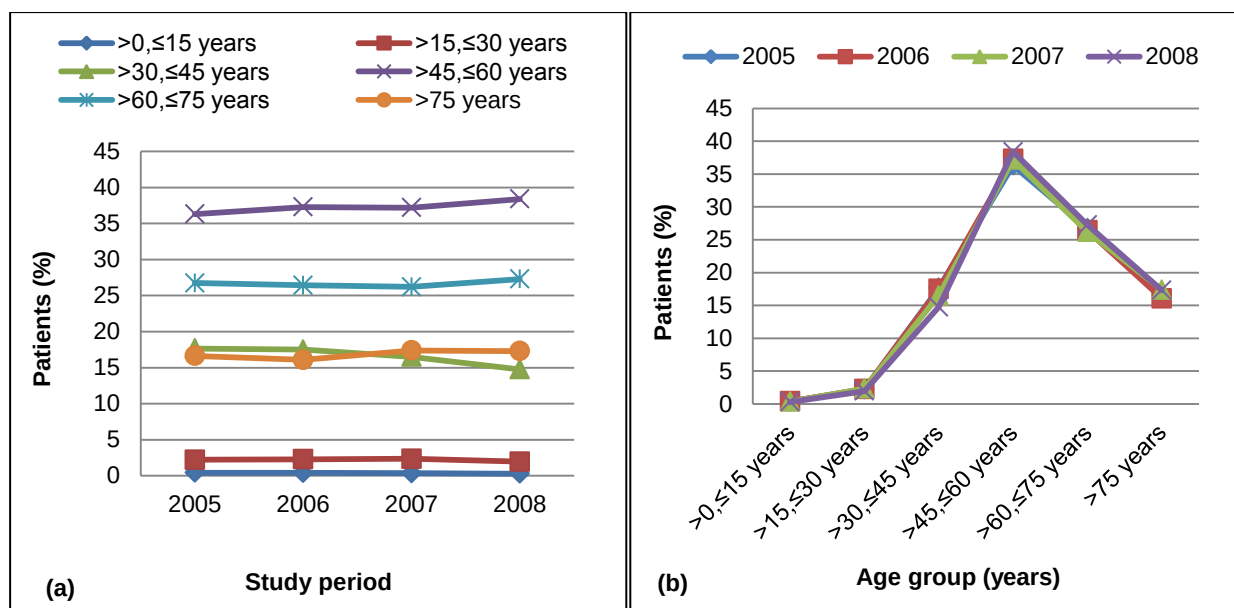


Figure 4.7: Distribution of patients from the antihypertensive category in relation to study period and age group (years) (2005-2008)

4.4.5.2 General prescribing patterns pertaining to the antihypertensive category

Table 4.12 shows that the number of prescriptions claimed in the antihypertensive category as percentage of the total number of prescriptions claimed for the data subset decreased continuously from 61.3% ($n = 1\,911\,296$) in 2005 to 59.5% ($n = 2\,081\,849$) in 2006, 56.9% ($n = 1\,943\,498$) in 2007 and 56.1% ($n = 1\,848\,474$) in 2008 [a relative decrease of 5.2% over the study period vs. the 3% decrease observed in the total data subset (refer to section 4.4.2)]. The number of prescriptions subsequently represented 14.0% ($n = 8\,391\,836$) of the number of prescriptions from the dataset in 2005, compared with 13.9% ($n = 8\,906\,344$) in 2006, 14.0% ($n = 7\,911\,072$) in 2007 and 15.3% ($n = 6\,775\,863$) in 2008 (refer to Tables 4.1 and 4.12) – representative of an overall 1.3% increase over the study period.

The number of antihypertensive medicine items claimed decreased by 5.1% over the study period, from 29.1% ($n = 3\,081\,832$) in 2005, to 27.1% ($n = 3\,458\,538$) in 2006, 25.2% ($n = 3\,304\,273$) in 2007 and 24.0% ($n = 3\,214\,534$) in 2008 (refer to Tables 4.8 and 4.12). An average 1.3 ± 0.57 antihypertensive items was claimed per prescription in 2005 vs. 1.3 ± 0.59 in 2006, 1.3 ± 0.60 in 2007 and 1.3 ± 0.61 in 2008. The d -value calculated for difference in the average number of antihypertensive items claimed per prescription was zero.

The choice of antihypertensive agent utilised depends on the indication thereof. For example,

in the treatment of hypertension, therapy should be initiated using diuretics (low dose thiazide or thiazide-like diuretics), followed by a second, third or even fourth medication, or combination of medications (either as multiple individual agents or as fixed-dose combinations) until blood pressure control is obtained (refer to paragraph 2.9.3.5.2). A patient with hypertension may therefore be treated easily with 4 or more antihypertensive agents. Results from this empirical investigation shows that a maximum of 8-10 antihypertensive medicine items (minimum 1) was claimed per prescription per year for patients from the antihypertensive category (i.e. 2005 – 2008).

4.4.5.3 Direct medicine treatment cost associated with the antihypertensive category

The direct medicine treatment cost associated with the antihypertensive category in 2005 totalled to R1.22 million, increasing to R1.24 million in 2006, with a subsequent decline to R1.16 million in 2007 and R1.04 million in 2008 (refer to Table 4.12) – a 15.2% relative decrease in cost. These costs represent 31.1% of the cost associated with the medicine treatment from the total data subset during 2005 ($n = R394\ 586\ 482.52$) vs. 28.7% in 2006 ($n = R432\ 361\ 357.98$), 27.4% in 2007 ($n = R1\ 918\ 284\ 177.00$) and 26.0% ($n = R400\ 155\ 046.30$) in 2008 (refer to Tables 4.8 and 4.12). The costs subsequently also represented 6.8% of the cost associated with the medicine treatment from the dataset during 2005 ($n = R1\ 819\ 865\ 251.64$) vs. 6.3% in 2006 ($n = R1\ 959\ 738\ 734.13$), 6.1% in 2007 ($n = R1\ 918\ 284\ 176.64$) and 5.8% ($n = R1\ 785\ 871\ 013.83$) in 2008 (refer to Tables 4.1 and 4.12).

Medical aid schemes contributed 87.8% ($n = R394\ 586\ 482.52$) towards the direct medicine treatment cost of patients in the antihypertensive category of 2005 vs. 86.4% ($n = R432\ 361\ 357.98$) during 2006, 84.3% ($n = R424\ 665\ 162.64$) in 2007 and 79.9% ($n = R401\ 155\ 046.30$) in 2008 (Table 4.12). This translates to an average scheme contribution of $R92.01 \pm 70.67$ (median R77.49) in 2005 vs. $R86.48 \pm 67.16$ (median R74.35) in 2006, $R88.62 \pm 66.00$ (median R81.34) in 2007 and $R80.16 \pm 60.96$ (median R73.43) in 2008.

Patients paid the excess 12-20% medicine treatment cost out-of-pocket for co-payments on medicine items at an average $R12.76 \pm 25.03$ (median R0.00) per item for 2005 compared with $R13.66 \pm 26.79$ (median R0.00) during 2006, $R16.47 \pm 29.82$ (median R1.54) in 2007 and $R20.22 \pm 33.55$ (median R4.56) in 2008. As indicated by the median, more than half of patients did not have a co-payment, or co-paid approximately R5.00 per medicine item. Possible explanations for the zero median were explored in paragraph 4.4.3. In the absence of diagnosis, however, it may also be possible that co-payments were levied for the treatment of other conditions/illnesses not considered CDL prescribed minimum benefits with medication

from the class of antihypertensives. Co-payments may furthermore be levied under certain circumstances as highlighted in paragraph 4.4.3. The *d*-values calculated for the difference in the average contribution of patients' and medical aid scheme's contribution over the study period approached small levels ($d \leq 0.22$), indicating no practically significant difference (Table 4.13).

Table 4.13: Effect sizes: average contribution per medicine item from the antihypertensive category (2005-2008)

	Average scheme contribution			Average patient co-payment		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.08	-	-	0.03	-	-
2007	0.05	0.03	-	0.12	0.09	-
2008	0.17	0.09	0.13	0.22	0.20	0.11

The annual direct cost of medicine treatment for a patient from the antihypertensive category from this empirical investigation was R871.22 ± 1 141.96 (median R361.76) in 2005 vs. R866.20 ± 1 117.54 (median R383.24) in 2006, R1 008.17 ± 1 201.51 (median R563.90) in 2007 and R984.69 ± 1 173.20 (median R563.53) in 2008. These amounts were less than that of any other patient from the different datasets (refer to paragraph 4.4.3). Based on Cohen's *d*-values of 0.11 for both 2005 and 2006, and 0.12 and 0.13 for 2007 and 2008, respectively, these differences in costs were practically insignificant. The annual costs per patient, however, excluded other medication taken concurrently. The actual cost per patient from the antihypertensive category, similar to patients from the antidiabetic category, will therefore certainly be higher. For example, according to the National Academy on an Aging Society (2000:5) a presence of hypertension may result in a 17% higher medical expenditure per patient.

4.4.6 Hipolipidaemic category

In this section, a detailed overview of patients receiving hipolipidaemics only (i.e. patients receiving hipolipidaemic agents in the absence of medicine items from two other medication classes, i.e. antidiabetics and antihypertensives) is presented, based on the summary in Table 4.14.

The following discussion includes an overview of the total number of patients in the category and the utilisation trends for prescriptions and medicine items claimed over the 4-year study period, in relation to age and gender. A discussion on the total direct cost of treatment associated with the hipolipidaemic category (also stratified by age and gender) follows in

paragraph 4.4.6.3.

Table 4.14: General characteristics of the hipolipidaemic category (2005-2008)

	2005	2006	2007	2008
Number of patients (n)	28 264	28 427	22 161	21 248
Females	13 119	13 294	10 467	10 259
Males	15 126	15 123	11 692	10 989
Unknown gender	19	10	2	0
Age group 1 (>0, ≤15 years)	701	530	49	223
Age group 2 (>15, ≤30 years)	805	795	563	572
Age group 3 (>30, ≤45 years)	4 747	4 476	3456	3 208
Age group 4 (>45, ≤60 years)	11 073	11 143	8899	8 371
Age group 5 (>60, ≤75 years)	8 880	9 187	7320	7 041
Age group 6 (>75 years)	2 058	2 296	1874	1 833
Number of prescriptions (n)	168 645	175 548	156 086	146 514
Number of medicine items (n)	171 303	179 985	160 293	150 299
Medicine treatment cost (R)	29 529 661.55	30 631 455.40	26 352 183.48	23 634 730.31
Scheme contribution	26 793 149.82	27 380 924.55	22 991 287.77	19 980 615.91
Patient co-payment	2 736 511.73	3 250 530.85	3 360 895.71	3 654 114.40

4.4.6.1 Demographic overview of the hipolipidaemic category

Patients from the hipolipidaemic category represented 10.8% (n = 261 036) of patients from the total data subset in 2005, followed by a slight decrease to 10.5% (n = 269 452) in 2006 and 9.8% (n = 226 264) in 2007 and a subsequent marginal increase to 9.9% (n = 214 109) in 2008 (refer to Tables 4.8 and 4.14). Overall, these patients represented 1.9% of the total number of patients from the total dataset in 2005 (n = 1 509 621) compared with 1.8% in 2006 (n = 1 558 090), 1.9% in 2007 (n = 1 178 596) and 2.2% (n = 974 497) in 2008 (refer to Tables 4.1 and 4.14).

Hipolipidaemic agents are prescribed for a number of diseases/conditions other than dyslipidaemia, *inter alia*, hypertension, diabetes, reducing the risk for cardiovascular events, obesity and sitosterolaemia (refer to paragraphs 2.9.5.2, 2.9.3.5.2 and 2.9.4.5.2); therefore, no definitive conclusions can be drawn from Table 4.14. However, results of the 1998 SADHS showed that more male than female patients utilised lipid-lowering agents for the treatment of hyperlipidaemia (Department of Health, 2002). In accord, the demographic data from the hipolipidaemic category showed that slightly more than half of the patients receiving hipolipidaemic agents in 2005 were male, i.e. 53.5% (n = 16 239) vs. 53.2% (n = 16 549) in 2006, 52.8% (n = 13 136) in 2007 and 51.7% (n = 12 026) in 2008. Similar to the demographic profile of all patients from the total dataset (refer to paragraph 4.3.1), the average prevalent age

appeared earlier in males than in females by 3 years, at average (+SD) ages of:

- 53.5 ± 15.26 years for males vs. 56.4 ± 15.49 years for females in 2005 ($d = 0.19$).
- 54.2 ± 14.83 years for males vs. 57.2 ± 14.97 years for females in 2006 ($d = 0.20$).
- 55.3 ± 13.22 years for males vs. 58.5 ± 13.22 years for females in 2007 ($d = 0.24$).
- 55.1 ± 14.12 years for males vs. 57.9 ± 14.14 years for females in 2008 ($d = 0.20$).

The d -values calculated in the preceding paragraph for the difference in the average age between males and females from the hipolipidaemic category, approached a small level ($0.19 \geq d \leq 0.24$). Based on the 0.8 cut-off point for Cohen's d , this difference is of no practical significance. The d -values calculated for the difference per gender group over the 4-year study period were also small ($d \leq 0.14$) - thus also indicating no practically significant difference in average age of patients between the respective study periods.

Stratification of the hipolipidaemic category by study period [Figure 4.8(a)] shows that the number of patients in the hipolipidaemic category remained relatively constant over the 4-year study period, with only minor changes in the number of patients aged ≤ 15 years and 31-45 years (where marginal decreases of 1.5% and 1.7%, respectively were observed) and in patients aged older than 60 years, where a more pronounced 3.0% increase over the study period was observed.

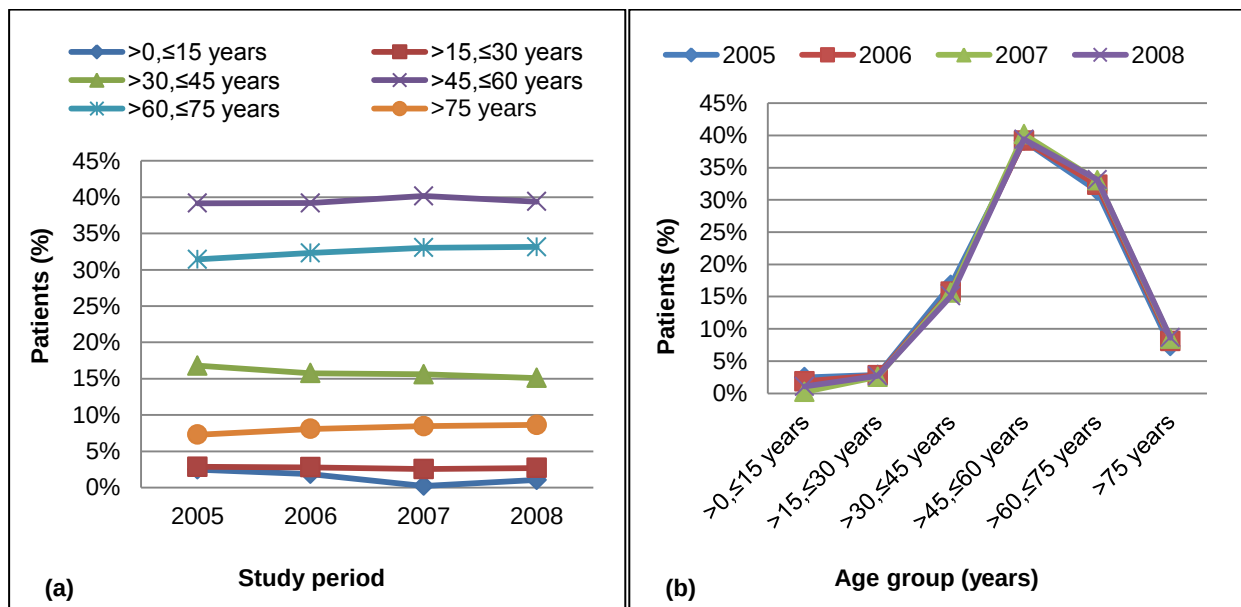


Figure 4.8: Distribution of patients from the hipolipidaemic category in relation to age group (years) and study period (2005-2008)

Stratification by age group [Figure 4.8(b)] shows a relatively low utilisation frequency in patients ≤ 30 years and in those older than 75 years, with prevalence rates peaking in patients aged

46-60 and 61-75 years. Patients aged 31-75 years furthermore represented the majority of patients from the hipolipidaemic category, at 87.4% (n = 261 036) for 2005, compared with 87.2% in 2006 (n = 269 452), 88.8% in 2007 (n = 226 264) and 87.6% (n = 214 109) in 2008 (refer to Table 4.14). These utilisation patterns may well fit in with the prevalence patterns of dyslipidaemia among South Africans (refer to paragraph 2.9.2.2).

4.4.6.2 General prescribing patterns pertaining to the hipolipidaemic category

The hipolipidaemic category contained 168 645 prescriptions, which increased by 4.1% to 175 548 in 2006 (Table 4.14). An 11.1% decrease to 156 086 was then observed in 2007, followed by a further 6.1% reduction to 146 514 prescriptions in 2008 [a relative decrease of 13.1% over the study period vs. the 3% decrease observed in the total data subset (refer to paragraph 4.4.2)]. The number of prescriptions represented 8.8% (n = 1 911 296) of the number of prescriptions from the total data subset in 2005, compared with 8.4% (n = 2 081 849) in 2006, 8.0% (n = 1 943 498) in 2007, and 4.6% (n = 3 214 534) in 2008 (refer to Tables 4.8 and 4.14). The number of hipolipidaemic medicine items claimed, decreased marginally from 5.6% (n = 3 081 832) in 2005 to 5.2% (n = 3 458 538) in 2006, 4.9% (n = 3 304 273) in 2007 and 4.7% (n = 3 214 534) in 2008 (refer to Tables 4.8 and 4.14). The average number of hipolipidaemic items claimed per prescription was 1.0 ± 0.13 in 2005 compared with 1.0 ± 0.16 in 2006, 1.0 ± 0.17 in 2007 and 1.0 ± 0.16 in 2008. The *d*-value calculated for difference in the average hipolipidaemic item claim rate in this subset was zero.

Based on the treatment guidelines for a patient with dyslipidaemia (refer to paragraph 2.9.2.5.2), aggressive combination lipid-lowering therapy in subjects at high risk of cardiovascular disease, i.e. patients who have familial hypercholesterolaemia or familial combined hyperlipidaemia (Durrington, 2003:719) or where patients have not reached target LDL-cholesterol levels of fewer than 70 mg/dL (1.8 mmol/L) with monotherapy (Tannok, 2008:369), is recommended. A patient with dyslipidaemia may therefore easily be treated with a combination of three or more lipid-lowering agents. In accordance to this guideline, a maximum of 4 hipolipidaemic medicine items (median 1) was claimed per prescription per year for patients from the hipolipidaemic category (i.e. 2005 – 2008).

4.4.6.3 Direct medicine treatment cost associated with the hipolipidaemic category

The total direct medicine item cost associated with the hipolipidaemic category in 2005 was R2.95 million, increasing to R3.06 million in 2006, with a subsequent decline to R2.6 million in 2007 and R2.4 million in 2008 – an overall decrease in cost of 20% over the 4-year period (Table 4.14). These costs represent 7.5% of the cost associated with the medicine treatment

from the total data subset during 2005 ($n = R394\ 586\ 482.52$) compared with 7.1% in 2006 ($n = R432\ 361\ 357.98$), 6.2% in 2007 ($n = R424\ 665\ 162.64$) and 5.9% ($n = R400\ 155\ 046.30$) in 2008 (refer to Tables 4.8 and 4.14). Based on the cost-prevalence index indicator, the hipolipidaemic medicine items were relatively expensive over the study period (i.e. CPIs > 1.4).

Medical aid schemes contributed 90.7% ($n = R29\ 529\ 661.55$) towards the direct medicine treatment cost of patients on the hipolipidaemic category of 2005 compared with 89.4% ($n = R30\ 631\ 455.40$) during 2006, 87.3% ($n = R26\ 352\ 183.48$) in 2007 and 84.5% ($n = R23\ 634\ 730.31$) in 2008 (Table 4.14). This translates to an average scheme contribution of $R156.41 \pm 69.79$ (median $R152.11$) per item in 2005 compared with $R152.13 \pm 72.56$ (median $R142.92$) in 2006, $R143.43 \pm 70.34$ (median $R135.06$) in 2007 and $R132.94 \pm 64.54$ (median $R119.97$) in 2008. Patients paid the excess 9-15% of medicine treatment costs out-of-pocket for co-payments at an average $R15.97 \pm 33.86$ (median $R0.00$) per item for 2005 compared with $R18.06 \pm 38.17$ (median $R0.00$) during 2006, $R20.97 \pm 40.59$ (median $R0.00$) in 2007 and $R24.31 \pm 42.20$ (median $R3.58$) in 2008. The d -values calculated for the difference in the average contribution of patients and medical aid schemes over the study period approach small to medium levels ($0.03 \leq d \leq 0.34$) (Table 4.15). Based on the 0.8 cut-off point for Cohen's d , this difference is of no practical significance.

Table 4.15: Effect sizes: average contribution per medicine item from the hipolipidaemic category (2005-2008)

	Average scheme contribution			Average patient co-payment		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.03	-	-	0.05	-	-
2007	0.18	0.06	-	0.12	0.07	-
2008	0.34	0.26	0.15	0.20	0.15	0.08

The direct medicine treatment cost per year for a patient from the hipolipidaemic category was $R1\ 044.78 \pm 973.28$ (median $R794.49$) in 2005 compared to $R1\ 077.55 \pm 1\ 026.15$ (median $R835.92$) in 2006, $R1\ 189.12 \pm 1\ 028.23$ (median $R1\ 039.50$) in 2007 and $R1\ 112.33 \pm 997.14$ (median $R962.31$) in 2008. Compared with any other patient from the total dataset (refer to paragraph 4.3.3), the yearly cost of a patient receiving at least one hipolipidaemic item, was 15.4% lower in 2005 compared with 16.7% in 2006, 36.9% in 2007 and 64.8% in 2008. Calculated d -values for this difference in annual direct medicine treatment cost between patients from the hipolipidaemic category and those from the respective datasets (paragraph 4.3.3) totalled 0.05 for 2005, 0.01 for 2006, 0.04 for 2007 and 0.07 for 2008, respectively and were therefore practically insignificant. These annual costs per patient, however, excluded other medication taken concurrently. The total medicine cost per patient

from the hipolipidaemic category may therefore be even higher.

4.4.7 Antidiabetic/antihypertensive category

In this section, a detailed overview of patients receiving both antidiabetics and antihypertensives is presented, based on the summary in Table 4.16.

Table 4.16: General characteristics of the antidiabetic/antihypertensive category (2005-2008)

	2005	2006	2007	2008
Number of patients (n)	18 312	20 710	18 128	18 027
Females	9 542	10 846	9 668	9 527
Males	8 759	9 859	8 460	8 500
Unknown gender	11	5	0	0
Age group 1 (>0, ≤15 years)	31	25	24	18
Age group 2 (>15, ≤30 years)	243	279	252	237
Age group 3 (>30, ≤45 years)	2 940	3 200	2 613	2 359
Age group 4 (>45, ≤60 years)	7 934	9 157	8 112	8 269
Age group 5 (>60, ≤75 years)	4 907	5 561	4 787	4 942
Age group 6 (>75 years)	2 257	2 488	2 340	2 202
Number of prescriptions (n)	159 413	199 814	172 155	184 367
Number of medicine items (n)	348 384	440 530	381 528	414 829
Medicine treatment cost (R)	41 351 687.12	52 364 199.07	47 846 760.88	50 604 256.67
Scheme contribution	37 745 773.47	47 401 095.65	42 794 312.26	43 614 836.15
Patient co-payment	3 605 913.65	4 963 103.42	5 052 448.62	6 989 420.52

The following discussion includes an overview of the total number of patients in the category and the utilisation trends for prescriptions and medicine items claimed over the 4-year study period, stratified by age and gender. A discussion on the total direct cost of treatment associated with the antidiabetic/antihypertensive category (also in relation to age and gender) follows in paragraph 4.4.7.3.

4.4.7.1 Demographic overview of the antidiabetic/antihypertensive category

Patients from the antidiabetic/antihypertensive category represented 7.0% (n = 261 036) of patients from the total data subset in 2005. This was followed by a continuous marginal increase in prevalence to 7.7% (n = 269 452) in 2006, 8.0% (n = 226 264) in 2007 and 8.4% (n = 214 109) in 2008 (refer to Tables 4.8 and 4.16). Overall, these patients represented 1.2% of the total number of patients from the dataset in 2005 (n = 1 509 621) compared with 1.3% in 2006 (n = 1 558 090), 1.5% in 2007 (n = 1 178 596) and 1.9% (n = 974 497) in 2008 (refer to

Tables 4.1 and 4.16).

Both antidiabetics and antihypertensives may be used for the treatment of a variety of conditions, *inter alia* hypertension and diabetes. The prevalence of hypertension is approximately twice as high in diabetic patients as in the non-diabetic population (refer to paragraphs 2.6.1 and 2.9.3.3), with co-morbidities more common among men (Qvarnström *et al.*, 2010:2). In contrast, more than half of the patients in the data subsets that received both antidiabetics and antihypertensives were female, i.e. 52.1% ($n = 18\,312$) in 2005, 52.4% ($n = 20\,710$) in 2006, 53.3% ($n = 18\,128$) in 2007 and 52.9% ($n = 18\,027$) in 2008. The average ($\pm$ SD) ages of patients in this subset were similar, i.e.:

- 57.9 ± 13.14 years for males *viz.* 57.1 ± 14.23 years for females in 2005 ($d = 0.06$).
- 57.9 ± 12.88 years for males *viz.* 57.1 ± 14.19 years for females in 2006 ($d = 0.06$).
- 58.3 ± 12.81 years for males *viz.* 57.3 ± 14.25 years for females in 2007 ($d = 0.07$).
- 58.5 ± 12.41 years for males *viz.* 57.6 ± 13.97 years for females in 2008 ($d = 0.06$).

The d -values calculated in the preceding paragraph for the difference in the average age between males and females from the antidiabetic/antihypertensive category approached a very small difference level ($0.06 \leq d \leq 0.07$). Based on the 0.8 cut-off point for Cohen's d , this difference is of no practical significance. The d -values calculated for the difference per gender group over the 4-year study period were also very small ($d \leq 0.04$) - thus also indicating no practically significant difference in average age of patients between the respective study periods. Figure 4.9 shows the distribution of patients from the antidiabetic/antihypertensive category in relation to age group (years) and gender.

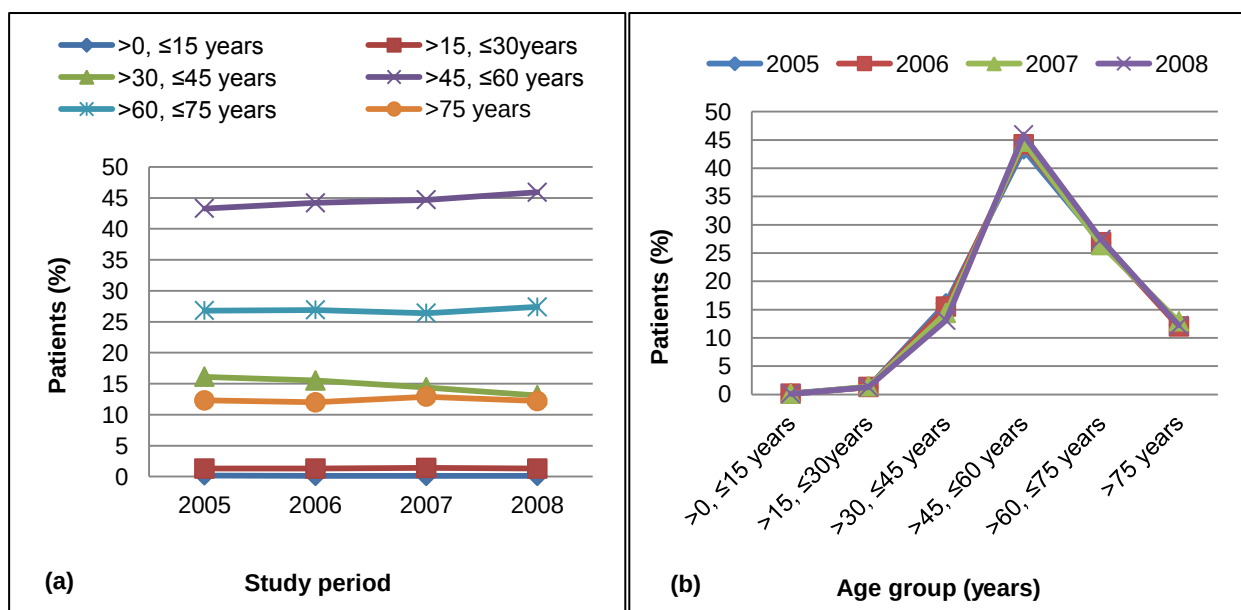


Figure 4.9: Distribution of patients from the antidiabetic/antihypertensive category in relation to study period and age group (years) (2005-2008)

Based on Figure 4.9(a), the number of patients in the antidiabetic/antihypertensive category remained relatively constant over the 4-year study period, except for patients aged 31-45 years (where a 3.0% decrease was observed) and those aged 46-60 years, where a 2.5% increase over the study period was observed. Stratification of the antidiabetic/antihypertensive category by age group [refer to Figure 4.9(b)] shows a relatively low “prevalence” in patients ≤ 30 years, thereafter increasing steeply to peak in patients aged 46-60 years, followed by another decline to “prevalence” values of approximately 27% for those aged 61-75 years and 12% for patients older than 75 years.

The prevalence of co-existing hypertension and diabetes appeared to be increasing with age (Epstein & Sowers, 1992:415; Movahed *et al.*, 2010:200). Among those with type 1 diabetes, the incidence of hypertension rose from 5% at age 10 years to 33% at 20 years and 70% at 40 years (Parving *et al.*, 1988:156). In patients with type 2 diabetes the prevalence of essential hypertension among diabetic adults increased by decade of life from 36% at ages 30-39 years to 70% at ages 70-79 years, reducing slightly thereafter to 67% among people over 80 years of age. The findings from a study by Jacober *et al.* (2006) showed that essential hypertension was also present in ~26% of children (aged 1-11 years) with type 2 diabetes and ~10% of adolescents aged 12 to 19 years.

Despite no diagnosis being available, it seems that the antidiabetic/antihypertensive category follows a similar pattern to that of the type 2 diabetics as described by Jacober and colleagues, although peaking earlier, with lower “prevalence” rates among patients ≤ 30 years. Patients from age groups 3 to 6, that is patients older than 30 years, furthermore represented the majority of patients from the antidiabetic/antihypertensive category, at 82.4% ($n = 18\,312$) for 2005, compared with 83.1% in 2006 ($n = 20\,710$), 84.0% in 2007 ($n = 18\,128$) and 85.5% ($n = 18\,027$) in 2008 (Table 4.16).

4.4.7.2 General prescribing patterns pertaining to the antidiabetic/antihypertensive category

The 2005-antidiabetic/antihypertensive category contained 159 413 prescriptions, which increased by 25.3% to 199 814 in 2006. A 13.8% decrease to 172 155 was then observed in 2007, followed by another 7.0% increase to 184 367 prescriptions in 2008 [an overall relative 16.0% increase vs. the 3% decrease observed in the total data subset (refer to paragraph 4.4.2)]. The number of prescriptions subsequently represented 1.9% ($n = 8\,391\,836$) of the number of prescriptions from the total dataset in 2005 compared with 2.2% in both 2006 ($n = 8\,906\,344$) and 2007 ($n = 7\,911\,072$) and 2.7% ($n = 6\,775\,863$) in 2008 (refer to Tables 4.1 and 4.16).

The number of medicine items claimed by the antidiabetic/antihypertensive category increased from 11.3% (n = 3 081 832) in 2005 to 12.7% (n = 3 458 538) in 2006, 11.6% (n = 3 304 273) in 2007 and 12.9% (n = 3 214 534) in 2008 (refer to Tables 4.8 and 4.16). The average number of medicine items per prescription claimed, was 2.2 ± 1.11 in 2005, compared with 2.2 ± 1.14 in 2006, 2.2 ± 1.15 in 2007 and 2.3 ± 1.18 in 2008. The *d*-value calculated for difference in the average number of medicine items claimed per prescription over the study period was less than 0.1 and therefore not practically significant.

The optimal management of patients with diabetes mellitus requires multiple medications - not only for glycaemic control but also for nephroprotection and for reducing cardiovascular risk. Hyperglycaemia, *per se*, may be treated easily with five or more antidiabetics (refer to paragraph 4.9.4.5.2). Based on treatment guidelines for hypertension in patients with type 2 diabetes, thiazide diuretics, angiotensin II receptor blockers and ACE inhibitors may be the best first-line treatments, although other agents are usually necessary and goals may not be achieved even with three or more agents (Vijan & Hayward, 2003:600). Up to five agents may be necessary to treat hypertension in patients with type 1 diabetes (Maahs *et al.*, 2005:303). In addition, all persons with diabetes should be treated with lipid-lowering agents as if they had prior coronary heart diseases (Juutilainen *et al.*, 2005:2905) and with low-dose aspirin to reduce adverse clinical outcomes (Clowell, 2003:S87). A patient with concomitant diabetes and hypertension may therefore easily be treated with six medicine agents (i.e. two oral antidiabetics, a statin, aspirin and two antihypertensives) (Poulter, 2010:110). The findings of this empirical investigation showed that patients from the antidiabetic/antihypertensive category received a maximum of 10 medicine items per prescription in 2005, increasing yearly over the study period to a maximum of 16 in 2008.

4.4.7.3 Direct medicine treatment cost associated with the antidiabetic/ antihypertensives category

The total direct medicine item treatment cost from the antidiabetic/antihypertensive category increased from R41.4 million in 2005 to R50.6 million in 2008 (a relative increase of 22.4%), after an initial 26.6% increase to R52.4 million in 2006 and subsequent 8.6% decline to R47.8 million in 2007 (Table 4.16). These costs represent 10.5% of the cost associated with the medicine treatment from the total data subset during 2005 (n = R394 586 482.52), compared with 12.1% in 2006 (n = R432 361 357.98) and 11.3% in 2007 (n = R424 665 162.64) and 12.6% (n = R400 155 046.30) in 2008 (refer to Tables 4.8 and 4.16). Medical aid schemes contributed 91.3% (n = R41 351 687.12) towards the direct medicine treatment cost of patients in 2005, decreasing to 90.5% (n = R52 364 199.07) during 2006, 89.4% (n = R47 846 760.88) in 2007 and 86.2% (n = R50 604 256.67) in 2008. This translates to an average scheme

contribution of $R108.35 \pm 133.43$ (median $R62.07$) in 2005, compared with $R107.60 \pm 136.96$ (median $R60.18$) in 2006, $R112.17 \pm 144.61$ (median $R65.29$) in 2007 and $R105.14 \pm 145.81$ (median $R60.64$) in 2008 (Table 4.16). Patients paid the excess out-of-pocket for co-payments on medicine items at an average $R10.35 \pm 30.17$ (median $R0.00$) per item per year for 2005, increasing to $R11.27 \pm 32.08$ (median $R0.00$) during 2006, $R13.24 \pm 32.47$ (median $R0.00$) in 2007 and $R16.85 \pm 37.14$ (median $R2.02$) in 2008.

The d -values calculated for the difference in the average contribution of patients' co-payment and medical aid schemes over the study period approached small levels ($0.01 \geq d \leq 0.18$) (Table 4.17). Based on the 0.8 cut-off point for Cohen's d , this difference is of no practical significance.

Table 4.17: Effect sizes: average contribution per medicine item from the antidiabetic/antihypertensive category (2005-2008)

	Average scheme contribution			Average patient co-payment		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.01	-	-	0.03	-	-
2007	0.03	0.03	-	0.09	0.06	-
2008	0.02	0.02	0.05	0.18	0.15	0.10

The average annual direct medicine treatment cost for a patient from the antidiabetic/antihypertensive category was $R2\ 258.17 \pm 2\ 719.75$ (median $R1\ 284.83$) in 2005, increasing to $R2\ 528.45 \pm 2\ 958.78$ (median $R1\ 528.21$) in 2006, $R2\ 784.38 \pm 3\ 131.45$ (median $R1\ 799.46$) in 2007 and $R2\ 807.14 \pm 3\ 190.56$ (median $R1\ 780.56$) in 2008. The annual cost of a patient receiving at least one antidiabetic and antihypertensive concomitantly, was therefore almost one and a half times to double that of any other patient from the total dataset (refer to paragraph 4.3.3). Calculated d -values for this difference in annual direct medicine treatment cost between patients from the antidiabetic/antihypertensive category and those from the respective datasets (paragraph 4.3.3) approached medium effect size levels in both 2005 and 2006 ($d = 0.4$), to small levels for 2007 ($d = 0.2$) and 2008 ($d = 0.15$), respectively and were therefore practically insignificant. These annual costs per patient again excluded other medication taken concurrently. The total cost per patient from this subset will therefore be much higher than that of any other patient not receiving these two medicine items in combination.

4.4.8 Antihypertensive/hipolipidaemic category

In this section, a detailed overview of patients receiving both antihypertensives and hipolipidaemic agents is presented, based on the summary in Table 4.18.

Table 4.18: General characteristics of the antihypertensive/hipolipidaemic category (2005-2008)

	2005	2006	2007	2008
Number of patients (n)	39 594	39 999	36 930	36 253
Females	19 269	19 465	17 985	17 914
Males	20 308	20 515	18 943	18 339
Unknown gender	17	19	2	0
Age group 1 (>0, ≤15 years)	29	18	15	2
Age group 2 (>15, ≤30 years)	191	150	128	105
Age group 3 (>30, ≤45 years)	2 778	2 506	2 153	1 922
Age group 4 (>45, ≤60 years)	12 599	12 466	11 201	10 859
Age group 5 (>60, ≤75 years)	17 183	17 646	16 129	15 963
Age group 6 (>75 years)	6 814	7 213	7 304	7 402
Number of prescriptions (n)	398 547	425 179	436 855	407 784
Number of medicine items (n)	754 334	820 454	841 791	803 351
Medicine treatment cost (R)	106 024 255.88	111 399 745.79	112 843 244.42	103 542 084.98
Scheme contribution	93 945 401.90	97 118 565.73	97 112 065.09	85 600 742.09
Patient co-payment	12 078 853.98	14 281 180.06	15 732 351.54	17 941 342.89

The following discussion includes an overview of the total number of patients in the subset and the utilisation trends for prescriptions and medicine items claimed over the 4-year study period, stratified by age and gender. A discussion on the total direct cost of treatment associated with the antihypertensive/ hipolipidaemic category (also in relation to age and gender) follows in paragraph 4.4.8.3.

4.4.8.1 Demographic overview of the antihypertensive/hipolipidaemic category

Patients from the antihypertensive/hipolipidaemic category increased from 15.2% (n = 261 036) from the total data subset in 2005 to 16.3% (n = 226 264) in 2007 and 16.9% (n = 214 109) in 2008, after an initial decrease to 14.8% (n = 269 452) in 2006 (refer to Tables 4.8 and 4.18). Overall, these patients represented 2.6% of the total number of patients from the dataset in both 2005 (n = 1 509 621) and 2006 (n = 1 558 090) compared with 3.1% in 2007 (n = 1 178 596) and 3.7% (n = 974 497) in 2008 (refer to Tables 4.1 and 4.18).

Antihypertensives and hipolipidaemics may be used for the treatment of a variety of conditions, *inter alia*, hypertension and high serum cholesterol levels or low HDL-cholesterol levels. Hypercholesterolemia and hypertriglyceridemia are common in patients with high blood pressure (Ruixing *et al.*, 2009:251). The presence of these conditions is related to the severity of hypertension, age and gender of the patient (Sander & Giles, 2002:460). For example, in a study by O'Meara *et al.* (2004:1315) among American hypertensive patients, concomitant

dyslipidaemia was significantly more common among men than women. Similar findings from the Framingham Heart Study were published in the late 1990s (Lloyd-Jones *et al.*, 1999:2210) estimating a prevalence rate of 40-53% among men, compared with 33-43% of women. Although diagnosis was not available in this empirical investigation, the findings showed that in contrast to the findings of these authors, approximately half of the patients that received both antihypertensives and hipolipidaemic agents were male, at rates of 51.3% ($n = 39\,594$) in 2005, 2006 ($n = 39\,999$) and 2007 ($n = 36\,930$), respectively, and 50.6% ($n = 36\,253$) in 2008. The average prevalent age appeared earlier in males than in females by 4 years, at an average (+SD) age of:

- 61.1 ± 12.16 years for males viz. 64.9 ± 11.78 years for females in 2005 ($d = 0.31$).
- 61.5 ± 12.11 years for males viz. 65.4 ± 11.56 years for females in 2006 ($d = 0.32$).
- 61.9 ± 12.26 years for males viz. 66.2 ± 11.49 years for females in 2007 ($d = 0.35$).
- 62.4 ± 11.96 years for males viz. 66.5 ± 11.62 years for females in 2008 ($d = 0.34$).

The d -values calculated in the preceding paragraph for the difference in the average age between males and females from the antihypertensive/hipolipidaemic category, approached a medium level ($0.31 \leq d \leq 0.35$). Based on the 0.8 cut-off point for Cohen's d , these differences are of no practical significance. The d -values calculated for the difference per gender group over the 4-year study period were very small ($d \leq 0.13$) - thus also indicating no practically significant difference in average age of patients between the respective study periods.

Figure 4.10 shows the distribution of the number of patients (percentage) in the antihypertensive/hipolipidaemic category, stratified by study period and age groups (years).

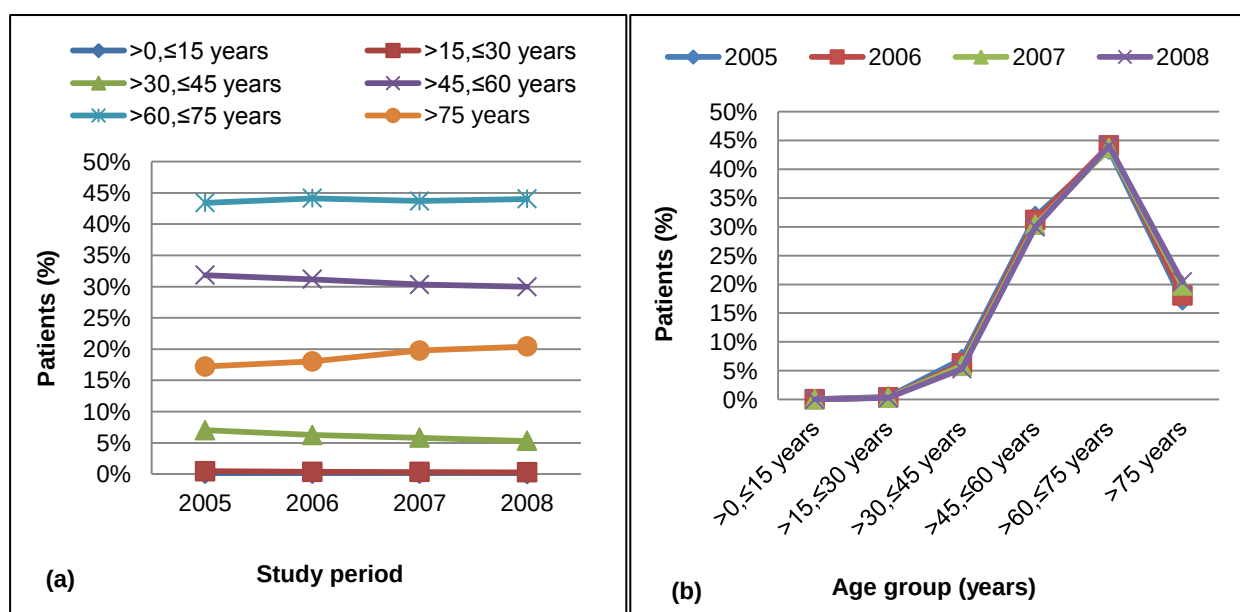


Figure 4.10: Distribution of patients from the antihypertensive/hipolipidaemic category in relation to study period and age group (years) (2005-2008)

Figure 4.10(a) shows that the number of patients in the antihypertensive/hipolipidaemic category remained relatively constant over the 4-year study period, except for patients aged 31-45 years and 46-60 years, where decreases of 1.7% and 1.9%, respectively were observed, and for those older than 75 years, where a 3.2% increase over the study period was observed. Stratification of the antihypertensive/hipolipidaemic category by age group [Figure 4.10(b)] showed a relatively low prevalence in patients aged ≤ 45 years, thereafter increasing steeply to approximately 30% in patients aged 46-60 years, peaking in patients aged 61-75 years at around 44%, followed by a decline to approximately 20% in patients older than 75 years.

According to Petrella and Merikle (2008:1152) patients aged >55 years are much more likely to be hypertensive, dyslipidaemic, or both, compared with those aged <55 years, except among those patients with a family history of coronary heart disease (CHD). In addition, the prevalence of hypertension and dyslipidaemia increases with age by decade until 75 years of age, after which the rates decline. Hendrix *et al.* (2005:14) furthermore showed that younger hypertensive patients with dyslipidaemia have fewer annual cholesterol measurements and are less likely to receive hipolipidaemic medication than older patients. Despite no diagnosis being available, it seems that the antihypertensive/hipolipidaemic category follow a pattern similar to hypertensive dyslipidaemic patients as described by Hendrix *et al.* (2005) and Petrella and Merikle (2008). Patients ≥ 45 years furthermore represented the majority of patients from the antihypertensive/hipolipidaemic category, at 92.4% ($n = 39\,594$) for 2005, compared with 93.3% in 2006 ($n = 39\,999$), 93.8% in 2007 ($n = 36\,930$) and 94.4% ($n = 36\,253$) in 2008 (Table 4.18).

4.4.8.2 General prescribing patterns pertaining to the antihypertensive/hipolipidaemic category

The number of prescriptions in the antihypertensive/hipolipidaemic category increased from 398 547 prescriptions in 2005 by 6.7% to 425 179 in 2006, and by another 2.8% to 436 855 in 2007 (Table 4.18). A 6.7% decline to 407 784 prescriptions in 2008 was observed thereafter [a relative 2.3% increase vs. the 3% decrease observed in the total data subset (refer to paragraph 4.4.2)]. Prescriptions subsequently represented 4.8% ($n = 8\,391\,836$) of the number of prescriptions from the dataset in 2005, compared with 4.8% in 2006 ($n = 8\,906\,344$), 5.5% ($n = 7\,911\,072$) in 2007; and 6.0% ($n = 6\,775\,863$) in 2008 (refer to Tables 4.1 and 4.18).

The number of medicine items claimed from the antihypertensive/hipolipidaemic category increased marginally from 24.5% ($n = 3\,081\,832$) in 2005 to 25.0% ($n = 3\,214\,534$) in 2008, after an initial 8.8% decline to 23.7% ($n = 3\,458\,538$) in 2006, followed by a 2.6% increase 25.5% ($n = 3\,304\,273$) in 2007 (refer to Tables 4.8 and 4.18). The number of medicine items claimed from this category furthermore represented 3.9% ($n = 19\,500\,774$) of the total number of medicine

items claimed from the datasets in 2005, compared with 3.9% ($n = 21\,113\,422$) in 2006, 4.4% ($n = 19\,075\,724$) in 2007; and 4.9% ($n = 16\,439\,253$) in 2008 (refer to Tables 4.1 and 4.18).

An average 1.9 ± 0.84 medicine item were claimed per prescription in 2005 compared with 1.9 ± 0.87 in 2006, 1.9 ± 0.88 in 2007 and 2.0 ± 0.90 in 2008. The d -value calculated for difference in the average number of medicine items claimed per prescription in this subset over the study period was less than 0.2 and therefore of no practical significance. Patients from the antihypertensive/hipolipidaemic category received a maximum of 11 medicine items per prescription in both 2005 and 2006 compared with a maximum of 10 in 2007 and 12 in 2008.

4.4.8.3 Direct medicine treatment cost associated with the antihypertensive/hipolipidaemic category

The total direct medicine treatment cost of the antihypertensive/hipolipidaemic category decreased from R10.6 million in 2005 to R10.3 million in 2008 (a relative decrease of 2.0%), after an initial increase to R11.2 million in 2006 and R11.2 million in 2007 (Table 4.18). These costs represent 26.9% of the direct medicine treatment cost from the total data subset during 2005 ($n = R394\,586\,482.52$) compared with 25.8% in 2006 ($n = R432\,361\,357.98$), 26.6% in 2007 ($n = R424\,665\,162.64$) and 25.9% ($n = R400\,155\,046.30$) in 2008 (refer to Tables 4.8 and 4.18). Medical aid schemes contributed 88.6% ($n = R106\,024\,255.88$) towards the direct medicine treatment cost of patients in 2005, decreasing to 87.2% ($n = R111\,399\,745.79$) during 2006, 86.1% ($n = R112\,843\,244.42$) in 2007 and 82.7% ($n = R103\,542\,084.98$) in 2008. This translated to an average scheme contribution of $R124.54 \pm 73.49$ (median R115.38) in 2005 compared with $R118.37 \pm 71.99$ (median R113.08) in 2006, $R115.36 \pm 69.06$ (median R111.00) in 2007 and $R106.55 \pm 63.86$ (median R105.42) in 2008. Patients paid the excess out-of-pocket for levies on medicine items at an average $R16.01 \pm 29.79$ (median R0.00) per item per year for 2005 compared with $R17.41 \pm 32.90$ (median R0.00) during 2006, $R18.69 \pm 34.57$ (median R0.16) in 2007 and $R22.33 \pm 36.51$ (median R8.64) in 2008. Table 4.19 shows the d -values calculated for the difference in the average contribution of patients' co-payment and medical aid schemes over the study period.

Table 4.19: Effect sizes: average contribution per medicine item from the antihypertensive/hipolipidaemic category (2005-2008)

	Average scheme contribution			Average patient co-payment		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.08	-	-	0.04	-	-
2007	0.12	0.04	-	0.08	0.04	-
2008	0.24	0.16	0.13	0.17	0.13	0.10

The d -values depicted in Table 4.19 approach medium levels ($0.04 \leq d \leq 0.24$) (Table 4.19). Based on the 0.8 cut-off point for Cohen's d , the difference in the average contribution of patients' co-payment and medical aid schemes is of no practical significance.

The direct medicine treatment cost per year for a patient from the antihypertensive/hipolipidaemic category summed to R2 677.79 $\pm$ 2 001.35 (median R2 356.22) in 2005 compared with R2 785.06 $\pm$ 1 956.51 (median R2 486.47) in 2006, R2 966.28 $\pm$ 1 956.51 (median R2 675.44) in 2007 and R2 856.10 $\pm$ 1 906.39 (median R2 547.18) in 2008. The direct medicine treatment cost per year of a patient receiving at least one antihypertensive and hipolipidaemic concomitantly was therefore one and a half times to double that of any other patient from the respective datasets (refer to paragraph 4.3.3). Calculated d -values for the differences in annual direct medicine treatment cost between patients from the antihypertensive/hipolipidaemic category and those from the respective datasets (paragraph 4.3.3) approached medium effect size levels in 2005 ($d = 0.5$), 2006 ($d = 0.4$), and 2007 ($d = 0.3$) to small levels for 2008 ($d = 0.15$), respectively and were therefore practically insignificant.

4.4.9 Antidiabetic/hipolipidaemic category

In this section, a detailed overview of patients receiving both antidiabetic and hipolipidaemic agents (i.e. antidiabetic/hipolipidaemic category) is presented (refer to Table 4.20).

Table 4.20: Demographic overview of the antidiabetic/hipolipidaemic category (2005-2008)

	2005	2006	2007	2008
Number of patients (n)	2 777	3 126	2 934	2 940
Females	1 133	1 285	1 202	1 212
Males	1 643	1 840	1 732	1 728
Unknown gender	1	1	0	0
Age group 1 (>0, $\leq$ 15 years)	8	4	5	7
Age group 2 (>15, $\leq$ 30 years)	71	66	63	68
Age group 3 (>30, $\leq$ 45 years)	539	607	561	533
Age group 4 (>45, $\leq$ 60 years)	1 225	1 388	1 323	1 344
Age group 5 (>60, $\leq$ 75 years)	779	868	791	814
Age group 6 (>75 years)	155	193	191	174
Number of prescriptions (n)	23 776	28 415	29 529	28 710
Number of medicine items (n)	42 926	52 253	55 224	53 928
Medicine treatment cost (R)	6 769 376.27	7 861 055.79	8 407 556.23	8 144 933.90
Scheme contribution	6 284 034.09	7 225 082.11	7 633 271.27	7 294 277.65
Patient co-payment	485 342.18	635 973.68	774 284.96	850 656.25

The discussion includes an overview of the total number of patients in the category and the

utilisation trends for prescriptions and medicine items claimed over the 4-year study period, stratified by age and gender. A discussion on the total direct cost of treatment associated with the antidiabetic/hipolipidaemic category (also in relation to age and gender) follows in paragraph 4.4.9.3.

4.4.9.1 Demographic overview of the antidiabetic/hipolipidaemic category

Patients from the antidiabetic/hipolipidaemic category represented 1.1% in both 2005 ($n = 261\ 036$) and 2006 ($n = 269\ 452$) of the number of patients from the data subset increasing marginally to 1.4% ($n = 226\ 264$) in both 2007 and 2008 ($n = 214\ 109$) (refer to Tables 4.8 and 4.20). Overall, these patients represented 0.2% of the total number of patients from the dataset in both 2005 ($n = 1\ 509\ 621$) and 2006 ($n = 1\ 558\ 090$) compared with 0.3% in both 2007 ($n = 1\ 178\ 596$) and 2008 ($n = 974\ 497$) (refer to Tables 4.1 and 4.20).

Antidiabetics and hipolipidaemics may be used for the treatment of a variety of conditions, *inter alia* hyperglycaemia and dyslipidaemia. Increased levels of serum triglycerides and decreased HDL-cholesterol are characteristic lipid abnormalities not only in patients with type 2 diabetes but also in those with impaired glucose tolerance (refer to paragraphs 2.9.4.3). For example, findings from the Framingham Heart Study (Kannel, 1985:1105) showed that the prevalence of low HDL-cholesterol levels in those with diabetes mellitus was almost twice as high as the prevalence in non-diabetic individuals (21% vs. 12% in men and 25% vs. 10% in women, respectively). The Framingham Heart Study also found that the prevalence of high plasma triglyceride levels in individuals with diabetes mellitus (19% in men and 17% in women) were significantly higher than in those without diabetes mellitus (9% of men and 8% of women). Similar results were found in the UK Prospective Diabetes Study (UKPDS, 1997:1685), the San Antonio Study (Mahaney *et al.*, 1995:3245) and the Cardiovascular Health Study (Kuller *et al.*, 1994:1174), establishing higher prevalence of diabetic dyslipidaemia among men compared with their female counterparts. In agreement to these findings, the results of this empirical investigation showed that about 60% of the patients that received both antidiabetics and hipolipidaemics were male [i.e. 59.2% ($n = 2\ 777$) in 2005, 58.9% in 2006 ($n = 3\ 126$) and 59.0% in 2007 ($n = 2\ 934$), respectively, compared with 58.8% ($n = 2\ 940$) in 2008] (Table 4.20). The average prevalent age appeared earlier in females than in males by 1 to 2 years, at average (+SD) ages of:

- 55.2 ± 12.10 years for males *viz.* 53.5 ± 13.82 years for females in 2005 ($d = 0.12$).
- 55.7 ± 12.16 years for males *viz.* 53.6 ± 13.24 years for females in 2006 ($d = 0.16$).
- 55.5 ± 12.29 years for males *viz.* 54.1 ± 13.42 years for females in 2007 ($d = 0.10$).
- 55.5 ± 11.96 years for males *viz.* 54.2 ± 13.51 years for females in 2008 ($d = 0.10$).

The d -values calculated in the preceding paragraph for the difference in the average age between

males and females from the antidiabetic/hipolipidaemic category approached a small level ($d \leq 0.16$). Based on the 0.8 cut-off point for Cohen's d , this difference is of no practical significance. The d -values calculated for the difference per gender group over the 4-year study period were very small ($0.01 \leq d \leq 0.05$) - thus also indicating no practically significant difference in average age of patients between the respective study periods. Figure 4.11 shows the distribution of the number of patients (percentage) in the antidiabetic/hipolipidaemic category, stratified by study period and age groups (years).

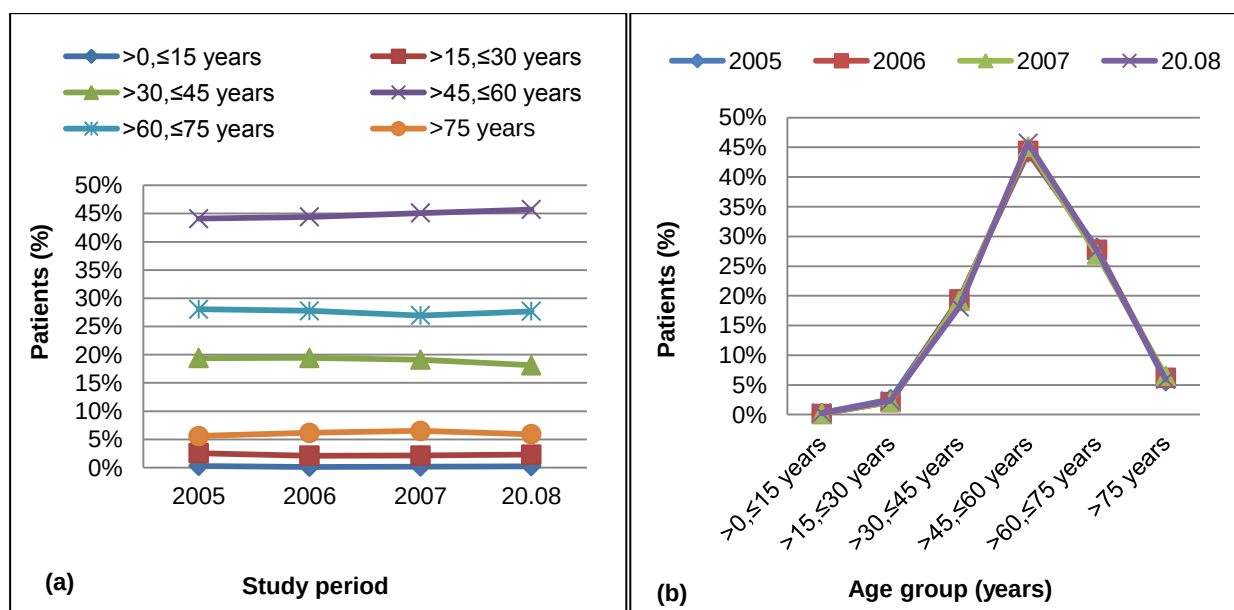


Figure 4.11: Distribution of patients from the antidiabetic/hipolipidaemic category in relation to study period and age group (years) (2005-2008)

Figure 4.11(a) shows that the number of patients in the antidiabetic/hipolipidaemic category decreased marginally over the 4-year study period, except for patients aged 46-60 years and those >75 years where increases of 1.6% and 0.3%, respectively were observed. Stratification of the antidiabetic/hipolipidaemic category by age group shows a relatively low prevalence in patients aged ≤30 years, thereafter increasing steeply to approximately 19% in patients aged 31-45 years, peaking in patients aged 46-60 years at around 45%, followed by decline to approximately 27% in patients aged 61-75 years and 6% in those older than 75 years [Figure 4.11(b)]. Patients aged 31-75 years furthermore represented the majority of patients from the antidiabetic/hipolipidaemic category, at 91.6% ($n = 2\,777$) for both 2005 and 2006 ($n = 3\,126$) compared with 91.2% in 2007 ($n = 2\,934$) and 91.5% ($n = 2\,940$) in 2008.

4.4.9.2 General prescribing patterns pertaining to the antidiabetic/hipolipidaemic category

Prescriptions from the antidiabetic/hipolipidaemic category increased by 19.5% from 23 776 in 2005 to 28 415 in 2006 and another 3.9% to 29 529 in 2007 (Table 4.20). A 3.0% decline to

28 710 prescriptions in 2008 was observed, thereafter [a relative increase of 20.8% vs. the 3% decrease observed in the total data subset (refer to section 4.4.2)]. Prescriptions subsequently represented 0.3% of the number of prescriptions from the dataset in 2005 ($n = 8\,391\,836$) and 2006 ($n = 8\,906\,344$) compared with 0.4% in both 2007 ($n = 7\,911\,072$) and 2008 ($n = 6\,775\,863$) (refer to Tables 4.1 and 4.20).

The number of medicine items claimed from the antidiabetic/hipolipidaemic category increased marginally from 1.4% ($n = 3\,081\,832$) in 2005 to 1.7% ($n = 3\,214\,534$) in 2008, after an initial increase to 1.5% ($n = 3\,458\,538$) in 2006, followed by a further 5.7% increase to 1.7% ($n = 3\,304\,273$) in 2007 (refer to Tables 4.8 and 4.20). The number of medicine items claimed from the antidiabetic/hipolipidaemic category furthermore represented 0.2% ($n = 19\,500\,774$) of the total number of medicine items claimed from the datasets in 2005 compared with 0.3% in 2006 ($n = 21\,113\,422$), 2007 ($n = 19\,075\,724$) and 2008 ($n = 16\,439\,253$) (refer to Tables 4.1 and 4.20). An average 1.8 ± 0.80 medicine item was claimed in 2005 compared with 1.8 ± 0.81 in 2006 and 1.9 ± 0.83 in 2007 and 1.9 ± 0.83 in 2008. The d -value calculated for difference in the average number of medicine items claimed per prescription over the study period was less than 0.3 and therefore of no practical significance. Patients from the antidiabetic/hipolipidaemic category received a maximum of 6 medicine items per prescription in 2005 compared with 8 in 2006, 7 in 2007 and 6 in 2008.

4.4.9.3 Direct medicine treatment cost associated with the antidiabetic/hipolipidaemic category

The total direct medicine treatment cost associated with the antidiabetic/hipolipidaemic category increased from R6.8 million in 2005 to R8.1 million in 2008 (a relative increase of 20.3%), after an initial increase to R7.9 million in 2006 and R8.4 million in 2007 (Table 4.20). These costs represent 2.0% of the cost associated with the medicine treatment from the data subset during 2005 ($n = R394\,586\,482.52$), 2007 ($n = R424\,665\,162.64$) and 2008 ($n = R400\,155\,046.30$) compared with 1.8% in 2006 ($n = R432\,361\,357.98$) (refer to Tables 4.8 and 4.20).

Medical aid schemes contributed 92.8% ($n = R6\,769\,376.27$) towards the direct medicine treatment cost of patients from the antidiabetic/hipolipidaemic category of 2005 compared with 91.9% ($n = R7\,861\,055.79$) during 2006, 90.8% ($n = R8\,407\,556.23$) in 2007 and 89.6% ($n = R8\,144\,933.90$) in 2008 (Table 4.20). This translated to an average scheme contribution of $R146.39 \pm 163.36$ (median R102.41) in 2005 compared with $R138.27 \pm 160.00$ (median R99.12) in 2006, $R138.22 \pm 164.21$ (median R98.78) in 2007 and $R135.26 \pm 170.95$ (median R94.69) in 2008. Patients paid the excess out-of-pocket for levies on medicine items at an average $R11.31 \pm 34.96$ (median R0.00) per item per year for 2005 compared with $R12.17 \pm 35.66$

(median R0.00) during 2006, $R14.12 \pm 39.91$ (median R0.00) in 2007 and $R15.77 \pm 37.66$ (median R1.04) in 2008. The d -values calculated for the difference in the average contribution of patients' co-payment and medical aid schemes over the study period approached medium levels ($0 \leq d \leq 0.12$) (Table 4.21). Based on the 0.8 cut-off point for Cohen's d , this difference is therefore of no practical significance.

Table 4.21: Effect sizes: average contribution per medicine item from the antidiabetic/hipolipidaemic category (2005-2008)

	Average scheme contribution			Average patient co-payment		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.05	-	-	0.02	-	-
2007	0.05	0.00	-	0.07	0.05	-
2008	0.07	0.02	0.02	0.12	0.10	0.04

The average direct medicine treatment cost per year for a patient from the antidiabetic/hipolipidaemic category was $R2\ 437.66 \pm 2\ 874.53$ (median R1 567.12) in 2005 compared with $R2\ 514.73 \pm 2\ 879.23$ (median R1 690.10) in 2006, $R2\ 865.56 \pm 3\ 163.88$ (median R1 932.93) in 2007 and $R2\ 770.39 \pm 3\ 093.52$ (median R1 844.92) in 2008. The yearly cost of a patient receiving at least one antidiabetic and hipolipidaemic agent concomitantly, was therefore again one and a half to double that of any other patient from the respective datasets (refer to paragraph 4.3.3). Calculated d -values for this difference in annual direct medicine treatment cost between patients from the antidiabetic/hipolipidaemic category and those from the respective datasets (paragraph 4.3.3) approached a large effect size level in 2006 ($d = 0.7$), medium effect size levels in 2005 ($d = 0.4$), compared with a small level for 2007 ($d = 0.2$) and 2008 ($d = 0.14$), respectively and were therefore practically insignificant. These annual costs per patient from the antidiabetic/hipolipidaemic category again excluded other medication taken concurrently. The total cost per patient from this category will therefore also be much higher than that of any other patient not receiving these two medicine items in combination.

4.4.10 Data subsets summary

The data subsets consisted of individual subsets of data for 2005, 2006, 2007 and 2008, respectively obtained after the application of inclusion criteria (refer to Table 3.3). All patients on the medicine claims database receiving ≥ 1 medicine item(s) at any given time during a specific study period (year) from any (but at least ≥ 1) of the following pharmacological medicine classes (based on the MIMS® classification): antidiabetics, antihypertensives (including diuretics) and hipolipidaemics were included. The patients from each data subset were further categorised into 6 "at risk" categories and a "metabolic syndrome" category (the study population, discussed in

Section 4.5) (refer to Table 3.4). The 6 “at risk” categories were discussed in paragraphs 4.4.4 to 4.4.9.

This analysis was conducted to position patients with one or more risk factor for the development of metabolic syndrome [as defined by the definitions of the American Heart Association/National Heart, Lung and Blood Institute, and the joint interim statement (refer to paragraph 3.4.1)] with regard to all patients from the respective datasets. The analysis was further conducted to establish baseline demographic and utilisation trends with regard to medicine claims patterns (prescriptions and medicine items) and associated direct treatment cost for “at risk” patients. The key findings of this analysis are described in paragraph 5.3.2 (Chapter 5) under the heading “conclusions derived from the empirical investigation”.

4.5 ANALYSIS OF THE METABOLIC SYNDROME CATEGORY

The study population or metabolic syndrome category consisted of all patients on the medicine claims database with a claim for at least one medicine item(s) per year from each of the pharmacological drug classes of antihypertensives (including diuretics) (based on the MIMS® classification 7.3 and 16.1), hipolipidaemics (MIMS® classification 7.7) and antidiabetics (MIMS® classification system for medicines 19.1), for the period January 1, 2005 through December 31, 2008 (refer to Step 3 of Figure 4.1). The discussion in this section entails an overview of the respective metabolic syndrome-categories obtained from the central database of a South African PBM from the period January 1, 2005 to December 31, 2008, based on the following specific objectives:

- Determine the prevalence and demographic profile of metabolic syndrome patients.
- Review claims patterns (prescriptions and medicine items) for metabolic syndrome patients, stratified by age and gender.
- Determine the direct medicine treatment cost of metabolic syndrome patients, stratified by age and gender.
- Determine a prescribing index for metabolic syndrome patients based on prescribing volume and cost of medicine items.

In addition, the 2008 data subset was used to determine the:

- prescribing volume, nature and direct cost of the most claimed treatment regimens used for metabolic syndrome patients, and
- prevalence of chronic conditions co-occurring in metabolic syndrome patients.

The total number of patients in the respective datasets (n) (refer to Table 4.1) was used as denominator for all calculations in this section, except where explicitly stated otherwise.

4.5.1 Demographic overview of the metabolic syndrome category

This section provides an overview on the prevalence and basic demographic characteristics of patients from the metabolic syndrome category over the 4-year study period. Table 4.22 provides a summary of these basic characteristics (values are frequencies). The discussion in subsequent paragraphs includes an overview of the total number of patients from each year, stratified by gender and age.

Table 4.22: Demographic overview of the metabolic syndrome category (2005-2008)

	2005	2006	2007	2008
Number of patients (n)	14 914	17 372	17 632	17 866
Females	6 792	7 968	8 230	8 234
Males	8 114	9 400	9 402	9 632
Unknown gender	8	4	0	0
Age group 1 (>0, ≤15 years)	4	5	4	2
Age group 2 (>15, ≤30 years)	63	60	56	53
Age group 3 (>30, ≤45 years)	1 078	1 119	1 093	992
Age group 4 (>45, ≤60 years)	5 005	5 762	5 819	5 768
Age group 5 (>60, ≤75 years)	6 378	7 487	7 460	7 641
Age group 6 (>75 years)	2 386	2 939	3 200	3 410

The data from this empirical investigation show that the number of patients identified as metabolic syndrome gradually increased from 1.0% of the total number of patients from the dataset in 2005 ($n = 1\,509\,621$) to 1.1% in 2006 ($n = 1\,558\,090$), 1.5% in 2007 ($n = 1\,178\,596$) and 1.8% in 2008 ($n = 974\,497$) (refer to Tables 4.1 and 4.22). Metabolic syndrome patients from 2005 therefore represented 5.7% ($n = 261\,036$) of all patients from the corresponding data subset for that year (refer to Table 4.8). This prevalence rate increased to 6.5% ($n = 269\,452$) in 2006, 7.8% ($n = 226\,264$) in 2007 and 8.3% ($n = 214\,109$) in 2008. Because the diagnosis of metabolic syndrome requires the presence of any three of the five risk factors, many combinations will lead to that diagnosis. The prevalence rate in this empirical investigation was calculated based on surrogate markers (i.e. the concurrent use of antidiabetics, antihypertensives and hipolipidaemic agents per patient as provided for by the American Heart Association and the new joint statement's diagnostic criteria (refer to paragraph 3.4.1); this "prevalence rate" is therefore likely to be a conservative estimate. Other shortcomings of the use of medication for prevalence estimating purposes have been addressed in paragraph 3.9.2.

In keeping with general epidemiological studies conducted on metabolic syndrome (refer to paragraph 2.5.1) (and subsequent contrast to that indicated by epidemiological studies conducted in South African populations (refer to paragraph 2.5.2), the demographic data of this empirical investigation show that more than half of the patients from the metabolic syndrome categories

(2005-2008) were male (female to male ratio: 1:1.2). Also in agreement with general epidemiological findings (paragraph 2.5.1), the average prevalent age appeared earlier in males than in females by 2 years, at average (+SD) ages of:

- 61.7 ± 11.54 years for males viz. 63.6 ± 12.40 years for females in 2005 ($d = 0.15$).
- 62.0 ± 11.59 years for males viz. 64.3 ± 12.06 years for females in 2006 ($d = 0.19$).
- 62.2 ± 11.59 years for males viz. 64.6 ± 12.32 years for females in 2007 ($d = 0.19$).
- 62.6 ± 11.61 years for males viz. 65.0 ± 12.26 years for females in 2008 ($d = 0.20$).

The d -values calculated in the preceding paragraph for the differences in the average age between males and females from the metabolic syndrome category, approached a small level ($d \leq 0.2$). Based on the 0.8 cut-off point for Cohen's d , this difference is of no practical significance. The d -values calculated for the difference per gender group over the 4-year study period (i.e. from 2005 to 2008) were also very small ($0.02 \leq d \leq 0.11$) - also indicating no practically significant difference in average age of males or females between the respective study periods.

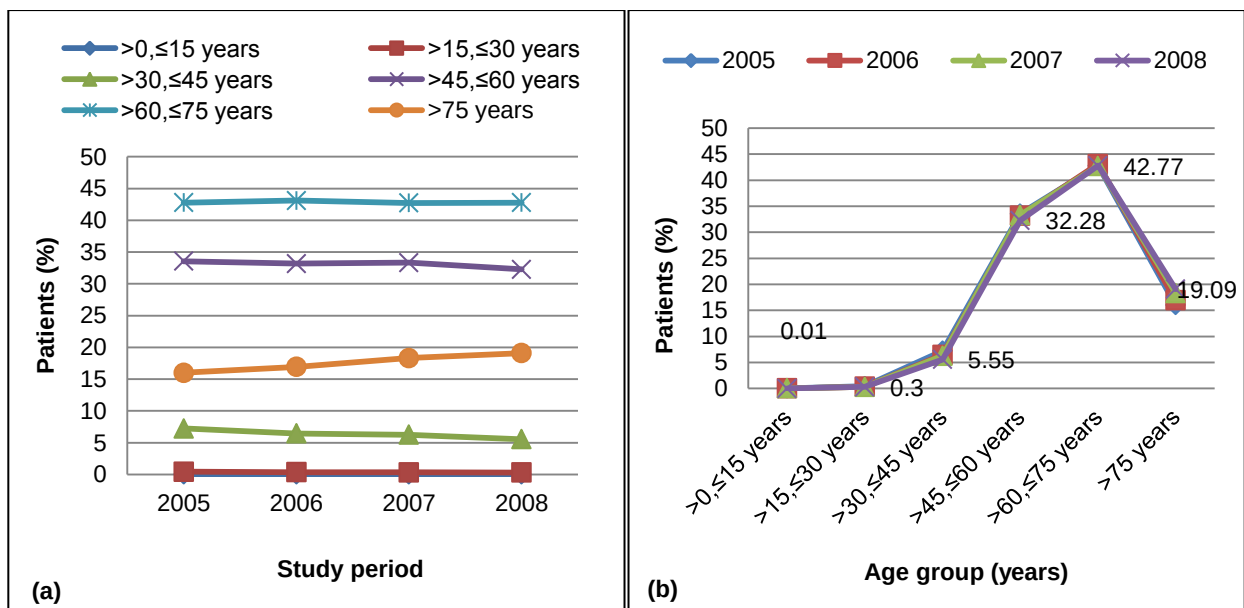


Figure 4.12: Distribution of patients from the metabolic syndrome category in relation to study period and age group (years) (2005-2008)

Figure 4.12(a) shows that the number of patients from age groups 1 to 4 (i.e. patients ≤60 years of age) in the data subset decreased marginally over the 4-year study period by 0.02%, 0.13%, 1.7% and 1.3%, respectively. The prevalence of the metabolic syndrome is highly age-dependent (refer to paragraph 2.5.1). In agreement, stratification of the metabolic syndrome category by age group showed a relatively low prevalence in patients from age groups 1 and 2, i.e. patients' ≤30 years, thereafter increasing to approximately 6% in patients aged 31-45 years. The prevalence rate from then on increased steeply to approximately 30% for patients aged 46-60 years, peaking in those

aged 61-75 years at around 40%, subsequently lowering to approximately 20% for mature patients older than 75 years [Figure 4.12(b)].

Age *per se* is a major risk factor for metabolic syndrome (refer to section 2.3); it is therefore not unexpected that the prevalence distribution increased with age. More than 90% of the metabolic syndrome category population were ≥ 45 years, at 92.3% ($n = 14\,914$) for 2005, increasing to 93.2% in 2006 ($n = 17\,372$), 93.5% in 2007 ($n = 17\,632$) and 94.1% ($n = 17\,866$) in 2008. Mature patients >75 years, however, represented between 3.7% ($n = 65\,356$) of the total number of patients in the corresponding age group from the 2005-dataset (refer to Tables 4.1 and 4.22), though increasing to 4.5% ($n = 65\,969$) in 2007, 5.9% in 2007 ($n = 54\,385$) and 6.2% in 2008 ($n = 51\,489$). Similar prevalence patterns were observed in patients aged 61-75 years, representing 4.1% ($n = 157\,443$) of all patients in that specific age group from the 2005-dataset, increasing to 4.6% ($n = 162\,882$) in 2006, 6.0% ($n = 123\,688$) in 2007 and 6.4% ($n = 118\,947$) in 2008 (refer to Table 4.1).

4.5.2 General medicine prescribing patterns for the metabolic syndrome category

The following section includes an overview of the utilisation trends of prescriptions and medicine items claimed over the 4-year study period for patients from the metabolic syndrome category, in relation to gender and age, based on the data provided in Table 4.23 (values are frequencies). A discussion on the rationale and potential indications for the use of the most claimed medicines or active substances over the study period, follows in paragraph 4.5.2.3.

Table 4.23 shows that the 2005 metabolic syndrome category contained 191 747 prescriptions, increasing by 23.9% to 237 503 in 2006. A further 4.1% increase was then observed to 247 322 in 2007, followed by a marginal 0.4% decline to 246 279 prescriptions in 2008 [a crude difference of 28.4% vs. the 19% decrease observed in the datasets over the study period (refer to paragraph 4.3.2)]. Prescriptions from the metabolic syndrome category furthermore represented 2.3% ($n = 8\,391\,836$) of the number of prescriptions from the dataset in 2005, compared with 2.7% ($n = 8\,906\,344$) in 2006, 3.1% ($n = 7\,911\,072$) in 2007; and 3.6% ($n = 6\,775\,863$) in 2008 (refer to Tables 4.1 and 4.23).

Medicine items for this patient category increased by an overall 35.1% from 2005 to 2008, after an initial steep increase of 25.2% to 616 359 in 2006. This was followed by a further 7.6% increase to 663 052 in 2007 (Table 4.23). The number of medicine items claimed from the metabolic syndrome category represented 2.5% ($n = 19\,500\,774$) of all items claimed from the dataset in 2005, increasing to 2.9% ($n = 21\,113\,422$) in 2006, 3.5% ($n = 19\,075\,724$) in 2007 and 4.1% ($n = 16\,439\,253$) in 2008 (refer to Tables 4.1 and 4.23).

Table 4.23: Prescriptions and medicine items provided for the metabolic syndrome category (2005-2008)

	2005	2006	2007	2008
Number of prescriptions (n)	191 747	237 503	247 322	246 279
Female	88 842	110 242	113 476	115 372
Male	102 794	127 192	133 846	130 907
Unknown gender	111	69	0	0
Age group 1 (>0, ≤15 years)	28	16	23	11
Age group 2 (>15, ≤30 years)	505	612	484	579
Age group 3 (>30, ≤45 years)	10 607	12285	12 733	11 111
Age group 4 (>45, ≤60 years)	59 603	73459	77 373	73 948
Age group 5 (>60, ≤75 years)	85 366	106175	107 425	109 045
Age group 6 (>75 years)	35 638	44956	49 284	51 585
Number of medicine items (n)	492 333	616 359	663 052	664 969
Female	219 332	274 139	292 253	296132
Male	272 745	342 036	370 799	368 837
Unknown gender	256	184	0	0
Age group 1 (>0, ≤15 years)	62	29	51	25
Age group 2 (>15, ≤30 years)	1 124	1 352	1 311	1 374
Age group 3 (>30, ≤45 years)	26 802	32 473	34 033	30 168
Age group 4 (>45, ≤60 years)	157 570	198 388	214 779	208 011
Age group 5 (>60, ≤75 years)	224 048	279 283	292 986	300 200
Age group 6 (>75 years)	82 727	104 834	119 892	125 191

It seems that there are currently no established guidelines for the treatment of the metabolic syndrome *per se*. Furthermore, there are no therapeutic agents approved specifically for the treatment of the metabolic syndrome independent of those most appropriate for specific abnormal risk factors (refer to Sections 2.9 and 2.10). Pharmacological treatment of patients with the metabolic syndrome thus typically leads to polypharmacy - especially in those patients with type 2 diabetes or dyslipidaemia, where treatment with ten or more different kinds of medications is second nature (refer to paragraph 1.1). For example, Boyd *et al.* (2009:300) determined that metabolic syndrome patients with diabetes prescribed dual therapy for glucose control, antihypertensives, lipid-lowering agents and aspirin, had an average pill burden (average number of prescribed administrations per day) of 13.1. For the purpose of the present study, an average “pill burden per prescription” was calculated. Based on this calculation, an average 2.6 ± 1.43 medicine items was claimed per prescription during 2005 (compared with 2.6 ± 1.47 in 2006, 2.7 ± 1.52 in 2007 and 2.7 ± 1.53 in 2008). The number of items claimed per patient, however, ranged from a minimum of 1 item to a maximum of 16 items in 2005, 14 in 2006 and 2007, respectively and 19 in 2008.

4.5.2.1 Prescriptions and medicine items claimed per study period, in relation to gender

Stratification of the number of prescriptions and medicine items claimed per study period by

gender shows that coinciding with the larger number of males from the metabolic syndrome category (refer to paragraph 4.5.1), both prescriptions and medicine items claimed, were highest for this gender group (refer to Table 4.23). Approximately 54% of prescription claims in 2005 were for male patients, containing roughly 55% of claims for medicine items in the metabolic syndrome category vs. a 46% of prescriptions and 45% of medicine claims for females in 2005. This was a consistent finding over the study period (refer to Table 4.23). The specific medicine items claimed by each gender group (grouped based on pharmacological classification and active ingredient) are depicted in Tables C.7-C.9 (Annexure C). A summary of these claims patterns and the data summarised in Table 4.23, are provided here.

- **Antidiabetics**

Approximately a quarter of medicine item claims for female patients in the metabolic syndrome category was for antidiabetics [i.e. 25.4% (n = 219 332) in 2005 vs. 23.7% in 2006 (n = 274 139), 26.7% (n = 292 253) in 2007, and 24.9% (n = 296 132) in 2008]. Claims for antidiabetics in males represented a third of all claims in this gender group, remaining relatively constant over the study period, at 30.3% (n = 272 745) in 2005, compared with 29.0% (n = 342 036) in 2006, 30.8% (n = 370 799) in 2007 and 30.0% (n = 368 837) in 2008 (refer to Tables C.7, C.8 and C.9, Annexure C).

Tables C.7 and C.8 (Annexure C) show that metformin was by far the most notably claimed agent over the study period in both gender groups, increasing continuously from 47.1% (n = 55 635) in 2005 to 50.9% (n = 73 736) in 2008 in females, vs. 43.5% (n = 82 621) to 47.5% (n = 110 479) in 2005 and 2008, respectively for males. Tables C.7 and C.8 (Annexure C) furthermore, show that insulin was claimed second most of all antidiabetics for both gender groups, increasing marginally from 2005 to 2008 at 19.5% (n = 55 635) to 19.8% (n = 73 736) for females vs. 20.0% (n = 82 621) to 20.7% (n = 110 479) for males. Gliclazide was claimed third most, however decreasing from 16.4% in 2005 (n = 55 635) to 14.9% (n = 73 736) in 2008 in females and correspondingly from 16.4% (n = 82 621) to 15.1% (n = 110 479) in males. Claims for both glimepiride and glibenclamide also decreased over the study period, from 6.1% and 4.6% (n = 55 635), respectively in females [vs. 7.6% and 5.4% (n = 82 621) in males] in 2005 to a corresponding 4.3% and 3.5% (n = 73 736) for females and 5.3% and 4.2% (n = 110 479) for males in 2008. Other oral antidiabetics claimed for both gender groups from the metabolic syndrome category included pioglitazone, rosiglitazone, the fixed-dose combination of metformin and glibenclamide, glipizide, the meglitinides (nateglinide and repaglinide), chlorpropamide and acarbose.

A small number of claims for insulin glulisine, insulin lispro, biphasic insulin, pre-mixed insulin

isophane and regular insulin was reported for both groups (refer to Tables C.7 and C.8, Annexure C).

- **Hipolipidaemics**

Approximately a quarter of all claims from 2005 to 2008 for both males and females from the metabolic syndrome category were for hipolipidaemic agents (refer to Tables C.7 and C.8, Annexure C).

Simvastatin (monotherapy and in combination with ascorbic acid, citric acid monohydrate and butylated hydroxyanisole) was the most significantly claimed hipolipidaemic in both gender groups, representing approximately half of all claims in these two groups (refer to Tables C.7 and C.8, Annexure C). Atorvastatin was claimed second most, although decreasing from 36.5% (n = 55 235) in 2005 to 29.3% (n = 74 435) in 2008 for females and from 39.7% (n = 64 914) in 2005 to 30.3% (n = 89 681) in 2008 for males. Claims for both fluvastatin and pravastatin also decreased over the study period, from 3.9% and 4.9%, respectively in 2005 (n = 55 235), to a corresponding 1.9% and 2.9% in 2008 (n = 73 736) for females vs. a decrease from 3.0% and 4.2% (n = 64 914) in 2005, respectively to 1.5% and 2.5% (n = 89 681) in 2008 for males. Claims for lovastatin and rosuvastatin on the other hand both increased over the study period i.e. utilisation of lovastatin increased by 0.5% for females (vs. 0.2% for males), whereas that of rosuvastatin increased by almost 8% for females to 11% for males from 2006 to 2008. Among the fibrates, bezafibrate was most claimed for both gender groups. Other hipolipidaemic agents claimed, included ezetimibe, cholestyramine, acipimox and nicotinic acid (refer to Tables C.7 and C.8, Annexure C).

- **Antihypertensives**

About half of all medicine items claimed over the study period for females from the metabolic syndrome category was antihypertensives. Males received less antihypertensive medicine items than females, representing 46.3% (n = 272 745) of all claims in 2005 to 45.8% (n = 368 837) in 2008 (refer to Tables C.7 and C.8, Annexure C).

Most claims for females were diuretics, accounting for almost 31% of claims (n = 111 462) in 2005, decreasing to 26.5% (n = 147 961) in 2008. In particular, the agents indapamide and furosemide. Indapamide represented 24.2% (n = 34 231) and 24.1% (n = 39 263) of all diuretics claimed in 2005 and 2008 respectively, followed by furosemide, at 22.6% (n = 34 231) in 2005, and 23.4% (n = 39 263) in 2008. Claims for the fixed-dose combination of amiloride with hydrochlorothiazide represented 17.1% (n = 34 231) in 2005 and 16.5% in 2008 (n = 39 263)

(refer to Tables C.7 and C.8, Annexure C).

The pharmacological drug class of ACE inhibitors were claimed second most for females, accounting for 22-23% of claims, in particular perindopril (as monotherapy and in combination with indapamide) at 32.1% (n = 32 446) in 2005, increasing to 39.7% (n = 41 661) in 2008 and enalapril (as monotherapy and in combination with hydrochlorothiazide) at 25.4%, n = 32 446) in 2005, however, decreasing to 23.2% (n = 41 661) in 2008. Claims for lisinopril (monotherapy and in combination with hydrochlorothiazide) also increased marginally over the study period, from 18.8% in 2005 (n = 32 446) to 20.0% (n = 41 661) in 2008. In comparison, the ACE inhibitors were claimed most for males from the metabolic syndrome category, accounting for 35.4% of claims (n = 272 745) in 2005, decreasing to 33.8% (n = 368 837) in 2008. Similar to utilisation patterns in females, perindopril (as monotherapy and in combination with indapamide) in particular, were the most significantly claimed agents in this pharmacologic medicine class for males, at 32.4% (n = 44 685) in 2005, increasing to 41.5% (n = 57 033) in 2008, followed by claims for enalapril (as monotherapy and in combination with hydrochlorothiazide) representing 23.7%, n = 44 685) of ACE inhibitor claims in 2005, decreasing to 20.9% (n = 57 033) in 2008. Lisinopril (monotherapy and in combination with hydrochlorothiazide) was also significantly claimed in males, representing 18.0% (n = 44 685) of ACE inhibitor claims in 2005, and 19.2% (n = 57 033) in 2008 (refer to Tables C.7 and C.8, Annexure C).

Diuretics were claimed second most in males, accounting for 23.9% (n = 156 922) of antihypertensive claims in 2005, decreasing to 20.2% (n = 168 884) in 2008. The agents most claimed within this class were furosemide, representing 27.3% (n = 30 167) to 30.5% (n = 34 044) of all diuretics claimed in 2005 and 2008 respectively, and indapamide, representing 24.7% (n = 30 167) in 2005 to 23.1% (n = 34 044) in 2008. Claims for spironolactone (monotherapy and in combination with isobutyl hydrochlorothiazide) were claimed third most of all diuretics claimed for males, representing 15.9% (n = 30 167) in 2005, increasing to 18.7% in 2008 (n = 34 044) (refer to Table C.8, Annexure C).

Angiotensin II receptor blockers (ARBs) represented 14.5% (n = 111 462) of claims in females in 2005, increasing marginally over the study period to 15.9% (n = 147 961) in 2008. Claims for males remained relatively stable over the study period, with ARBs representing 14.2% (n = 272 745) of antihypertensive medicine items claimed in 2005 and 14.3% (n = 368 837) in 2008 (refer to Tables C.7 and C.8, Annexure C). Individual ARBs most frequently claimed for females included candesartan [representing 24.2% (n = 16 183) of claims in 2005, decreasing to 16.9% (n = 23 459) in 2008], losartan (monotherapy and in combination with hydrochlorothiazide) at 24.0% (n = 16 183) in 2005, decreasing again to 21.7% (n = 23 459) in 2008, and valsartan (monotherapy and in combination with hydrochlorothiazide), accounting for 25.6% (n = 16 183)

and 28.9% (n = 23 459) of claims in 2005 and 2008, respectively. These three individual ARBs were also the most frequently claimed ARBs in male patients, however, in different ranking order based on prescribing volume. For example, valsartan (monotherapy and in combination with hydrochlorothiazide) was claimed most significantly in males, accounting for 28.3% (n = 17 945) of ARB-claims in 2005, decreasing to 26.9% (n = 24 095) in 2008. Candesartan was claimed second most in this medicine class, at 24.6% (17 945) in 2005, also decreasing to 16.3% (24 095) in 2008. Claims for losartan in males remained stable over the study period, ranging from 22.4% (n = 17 945) in 2005 to 22.6% (n = 24 095) in 2008. The utilisation of eprosartan and telmisartan (monotherapy and in combination with hydrochlorothiazide) increased significantly over the study period in both gender groups, with a 5.8% increase in females vs. a 4.9% increase in males for eprosartan and a 1.3% increase in the utilisation of telmisartan in females vs. a more pronounced 5.1% increase in males (refer to Tables C.7 and C.8, Annexure C).

Claims for adrenergic receptor blockers increased marginally from 14.3% (n = 111 462) of antihypertensive claims in females from 2005 to 15.7% (n = 147 961) in 2008; claims in males increased correspondingly from 17.8% (n = 126 165) to 19.7% (n = 168 884) (refer to Tables C.7 and C.8, Annexure C). Bisoprolol (monotherapy and in combination with hydrochlorothiazide) was claimed most significantly within this medicine class, representing 45.2% (n = 17 347) of claims in females from 2005, vs. 53.9% (n = 24 691) in 2008 [Claims in males represented 37.6% (n = 22 437) and 46.9% (n = 33 309) in 2005 and 2008, respectively]. Claims for carvedilol represented 28.4% (n = 17 347) of claims in 2005, decreasing to 15.7% (n = 24 691) in 2008 in females; in males, claims represented 32.4% (n = 22 437) and 30.6% (n = 33 309) in 2005 and 2008, respectively (refer to Tables C.7 and C.8, Annexure C).

4.5.2.2 Prescriptions and medicine items claimed per study period, in relation to age

In this section an overview of the number of prescriptions and medicine items and classification of medicine items claimed from the metabolic syndrome category, according to age group is provided. The specific medicine items claimed by each gender group (grouped based on pharmacological classification and active ingredient) are depicted in Tables C.10-C.15 (Annexure C). A summary of these claims patterns is provided here.

- **Children and pre-adolescents >0,≤15 years (age group 1)**

Children up to the age of 15 years (age group 1, n = 4) received 28 prescriptions in 2005 (0.01%, n = 191 747), containing 62 medicine items (0.01%, n = 492 333). Both prescriptions and medicine items thereafter decreased from 16 prescriptions (0.01%, n = 237 503) and 29 items (0.005%, n 616 359), respectively in 2006 to 11 prescriptions (0.004%, n = 246 279) and 25

medicine items (0.004%, n = 664 969) in 2008 (refer to Table 4.23).

Table C.10 (Annexure C) shows that about 25% (n = 62) of claims for children ≤15 years in the metabolic syndrome category in 2005 was for antidiabetics, declining steeply to 13.8% in 2006 (n = 29) and 5.9% (n = 51) in 2007, afterwards increasing to 24.0% (n = 25) in 2008. Insulin was by far the most claimed agent over the study period, although decreasing from 17.7% (n = 62) in 2005 to 12.0% (n = 25) in 2008. Table C.10 (Annexure C) furthermore shows that one claim for insulin glulisine (rapid-acting analogue) was recorded in 2008 (0.4%, n = 25). Fewer than 8.1% of claims over the study period were for oral antidiabetics. Metformin was claimed most of the oral antidiabetics and second most of all antidiabetics claimed for children and pre-adolescents ≤15 years over the study period, increasing from 6.4% (n = 62) of claims in 2005 to 8% (n = 25) in 2008 after an initial decline to 3.5% in 2006. One claim for glibenclamide was recorded in 2005 (1.6%, n = 62) and one for the combination of glibenclamide with metformin in 2006 (3.5%, n = 29) (refer to Table C.10, Annexure C).

Between 2005 and 2008, approximately 23% to 32% of claims for children and pre-adolescents ≤15 years were for hipolipidaemic agents [after an initial decline to 13.8% (n = 29) in 2006] (refer to Table C.10, Annexure C). Atorvastatin was the most significantly claimed hipolipidaemic in this patient group in 2005, at 16.1% (n = 62). From 2006 to 2008, however, claims decreased from 13.8% (n = 29) to 8.0% (n = 25), whilst that for simvastatin increased from 6.5% (n = 62) in 2005 to 24.0% (n = 25) in 2008. No other hipolipidaemics were claimed for this age group.

Slightly more than half of the medicine items claimed in 2005 (n = 62) were antihypertensives, increasing to 58.6% (n = 29) in 2006 and 64.7% (n = 51) in 2007, followed by a decline to 44.0% (n = 25) in 2008 (refer to Table C.10, Annexure C). Antihypertensives claimed most frequently in 2005 were the ACE inhibitors perindopril and ramipril, together accounting for 22.6% (n = 62) of claims in this age group, the angiotensin II receptor blockers losartan and amlodipine (both 8.1%, n = 62). In 2006, the diuretic spironolactone was mostly claimed (37.9%, n = 29), followed by perindopril at 6.9% (n = 29). In 2007 the ACE inhibitors were once again claimed the most, in particular enalapril (25.5%, n = 51) and captopril (7.8%, n = 51). Spironolactone represented almost 12% of claims in 2007 (n = 51). In 2008 the diuretic spironolactone was mostly claimed (16.0%, n = 25), followed by hydrochlorothiazide at 12.0% (n = 25) (refer to Table C.10, Annexure C). Claims for β-blockers (in particular bisoprolol as monotherapy and in combination with hydrochlorothiazide) represented 3.2% (n = 62) of claims for this age group in 2005, compared with 3.5% (n = 29) in 2006 and 2.0% (n = 51) in 2007. Other antihypertensives claimed, included the ACE inhibitors captopril (claimed only in 2007 at 7.8%, n = 51), lisinopril (claimed only in 2006 at 3.5%, n = 29) and the fixed-dose combination of perindopril and indapamide, claimed

at a rate of 3.9% (n = 51) in 2007; felodipine [claimed in 2005 at 4.8% (n = 62)], valsartan [claimed in 2006 at 3.5% (n = 29)], doxazosin [claimed in 2005 at 4.8% (n = 62)] and furosemide [claimed in 2007 at 3.9% (n = 51)] (refer to Table C.10, Annexure C).

In brief, the utilisation of individual agents such as insulin glulisine, metformin, simvastatin and hydrochlorothiazide increased relatively by 4.0%, 1.6%, 17.5% and 4.2%, respectively from 2005 to 2008, whilst that of other agents claimed for this age group, decreased. Table C.10 (Annexure C) furthermore shows that more than 96% of medicine items claimed for children and pre-adolescents up to the age of 15 years from the metabolic syndrome category were received as products containing one active ingredient. It is however possible that patients from this age group may have received some of these medicine items separately that may together form a product similar to a fixed-dose combination, for example, the metformin and glibenclamide (vs. the fixed-dose combination of metformin plus glibenclamide) and bisoprolol and hydrochlorothiazide, also available as a fixed-dose combination product (refer to Table C.10, Annexure C).

- **Adolescents, late adolescents and young adults >15, ≤30 years (age group 2)**

Adolescents and young adults aged 16 to 30 years (age group 2) received 505 prescriptions (0.26%, n = 191 747), containing 1 124 medicine items (0.23%, n = 492 333) in 2005 (Table 4.23). Both prescriptions and medicine items remained relative stable thereafter at 612 prescriptions (0.01%, n = 237 503) containing 1 352 items (0.22%, n 616 359) in 2006 to 484 prescriptions (0.20%, n = 247 322) containing 1 311 medicine items (0.20%, n = 663 052) in 2007, and 579 prescriptions (0.24%, n = 249 279) containing 1 374 (0.21%) medicine items (n = 664 969) in 2008 (Table 4.23).

Table C.11 (Annexure C) shows that about one fourth of claims in metabolic syndrome category in 2005 for patients aged 16-30 years (n = 1 124) was for antidiabetics, remaining relatively stable at 36.9% in 2006 (n = 1 352), 38.4% (n = 1 311) in 2007 and 39.3% (n = 1 374) in 2008. Insulin was by far the most significantly claimed antidiabetics over the study period, though decreasing from 23.4% (n = 1 124) in 2005 to 17% (n = 1 374) in 2008, followed by claims for metformin and gliclazide, respectively increasing from 11.2% in 2005 to 13.0% in 2008 (metformin) and 2.1% in 2005 to 5.3% in 2008 (gliclazide) (refer to Table C.11, Annexure C). A greater diversity of antidiabetics were claimed for patients in age group two compared with those patients aged ≤15 years, for example, claims for antidiabetics included also agents such as glipizide [claimed only once in 2006 (0.07%, n = 1 124)], glimepiride (claimed once during 2005, 2006 and 2008, respectively), the benzoic acid derivative repaglinide (claimed in 2005 only, representing 0.4%, n = 1 124) and the thiazolidinediones pioglitazone (claimed 2006-2008) and rosiglitazone (claimed 2006 and 2008 only) (refer to Table C.11, Annexure C).

About a quarter of claims over the study period in this age group was for hipolipidaemic agents. Simvastatin was the most significantly claimed hipolipidaemic in adolescents and young adults aged 16-30 years at 13.1% (n = 1 124) in 2005, increasing marginally to 16.7% (n = 1 311) in 2007, subsequently decreasing to 12.7% (n = 1 374) in 2008 (refer to Table C.11, Annexure C). Atorvastatin was claimed second most for patients in this age group (decreasing from 8.2% in 2005 to 7.4% in 2008). In addition, a greater variety of hipolipidaemic agents were also claimed for this patient group compared with those patients aged ≥ 15 years, for example, other statins claimed included fluvastatin, lovastatin, pravastatin, rosuvastatin and the fixed-dose combination of simvastatin with ascorbic acid, citric acid monohydrate and butylated hydroxyanisole. Claims also included fibrates and bile acid sequestrant cholestyramine. The fibrate, bezafibrate, was only claimed from 2006 to 2008, decreasing in prevalence from 0.7% (n = 1 352) in 2006 to 0.3% (n = 1 374) in 2008. Fenofibrate was only claimed in 2008 at a prevalence rate of 0.8% (n = 1 374) (refer to Table C.11, Annexure C).

A total of 40.1% (n = 1 124) of the medicine items claimed in 2005 was antihypertensives, decreasing to 34.5% (n = 1 374) in 2008 (refer to Table C.11, Annexure C). . Antihypertensives claimed most commonly in 2005 were the ACE inhibitors enalapril and lisinopril (both as monotherapy and in fixed-dose combination with hydrochlorothiazide) at 8.0% and 3.5%, respectively (n = 1 124). perindopril (monotherapy and in fixed-dose combination with indapamide) was mostly claimed from 2006 to 2008 [(11.4%, n = 1 352) for 2006, (9.9%, n = 1 311) for 2007 and 11.5% (n = 1374) for 2008]]. The prescribing patterns for β -blockers showed a decrease in utilisation from 5.1% (n = 1 124) in 2005 to 1.1% (n = 1 374) in 2008. Individual β -blockers mostly claimed over the study period were bisoprolol (monotherapy and in fixed-dose combination with hydrochlorothiazide) and carvedilol. Claims for calcium channel blockers (mostly felodipine and amlodipine as monotherapy and in various combinations) represented 3.7% (n = 1 124), 3.3% (n = 1 352), 4.0% (n = 1 311) and 3.7% (n = 1 374), respectively over the study period (refer to Table C.11, Annexure C).

Claims for angiotensin II inhibitors (mostly irbesartan, candesartan, losartan and valsartan as monotherapy or in fixed-dose combination with hydrochlorothiazide) represented 4.9% (n = 1 124), 5.6% (n = 1 352), 7.0% (n = 1 311) and 4.2% (n = 1 374) of claims over the study period respectively (refer to Table C.11, Annexure C). Compared with patients aged ≥ 15 years, a wider variety of antihypertensives were also claimed, in particular, the ACE inhibitors (fosinopril, quinapril and trandolapril and the fixed-dose combinations of hydrochlorothiazide plus quinapril, lisinopril or enalapril, the combination of ramipril and the calcium channel blocker, felodipine and the combination of trandolapril with verapamil). Other antihypertensives claimed (not claimed for children from age group one) included the calcium channel blockers, verapamil (monotherapy), lercanidipine and nifedipine; the angiotensin II receptor blockers candesartan, eprosartan and

irbesartan, losartan and telmisartan in combination with hydrochlorothiazide; the α -receptor blockers alfuzosin and prazosin, the β -blockers atenolol in combination with chlorthalidone, propranolol and nebivolol; the α/β blocker carvedilol; the diuretics acetazolamide, amiloride in combination with hydrochlorothiazide, indapamide, torasemide and the combination of bumetanide with potassium chloride; methyldopa, moxonidine and minoxidil (refer to Table C.11, Annexure C).

In brief, the utilisation of individual agents increased significantly over the study period, i.e. gliclazide (3.2% increase), metformin (1.8%), rosuvastatin, (2.7%) perindopril [monotherapy (30.9%) and in fixed-dose combination with indapamide (3.7%)], amlodipine (2.0%) and hydrochlorothiazide (1.0%). On the other hand, claims for insulin decreased by 6.4%, enalapril claims decreased by 4.1% and felodipine and carvedilol, respectively decreased with more than 2.1% over the study period (refer to Table C.11, Annexure C). Furthermore, approximately 10-12% of claims for patients aged 16-30 years from the metabolic syndrome category were for fixed-dose combination products (refer to Table C.11, Annexure C). It is however possible that these patients might have received medicine items that had originally been marketed as fixed-dose combination products, as separate active substances.

- **Young adults >30, ≤45 years (age group 3)**

Adults aged 31-45 years (age group 3) received 5.5% (n = 191 747) of prescriptions claimed in 2005 for patients from the metabolic syndrome category, decreasing to 4.5% (n = 246 279) in 2008 (n = 664 969) (refer to Table 4.23). A corresponding medicine claim pattern was observed in these patients, with medicine item claims decreasing marginally from 26 802 in 2005 (5.4%, n = 492 333) to 30 168 (4.5%) in 2008 (n = 664 969) (refer to Table 4.23).

Table C.12 (Annexure C) shows that about a third of claims in metabolic syndrome category from 2005 to 2008 was for antidiabetics. In contrast to age groups one and two, metformin was by far the most significantly claimed agent over the study period, ranging from 15.5% (n = 26 802) in 2005 to 16.1% (n = 30 168) in 2008, followed by claims for insulin and gliclazide representing between 10.4% and 3.5% in 2005 (n = 26 802) to 8.8% and 3.8% in 2008 (n = 30 168), respectively (refer to Table C.12, Annexure C). Similar to patients from age group two, patients from this age group received a greater variety of antidiabetics. Compared with patients from age group two, claims for antidiabetics in patients aged 31-45 years also included agents such as biphasic isophane human insulin (30% soluble insulin/70% isophane insulin), insulin lispro, the α -glucosidase inhibitor acarbose and the meglitinide, nateglinide (refer to Table C.12, Annexure C).

Approximately a quarter of claims over the study period for patients from this age group was for hipolipidaemic agents (refer to Table C.12, Annexure C). Similar to the claim patterns in adolescents and young adults, simvastatin (monotherapy or in combination with ascorbic acid, citric acid monohydrate and butylated hydroxyanisole) was the most significantly claimed hipolipidaemic in adults aged 31-45 years at 45.0% (n = 6 454) in 2005, compared with 50.2% (n = 8 077) in 2006, 48.3% (n = 7 988) in 2007 and 45.8% (n = 7 359) in 2008. Atorvastatin was claimed second most for patients in this age group, decreasing from 40.6% in 2005 (n = 6 454) to 29.1% (n = 7 359) in 2008. Similar to patients from age group two, other statins claimed for patients from age group three included pravastatin, fluvastatin, rosuvastatin and lovastatin. Among the fibrates, bezafibrate was claimed most commonly over the study period, 79.8% (n = 381) in 2005, compared with 89.5% (n = 449) in 2006, 85.3% (n = 463) in 2007 and 79.2% (n = 524) in 2008. Other hipolipidaemic agents (not claimed for age groups one and two) included here were gemfibrozil, ezetimibe, acipimox and nicotinic acid (refer to Table C.12, Annexure C).

The remaining 41-42% of medicine items claimed for these adults were for antihypertensives (refer to Table C.12, Annexure C). The ACE inhibitors, perindopril (both as monotherapy and in fixed-dose combination with indapamide) and enalapril and lisinopril (both as monotherapy and in fixed-dose combination with hydrochlorothiazide), were claimed most frequently in 2005 representing 16.5% of all claims from the metabolic syndrome category in 2005. In 2006 and 2007, ACE inhibitors, in particular perindopril and lisinopril (as monotherapy and in combination with indapamide and hydrochlorothiazide, respectively) represented respectively 15.6% (n = 32 473) and 16.4% (n = 34 033) of all medicine items claimed (refer to Table C.12, Annexure C). Similar to 2005 the majority of medicine items claimed in 2008 (16.1%, n = 30 168) were from the class of ACE inhibitors. Perindopril (both as monotherapy and in fixed-dose combination with indapamide) and enalapril and lisinopril (both as monotherapy and in fixed-dose combination with hydrochlorothiazide) were most significantly claimed (refer to Table C.12, Annexure C).

Claims for β -blockers increased marginally over the study period from 4.7% (n = 26 802) in 2005 to 5.3% (n = 30 168) in 2008. The prevalence of angiotensin II inhibitors (mostly irbesartan, candesartan, losartan, valsartan and telmisartan as monotherapy or in fixed-dose combination with hydrochlorothiazide) also increased marginally from 6.9% (n = 26 802) in 2005 to 7.2% (n = 30 168) in 2008. Other antihypertensives claimed (not claimed for patients from age group two) included the ACE inhibitors benazepril, captopril, cilazapril and fosinopril (in combination with hydrochlorothiazide), the calcium channel blocker, isradipine; the α -receptor blocker terazosin; the β -blockers acebutolol, sotalol and atenolol (monotherapy); the diuretics bumetanide, hydrochlorothiazide in combination with triamterene, piretanide and spironolactone in combination

with isobutyl hydrochlorothiazide; dihydroergocristine in combination with clopamide and reserpine, reserpine (monotherapy) and hydralazine (refer to Table C.12, Annexure C).

In brief, the utilisation of individual agents claimed for patients aged 31-45 years remained relatively constant over the 4-year study period (i.e. $\geq 1\%$ crude difference from 2005 to 2008), with the exception of insulin and atorvastatin (decreasing by 1.6% and 2.7%, respectively) and rosuvastatin, perindopril/indapamide fixed-dose combination and amlodipine that increased by 3.6%, 1.9% and 2.0%, respectively over the study period. About 12-14% of claims for patients aged 31-45 years from the metabolic syndrome category were for fixed-dose combinations (refer to Table C.12, Annexure C). Similar to patients from age groups 1 and 2, these patients could have also have received medicine items that had originally been marketed as fixed-dose combination products, as separate active substances.

- **Middle-aged adults >45,≤60 years (age group 4)**

Adults aged 46-60 years (age group 4) received approximately a third of prescriptions and medicine items claimed during 2005 and 2008 (refer to Table 4.23). About 32-33% of these medicine claims during 2005 (n = 157 570) and 2008 (n = 208 011) was for antidiabetics (refer to Table C.13, Annexure C). In accordance with the findings in age group three, metformin was by far the most significantly claimed agent over the study period, increasing from 14.4% (n = 157 570) in 2005, to 15.7% (n = 208 011) in 2008, followed by claims for insulin and gliclazide representing between 6.2% and 4.4% in 2005 (n = 157 570), to 6.8% and 4.2% in 2008 (n = 208 011) respectively. Other antidiabetics (not claimed for age groups one, two, or three) included here were biphasic isophane insulin [claimed only in 2008 at a prevalence of 0.002% (n = 208 011)] and the first generation sulphonylurea, chlorpropamide [claimed only in 2006 at a prevalence of 0.001% (n = 198 388)] (refer to Table C.13, Annexure C).

Roughly a quarter of claims from 2005 (n = 157 570) to 2008 (n = 208 011) was for hipolipidaemic agents (refer to Table C.13, Annexure C). Similar to the claim patterns in adolescents and young adults (i.e. patients from age groups two and three, simvastatin (monotherapy and in combination with ascorbic acid, citric acid monohydrate and butylated hydroxyanisole) was the most significantly claimed hipolipidaemic in adults aged 46-60 years at 46.9% (n = 37 384) in 2005 decreasing marginally to 46.7% (n = 50 484) in 2008. Atorvastatin was claimed second most for these patients, decreasing from 40.6% (n = 37 384) in 2005 to 30.4% (n = 50 484) in 2008. Other statins claimed over the study period, included pravastatin, fluvastatin, lovastatin and rosuvastatin. Among the fibrates, bezafibrate was claimed most over the study period, representing 85.7% (n = 1 712) of all fibrate-claims in the metabolic syndrome category from 2005, compared with 94.9% (n = 2 213) in 2006, 95.0% (n = 2 317) in 2007 and

87.0% (n = 2 537) in 2008 (refer to Table C.13, Annexure C). Other hipolipidaemic agents claimed were ezetimibe, acipimox, nicotinic acid and cholestyramine. Essential phospholipids were also claimed in 2005 at a prevalence of 0.003% (n = 157 570).

About one-fourth of medicine items claimed over the study period for this patient group were antihypertensives (refer to Table C.13, Annexure C). The ACE inhibitors, perindopril (monotherapy and in fixed-dose combination with indapamide), enalapril and lisinopril (both as monotherapy and in fixed-dose combination with hydrochlorothiazide) were most frequently claimed. Claims for diuretics decreased from 10.6% (n = 157 570) in 2005 to 8.7% (n = 208 011) in 2008, whereas claims for angiotensin II inhibitors (mostly irbesartan, candesartan, losartan, valsartan, eprosartan and telmisartan as monotherapy or in fixed-dose combination with hydrochlorothiazide) increased marginally from 6.7% (n = 157 570) in 2005 to 7.1% (n = 208 011) in 2008. Claims for β -blockers remained stable over the study period at 4.4% (n = 157 570) in 2005 to 4.7% (n = 208 011) in 2008 (refer to Table C.13, Annexure C). Other antihypertensives claimed (not claimed for patients from age groups two and three) included the β -blockers metoprolol, nadolol (monotherapy and in combination with bendoflumethiazide) and the fixed-dose combination of timolol with amiloride and hydrochlorothiazide; the non-selective adrenergic receptor blocker labetalol; the diuretics chlorthalidone (monotherapy and in combination with reserpine), hydroflumethiazide in combination with reserpine and hydrochlorothiazide and xipamide (refer to Table C.13, Annexure C).

In brief, the utilisation of individual agents claimed for patients aged 46-60 years remained relatively constant over the 4-year study period (i.e. $\geq 1\%$ crude difference from 2005 to 2008), with the exception of atorvastatin (decreasing by 2.2% over the study period) and metformin, the fixed-dose combination of perindopril and indapamide and amlodipine (increasing by 1.3%, respectively) and rosuvastatin (increasing by 2.5% from 2006 to 2008). About 13-14% of claims for patients aged 46-60 years from the metabolic syndrome category were for fixed-dose combination products (refer to Table C.13, Annexure C). Again, these patients also could have received medicine items that had originally been marketed as a fixed-dose combination product, as separate active substances.

- **Elderly patients >60, ≤ 75 years (age group 5)**

The majority of prescriptions and medicine items claimed from the metabolic syndrome category were for adults aged 61-75 years (age group 5) (refer to Table 4.23). A total of 26.7% (n = 224 048) of medicine claims from 2005 to 27.6% (n = 208 011) in 2008 for this age group was for antidiabetics (refer to Table C.14, Annexure C). In agreement to the findings in age group three and four, metformin was by far the most significantly claimed agent over the study period,

increasing from 12.5% (n = 224 048) in 2005 to 13.7% (n = 300 200) in 2008, followed by claims for insulin and gliclazide representing approximately 5% and 4% in 2005 and 2008, respectively. Other antidiabetics claimed, included glimepiride, glibenclamide, pioglitazone, rosiglitazone, repaglinide, nateglinide, glipizide and acarbose (refer to Table C.14, Annexure C).

About 25% of claims was for hipolipidaemic agents (refer to Table C.14, Annexure C). Similar to the claim patterns in age groups two, three and four, simvastatin (monotherapy or in combination with ascorbic acid, citric acid monohydrate and butylated hydroxyanisole) was the most frequently claimed hipolipidaemic in adults aged 61-75 years at 50.6% (n = 53 468) in 2005, compared with 53.0% (n = 71 250) in 2006, 52.6% (n = 67 602) in 2007 and 50.7% (n = 73 525) in 2008. Atorvastatin was claimed second most for patients in this age group (however, decreasing from 36.6% in 2005 to 29.8% in 2008). Similar to patients from age groups two, three and four, other statins claimed, included pravastatin, fluvastatin, rosuvastatin and lovastatin. Among the fibrates, bezafibrate was again claimed most commonly over the study period, 83.9% (n = 1 993) in 2005, compared with 92.6% (n = 2 646) in 2006, 93.0% (n = 2 449) in 2007 and 89.0% (n = 2 679) in 2008 (refer to Table C.14, Annexure C). Other hipolipidaemic agents claimed again, similar to claims in age groups two, three and four, included ezetimibe, acipimox, nicotinic acid and cholestyramine.

About half of medicine items claimed in 2005 (n = 224 048) were antihypertensives, decreasing marginally to 48.0% (n = 300 200) in 2008 (refer to Table C.14, Annexure C). The ACE inhibitors, perindopril (monotherapy and in fixed-dose combination with indapamide), lisinopril, enalapril and quinapril (both as monotherapy and in fixed-dose combination with hydrochlorothiazide), ramipril, cilazapril and benazepril were most commonly claimed (refer to Table C.14, Annexure C). Claims for diuretics decreased from 13.1% (n = 224 048) in 2005 to 11.1% (n = 300 200) in 2008. In contrast, the prevalence of angiotensin II inhibitors (mostly irbesartan, candesartan, losartan, valsartan, eprosartan and telmisartan as monotherapy or in fixed-dose combination with hydrochlorothiazide) increased marginally from 6.7% (n = 224 048) in 2005 to 7.0% (n = 300 200) in 2008. Claims for β -blockers also increased over the study period, from 7.3% (n = 224 048) in 2005 to 8.2% (n = 300 200) in 2008 (refer to Table C.14, Annexure C).

Overall, the utilisation of individual agents claimed for patients aged 61-75 years remained relatively constant over the 4-year study period (i.e. $\geq 1\%$ crude difference from 2005 to 2008), with the exception of atorvastatin (again decreasing by 1.4% over the study period), whilst claims for metformin, rosuvastatin, amlodipine and bisoprolol increased by 1.5%, 2.3%, 1.4% and 1.3% respectively, from 2006 to 2008. About 13% of claims for patients aged 61-75 years from the metabolic syndrome category were for fixed-dose combination products (refer to Table C.14,

Annexure C). Similar to patients from age group 1-4, these patients could also have received medicine items that had originally been marketed as fixed-dose combination products, as separate active substances.

Four medicine items prescribed for patients aged 61-75 years appeared on the 2003-Beers criteria list (refer to Table B.2, Annexure B) for potentially inappropriate medication to use in older adults (Fick *et al.*, 2003:2719-2720), i.e. chlorpropamide and methyldopa (both agents high severity ratings) and doxazosin and reserpine (both low severity ratings). These items represented 1.3% of all claims for patients from age group 5 in 2005 (n = 224 048), decreasing to 1.1% in 2006 (n = 279 283), 2007 (n = 292 986) and 2008 (n = 300 200) (refer to Table C.14, Annexure C). According to Fick and colleagues (2003:2720), chlorpropamide has a prolonged half-life in elderly patients and could cause prolonged hypoglycaemia. Additionally, it is the only oral hypoglycaemic agent that causes syndrome of inappropriate antidiuretic hormone secretion, whereas methyldopa may cause bradycardia and exacerbate depression in elderly patients. Doxazosin shows potential for hypotension, dry mouth and urinary problems in elderly patients, whereas reserpine may induce depression, impotence, sedation and orthostatic hypotension at doses >0.25 mg (refer to Table B.2, Annexure B).

- **Mature patients >75 years (age group 6)**

Elderly patients older than 75 years (age group 6) received 18.6% (n = 191 747) of prescriptions claimed in 2005 for the metabolic syndrome category, marginally increasing to 21% (n = 246 279) in 2008. The number of medicine items claimed for this patient group correspondingly increased from 82 727 medicine items in 2005 (16.8%, n = 492 333) to 125 191 (18.8%) in 2008 (n = 664 969) (refer to Table 4.23).

Table C.15 (Annexure C) shows that about 21% (n = 82 727) of claims in metabolic syndrome category from 2005 was for antidiabetics, reducing to 19.2% (n = 125 191) in 2008. In accord to the findings in age groups three, four and five, metformin was by far the most significantly claimed agent over the study period, increasing marginally from 8.8% (n = 82 727) in 2005 to 9.1% (n = 125 191) in 2008, followed by claims for gliclazide and insulin (2006-2008) (refer to Table C.15, Annexure C).

Hipolipidaemic claims represented about 24% of claims in 2005, 26.4% (n = 104 834) in 2006, 22.9% (119 892) in 2007 and 25.8% (n = 25 191) in 2008 (refer to Table C.15, Annexure C). Simvastatin (monotherapy or in combination with ascorbic acid, citric acid monohydrate and butylated hydroxyanisole) was the most significantly claimed hipolipidaemic in elderly adults aged >75 years at 49.2% (n = 19 838) in 2005, compared with 53.5% (n = 27 710) in 2006,

55.8% (n = 27 441) in 2007 and 53.9% (n = 32 251) in 2008. Atorvastatin was claimed second most (however decreasing from 37.0% in 2005 to 29.1% in 2008). Claims for pravastatin decreased marginally from 5.9% in 2005 (n = 19 835) to 4.4% in 2007 (n = 27 441), whereas rosuvastatin was claimed third most in 2008 at 6.7% (n = 32 251). Among fibrates, bezafibrate again was claimed most from 2006 to 2008, increasing in prevalence from 79.2% (n = 408) to 91.3% (n = 647). Acipimox was only claimed in 2006 at a prevalence rate of 0.01% (n = 104 834) (refer to Table C.15, Annexure C).

The majority of claims for mature patients older than 75 years from the metabolic syndrome category were for medicine classified as antihypertensives (refer to Table C.15, Annexure C). The antihypertensive class claimed most commonly in 2005 was the diuretics, representing 19.7% (n = 82 727) of claims for patients older than 75 years, compared with 17.9% of claims in 2006 (n = 104 834), 17.3% in 2007 (n = 119 892) and 16.0% in 2008 (n = 125 191).

Furosemide was claimed most frequently, representing 32.4% (n = 15 326) of diuretic claims in 2005 and 33.4% (n = 125 191) in 2008. Indapamide and spironolactone (monotherapy) were respectively the second and third most claimed diuretics for this patient group, at a prevalence rate of 19.4% for indapamide and 14.6% for spironolactone in 2005 (n = 15 326), compared with 18.0% for indapamide and 19.3% for spironolactone in 2008 (n = 19 982). Enalapril, lisinopril, perindopril (monotherapy and in fixed-dose combination with indapamide) and ramipril were the most frequently claimed ACE inhibitors for patients older than 75 years (refer to Table C.15, Annexure C). These items claimed represented in total 75.6% (n = 12 863) of all ACE inhibitor claims for this age group in 2005, compared with 76.9% (n = 16 204) in 2006, 76.5% (n = 17 400) in 2007 and 77.7% (n = 18 174) in 2008. Claims for calcium channel blockers (mostly felodipine and amlodipine) represented 4.5% (n = 82 727) of claims in this age group for 2005, increasing to 5.3% (n = 104 834) in 2006, 5.7% (n = 119 892) in 2007 and 5.9% (n = 125 191) in 2008. Claims for β -blockers also increased over the study period, from 5.2% (n = 82 727) in 2005 to 6.0% (n = 125 191) in 2008. The individual β -blockers mostly claimed over the study period were bisoprolol (monotherapy and in fixed-dose combination with hydrochlorothiazide). Claims for angiotensin II inhibitors [in particular candesartan and losartan or valsartan (as monotherapy and in combination with hydrochlorothiazide)] increased from 6.9% (n = 82 727) in 2005 to 7.6% (n = 125 191) of claims in 2008 (refer to Table C.15, Annexure C).

To summarise, the utilisation of individual agents claimed for patients aged >75 years remained relatively constant over the 4-year study period (i.e. $\geq 1\%$ crude difference from 2005 to 2008), with the exception of atorvastatin (yet again decreasing by 1.4% over the study period), whilst claims for rosuvastatin increased by the same fraction over the study period (refer to Table C.15, Annexure C). Claims for simvastatin, amlodipine and bisoprolol furthermore increased by 2.2%,

1.6% and 1.7%, respectively, from 2006 to 2008. About 12.0-12.5% of claims for patients aged >75 years from the metabolic syndrome category were for fixed-dose combination products (refer to Table C.15, Annexure C). These patients could have received medicine items from two or more different pharmacological medication classes that might be equivalent to a specific fixed dose combination. Similar to patients from age group 5, mature patients older than 75 years were also prescribed four medicine items appearing on the 2003-Beers criteria list for potentially inappropriate medication used in older adults (Fick *et al.*, 2003:2719-2720), i.e. chlorpropamide and methyldopa (both agents high severity ratings), and doxazosin and reserpine (both low severity ratings). These items represented 1.0% of all claims for patients from age group 5 in 2005 (n = 224 048), 1.1% in 2006 (n = 279 283), 1.2% in 2007 (n = 292 986) and 1.1% in 2008 (n = 300 200).

4.5.2.3 Interpretation of prescribing patterns for patients from the metabolic syndrome category

The empirical investigation showed that more than half of the metabolic syndrome category patients were male; prevalence rates increased with age and peaked in the elderly. More than 90% of patients were ≥ 35 years of age (refer to paragraph 4.5.1). The analysis of the specific medicine items claimed, based on age, revealed that the oral antidiabetics, metformin and gliclazide, were the most claimed medicine items in patients from all age groups from the metabolic syndrome category (with the exception of children and adolescents for whom insulin was mostly claimed) (paragraph 4.5.2.2). Based on gender stratification, males received less oral antidiabetics, but more insulin than their female counterparts (paragraph 4.5.2.1).

A possible explanation of these prescribing patterns may include that, based on treatment guidelines (refer to paragraph 2.9.4.5.2), metformin should be the agent of first choice for the treatment of hyperglycaemia in both adults and children. According to Chehade and co-workers (2008:20), no other oral antidiabetic than metformin has been approved for use in paediatric patients, although sulphonylureas (in particular the short-acting formulations such as tolbutamide) may be considered for those for whom metformin is contra-indicated or not tolerated (Costello, 2006:409). Long-acting sulphonylureas such as glibenclamide (refer to paragraph 2.9.4.5.2) should preferably be avoided in children because of the greater risk of hypoglycaemia (Costello, 2011). Elderly patients may also be prone to hypoglycaemia with longer-acting sulphonylureas such as chlorpropamide or glibenclamide. In these cases, agents such as gliclazide, in particular, may be more suitable (Amiel *et al.*, 2008:252).

Metformin is furthermore used for the treatment of advanced onset of puberty in adolescent females to reduce the prevalence of hirsutism and androgen excess (Ibáñez *et al.*, 2011), and

for the treatment of oligomenorrhea in patients with polycystic ovary syndrome (Diamanti-Kandarakis *et al.*, 2010:199) (refer to paragraph 2.9.4.5.2). For the management of hyperglycaemia a second agent [from basal insulin therapy with intermediate or long-acting agents, i.e. insulin glargine and detemir and the intermediate-acting neutral protamine Hagedorn insulin (NPH), a sulphonylurea, or thiazolidinediones] should be added within two to three months of the initiation of therapy if glycaemic treatment goals are not met with lifestyle changes and the use of the maximal tolerated dose of metformin, or at any time when the HbA_{1c} goal is not achieved in adults.

The incidence of type 1 diabetes mellitus peaks at ages 4-6 years and 10-14 years (Haller *et al.*, 2005:1554) (refer to paragraph 2.9.4.2). According to Candalia and Lamba, (2001) more than 99% of children under the age of 16 years therefore present with type 1 diabetes - most children with diabetes therefore need insulin treatment (Chase & Eisenbarth, 2007:979) as was shown in this empirical investigation. Insulin is also indicated for the treatment of diabetic ketoacidosis in children (Cardella, 2005:52), whereas the rapid-acting insulin such as insulin glulisine is usually indicated for the treatment of medical emergencies or when fast onset of action is required, such as in young children with erratic eating routines (refer to paragraph 2.9.4.5.2). About half of all type 1 diabetics present as adults older than the age of 43 years, with a male predominance (Wild *et al.*, 2004:1050) (refer to paragraph 2.9.4.2), therefore also requiring insulin treatment. Similar results were found in this empirical investigation. Adults with HbA_{1c} levels greater than 7% may furthermore require short- or rapid-acting insulin (e.g. insulin lispro, -aspart and -glulisine) prior to meals in addition to basal insulin to control glycaemia (Levitt *et al.*, 2009:57-58). Almost all diabetic patients will, however, eventually fail to respond adequately to oral antidiabetics and therefore require insulin therapy (MacIsaac *et al.*, 2010:565; Van Avendonk & Rutten, 2009:415).

In this empirical investigation, males and females received equal amounts of hipolipidaemic medicine items over the study period. Simvastatin, followed by atorvastatin were the most notably claimed hipolipidaemic agents for both male and female genders. Among the fibrates, bezafibrate was claimed most. Simvastatin (monotherapy or in combination with ascorbic acid, citric acid monohydrate and butylated hydroxyanisole) was the most significantly claimed hipolipidaemic in patients >15 years, followed by atorvastatin in the second place. Ramjeeth and co-workers (2008:89) also found similar results in patients aged 18 to 80 years from the "South African Not at Goal Study (SA-NAG)". The reverse was true for children younger than 15 years of age in this empirical investigation. To achieve the goal for LDL-cholesterol, treatment is generally initiated with a LDL-lowering agent (usually a statin, although bile acid sequestrant or nicotinic acid can also be used), with dosages dependant on the baseline LDL-cholesterol level (NIH, 2002:3304) (refer to paragraph 2.9.2.5.2). Statins (in particular

atorvastatin, pravastatin and simvastatin) should furthermore be initiated as treatment of familial hypercholesterolemia in children at age ≥ 10 years in males and after the onset of menses in females (Kavey *et al.*, 2006:2725), which ensues at a median age of 12.4 years in South African females from African descent (95% CI: 12.2 - 12.6) and 12.5 years (95% CI 11.7 - 13.3) for Caucasians (Jones *et al.*, 2009:131). Atorvastatin may be used for the treatment of hyperlipidaemia (including familial hypercholesterolemia) in children 10-17 years of age, whereas pravastatin is licensed for use in children over the age of 8 years. Simvastatin may be used at an earlier age in children, i.e. from the age of 5-10 years (Costello, 2011) (refer to paragraph 2.9.2.5.2).

The South African Hypertension Guidelines (Seedat *et al.*, 2006:341) promote individualised antihypertensive treatment for adults and suggest that step 1 agents could include diuretics and that steps 2 and 3 could include ACE inhibitors or angiotensin II inhibitors, or calcium channel blockers (refer to paragraph 2.9.3.5.2). Younger (Caucasian) patients respond better to monotherapy with β -blockers and ACE inhibitors (and probably ARBs), whereas older patients respond better to monotherapy with diuretics (thiazides) and CCBs (in particular diltiazem) (Flack *et al.*, 2010:788; Kato *et al.*, 2011:333; Mpe, 2007:27; Schachter, 2006:28) (refer to paragraph 2.9.3.6). ARBs furthermore produce similar blood pressure reductions in both gender groups, as well as all age categories. Similar to ACE inhibitors, the ARBs appear less effective in patients from African descent, unless co-administered with diuretics or calcium channel blockers (Burnier, 2001:906; Plosker & Robinson, 2008:373) (refer to paragraph 2.9.3.5.2). In this empirical investigation, females were more often treated with antihypertensives than male patients. The majority of antihypertensives claimed for adolescents and adults up to the age of 75 years were from the classes of ACE inhibitors followed by diuretics, with males receiving more ACE inhibitors and females receiving more diuretics. Patients older than 75 years received mostly diuretics (refer to paragraphs 4.5.2.1-4.5.2.3). Qvarnström and colleagues (2010:4) reported similar findings among a large sample of Swedish patients, also adding that women were more often prescribed one or two agents, whereas males received combinations of three and four agents more frequently.

Most medications used for the treatment of adult hypertension may be used in children and adolescents (refer to paragraph 2.9.3.5.2); treatment should, however, be individualised, based on the child's age, cause of hypertension, concomitant medicine intake and degree of blood pressure elevation required (Falkner, 2005:611). β -blockers and ACE inhibitors, in particular, are considered standard first-line medical treatment (Sondheimer *et al.*, 2007:590) (refer to paragraph 2.9.3.6). The majority of claims for 2005 and 2007 for children from the metabolic syndrome category were from the class of ACE inhibitors. The majority of claims from 2006 and 2008, however, were from the class of diuretics – in particular spironolactone and

hydrochlorothiazide. Spironolactone can be used for the treatment of various conditions, *inter alia*, diuresis in congestive heart failure, ascites, oedema and nephritic syndrome reduction of hypokalaemia, induced by other diuretics or amphotericin and primary hyperaldosteronism (Tavakkolim, 2011). Hydrochlorothiazide may be used to manage the oedema due to mild-to-moderate congestive heart failure in children, oedema due to chronic hepatic or renal disease, nephrogenic diabetes insipidus, hypercalciuria and oedema associated with premenstrual tension (O'Brien *et al.*, 2005:2114-2118). Other diuretics such as furosemide may also be used for the treatment of hypertension in neonates and children from the age of one month onwards (Costello, 2011) and to reduce oedema in both acute and chronic cardiovascular, pulmonary and kidney diseases in paediatric patients (Prandota, 2001:287).

In general, antihypertensives can also be used for a variety of other conditions not necessarily related to hypertension in children, for example:

- ACE inhibitors may be used for heart failure and diabetic nephropathy in children, as well as for children with severe bilateral renal artery stenosis (or severe stenosis of the artery supplying a single functioning kidney) (Costello, 2006:127). The ACE inhibitor perindopril is considered effective in preventing the onset and progression of heart failure in children with Duchenne muscular dystrophy (Duboc *et al.*, 2007:E22), whereas ramipril appears to be effective and safe for children with chronic renal failure associated with hypertension (Wühl *et al.*, 2004:774). Enalapril may be used for the treatment of children with sickle nephropathy to reduce urinary protein excretion and normalise serum albumin levels (Fitzhugh *et al.*, 2005:983) and may be effective in improving haemodynamics in the relatively short-term treatment of infants and children with congestive heart failure due to postoperative volume overload or dilated cardiomyopathy (Seguchi *et al.*, 1992:17) and left ventricular mass (Kupferman *et al.*, 2010:1515). Enalapril is also effective in reducing urinary protein excretion in addition to preserving glomerular filtration in children with Alport syndrome (Proesmans & Van Dyck, 2004:273). Captopril and lisinopril are furthermore licensed for the treatment of hypertension, heart failure, proteinuria, nephritis and diabetic nephropathy in neonates and children from the age of one month onwards (Costello, 2011).
- The angiotensin II receptor inhibitor, losartan, may be used as an alternative to ACE inhibitors in children from the age of 6 years onwards (Shahinfar *et al.*, 2005:187) and may also be used in the treatment of proteinuria secondary to Alport syndrome (with or without hypertension) in children aged 1-17 years of age (Webb *et al.*, 2011:2524). Valsartan has also recently been shown to lower systolic blood pressure and diastolic blood pressure compared with placebo, in children <6 years of age, with no negative effects on growth and development (Flynn *et al.*, 2008:226).
- The calcium channel blocker amlodipine has been shown to effectively lower systolic

blood pressure in a dose-dependent manner in hypertensive children who require drug treatment (Flynn *et al.*, 2004:357), in particular those patients with chronic kidney diseases (Von Vigier *et al.*, 2001:389). The safety of felodipine has not yet been established in children (National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents, 2004:568), but may be used (unlabelled) in doses of 2.5 mg once daily to a maximum of 10 mg/day in paediatrics. In 2003, Trachtman and colleagues (2003:552) showed that a 5 mg dose of felodipine (extended release formulation) resulted in a significant decline in trough sitting, standing and supine diastolic blood pressure (placebo-adjusted, -4.6, -5.06 and -5.05 mmHg, respectively), compared with placebo. Trachtman *et al.* also showed that the side effects in paediatric patients were comparable with that in adults, except for a lower incidence of peripheral oedema.

- Doxazosin, prazosin and terazosin are also successful in selected children with voiding dysfunction and incomplete bladder emptying (Pachl *et al.*, 2008:S51), as well as for the treatment of distal urethral stones (Aydogdu *et al.*, 2009:2881).

In conclusion, paragraphs 4.5.2, 4.5.2.1 and 4.5.2.2 established real prescribing patterns for patients from the metabolic syndrome subset based on gender and age stratification. In this paragraph (4.5.2.3), an attempt was made at describing the rationale and potential indications for the use of the most claimed medicines or active substances over the study period.

4.5.3 Direct medicine treatment cost associated with the metabolic syndrome category

This section entails a discussion on the cost associated with the medicine treatment of patients from the metabolic syndrome category, in relation to gender (paragraph 4.5.3.1) and age (paragraph 4.5.3.2). Table 4.24 depicts the total costs associated with the medicine treatment of patients from the metabolic syndrome category.

Based on Table 4.24, the total direct medicine treatment cost from the metabolic syndrome category amounted to R71.7 million in 2005, increasing to R87.8 million in 2006 and R96 million in 2007, followed by a decline to R94.7 million in 2008 (Table 4.24). These costs represent 3.9% of the cost associated with medicine treatment from the dataset during 2005 ($n = R1\ 819\ 865\ 252.00$), compared with 4.5% in 2006 ($n = R1\ 959\ 738\ 734.00$), 5.0% in 2007 ($n = R1\ 918\ 284\ 177.00$) and 5.3% ($n = R1\ 785\ 871\ 014.00$) in 2008 (refer to Tables 4.1 and 4.24).

Medical aid schemes contributed 90.0% ($n = R71\ 724\ 445.88$) towards the direct medicine treatment cost of patients from the metabolic syndrome category of 2005, compared with 88.9%

(n = R87 786 565.60) during 2006, 88.6% (n = R96 119 774.20) in 2007 and 86.0% (n = R94 690 393.54) in 2008 (Table 4.24). The contribution of medical aid schemes towards patients from the metabolic syndrome category represented 4.0% (n = R1 602 447 649.42) of the total contribution of medical aid schemes to patients from the datasets in 2005 (refer to Tables 4.4 and 4.24), compared with 4.6% in 2006 (n = R1 698 709 951.40), 5.3% in 2007 (n = R1 615 007 032.90) and 5.5% in 2008 (n = R478 548 228.90). This translates to an average scheme contribution of R131.14 ± 135.64 (median R103.12) per medicine item in 2005, compared with R126.63 ± 133.65 (median R101.24) in 2006, R128.39 ± 141.69 (median R101.35) in 2007 and R122.45 ± 143.97 (median R94.27) in 2008.

Table 4.24: Direct medicine treatment cost associated with the metabolic syndrome category (2005-2008)

	2005	2006	2007	2008
Medicine treatment cost (R)	71 724 445.88	87 786 565.60	96 142 661.22	94 690 393.54
Scheme contribution (R)	64 562 286.12	78 048 571.08	85 128 148.18	81 423 820.89
Patient co-payment (R)	7 162 159.76	9 737 994.52	11 014 513.04	13 266 572.65
Female	30 651 508.25	37 401 733.98	40 617 178.33	40 434 994.35
Male	41 050 455.94	50 357 226.46	55 525 482.89	54 255 399.19
Unknown gender	22 481.69	27 605.16	0.00	0.00
Age group 1 (>0, ≤15 years)	12 453.75	4 137.74	4 329.55	3 586.00
Age group 2 (>15, ≤30 years)	258 997.13	263 571.30	270 134.46	290 602.10
Age group 3 (>30, ≤45 years)	4 567 170.09	5 500 430.26	5 599 184.44	4 871 570.28
Age group 4 (>45, ≤60 years)	24 414 190.77	30 178 079.68	33 394 769.48	31 585 555.25
Age group 5 (>60, ≤75 years)	31 629 942.14	38 789 219.74	41 683 757.09	42 109 519.05
Age group 6 (>75 years)	10 841 692.00	13 051 126.88	15 190 486.20	15 829 560.86

Patients paid the excess 10% (2005) to 14% (2008) of costs out-of-pocket for co-payments on medicine items at an average cost of R14.55 ± 34.26 (median R0.00) per item for 2005, compared with R15.80 ± 38.04 (median R0.00) during 2006, R16.61 ± 38.01 (median R0.00) in 2007 and R19.95 ± 40.06 (median R2.28) in 2008. As indicated by the (almost) zero median, more than half of patients did not have a co-payment. A possible explanation for this trend was explored in paragraph 4.4.3.

Patient co-payments for this subset represented 3.3% (n = R217 417 602.22) of the all patient co-payments from the dataset during 2005, compared with 3.7% (n = R261 028 782.73) during 2006, 3.6% (n = R303 277 143.74) in 2007 and 4.3% (n = R307 322 784.93) in 2008 (refer to Tables 4.4 and 4.24). The calculated *d*-values for the difference in the average contribution of patients- and medical aid scheme over the study period approached small levels ($0.01 \leq d \leq 0.13$), indicating no practically significant difference over the 4-year period (Table 4.25).

Table 4.25: Effect sizes: average contributions per medicine item from the metabolic syndrome category (2005-2008)

	Average scheme contribution			Average patient co-payment		
	2005	2006	2007	2005	2006	2007
2005	-	-	-	-	-	-
2006	0.03	-	-	0.03	-	-
2007	0.02	0.01	-	0.05	0.02	-
2008	0.06	0.03	0.04	0.13	0.10	0.08

The average annual direct medicine treatment cost for a patient from the metabolic syndrome category was R4 809.20 $\pm$ 4 057.46 (median R3 850.67) in 2005, compared with R5 053.34 $\pm$ 4 033.85 (median R4 041.16) in 2006, R5 503.88 $\pm$ 4 348.67 (median R4 357.79) in 2007 and R5 300.03 $\pm$ 4 433.93 (median R4 100.06) in 2008. These costs therefore increased by approximately 10% from 2005 to 2008 in comparison to the ~8% change in the general inflation rate from 2005 to 2008 (Statistics South Africa, 2011). Calculated *d*-values, however, showed that the differences in costs were practically insignificant (i.e. *d* for 2005/2006 was 0.06, compared with 0.1 for 2006/2007 and 0.05 for 2007/2008).

4.5.3.1 Direct medicine item cost associated with the metabolic syndrome category, in relation to gender

Stratification of the direct medicine treatment cost claimed by gender group (Table 4.24) shows that the costs claimed were highest for male patients, in accordance with the larger number of male patients from the metabolic syndrome category (refer to paragraph 4.5.1) and the higher total number of medicine items claimed for these patients (refer to paragraph 4.5.2.1). In 2005 the direct medicine treatment cost for males accounted for 57.2% of the total medicine treatment cost of patients from the metabolic syndrome category in that year, compared with 42.7% (*n* = R71 724 445.88) in their female counterparts. Similar trends were observed from 2006 onwards (refer to Table 4.24).

4.5.3.2 Direct medicine item cost associated with the metabolic syndrome category, in relation to age

Figure 4.13 shows the distribution of the direct cost of treatment (as percentage) in the metabolic syndrome category, stratified by study period and age groups (years). Figure 4.13(a) shows that the direct medicine treatment cost of patients aged >0, $\leq$ 30 years from the metabolic syndrome subset remained relatively constant over the 4-year study period, whereas the costs for patients aged 30-60 years decreased marginally. The direct cost of treatment for patients aged 61-75 years remained stable at 44.1% in 2005 and 44.4% in 2008, whereas that for

patients older than 75 years were stable at 15.1% in 2005 and 16.7% in 2008 (refer also to Table 4.24).

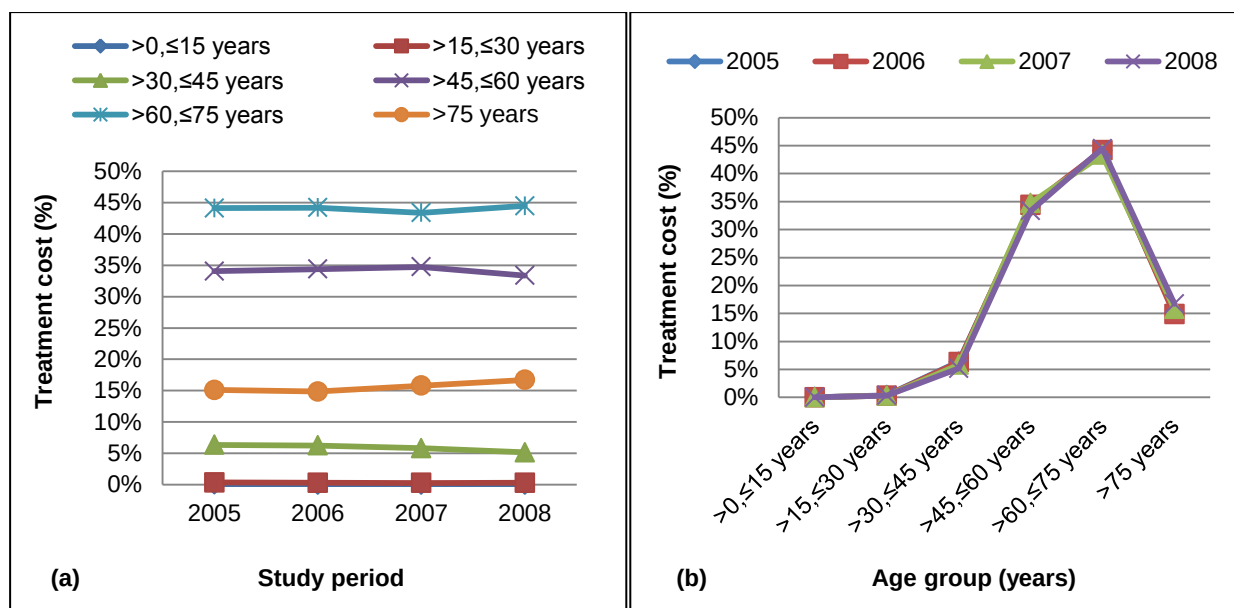


Figure 4.13: Distribution of the direct cost of treatment (as percentage) in the metabolic syndrome category in relation to age group (years) and study period (2005-2008)

Stratification of the direct medicine treatment cost claimed by age group [Figure 4.13(b)] shows that the total cost of medicine item claims increased with age over the study period, and was highest for patients in age group 5 (i.e. those aged 61-75 years) at approximately 44-45% of total costs incurred by patients from the metabolic syndrome category. This coincides with the higher prevalence trends of patients aged 61-75 years in this category (refer to paragraph 4.5.1), as well as the higher total number of medicine items claimed for this group (refer to paragraph 4.5.2.2). The direct cost of medicine treatment for patients aged 61-75 years from the metabolic syndrome category furthermore represented 7.1% ($n = R444\ 749\ 542.72$) of the treatment cost for patients in age group 5 from the 2005 dataset (refer to Table 4.1), increasing to 8.7% in 2008 ($n = R483\ 850\ 628.91$). A similar cost utilisation pattern was observed in mature patients older than 75 years, representing 4.7% ($n = R229\ 608\ 307.85$) of costs for patients in that specific age group from the 2005 dataset, increasing to 6.1% ($n = R260\ 164\ 902.74$) in 2008 (refer to Tables 4.1 and 4.24).

In conclusion, this section estimated the direct medicine treatment cost associated with medicine use by patients from the metabolic syndrome category, stratified by gender and age. The next paragraph (4.5.4) will focus on the cost and prevalence of the 20 foremost claimed medicine items in the metabolic syndrome category, over the study period.

4.5.4 Prescribing index for metabolic syndrome patients

In this section, a prescribing index, consisting of the 20 foremost claimed medicine items for patients from the metabolic syndrome category over the study period (i.e. the active ingredients most prescribed – either alone or in combination with other active ingredients) and their associated direct cost are discussed. The prescribing index was determined for each study period as indicated in Table 4.26 (values in parentheses indicate ranking order based on prescribing volume).

Table 4.26: Prescribing index based on prescribing volume, for metabolic syndrome patients (2005-2008)

	2005	2006	2007	2008
Number of medicine items (n)	492 333	616 359	663 052	664 969
Metformin	62 194 (1)	77 950 (1)	91 128 (1)	90 021 (1)
Simvastatin	57 047 (2)	75 997 (2)	78 478 (2)	81 751 (2)
Atorvastatin	44 796 (3)	53 754 (3)	46 724 (3)	48 929 (3)
Insulin	24 504 (4)	29 302 (4)	35 729 (4)	34 724 (4)
Gliclazide	22 710 (5)	25 706 (5)	29 334 (5)	27 674 (5)
Perindopril	17 379 (6)	22 905 (6)	24 603 (6)	22 542 (7)
Furosemide	15 981 (7)	18 436 (8)	21 709 (8)	19 553 (9)
Indapamide	15 742 (8)	18 931 (7)	18 124 (10)	17 348 (10)
Enalapril	13 145 (9)	15 435 (11)	14 076 (14)	14 477 (14)
Lisinopril	11 903 (10)	14 671 (12)	14 371 (13)	15 180 (15)
Carvedilol	11 793 (11)	15 006 (13)	17 205 (11)	16 839 (11)
Amlodipine	11 742 (12)	17 628 (9)	23 867 (7)	25 679 (6)
Bisoprolol	10 629 (13)	16 227 (10)	20 229 (9)	22 474 (8)
Glimepiride	9 703 (14)	10 534 (17)	10 558 (16)	9 023 (19)
Amiloride/Hydrochlorothiazide	8 966 (15)	10 952 (15)	9 833 (18)	9 554 (17)
Spironolactone	8 584 (16)	10 608 (16)	12 135 (15)	12 062 (16)
Hydrochlorothiazide	8 248 (17)	9 725 (18)	8 920 (19)	9 431 (18)
Rosuvastatin	-	-	10 530 (17)	16 276 (13)
Indapamide/Perindopril	7 520 (18)	12 706 (14)	15 927 (12)	16 682 (12)
Glibenclamide	7 014 (19)	7 639 (19)	7 839 (20)	-
Ramipril	6 369 (20)	-	-	-
Enalapril/Hydrochlorothiazide	-	6 892 (20)	-	-
Candesartan	-	-	-	7 889 (20)

The medicine items encompassing the prescribing index represented 76.4% of all items claimed in the metabolic syndrome category in 2005 (n = 492 333) and 2006 (n = 616 359) respectively, compared with 77.1% in 2007 (n = 663 052) and 77.9% (n = 664 969) in 2008 (refer to Table 4.8). The direct cost of these top 20 medicine items represented 72.2% of the total cost of all items claimed from the data subsets in 2005 (n = R71 724 445.88), compared with 71.3% in

2006 (n = R87 786 565.60), 72.9% in 2007 (n = R96 142 661.22) and 75.7% (n = R94 690 393.54) in 2008 (refer to Table 4.12 and Tables C.16-19, Annexure C).

Based on Table 4.26 five from the prescribing index medicine items claimed over the study period were antidiabetics, representing 25.6% (n = 492 333) of medicine items in the 2005 metabolic syndrome category, compared with 24.2% (n = 616 359) in 2006, 26.3% in 2007 (n = 663 052) and 24.3% in 2008 (n = 664 696) (refer to Table 4.23). Claims for these antidiabetics accounted for 30.5% (n = R71 724 445.88) of all medicine items claimed in the 2005 metabolic syndrome category, compared with 29.3% (n = R87 786 565.60) in 2006, 32.2% in 2007 (n = R96 142 661.22) and 32.3% in 2008 (n = R94 690 393.54) (refer to Tables 4.24 and C.16-19, Annexure C).

Metformin, insulin and the sulphonylureas gliclazide, glimepiride and glibenclamide were the most commonly prescribed antidiabetics over the study period. Metformin was ranked first in 2005, 2007 and 2008 based on prevalence, accounting for 12.6% (n = 492 333) of all medicine items claimed from the 2005 metabolic syndrome category, compared with 12.3% (n = 616 359) in 2006, 13.7% (n = 663 052) in 2007 and 13.5% (n = 664 969) in 2008. Metformin accounted for 4.1% (n = R71 724 445.88) of all medicine items claimed in 2005, compared with 4.0% (n = R87 786 565.60) in 2006, and 4.5% in both 2007 (n = R96 142 661.22) and 2008 (n = R94 690 393.54). Metformin had the lowest average cost per item, second to glibenclamide amongst the oral antidiabetics on the prescribing index medicine item list, ranging from R47.18 ± 19.83 (median R51.22) in 2005, to R47.29 ± 20.26 (median R49.20) in 2008. Based on CPI values, metformin was relatively inexpensive, with CPI values at 0.3 across the 4-year study period. In contrast, insulin ranked fourth, based on prevalence [representing 5.0% for 2005 (n = 492 333), compared with 4.8% in 2006 (n = 616 359), 5.4% for 2007 (n = 663 052) and 5.2% for 2008 (n = 664 969) (Table 4.26)] representing 21.3% of all metabolic syndrome category medicine item cost in 2005, increasing to 23.8% in 2008. Insulin was therefore not only the most expensive antidiabetic but also the most expensive medicine item on the prescribing index claimed over the study period, with an average cost of R568.22 ± 244.93 (median R480.41) in 2005, increasing to R575.25 ± 237.83 (median R488.41) in 2006, R588.20 ± 243.31 (median R499.96) in 2007 and R608.84 ± 267.53 (median R533.21) in 2008. In agreement, CPIs ranged from 3.8 during 2005 to 4.0 in both 2006 and 2007 and 4.2 in 2008 (refer to Tables 4.24 and C.16-19, Annexure C).

Gliclazide was ranked fifth over the study period at 4.6% for 2005 (n = 492 333), compared with 4.2% in 2006 (n = 616 359), 4.4% for 2007 (n = 663 052) and 4.2% for 2008 (n = 664 969). This item was relatively inexpensive over the study period, with CPI values at 0.5 for both 2005 and 2006, and 0.6 for 2007 and 2008. Average cost per item ranged from R77.21 ± 42.91

(median R69.02) in 2005 to R87.06±50.11 (median R72.40) in 2008. On the other hand, glimepiride, ranked at position 14 in 2005, moving down to position 17 in 2006, 16 in 2007 and 19 in 2008 based on prevalence, was relatively expensive over the study period, with CPI values calculated at 1.1 across all metabolic syndrome-categories (i.e. 2005-2008). Average costs associated with glimepiride ranged from R163.39±81.08 (median R144.43) in 2005, down to R159.27±85.89 (median R131.56) in 2008 (refer to Tables 4.24 and C.16-19, Annexure C).

Only three of the prescribing index medicine items from Table 4.26 were hipolipidaemic agents. All these items were from the pharmacological class of statins, with simvastatin and atorvastatin ranking at positions 2 and 3, respectively based on prevalence over the 4-year study period, accounting for 11.6% and 9.1% respectively of all items claimed in the metabolic syndrome category in 2005 (n = 492 333) (Table 4.26). In 2006 claims for simvastatin and atorvastatin accounted for 8.7% and 4.8% respectively (n = 616 359), compared with 11.8% and 7.0% (n = 663 052) in 2007 and 12.3% and 7.4% (n = 664 969) in 2008. Rosuvastatin occupied position 17 in 2007 at 1.6% (n = 663 052), compared with position 13 in 2008 at 2.5% (n = 664 969). Simvastatin and atorvastatin accounted for 9.3% and 13.7% respectively of all items claimed in the metabolic syndrome category in 2005 (n = R71 724 445.88) (refer to Tables 4.24 and C.16, Annexure C). In 2006 claims for simvastatin and atorvastatin accounted for 10.1% and 13.7% respectively (n = R87 786 565.60), compared with 9.4% and 10.0% (n = R96 142 661.22) in 2007 and 9.8% and 9.4% (n = R94 690 393.54) in 2008 (Tables 4.24 and C.17-19, Annexure C). Based on CPI values, simvastatin was relatively inexpensive, with values at 0.8 for all metabolic syndrome categories, whereas atorvastatin was relative expensive (CPIs ranging from 1.5 in 2005 to 1.3 in 2008). The average cost per item for these two agents however decreased over the study period, from R116.93 ± 27.56 and R219.38 ± 57.14 respectively in 2005 to a corresponding R113.06 ± 26.30 and R181.29 ± 60.33 in 2008. The average cost of rosuvastatin, in contrast, increased from R210.62 ± 60.45 in 2007 to R220.54 ± 61.10 in 2008 (the median cost for both study periods remained at R199.63). Rosuvastatin was relatively expensive, based on CPI calculation, at 1.5 for both 2007 and 2008.

The majority (15 from 20) of medicine items in the prescribing index for patients from the metabolic syndrome category were antihypertensives, representing 30.1% (n = 492 333) of medicine items in the 2005 metabolic syndrome category, compared with 32.1% (n = 616 359) in 2006 and 31.5% in both 2007 (n = 663 052) and 2008 (n = 664 696) (refer to Table 4.26). These items represented 18.7% (n = R71 724 445.88) of the total direct cost of medicine items in the 2005 metabolic syndrome category, increasing to 20.4% (n = R94 690 393.54) in 2008 (refer to Tables 4.24, C.16 and C.19). Diuretics, ACE inhibitors, β-blockers, calcium channel blockers and angiotensin II receptor blockers (ARBs) were the most commonly prescribed

antihypertensive therapeutic groups in the prescribing index. The individual ACE inhibitors most frequently claimed included perindopril (monotherapy and as fixed-dose combination with indapamide), enalapril (and enalapril with hydrochlorothiazide as a fixed-dose combination), lisinopril and ramipril (refer to Table 4.26). The individual diuretics most claimed, included furosemide, indapamide (alone and in fixed-dose combination with perindopril), hydrochlorothiazide (alone and in fixed-dose combination with amiloride or enalapril) and spironolactone. The two β -blockers included in the prescribing index were carvedilol and bisoprolol, whereas the only calcium channel blocker in this list was amlodipine and the only angiotensin II receptor blocker, candesartan (refer to Table 4.26).

The most prevalent antihypertensives in 2005 were perindopril and furosemide, occupying ranking positions 6 and 7, respectively of the prescribing index, at 3.5% for perindopril and 3.2% for furosemide. Similar patterns were observed during 2006 and 2007 for perindopril, whereas in 2008 the ranking moved 1 place down to number 7. Furosemide occupied position 8 in both 2006 and 2007, moving 1 place down to position nine in 2008 (refer to Table 4.26). Perindopril and furosemide accounted for 3.2% and 2.1% respectively of the total cost of all items claimed in the metabolic syndrome category in 2005 ($n = R71\ 724\ 445.88$), whereas in 2006 perindopril and furosemide accounted for 3.5% and 1.9% of the cost of claims respectively ($n = R87\ 786\ 565.60$), compared with 3.5% and 2.2% ($n = R96\ 142\ 661.22$) in 2007 and 3.3% and 1.9% ($n = R94\ 690\ 393.54$) in 2008 (refer to Tables 4.24 and C.16-19). Based on CPI values, both perindopril and furosemide were relatively inexpensive, with CPI values ranging from 0.9 (perindopril) and 0.6 (furosemide) in 2005 to a corresponding 1.0 and 0.6, respectively in 2008. Perindopril is available in a fixed-dose combination with indapamide. The latter product also proved relatively inexpensive with CPI values of 0.3 for all study periods. Perindopril in the fixed-dose combination with indapamide was however relatively expensive with CPIs ranging from 1.2 in 2005 to 1.1 in 2008. Tables C.16-19 (Annexure C) show that the average cost of the fixed-dose combination product was 4.3% higher than the summed average cost per year of the two medicines obtained as separate products for 2005. From 2006 to 2008 the average cost of the combination product dropped by approximately 14%, whilst the summed cost of the separate products increased by 2.8%. This may be a possible explanation for the increase in prevalence for the combination product from 1.5% ($n = 492\ 333$) in 2005 to 2.5% ($n = 664\ 969$) in 2008, whilst claims for the separate products both decreased (i.e. claims for perindopril decreased by 0.1%, and claims for indapamide by 0.6%) (refer to Table 4.26).

Carvedilol and amlodipine also represented a notable portion of the total cost of medicine treatment for the metabolic syndrome category. For example, carvedilol represented approximately 2% of the total costs of claims from the metabolic syndrome category across the study period, whereas the total treatment costs for amlodipine was even higher, accounting for

2.4% of costs in 2005 ($n = R71\,724\,445.88$), increasing to 3.1% ($n = R94\,690\,393.54$) in 2008. Both these products were nevertheless relatively inexpensive (CPIs <0.9). Hydrochlorothiazide, the evidence-based preferred diuretic for first-line antihypertensive therapy, was the second least expensive antihypertensive available on the prescribing index (Table C.16-19, Annexure C), at an average cost of $R12.78 \pm 7.83$ (median $R10.27$) for 2005, increasing to $R15.37 \pm 9.10$ (median $R11.50$) in 2008. The lowest average cost per year for products on the prescribing index was reported for the fixed-dose combination of amiloride with hydrochlorothiazide, at an average cost of $R10.40 \pm 8.83$ (median $R6.74$) for 2005, increasing to $R11.37 \pm 8.70$ (median $R7.55$) in 2008.

In conclusion, with the exception of rosuvastatin, glibenclamide, ramipril, the fixed-dose combination of enalapril and hydrochlorothiazide and candesartan, the top 20 claimed items based on prescribing volume, remained relatively idem over the 4-year study period. These 20 claimed medicine items for patients from the metabolic syndrome category, based on prescribing volume and cost in this section, were determined to serve as a prescribing index in patients with metabolic syndrome.

4.5.5 Co-prescribed medicine items (treatment regimens)

The following section entails a discussion on the different co-prescribedⁿ medicine items (i.e. treatment regimens) identified for patients from the 2008-metabolic syndrome category, based on the data summarised in Tables 4.27 and C.20-C.31 (Annexure C). The rationale for the treatment combinations is difficult to ascertain in the absence of a definite diagnosis – which lacked in this empirical investigation (refer to paragraph 3.4.1). The potential rationale for the co-prescribing of these treatment combinations are explored in paragraph 4.5.5.2. The different treatment regimens (co-prescribed active substances) were calculated “per prescription”, recognising, however, that patients could have received more than one prescription containing different active ingredients simultaneously.

There were 17 716 different treatment regimens; these were further grouped, based on the number of active ingredients claimed simultaneously per prescription (refer to Section 4.1), into 12 different “treatment regimen groups”, summarised in Table 4.27.

4.5.5.1 General overview of the treatment regimen groups

Table 4.27 provides a summary of the prescribing volume (frequency), weighted average cost

ⁿ Co-prescribing is defined as “the jointly prescribing of more than one drug by the same prescriber on the same day” (Tobi et al., 2007:407).

(plus weighted standard deviation) and total direct medicine treatment cost associated with the different treatment regimen groups.

Table 4.27: Basic characteristics of the treatment regimen groups (2008)

Treatment regimen groups	Frequency (n)	Average weighted cost (+SD)	Total cost (R)
One active substance treatment regimen group	61 523	165.41 ±161.58	10 176 315.15
Two active substances treatment regimen group	43 956	232.67 ±161.64	10 227 149.19
Three active substances treatment regimen group	45 620	342.18 ±215.28	15 610 178.88
Four active substances treatment regimen group	35 597	465.66 ±272.28	16 576 025.88
Five active substances treatment regimen group	38 867	607.63±343.05	23 616 616.78
Six active substances treatment regimen group	14 272	784.57±430.69	11 197 375.35
Seven active substances treatment regimen group	4 667	1 033.14±470.39	4 821 664.58
Eight active substances treatment regimen group	1 353	1 272.66±530.45	1 721 908.98
Nine active substances treatment regimen group	323	1 710.44±647.83	552 472.12
Ten active substances treatment regimen group	86	1 849.94±913.77	159 094.55
Eleven active substances treatment regimen group	14	2 152.49±298.79	30 134.80
Twelve active substances treatment regimen group	1	1 456.93±0.00	1 456.93

A top 20 foremost list (or an all-inclusive list for regimen groups with less than 20 treatment regimens) was determined for each treatment regimen group based on the prescribing prevalence, as summarised in Tables C.20 to C.31 (Annexure C). A brief description of these regimens follow in subsequent paragraphs, based on these data summaries provided in Table 4.27 and Tables C.20-C.31 (Annexure C).

- **One and two active substance treatment regimen group**

Table 4.27 shows that more than 40% of patients from the 2008 metabolic syndrome category received prescriptions containing ≤ 2 active substances. Patients from the metabolic syndrome category were selected based on their concurrent use of antidiabetics, hipolipidaemics and antihypertensives (including diuretics) (refer to paragraphs 3.4.1 and 3.4.2), therefore implying that patients from this patient category should have received at least 3 active substances (1 from each pharmacological class) during the study period. Because the analysis in this section was conducted “per prescription”, it could have been possible for a patient to receive different prescriptions for the medicine item(s) from the different pharmacological classes. The number of active substances per fixed-dose combination products was furthermore counted separately in this analysis. For example, the fixed-dose combination of perindopril plus indapamide was regarded as two separate products and thus incorporated in the two active substance treatment regimen group.

The associated direct medicine treatment cost of prescriptions containing ≤ 2 active substances summed to 21.6% ($n = R94\ 690\ 393.54$) of all prescription claims for metabolic syndrome category patients in 2008 (refer to Table 4.24). Per group, these treatment regimens were relatively inexpensive, at CPI values of 0.5 for treatment regimens containing one active substance, compared with 0.6 for those containing two active substances. The top 20 “one active substance treatment regimens”, based on prescribing volume (refer to Table C.20, Annexure C), represented 87.1% ($n = 61\ 523$) of these prescriptions, and subsequently 21.7% ($n = 246\ 279$) of all prescriptions claimed for metabolic syndrome category patients during 2008 (refer to Tables 4.23). The cost associated with the “one active substance treatment regimens” represented 10.7% ($n = R94\ 690\ 393.54$) (refer to Tables 4.24 and 4.27) of all prescription costs for patients from the metabolic syndrome category for 2008, at a weighted average cost per treatment regimen group of $R165.41 \pm 161.58$. The cost associated with the top 20 list (refer to Table C.20, Annexure C) represented 84.7% ($n = R10\ 176\ 315.15$) of all one active substance treatment regimens.

Among the one active substance treatment regimens (Table C.20, Annexure C) simvastatin had the highest prescribing volume (16.7%, $n = 53\ 564$), followed by metformin (13.6%), atorvastatin (11.3%) and insulin (10.3%, $n = 53\ 564$). The top 20 “one active substance treatment regimens” compared with the top 20 medicine items from the prescribing index (refer to Table 4.26), with the exception of lisinopril, valsartan, pravastatin and losartan also appearing on the list of one active substance treatment regimen group (refer to Table C.20, Annexure C).

There were 43 956 prescriptions containing “two active substance treatment regimens”, representing 17.8% ($n = 246\ 279$) of all prescriptions claimed during 2008. The top 20 two active substances treatment regimens represented 42.3% ($n = 43\ 956$) of these prescriptions (refer to Table C.21, Annexure C). The active substances most prescribed in combinations of two per prescription (Table C.21) were indapamide and perindopril (representing 0.9% of prescription claims for 2008 ($n = 246\ 279$), followed by simvastatin in combination with metformin (0.7%), and hydrochlorothiazide in combination with amiloride (0.6%) or valsartan (0.5%, $n = 246\ 279$) respectively (refer to Tables 4.23 and C.21, Annexure C). The total costs associated with the prescriptions consisting of two active substances treatment regimens (refer to Table 4.27) summed to 10.8% ($n = R94\ 690\ 393.54$) of the total direct medicine treatment cost of claims for metabolic syndrome patients in 2008 (Table 4.24).

- **Three active substance treatment regimen group**

Prescriptions containing three active substance treatment regimens represented 18.5% ($n = 246\ 279$) of all prescriptions claimed for patients from the metabolic syndrome category

during 2008 (refer to Table 4.23). The top 20 three active substance treatment regimens (Table C.22, Annexure C) represented 27.7% ($n = 45\,620$) of all these prescriptions. The costs of prescriptions containing three active substance treatment regimens represented 16.5% ($n = R94\,690\,393.54$) of all prescription costs for patients from the metabolic syndrome category in 2008 (Table 4.24), at a weighted average cost of $R342.18 \pm 215.28$ per regimen group. Based on the ratio of cost to prevalence percentage (CPI) (Serfontein, 1989:180) the three active substance treatment regimen group was relatively expensive (CPIs = 1.12) (refer to Table 4.27).

The active substances most prescribed in this treatment regimen group were the combination of amlodipine, indapamide and perindopril, representing 1.1% ($n = 246\,279$) of all prescription claims during 2008, at a weighted average cost of $R221.02 \pm 11.48$ per prescription. This was followed by a number of regimens containing simvastatin in several different combinations, e.g. with perindopril and indapamide (0.43%, $n = 246\,279$), perindopril and metformin (0.35%); lisinopril and metformin (0.34%), lisinopril and hydrochlorothiazide (0.18%), enalapril and hydrochlorothiazide (0.33%), enalapril and metformin (0.29%), hydrochlorothiazide and amiloride (0.22%), hydrochlorothiazide and valsartan (0.17%), hydrochlorothiazide and bisoprolol (0.14%), hydrochlorothiazide and losartan (0.12%), metformin and gliclazide (0.19%), metformin and indapamide (0.14%), metformin and glibenclamide (0.12%) and atenolol and chlorthalidone (0.12%, $n = 246\,279$) (Table C.22, Annexure C).

- **Four active substance treatment regimen group**

Prescriptions containing four active substance treatment regimens represented 14.5% ($n = 246\,279$) of all prescriptions claimed for patients from the metabolic syndrome category during 2008 (refer to Table 4.23), whereas the top 20 four active substance treatment regimens (Table C.23, Annexure C) represented 19.8% of these. The costs of prescriptions containing four active substance treatment regimens represented 17.5% ($n = R94\,690\,393.54$) of all prescription costs for patients from the metabolic syndrome category in 2008 (refer to Table 4.24), at a weighted average cost of $R465.66 \pm 272.28$ per regimen group. Based on the ratio of cost to prevalence percentage (CPI) (Serfontein, 1989:180) this treatment regimen group was relatively inexpensive (CPIs = 0.8) (refer to Table C.23, Annexure C).

The two four active substance treatment regimens with the highest prevalence (Table C.23, Annexure C) both contained simvastatin and metformin, in combination with indapamide and perindopril (0.42%, $n = 246\,279$) and enalapril and hydrochlorothiazide (0.25%, $n = 246\,279$) respectively. The total direct treatment cost associated with these two regimens represented 0.35% and 0.16% ($n = R94\,690\,393.54$) respectively of all prescription costs for metabolic

syndrome patients for 2008. The majority of regimens in the top 20 four active substance treatment regimens list contained only one antidiabetic and hipolipidaemic agent, with two antihypertensives – mostly the diuretics hydrochlorothiazide and indapamide, or a combination of a diuretic with an ACE inhibitor (e.g. perindopril, enalapril or lisinopril) or with an angiotensin II receptor inhibitor such as valsartan or losartan (refer to Table C.23, Annexure C).

- **Five active substance treatment regimen groups**

Prescriptions containing five active substance treatment regimens represented 15.8% (n = 246 279) of all prescriptions claimed for patients from the metabolic syndrome category during 2008 (refer to Tables 4.23 and 4.27). The top 20 five active substance treatment regimens (Table C.24, Annexure C) represented 3 582 or 9.2% of these prescriptions, at an associated total direct treatment cost of 24.9% of all prescription costs for 2008 (n = R94 690 393.54). This treatment regimen group was relatively expensive (CPI = 1.6).

Similar to the four active substance treatment regimens, the two five active substance treatment regimens with the highest prescribing prevalence (refer to Table C.24, Annexure C) contained simvastatin, metformin and gliclazide, in combination with indapamide plus perindopril (0.21%) or enalapril plus hydrochlorothiazide (0.16%, n = 246 279). The total direct medicine treatment cost associated with these two regimens accounted for 0.2% and 0.1% (n = R94 690 393.54), of all metabolic syndrome patients for 2008 (refer to Table 4.23). The top 20 five active substance treatment regimens (Table C.24, Annexure C) consisted mainly of 1 hipolipidaemic agent (simvastatin or atorvastatin), 2 antidiabetics (mainly metformin in combination with either gliclazide or glibenclamide) and 2 antihypertensives (from the pharmacological classes of ACE inhibitors: perindopril, enalapril and lisinopril). The only β -blocker that featured in these five active substance treatment regimens was bisoprolol, whereas the diuretics indapamide and hydrochlorothiazide respectively featured in all regimens displayed in Table C.24 (Annexure C).

- **Six active substance treatment regimen groups**

Prescriptions containing six active substance treatment regimens represented 5.8% (n = 246 279) of all prescriptions claimed during 2008 for patients from the metabolic syndrome category, at a cost representative of 11.8% (n = R94 690 393.54) of all prescription costs for metabolic syndrome category patients in 2008 (refer to Tables 4.24 and 4.27). The weighted average cost of the six active substance treatment regimen group was R784.57 $\pm$ 430.69. Serfontein's CPI was calculated at 2.0 – this regimen group was therefore relatively expensive. The top 20 six active substance treatment regimens (refer to Table C.25, Annexure C) represented 6.9% of all prescriptions containing six active substances, and

subsequently 0.4% (n = 246 279) of all prescriptions claimed for patients from the metabolic syndrome category in 2008.

The two six active substance treatment regimens with the highest prevalence (Table C.25, Annexure C) both contained simvastatin, amlodipine, metformin, indapamide and perindopril, in combination with either gliclazide (0.04%) or insulin (0.03%, n = 246 279). The direct medicine treatment cost associated with these two treatment regimens accounted for 0.05% and 0.09% of total cost for metabolic syndrome patients from 2008, respectively. The top 20 six active substance treatment regimens consisted mainly of 1 hipolipidaemic agent (simvastatin or atorvastatin), 1-2 antidiabetics (mainly metformin in combination with gliclazide or insulin) and 2-3 antihypertensives - mainly 1 diuretic (indapamide, hydrochlorothiazide, amiloride or chlorthalidone), 1 ACE inhibitor (perindopril, lisinopril or enalapril) or ARB (valsartan or losartan), or β -blocking agent (from bisoprolol, atenolol or carvedilol).

- **Seven active substance treatment regimen groups**

Prescriptions containing 7-active substance treatment regimens represented 1.9% (n = 246 279) of all prescriptions claimed during 2008 for patients from the metabolic syndrome category, at a cost representative of 5.1% (n = R94 690 393.54) of all prescription costs for these patients in 2008 (refer to Tables 4.24 and 4.27). The weighted average cost of the 7-active substance treatment regimen group was R1 033.14 $\pm$ 470.39. Serfontein's CPI was calculated at 2.7 – this treatment regimen group was therefore relatively expensive.

The top 20 treatment regimens containing 7 active substance (Table C.26, Annexure C) represented 6.8% of both all prescriptions containing 7-active substances (n = 4 667) and the direct medicine treatment cost associated therewith (n = R4 821 664.58) (refer to Tables 4.24 and C.26, Annexure C). These treatment regimens consisted mainly of 1 hipolipidaemic agent (simvastatin or atorvastatin), 2-3 antidiabetics (mainly metformin, gliclazide, glibenclamide or insulin) and 2-4 antihypertensives - mainly 1 diuretic (from indapamide, hydrochlorothiazide, furosemide, spironolactone, amiloride or chlorthalidone), 1 calcium channel blocker (amlodipine, felodipine or nifedipine), 1 ACE inhibitor (perindopril, lisinopril, ramipril, quinapril or enalapril), or ARB (valsartan, losartan, telmisartan or candesartan), and 1 β -blocking agent (from bisoprolol, atenolol or carvedilol) (refer to Table C.26, Annexure C).

- **Eight active substance treatment regimen groups**

Prescriptions containing 8-active substance treatment regimens represented 0.55% (n = 246 279) of all prescriptions claimed during 2008 for patients from the metabolic

syndrome category, at a cost representative of 1.82% ($n = R94\ 690\ 393.54$) of all prescription costs for these patients in 2008 (refer to Tables 4.24 and 4.27). The weighted average cost of regimens within the 8-active substance treatment regimen group was $R1\ 272.66 \pm 530.45$ (CPI = 3.3). This treatment regimen group was therefore relatively expensive.

The top 20 8-active substance treatment regimens (refer to Table C.27) represented 17.9% of all prescriptions containing 8-active substances ($n = 1\ 353$), and subsequently 0.1% ($n = 246\ 279$) of all prescriptions claimed for patients from the metabolic syndrome category in 2008. The total direct treatment cost associated with the top 20 regimens in this group accounted for 16.8% ($n = R1\ 721\ 908.98$) of all prescriptions containing 8-active substances [corresponding to 0.5% ($n = R94\ 690\ 393.54$) of all prescription costs for metabolic syndrome patients in 2008 (refer to Tables 4.24 and 4.27)].

These treatment regimens contained between 1 and 3 hipolipidaemic agents (e.g. simvastatin or atorvastatin in combination with bezafibrate and/or ezetimibe), 1-4 antidiabetics (mainly metformin, gliclazide, glimepiride, glibenclamide, insulin and pioglitazone) and 2-6 antihypertensives, for example 1-2 substances from the class of diuretics (e.g. furosemide, indapamide, spironolactone, hydrochlorothiazide, amiloride or chlorthalidone), 1 calcium channel blocker (amlodipine, felodipine or nifedipine), 1 ACE inhibitor (perindopril, lisinopril, ramipril, quinapril, captopril or enalapril), or ARB (valsartan, losartan or irbesartan), 1 β -blocking agent (from bisoprolol, atenolol, nebivolol or carvedilol) and 1 α_1 -selective blocker (doxazosin) or vasodilator (minoxidil) or peripheral sympatholytic agents (reserpine) or central sympatholytic agents (moxonidine) (refer to Table C.27, Annexure C).

- **Nine active substance treatment regimen groups**

Prescriptions containing 9-active substance treatment regimens represented 0.07% ($n = 246\ 279$) of all prescriptions claimed during 2008 for patients from the metabolic syndrome category. The total treatment cost associated with these regimens summed to 0.3% ($n = R94\ 690\ 393.54$) of all prescription costs for these patients in 2008 (refer to Tables 4.24 and 4.27), at a weighted average cost of $R1\ 710.44 \pm 647.83$ per regimen group. This regimen group was relatively expensive, with a calculated CPI of 4.3.

The top 20 9-active substance treatment regimens (Table C.28, Annexure C) represented 50.2% of all prescriptions containing 9 active substances, and subsequently also 0.07% ($n = 246\ 279$) of all prescriptions claimed for patients from the metabolic syndrome category in 2008. The direct medicine treatment cost associated with these top 20 9-active substances regimens accounted for 51.2% ($R552\ 472.12$) of costs for this regimen group, and a

corresponding 0.3% (n = R94 690 393.54) of direct medicine treatment costs for 2008-metabolic syndrome patients.

The top 20 9-active substance treatment regimens contained between 1 and 2 hipolipidaemic agents (from simvastatin, rosuvastatin or atorvastatin in combination with bezafibrate or fenofibrate), 1-4 antidiabetic agents (from insulin, insulin glulisine, metformin, glibenclamide, glimepiride, gliclazide, pioglitazone and rosiglitazone) and between 5-6 antihypertensives. This latter group included mainly one calcium channel blocker (from felodipine, nifedipine and amlodipine), one ARB (from losartan, irbesartan, candesartan, valsartan, eprosartan and telmisartan) or ACE inhibitor (from enalapril, quinapril, perindopril and lisinopril), 1-2 diuretics (from hydrochlorothiazide, furosemide, chlorthalidone, clopamide, spironolactone, indapamide and torasemide) and one β -locking agent (from bisoprolol, atenolol, carvedilol and nebivolol) per prescription. Other substances that featured in these 9-drug per prescription regimens were doxazosin, methyldopa, dihydroergocristine in combination with reserpine, prazosin and hydralazine (refer to Table C.28, Annexure C).

- **Ten active substance treatment regimen groups**

Prescriptions containing 10-active substance treatment regimens represented 0.03% (n = 246 279) of all prescriptions claimed during 2008 for patients from the metabolic syndrome category, at an associated 0.17% (n = R94 690 393.54) of all prescription costs for 2008 for these patients. The weighted average cost per treatment regimen group was R1 849.94 $\pm$ 913.77, with a CPI-value of 5.7. This regimen group was therefore relatively expensive.

The top 20 10-active substance treatment regimens based on prescribing volume (Table C.29, Annexure C) represented 86.1% of all prescriptions containing 10-active substance treatment regimens, and 0.03% (n = 246 279) of all prescriptions claimed during 2008 for patients from the metabolic syndrome category. The direct medicine treatment costs corresponding with these top 20 10-active substance containing regimens accounted for 0.13% (n = R94 690 393.54) of costs for metabolic syndrome patients in 2008 (refer to Table 4.24), and 79.8% (n = R159 094.55) of the costs associated with the top 20 regimens containing 10-active substances (refer to Tables 4.27 and C.28, Annexure C).

The 20 foremost regimens claimed in this regimen group contained between one and two hipolipidaemic agents (from atorvastatin, fluvastatin, simvastatin, pravastatin, rosuvastatin, bezafibrate, gemfibrozil and ezetimibe), 3-4 antidiabetics (from rosiglitazone, gliclazide, metformin, glibenclamide, insulin, pioglitazone, glimepiride, repaglinide and insulin glulisine).

The treatment regimen further includes 4-7 antihypertensive substances, from the pharmacological classes of β -blocking agents (e.g. bisoprolol, carvedilol, sotalol and nebivolol); diuretics (e.g. indapamide, furosemide, spironolactone, hydrochlorothiazide bumetanide KCL amiloride, clopamide and torasemide); ACE inhibitors (from perindopril, captopril, verapamil and trandolapril); calcium channel blockers (from amlodipine, felodipine, nifedipine, lercanidipine); and ARBs (from candesartan, losartan, telmisartan, valsartan and irbesartan). Other substances that featured in these 10-drug per prescription regimens were doxazosin, dihydroergocristine in combination with reserpine, minoxidil, moxonidine, methyldopa and hydralazine (refer to Table C.29, Annexure C).

- **Eleven active substance treatment regimen groups**

There were six different treatment regimens each containing 11 medicine items during 2008 (refer to Table 4.27). These prescriptions represented 0.006% ($n = 246\ 279$) of all prescriptions claimed during 2008 for patients from the metabolic syndrome category, at an associated 0.03% of all prescription costs in 2008 for these patients (refer to Tables 4.8, 4.24 and 4.27), and a weighted average cost of R2 152.49 $\pm$ 298.79 for the regimen group. A CPI-value of 5.0 indicates that this regimen group was relatively expensive.

These 11-active substance treatment regimens (Table C.30, Annexure C) contained between one and two hipolipidaemic agents (from atorvastatin, simvastatin, rosuvastatin, bezafibrate and ezetimibe), 3-5 antidiabetics (from rosiglitazone, gliclazide, metformin, glibenclamide, insulin and glipizide). The treatment regimens further included 3-7 antihypertensive substances, from the pharmacological classes of β -blocking agents (e.g. bisoprolol, carvedilol, nebivolol and atenolol); diuretics (e.g. indapamide, furosemide, spironolactone, hydrochlorothiazide amiloride and chlorthalidone); ACE inhibitors (from perindopril and enalapril), calcium channel blockers (amlodipine); and the ARB, losartan. Other substances that featured in these 11-active substance treatment regimens were doxazosin, moxonidine, methyldopa and prazosin.

- **Twelve active substance treatment regimen**

One prescription claimed during 2008 contained 12 active substances (refer to Table C.31, Annexure C). The average cost of this treatment regimen amounted to R1 456.93 and was therefore relatively expensive (CPI = 5). This treatment regimen contained one hipolipidaemic (rosuvastatin), three antidiabetic agents (gliclazide, metformin and insulin) and eight antihypertensives.

In conclusion, the different treatment regimens (the active ingredients claimed simultaneously

per prescription during a specific study period) used for the treatment of patients identified metabolic syndrome during 2008 are discussed in this section. The majority of treatment regimens for these patients contained between 3-7 different active substances per prescription, with a further 3.3% of prescriptions containing eight or more active substances each to a maximum of 12 different substances per prescription. The combination of amlodipine with indapamide and perindopril (refer to Table C.22, Annexure C) had the highest prevalence among treatment regimens containing three or more medicine items per prescription. This treatment regimen was followed by the combination of simvastatin with indapamide plus perindopril in second position based on prescribing volume (Table C.22, Annexure C), and the combination of simvastatin with metformin, indapamide and perindopril (Table C.23, Annexure C) in third position.

The calculated *d*-values for the difference in the weighted average cost per treatment regimen group in 2008 are depicted in Table C.32 (Annexure C). Table C.32 shows that the difference in weighted average cost between sequential regimen groups (up to regimen groups containing 10 medicine items) approached small to medium levels (i.e. $0.15 \leq d \leq 0.7$) and was therefore not practically significant. The effect sizes calculated for the difference in weighted average cost per treatment regimen group were also at a medium level between the 8-active substance treatment regimen group and the 10-medicine item and 12-active substance treatment regimen group respectively; for the 9-active substance treatment regimen group compared with the 11-medicine item and 12-active substance treatment regimen group respectively, and for the 10-active substance treatment regimen group compared with the 12-active substance treatment regimen group. These small to medium effect sizes may be ascribed to larger standard deviations in the average cost per treatment regimen. The larger standard deviations, in turn, may be due to cost outliers.

The treatment regimen with the highest weighted average cost overall (R8 371.35, $n = 1$) consisted of the substances pioglitazone, candesartan, carvedilol, metformin, glibenclamide, hydrochlorothiazide, insulin, furosemide, atorvastatin and spironolactone. This treatment regimen was followed by a combination of bisoprolol, valsartan, hydrochlorothiazide, insulin, furosemide and atorvastatin in second position based on cost (weighted average cost = R6 703.78 $\pm$ 7 559.714, $n = 2$) and a combination of ezetimibe, glimepiride, atorvastatin and ramipril in third position (weighted average cost of R6 079.26, $n = 1$).

4.5.5.2 Rationale for the most prevalent treatment regimens

This section entails a discussion on the rationale for the most prevalent treatment regimens, based on prescribing volume among all regimens containing three or more active substances.

The most prevalent combinations were amlodipine with indapamide and perindopril (Table C.22, Annexure C), simvastatin with indapamide and perindopril (Table C.22, Annexure C) and simvastatin with indapamide and perindopril and metformin (Table C.23, Annexure C).

- **Amlodipine plus indapamide and perindopril**

The rationale for the combination of ACE inhibitors (e.g. perindopril) and thiazide diuretics (e.g. indapamide) were described in paragraph 2.9.3.5.2 (refer to “combination therapy with antihypertensives”). A combination of these agents provides a synergistic effect in that ACE inhibitor counteracts the activation and effects of the renin-angiotensin system incited by diuretics, leading to decreased sodium retention along with decreased angiotensin-mediated vasoconstriction and thus an enhanced antihypertensive effect (Sood *et al.*, 2010:886). The combination is particularly effective in the elderly and patients from African descent in whom ACE inhibitor/ARB monotherapy has been shown to be less effective because of low plasma renin levels (Rao *et al.*, 2007:150; Rayner, 2007:32). ACE inhibitors also decrease the occurrence of metabolic effects and electrolyte imbalances linked with diuretic monotherapy, such as hypokalaemia and new onset diabetes (Gillespie *et al.*, 2005:2261; Schultz, 2009:26). Perindopril and indapamide *per se* are both well-established effective agents that are used as first line antihypertensive treatment (refer to paragraph 2.9.3.5.2). The PROGRESS (Perindopril Protection Against Recurrent Stroke) study furthermore established distinct benefits of a treatment regimen involving perindopril and indapamide for stroke (PROGRESS Collaborative Group, 2001:1039) and both coronary events and congestive heart failure (PROGRESS Collaborative Group, 2003:482). The FALCO FORTE (StratiFication of cArdiovascuLar risk and evidence based mediCine hypertensiOn treatment FORTE) programme illustrated similar findings with perindopril/indapamide dosages of up to 10/2.5 mg, also showing a significant reduction in blood pressure, regardless of cardiovascular risk, with 87% of patients reaching blood pressure targets (Pella, 2011:110). The HYVET (HYpertension in the Very Elderly Trial) study (Beckett *et al.*, 2008:1896) likewise showed significant reductions in strokes and all-cause mortality with blood pressure reduction (using a combination of indapamide and perindopril) in mature elderly patients over the age of 80 years.

The rationale for the combination of an ACE inhibitor and calcium channel blocker was also addressed in paragraph 2.9.3.5.2 (refer to “combination therapy with antihypertensives”). This combination also works in synergy, leading to more efficient blood pressure lowering, improved fibrinolytic function and reduction of secondary effects (Ferrari, R., 2008:3555). In addition, the combination of a dihydropyridine calcium antagonist with ACE inhibitors significantly reduces the incidence of peripheral oedema and reflex tachycardia (Sica, 2006:56; Weir, 2003:330).

The combination of calcium channel blockers and renin-angiotensin system inhibitors is furthermore neutral to beneficial for glucose metabolism (Bahl *et al.*, 2009:140; Schmieder, 2010:40; Schultz, 2009:26; refer also to paragraph 2.9.3.5.2), furthermore offering all-purpose cardiovascular and cerebrovascular prevention. The combination of amlodipine and perindopril, in particular, has been shown to be effective for the management of hypertension, especially in high-risk patients (Mourad *et al.*, 2010:2274). Calcium channel blockers are also effective in combination with other ACE inhibitors (e.g. benazapril) as illustrated by Jamerson and colleagues (2004:497) in patients with stage 2 hypertension or in combination with ARBs (e.g. olmesartan) are recently shown by Erdine (2012) in special populations. The potential adverse effect with the use of ACE-inhibitors (e.g. cough and angioedema) may be reduced with the use of an ARB (refer to paragraph 2.9.3.5.2, under “combination therapy with antihypertensives”). The combination of perindopril, indapamide and amlodipine therefore presents a valuable option for the management of patients with hypertension and diabetes mellitus, offering all-purpose cardiovascular and cerebrovascular prevention, particularly in the elderly and patients from African descent in whom ACE inhibitor/ARB monotherapy has been shown to be less effective because of low plasma renin levels (Rao *et al.*, 2007:150; Rayner, 2007:32).

- **Simvastatin plus indapamide and perindopril**

The rationale for the combination of indapamide and perindopril has been addressed above. By the addition of simvastatin (40 mg) to existing treatments in high-risk patients (i.e. patients with a history of previous coronary heart disease, stroke or transient ischaemic attack, or diabetes), the rates of myocardial infarction, of stroke, and of revascularisation are reduced by about 25% (Heart Protection Study Collaborative Group, 2002:22). Similar results were shown with the combination of other statins with perindopril and/or other ACE inhibitors, for example Mamedov *et al.* (2003) established that by combining atorvastatin and perindopril, systolic and diastolic blood pressure were reduced by 11% and total cholesterol serum concentrations by one-third. Mamedov *et al.* furthermore showed a combination of simvastatin and indapamide to lower total serum cholesterol levels by 20%, triglycerides by 21%, and to increase HDL-cholesterol levels. Both combinations resulted in a lowered total coronary risk in patients with metabolic syndrome of 57.4-70%.

Based on an earlier study by Nazzaro *et al.* (1999:723), the combination of simvastatin and enalapril improved blood pressure control in hypertensive patients with hyperlipidaemia, in addition to delivering a significant additive effect on hypercholesterolemia, structural vascular damage, blood pressure and vascular resistance. Even more pronounced blood pressure lowering effects were shown by Sposito *et al.* (1999:1495) with the combination of lovastatin (20 mg/d) or pravastatin (10 mg/d) and enalapril (20 mg/d) or lisinopril (40 mg/d) in

hypercholesterolaemic patients. Danaoğlu *et al.* (2003:335) showed that by combining simvastatin with an ACE inhibitor, peripheral pulse pressure in normolipidaemic patients might be reduced by 25%.

- **Simvastatin plus indapamide, perindopril and metformin**

The rationale for the combination of indapamide and perindopril plus simvastatin has been addressed above. Type 2 diabetes mellitus is associated with an increased risk of coronary heart disease (CHD) (refer to paragraphs 2.6.1 and 2.9.4.3). In addition to its glucose-lowering effect, metformin treatment has been suggested to improve lipidaemia in patients with type 2 diabetes (refer to paragraph 2.9.4.5.2, under “biguanides”). Combined therapy with an antihyperglycaemic agent such as metformin and a statin is therefore indicated for the treatment of diabetic patients at risk of coronary heart disease. Metformin is also considered the first therapeutic option in type 2 diabetes patients who are overweight or obese because it may also prevent vascular complications and mortality by preventing the elevation of blood glucose concentrations that impair endothelial function and promotes atherogenesis (refer to paragraph 2.9.4.3). According to Tousoulis *et al.* (2010:1725), the combination of metformin and statin therapy may be particularly beneficial to prevent the glucose-induced impairment in endothelium-dependent dilation in patients with newly diagnosed type 2 diabetes mellitus. Adding metformin to statin therapy furthermore significantly lowers proatherogenic cholesterolaemia levels (the combination lowered levels of LDL and non-HDL-cholesterol by approximately 0.5 mmol/l compared with placebo) in patients with poorly controlled type 1 diabetes mellitus (Lund *et al.*, 2009:975). The combination of statins and metformin also has additive effects on low-grade inflammation (Bulcão *et al.*, 2007:222).

In conclusion, the combination of perindopril, indapamide, simvastatin and metformin provided concurrently to high-risk patients would therefore be expected to reduce the risks of major vascular events by more than half, and result in enhanced activity against inflammatory cytokines in type 2 diabetic individuals (refer to paragraph 2.9.2.5.2). Orloff (2005:30K) describes this combination as “additive”, in that it affects the same pharmacodynamic endpoint/accepted marker/surrogate with presumed additive effect to reduce risk, and as a “combination of convenience”, in that it addresses the distinct risk factors/diseases coexisting in a large number of patients (Orloff, 2005:30K).

4.5.6 Chronic Disease List conditions in the 2008-metabolic syndrome category

Identifying individuals at risk for chronic diseases is the first step toward preventive measures. The discussion in this section focuses on chronic diseases co-occurring in patients from the

2008-metabolic syndrome category, within the framework of conditions specified in the Chronic Disease List (CDL) as part of the prescribed minimum benefit package (refer to paragraph 3.5.5 and Table B.3, Annexure B).

4.5.6.1 Chronic disease count

The empirical investigation showed that 7 050 patients (39.5%, $n = 17\ 866$) or approximately every third patient from the metabolic syndrome category in 2008, had ≥ 1 "Chronic Disease List (CDL) condition", at an average "chronic disease count" of 1.4 ± 0.63 (median 1), per patient. Up to a maximum of five different CDL conditions co-occurred in patients from the metabolic syndrome category during 2008 (depicted in Table 4.28) – these conditions were additional to diagnosis (per definition consisting of at least 3 chronic conditions, *inter alia* diabetes, hypertension and dyslipidaemia).

Table 4.28: Prevalence of Chronic Disease List conditions co-occurring in metabolic syndrome category patients (2008) ($n = 7\ 050$)

Number of Chronic Disease List conditions	Frequency n (%)
One Chronic Disease List condition	5 061 (71.8)
Two Chronic Disease List conditions	1 627 (23.1)
Three Chronic Disease List conditions	300 (4.3)
Four Chronic Disease List conditions	56 (0.8)
Five Chronic Disease List conditions	6 (0.1)

4.5.6.2 Chronic disease combinations

The discussion in this section focuses on the different Chronic Disease List (CDL) condition combinations, based on the data summarised in Table 4.28 and Tables C.33-C.37 (Annexure C). Table 4.28 show that approximately 28.3% ($n = 17\ 866$) of patients from the 2008-metabolic syndrome category had one co-occurring CDL condition. The top 10 CDL conditions (based on prevalence) from this group are depicted in Table C.33 (Annexure C). Table C.33 shows that among this group of patients with one co-occurring CDL condition ($n = 5\ 061$), approximately a third presented with hypothyroidism, followed by coronary artery disease (18.9%, $n = 5\ 061$), cardiac failure (14.9%, $n = 5\ 061$) and asthma (10.2%, $n = 5\ 061$). Approximately 1 in 16 patients ($n = 5\ 061$) apparently had dysrhythmias and glaucoma respectively, whereas 1 in 20 had cardiomyopathy. A further 1 in 33 metabolic syndrome category patients ($n = 17\ 866$) had epilepsy, compared with 1 in 86 with chronic obstructive pulmonary disease and 1 in 89 that had Parkinson's disease.

A total of 1 627 (9.1%, $n = 17\ 866$) patients from the metabolic syndrome category had at least

two co-occurring CDL conditions during 2008. There were 72 different two CDL condition combinations, of which the top 10 combinations (based on prevalence) (depicted in Table C.34, Annexure C) presented 66.1% (n = 1 627). Table C.34 (Annexure C) furthermore shows that patients from the 2008-metabolic syndrome category with the top 10 list of two CDL chronic conditions (n = 1 075), had mostly cardiac failure in combination with either coronary artery disease 14.1%, n = 1 075) or with hypothyroidism (12.9%, n = 1 075). A further 13.4% of patients had a combination of dysrhythmias and hypothyroidism, whereas 12.3% had co-occurring coronary artery disease and hypothyroidism (n = 1 075). Asthma appeared twice on the top 10 list of co-occurring two-CDL conditions (Table C.34, Annexure C), either in combination with hypothyroidism (11.6%, n = 1 075) or cardiac failure (6.2%, n = 1 075); glaucoma combined with hypothyroidism was present in 4.8% (n = 1 075) of patients from the 2008-metabolic syndrome category.

Approximately 2% (n = 17 866) of patients from the metabolic syndrome category had three co-occurring chronic disease list conditions during 2008. Overall, 89 different disease combinations consisting of three-CDL conditions were observed. The top 10 combinations consisting of three-CDL conditions (based on prevalence, refer to Table C.35, Annexure C) represented 46.7% (n = 300) of these. Table C.35 furthermore shows that 108 patients (77.1%, n = 140) among those with the combinations described in the top 10 list (Table C.35, Annexure C) had cardiac failure, whereas 97 (69.3%, n = 140) had coronary artery disease, and 43 (30.7%) had cardiomyopathy and dysrhythmia, respectively. A total of 42 (30%) patients with three co-occurring CDL conditions had asthma. Table C.35 (Annexure C) shows that patients from the 2008-metabolic syndrome category with at least three additional CDL chronic conditions, mostly suffered from the combination of cardiac failure and hypothyroidism, in addition to either asthma or coronary artery disease (both combinations 17.1%, n = 140).

Fifty-six metabolic syndrome patients (0.3%, n = 17 866) had at least four other CDL conditions during 2008. Overall, 33 different disease combinations consisting of four CDL conditions were observed. The top 10 disease combinations consisting of four CDL conditions (based on prevalence) that co-occurred in metabolic syndrome patients, represented 60.7% (n = 56) of all combinations consisting of four CDL conditions (refer to Table C.36, Annexure C). Four of the top 10 “four CDL condition” containing combinations contained asthma as a co-occurring condition (present in 38.2% of patients, n = 34), with another two combinations containing chronic obstructive pulmonary disease (present in 14.7% of patients, n = 34). Seven of the top 10 combinations shown in Table C.36 (Annexure C), contained hypothyroidism as co-occurring condition (present in 61.8% of patients, n = 34), compared with 7 combinations containing either dysrhythmia (82.4%, n = 34) or coronary artery disease (70.6%, n = 34). A further six combinations contained cardiac failure as co-occurring condition. It is therefore conceivable that

the two four-CDL condition combinations with the highest prevalence consisted of the combination of cardiac failure, dysrhythmia and hypothyroidism, in combination with either coronary artery disease (occurring in 6 metabolic syndrome patients) (10.7%, n = 56) or with asthma (8.9%, n = 56).

Six patients from the 2008-metabolic syndrome category had a combination of five CDL conditions (refer to Tables 4.28 and C.37, Annexure C). Although each patient had a unique combination of co-occurring CDL conditions, Table C.37 (Annexure C) shows that both asthma and cardiac failure were present in 5 patients (83.3%, n = 6) respectively. Chronic obstructive pulmonary disease and dysrhythmia was present in four patients respectively (both 66.7%, n = 6), whereas cardiomyopathy, coronary artery disease and hypothyroidism were present in three from six patients, respectively (each 50%, n= 6). One patient had systemic lupus erythematosus and another glaucoma (refer to Table C.37, Annexure C).

4.5.6.3 Top 10 Chronic Disease List conditions

The overall top 10 list of Chronic Disease List conditions co-occurring in patients from the 2008 metabolic syndrome category is depicted in Table 4.29 (values in parenthesis represent percentages, n = 7 050). This section entails a discussion on the possible association/interplay between the metabolic syndrome and/or its components, and the particular Chronic Disease List condition ranked descending, based on prevalence of co-occurrence.

Table 4.29: Top 10 Chronic Disease List condition combinations co-occurring in metabolic syndrome category patients (2008) (n = 7 050)

Chronic Disease List condition combination	Frequency, n (%)
Hypothyroidism	1 597 (22.7)
Coronary artery disease	956 (13.6)
Cardiac failure	755 (10.7)
Asthma	516 (7.3)
Glaucoma	318 (4.5)
Dysrhythmias	313 (4.4)
Cardiomyopathy	261 (3.7)
Epilepsy	152 (2.2)
Hypothyroidism / Cardiac failure	149 (2.1)
Hypothyroidism / Coronary artery disease	132 (1.9)

Based on Table 4.29, patients from the 2008-metabolic syndrome category mostly had endocrine, nutritional and metabolic diseases (e.g. hypothyroidism) and diseases of the circulatory system (e.g. coronary artery disease, cardiac failure, cardiomyopathy and dysrhythmias) or various combinations thereof. The presence of diseases of the circulatory

system co-occurring in patients with metabolic syndrome is conceivable as the metabolic syndrome, *per se*, is associated with a 2-fold increased risk for cardiovascular disease (refer to Figure 2.1 and paragraphs 2.6.1 and 2.10). The components of the metabolic syndrome too are risk factors for cardiovascular disease (refer to paragraphs 2.6.1, 2.9.1.3, 2.9.2.3, 2.9.3.3 and 2.9.4.3).

The association of the metabolic syndrome and its components with hypothyroidism have been described in various studies. For example, already in the late 1990s Bakker and colleagues (1999:1728) established that concentrations of free tri-iodothyronine were associated with hyperinsulinaemia and insulin production, and therefore postulated thyroid hormones as a link between blood pressure and what they called the “insulin resistance syndrome”. Similar results were revealed by a more recent study by Roos *et al.* (2007:493) in euthyroid individuals. Overt hypothyroidism is furthermore associated with increased systemic vascular resistance, decreased cardiac contractility and decreased cardiac output, causing *inter alia* bradycardia, mild diastolic hypertension, hyperlipidaemia (in particular higher triglyceride and lower HDL-cholesterol levels) (Biondi *et al.*, 2002: 972-973; Klein & Danzi, 2007:1731-1732), low grade chronic inflammation, altered coagulation parameters (Lai *et al.*, 2011b:28) and ventricular dysrhythmias (Klein, 2005:2051). Patients with overt and subclinical^o hypothyroidism are therefore associated with an increased risk for atherosclerotic cardiovascular disease, coronary artery disease and the metabolic syndrome and its components (Shantha *et al.*, 2009). This effect of thyroid dysfunction is more pronounced in elderly females (Lai *et al.*, 2011a:27; Uzunlulu *et al.*, 2007:74) and (possibly) those with greater adiposity (De Moura Souza & Sichieri, 2011:13) or larger waist circumference (Erdogan *et al.*, 2011:490). Hyperthyroidism occasionally also co-occurs in asthmatic patients (Boulet & Boulay, 2011:384) and has been shown to exacerbate asthma attacks (Zacharisen & Fink, 2000:73).

Findings from a recent review by Tesse and co-workers (2011:105-110) indicate that hormones and inflammation might interact in the pathogenesis of asthma, consequently determining its course. Tesse *et al.* (2011) furthermore suggested that the same principles might apply for certain endocrine disorders, such as obesity and type 2 diabetes mellitus. In their argument, they stated that the prevalence of asthma increased parallel with the increase in obesity, and that this relation was stronger in females than in males. Since obesity is a well-known and documented risk factor for developing insulin resistance and metabolic syndrome, it suggests that both conditions could be influenced by shared “environmental factors”. Endocrine diseases and asthma may also share common genetic determinants (Tesse *et al.*, 2011:108).

^o Subclinical hypothyroidism or thyroid failure, is “diagnosed when peripheral thyroid hormone levels are within normal reference laboratory range but serum thyroid-stimulating hormone (TSH) levels are mildly elevated” (Fatourech, 2009:65.)

Agrawal and colleagues (2011:273) further used the term “obese-asthma sub phenotype” to describe a condition associated with marked symptoms, poor response to glucocorticoids and peripheral airway dysfunction, although with a lack of inflammation. They therefore suggested other mechanisms, independent of inflammatory cells, such as hyperglycaemia, hyperinsulinaemia, the influence of insulin-like growth factors on airway structure and function, and nitric oxide-arginine metabolism abnormalities and oxonitrosative stress in lungs as plausible causes. Some of these “mechanisms” are considered risk factors for the metabolic syndrome (refer to Figure 2.1). Lee *et al.* (2009:340) furthermore established the metabolic syndrome, *per se*, as an important contributing factor for the development of asthma-like symptoms. Besides obesity, their study also implicated hypertension as a risk factor for asthma-like symptoms such as wheeze, resting dyspnoea and post-exercise dyspnoea. On the other hand, a study by Uzunlulu and colleagues (2011:50) indicated that the prevalence of metabolic syndrome in asthmatic patients was only slightly, and not statistically significantly higher than that found in a control patient group. It should, however, be noted that the study by Uzunlulu *et al.* was conducted using a relatively small sample.

Glaucoma is defined as “an optic nerve disease that is associated with a disorder of blood supply and optic disc cupping, caused by an elevated intraocular pressure” (Bonomi *et al.*, 1998:209.). Elevated intraocular pressure, in turn, is dependent on age (Rochtchina *et al.*, 2002:173), gender (Vajaranant *et al.*, 2010:97), body mass index (Zafar *et al.*, 2010:86) and blood pressure level (Costa *et al.*, 2009:1280). Intraocular pressure is furthermore associated with diabetes mellitus and impaired fasting glucose levels (Oh *et al.*, 2005:438). Because of the association of the metabolic syndrome with most of the aforementioned factors, it is possible that a correlation exists between metabolic syndrome and intraocular pressure, and subsequent glaucoma (Park *et al.*, 2010:125; Tan *et al.*, 2009:1360).

Epileptic women are more prone to hormonal or metabolic irregularities than those who are healthy (Morrell, 2003:12-14); this may be due to neuro-endocrine effects caused by the seizure or epilepsy itself, the side effect of chronic use of anti-epileptic medication, in particular valproate, such as weight gain (Kim & Lee, 2007:1366), or it may be due to genetic factors that influence the several molecular pathways in energy homeostasis (e.g., insulin receptor signalling pathway and lipid metabolism) (Verotti *et al.*, 2010:271). The hormonal and/or metabolic irregularities typically found in female epileptic patients include *inter alia* obesity, amenorrhea, oligomenorrhea, abnormally prolonged or shortened menstrual cycles, anovulation, polycystic ovary syndromes, hyperandrogenism and dyslipidaemia (Isojärvi *et al.*, 2001:297; Luef *et al.*, 2002:1276). Treatment with valproate in males, in addition, is associated with hyperinsulinaemia (Pylvänen *et al.*, 2003:573). The majority of these hormonal and/or metabolic irregularities are associated with metabolic syndrome, and/or some of its components

(refer to Figure 2.1).

4.6 Metabolic syndrome category summary

Medicine claims were used as a proxy for diagnosis of the “metabolic syndrome”, subsequently defined as *“an individual on the medicine claims database with a claim for at least one medicine item(s) per year from each of the pharmacological drug classes of antihypertensives (including diuretics) (based on the MIMS® classification 7.3 and 16.1), hipolipidaemics (MIMS® classification 7.7) and antidiabetics (MIMS® classification system for medicines 19.1)”*. Although these medicines can be used for a number of other conditions, the conceptual importance for the purpose of this empirical investigation lies in the chance that they are prescribed concurrently to a particular patient. The limitations of using medicine as a proxy measure for disease identification were described in paragraph 3.9.

This analysis was conducted to fill the gap in the literature with respect to understanding the disease profile, treatment patterns and direct cost associated with drug regimens among South African private health care patients, identified as “metabolic syndrome” using real-world data. Paragraph 4.5.3 focused on the total direct treatment cost of patients from the metabolic syndrome subset, comprised of a medical aid scheme contribution and patient co-payment. The direct cost of treatment in relation to age and gender was addressed in paragraphs 4.5.3.1-4.5.3.2, whereas paragraph 4.5.4 focused on a prescribing index for metabolic syndrome patients. In paragraph 4.5.5, the prescribed treatment regimens for patients from the 2008 metabolic syndrome category were examined. Paragraph 4.5.6 focused on Chronic Disease List conditions co-occurring in metabolic syndrome patients. The key findings of this analysis are described in paragraph 5.2.2 (Chapter 5) under the heading “conclusions derived from the empirical investigation”.

4.7 CHAPTER SUMMARY

In this chapter the results obtained through the empirical investigation phase of the study (retrospective drug utilisation review), were presented and discussed. This included an analysis of medicine claims data (from 2005, 2006, 2007 and 2008, respectively) with reference to the private health care sector of South Africa, and an analysis concerning patients “at risk” for the development of metabolic syndrome. Finally, the results of the analysis regarding metabolic syndrome patients were presented. The next (final) chapter brings this investigation to a close and contains the conclusions and recommendations for future research and study, as well as limitations encountered during the study period.

CHAPTER 5

Conclusion and Recommendations

The main and specific objectives to be achieved by this study were indicated in paragraph 1.4 (Chapter 1), whereas the results of the empirical analysis were documented in Chapter 4. The purpose of this final chapter is to conclude the study by linking these objectives to what has been achieved. The chapter opens with a brief overview of the thesis content, followed by a summary of the most significant findings of the study in relation to the goal and specific objectives set for research. Finally, the strength and weaknesses of the study are highlighted, followed by recommendations for future research.

5.1 THESIS CONTENT

The thesis comprises five chapters. In chapter 1 a motivation of the research project was presented, and some background was given to place the study's contribution to the literature in context. The research questions were determined, and the goal and specific objectives of the study outlined. A brief overview of the phases of research was also presented. Chapter 2 contained a literature overview of the concept of metabolic syndrome, including a brief description of the origin and nomenclature, the definition and composing risk factors, the criteria for diagnosis, prevalence and epidemiology, the significance of the syndrome, aetiology, pathophysiology, and individual components and management thereof. The chapter concluded with a discussion on the management of metabolic syndrome.

Chapter 3 reported on the nature of the empirical investigation phase of the study, and included a description of the study design, research method, data source and the selection of the study population. The study measurement units were clarified and an explanation of the statistical techniques selected for data analysis was presented. The reliability and validity of the data and ethical aspects relevant to the empirical investigation were furthermore described.

Chapter 4 outlined the results and findings from the empirical investigation phase of the study that included a detailed discussion of the datasets, data subsets and study population. This final chapter attempts to summarise the results of the study in line with the goal and specific objectives.

5.2 CONCLUSIONS FROM THE STUDY

The main goal of this study was to determine the prevalence and impact (resource utilisation and direct treatment cost) associated with the metabolic syndrome and its components in the private health care sector of South Africa. The research method followed during this study was two-dimensional, comprising of a literature study followed by an empirical investigation phase. The empirical investigation entailed a quantitative, retrospective drug utilisation review study. The specific objectives aimed at achieving the goal were divided according to the two phases of study; the presentation of the conclusions from the study follows suite.

5.2.1 Conclusions derived from the literature study

These specific research objectives of the literature study were attained in chapters 1 through 2.

The evidence from the literature review suggests that the history of the concept of metabolic syndrome dates back to the 15th and 17th century. It is a complex disorder coexisting in an individual, characterised by a cluster of modifiable risk factors, including various combinations of abdominal obesity, glucose intolerance, hypertension and atherogenic dyslipidaemia (elevated triglyceride values, low high-density lipoprotein cholesterol levels and small dense low-density lipoprotein cholesterol particles). Several novel features are also associated with the syndrome based on frequent association therewith, including elevated lipoprotein(a), homocysteine, micro-albuminuria and creatine concentrations, and serum calcium levels (refer to Sections 2.2 and 2.3). Much debate has been raised on the topic and as such remains controversial because of the lack of a universal definition, and uncertainty about its existence (refer to Section 2.4). Regardless of the criteria used for diagnosis (of which there are currently 7 differing definitions for diagnosis in adults and two definitions for children and adolescents), the syndrome occurs rather frequently in the general population and has increased tremendously over the past decades, affecting up to a third of the general adult population of developed countries, or urban areas of developing countries where lifestyle changes towards a western urbanised pattern. The syndrome is furthermore highly age-dependent, affecting almost half of people over the age of 50 years, and up to 60% of individuals 70 years and older. Males are generally more affected, although prevalence rates may vary within men and women of the same age range. Other factors that may influence prevalence rates include differences in genetic background, age, gender, ethnicity and lifestyle factors such as diet, levels of physical activity, obesity, use of alcohol and smoking, levels of over- and under-nutrition, birth weight, co-morbidity, economic and social status, level of education and place of residence (refer to paragraph 2.5.1).

The prevalence of the metabolic syndrome in sub-Saharan Africa (South Africa included) is

uncertain due to a paucity of population-based information. Available South African studies of populations where the prevalence of the metabolic syndrome or its components was measured (either as primary or secondary outcomes of the study) indicate large gender, age and inter-ethnic diversity in its manifestation, also depending on the specific diagnostic criteria used. Similar to general epidemiological studies published, the syndrome appears to be highly obesity dependent in South Africa. In contrast, however, most published South African studies indicate a higher prevalence rate in females. Prevalence rates furthermore appear to be higher in South African Caucasians when compared with their African counterparts.

There is some controversy over the clinical value of metabolic syndrome, with inconsistent findings from various studies (refer to paragraph 2.6.1). Despite its apparently limited utility, the diagnosis of metabolic syndrome presents an opportunity to rationalise health services delivering coordinated care to those with one or more risk factors for the metabolic syndrome (refer to paragraph 2.6.1). Some of these risk factors (e.g. obesity, elevated blood pressure, dyslipidaemia and hyperglycaemia) are major and independent risk factors for diabetes and cardiovascular disease, each directly promoting atherosclerosis risk for type 2 diabetes (refer to section 2.9). Individuals with metabolic syndrome also appear to be susceptible to other medical conditions, *inter alia* respiratory diseases, hormonal disorders, central nervous system disorders and some types of cancer (refer to paragraph 2.6.1).

The recommended intervention for patients with metabolic syndrome is lifestyle modification (including weight control, increased physical activity and an atherogenic diet); however, about 50% of people with the metabolic syndrome do not reach treatment goals with lifestyle interventions only (Hanefeld & Schaper, 2005:390) and thus require pharmacological intervention to reduce major risk factors in patients (e.g. dyslipidaemia, elevated blood pressure and hyperglycaemia).

First-line dyslipidaemic therapy with pharmacological agents in individuals with metabolic syndrome should always be directed towards LDL-cholesterol and non-HDL-cholesterol, with statin therapy (refer to paragraphs 2.9.2.5.2 and 2.10). Second- and third-line treatments are then directed towards high triglyceride levels and low HDL-cholesterol levels, typically with agents such as fibrates and niacin (refer to paragraph 2.9.2.5.2). Other agents including ezetimibe, the bile acid sequestrants and omega-3 fatty acids may also provide benefit. Elevated blood pressure levels should preferably be treated with calcium channel blockers, ACE inhibitors or angiotensin II receptor blockers. Other agents that may provide additional benefits include the central sympatholytic agents (particularly the I₁-imidazoline agents such as rilmenidine and moxonidine) and low-dose diuretics (refer to paragraphs 2.9.2.5.2 and 2.10). No pharmacological treatment is currently recommended for use in patients with impaired

fasting glucose levels or prediabetes (refer to paragraph 2.9.4.5.2). Diabetes in patients with metabolic syndrome may, however, be treated with weight-loss promoting agents (i.e. orlistat), exenatide, metformin, pioglitazone, α -glucosidase inhibitors, nateglinide, the DPP-4 inhibitors and insulin. Aspirin or clopidogrel and statins or renin-angiotensin system inhibitors may further be used in the treatment of the pro-inflammatory state (refer to Sections 2.9 and 2.10).

Drug treatment in patients with the metabolic syndrome typically leads to polypharmacy – especially in those patients with type 2 diabetes or dyslipidaemia, where treatment with ten or more different kinds of drugs may be required (Hanefeld & Schaper, 2005:383). As the number of drugs required to better control risk factors and complications increase, so do the possibilities of untoward effects – drug side effects, drug-drug interactions, non-adherence, medication errors and increased risk of hospitalisation – and so does the cost of therapy (directly mainly due to medication and indirectly to the cost of treating adverse events) (Rollason & Vogt, 2003:820-821). For example, patients with metabolic syndrome have a higher utilisation rate of inpatient stay and cost, higher primary care visits and cost, higher other outpatient visits, i.e. speciality and mental health, higher pharmacy services and higher indirect costs associated with the treatment than patients without the syndrome (refer to paragraph 2.6.3). In addition, it was estimated annual costs associated with the metabolic syndrome increased by an average of 24% per additional risk factor (Boudreau *et al.*, 2009:308) (refer to paragraph 2.6.2). Obesity and hypertension are both associated with a higher total annual health care cost, a higher pharmacy cost and higher service utilisation rate, along with a decreased quality of life. Median costs further increase by 1.9% for every one-unit increase in BMI (refer to paragraphs 2.9.1.4 and 2.9.3.4). Furthermore, hypertriglyceridemia is associated with a 33-38% greater medical cost per annum (refer to paragraph 2.9.2.4), whereas an elevated level of blood glucose accounts for an additional 10% increase in hospital outpatient's visits per year, along with an additional 2.7 prescriptions per year. Both types 1 and 2 diabetics have an additional economic burden per case (refer to paragraph 2.9.4.4). Because of this magnitude of impact in terms of human life and health care expenditures conveyed by its components and by the syndrome *per se*, the metabolic syndrome must be addressed pro-actively by health care providers and decision makers from a managed health care perspective. Decision makers, however, require evidence on the cost, effectiveness and impact of health care interventions to facilitate transparent decision-making. Managed care organisations also need to be able to estimate the prevalence of health states to manage health care appropriately – especially for conditions that are carrying a high disease burden such as the metabolic syndrome (Hollenbeak *et al.*, 2007:S4). Effective strategies for metabolic syndrome disease management can be developed and resource allocation planned when it is clear how the syndrome and the clustering of risk factors translate into health care utilisation at a population level (Boudreau *et al.*, 2009:306) (refer to Sections 1.1 and 1.2).

In conclusion, this literature review revealed that although the metabolic syndrome has been studied in South Africa, very little is known about its impact (in terms of prevalence and cost) in the private health care sector. The lack of a detailed clinical population-based database and poor use of ICD-10 diagnostic codes in South Africa further complicate this assessment. The current study aims at filling the gap in the literature by providing a prevalence estimate and epidemiological trend in patients from a segment of the private health care sector from South Africa, and aims to provide baseline information with respect to understanding the treatment patterns and direct cost associated with drug regimens among South African private health care patients using real-world data.

5.2.2 Conclusions derived from the empirical investigation

The specific research objectives for the empirical investigation (refer to paragraph 1.5.2) were attained in chapter 4. Specific empirical objectives 1 to 3 relate to the respective datasets. Objectives 4 to 6 relates to the respective data subsets, as well as the “at risk” categories, whereas objectives 7 to 12 relate to the study population, i.e. the “metabolic syndrome” patients (refer to paragraph 3.8). The presentation of the conclusions from the study is group-based on these three main headings (i.e. dataset, data subsets and “at risk” categories, and study population or metabolic syndrome category).

- **Specific empirical objectives 1-3: Datasets**

Review the demographic profile, the nature of prescriptions and medicine items claimed, and the cost associated with prescriptions and medicine claims for patients from the datasets, for the period January 1, 2005 to December 31, 2008.

The data employed in the study were a convenience set sourced from the central medicine claims database of a South African Pharmaceutical Benefit Management (PBM) company. The Pharmaceutical Benefit Management (PBM) Company, providing the data for the study is a privately owned South African managed care organisation and currently provides real-time electronic pharmaceutical claims processing services to approximately 39 medical schemes in South Africa, or more than 1.6 million medical scheme beneficiaries. Data for a 4-year period, starting January 1, 2005 through December 31, 2008 were obtained as individual annual files. Exclusion criteria were applied to obtain four individual datasets for each study period.

Patients from the respective datasets (2005-2008) represented more than 10% of all beneficiaries covered by medical aid schemes registered in South Africa from 2005 to 2008. Patients from the respective datasets furthermore resembled a similar demographic profile (e.g. more females

than males and female patients slightly older than their male counterparts) compared with all beneficiaries covered by medical aid schemes registered in South Africa from 2005 to 2008. In contrast to all beneficiaries covered by medical aid schemes, however, the mean prevalent age of patients appeared later by 5 years (2005) to 8 years (2008). The mean prevalent age of patients from the respective datasets furthermore appeared earlier in males than in females by 2 years.

According to Bester (2010), the South African medically insured population is aging, adding to a higher prevalence of chronic diseases and contributing to increasing medicine expenditure in the private South African health care sector. In agreement, the empirical investigation showed that the largest percentage of patients from the datasets across all 4 study periods were in age groups 3 and 4, i.e. adult patients 31-45 years and those 46-60 years of age. Patients older than 60 years represented approximately 15% to 18% of all patients from 2005 ($n = 1\,509\,621$) and 2008 ($n = 974\,497$), respectively. There were no practically significant differences between the respective study periods in terms of distribution of the number of patients by demographic parameters, the number of prescriptions and medicine items claimed and the corresponding direct medicine treatment cost. In general though, the utilisation (measure as prescribing volume of prescriptions and medicine items) trends were higher for females (1.5:1 compared with males). Utilisation were also higher in older patients; the average number of prescriptions claimed annually per patient ranged from about a median of two in children, adolescents and young adults, to approximately 14 in mature adults over the age of 75 years (refer to paragraph 4.3.2.2). These findings are similar to the (self-reported) results of the 2003-South African Demographic Health Survey (Department of Health, 2007).

The average annual cost per prescription increased marginally from $R216.86 \pm 342.30$ (median $R135.40$) in 2005 to $R263.56 \pm 789.01$ (median $R151.56$) in 2008, whereas the average cost per medicine item increased from $R93.32 \pm 166.36$ (median $R52.57$) in 2005 to $R108.63 \pm 436.75$ (median $R59.30$). The total annual direct cost of medicine treatment for a patient increased by 52.0% over the 4-year study period from $R1\,205.51 \pm 3\,044.30$ (median $R333.13$) in 2005 to $R1\,832.61 \pm 6\,668.66$ (median $R432.23$) in 2008. Total benefits paid for medicine items per dataset represented more than 15% of benefits paid for items dispensed by pharmacists and providers other than hospitals in the private South African health care industry from 2005 to 2008. The direct medicine treatment costs corresponding with medicine treatment were furthermore higher in female and older patients. Although an overall assessment of the prevalence/incidence of chronic conditions, hospitalisation and other medical interventions among the elderly in this project was not conducted, it appears as if the higher cost of medicine treatment observed in these older patients could have been driven by the age-dependant escalation in the average number of prescriptions claimed annually per patient (refer to paragraph 4.3.2.2).

In conclusion, this section established a baseline of prescribing patterns for patients from the different datasets, and positioned the database used for analysis with regard to the South African private health care sector. Medicine claim patterns were also compared with general prescribing patterns as found in recent literature. Hereby the specific objectives for the empirical investigation phase pertaining to the respective datasets have been answered.

- **Specific empirical objectives 4-6: Data subsets and “at risk”-category**

Review the prevalence and demographic profile, the nature of prescriptions and medicine items claimed and associated cost of medicine claims of patients from the respective data subsets and “at risk”-category for the period January 1, 2005 to December 31, 2008, stratified by age and gender.

Inclusion criteria were applied to the datasets to obtain all patients receiving ≥ 1 medicine item(s) at any given time during a specific study period (year) from any (but at least ≥ 1) of the following pharmacological medicine classes (based on the MIMS classification): antidiabetics, antihypertensives (including diuretics) and hipolipidaemics. The empirical investigation showed that all these patients identified, represented more than 17% of all patients from the respective datasets, or between 4% (2005-2006) and 3% (2007-2008) of all beneficiaries covered by medical schemes registered in terms of the Medical Schemes Act, (Act 131/1998), in South Africa. Other similarities between the data subsets, the respective datasets and all beneficiaries covered by medical schemes registered in terms of the Medical Schemes Act, (Act 131/1998), in South Africa, include that almost two-thirds of all patients from the data subsets (2005 through 2008) were female, and that these patients were marginally older than their male counterparts. In contrast, patients from the data subsets were about one-and-a-half times to twice the age of patients from the datasets and medical aid scheme beneficiaries in South Africa, respectively. Patients aged 46-60 years and 61-75 years formed the largest percentages of patients from the data subsets across all study periods, whereas in the total datasets, the largest percentage of patients were aged 31-45 years and those 46-60 years of age. Mature patients older than 75 years from the data subsets, represented more than two-thirds (i.e. ~60% in 2005 to 66% in 2008) of all patients from the datasets in that particular age group.

The number of prescriptions claimed for patients from the total data subset decreased over the 4-year study period, similar to the number of claims from the respective datasets (although to a lesser degree). These claims from the data subsets furthermore represented approximately one quarter of all claims from the respective datasets over the study period. Claims for medicine items on the data subsets, however, increased over the study period in contrast to the decreasing trend observed in medicine items claimed from the respective datasets. A median of one medicine item

was claimed per prescription per year by patients from the data subsets, compared with a median of two for patients from the datasets. Effect sizes calculated between the average numbers of medicine items claimed per prescription for the data subsets in comparison to that obtained per dataset, is at medium levels ($0.4 \leq d \leq 0.5$), and therefore not practically significant.

The total direct medicine treatment cost associated with the data subsets represented approximately 22% of the cost corresponding with the medicine treatment of all patients from the datasets over the 4-year study period, and subsequently between 5.5% and 3.6% of benefits paid for medicines dispensed by pharmacists and providers other than hospitals in the private health care industry in South Africa during 2005 (N = R7.2 billion) (CMS, 2006:49) and 2008 (CMS, 2009:126), respectively. Private insurers/medical aid schemes carried more than 80% of these costs over the 4-year study period. Patient contributions per item per year furthermore increased by 48% from 2005 to 2008. This increase, however, was much less than the ~307% increase in average co-payments experienced by all patients from the respective datasets during the same period. Cohen's *d*-values calculated for the difference in co-payments between patients from the data subsets and patients from the respective datasets over the study period approached a small level, i.e. *d* = 0.06 (2005) vs. 0.17 (2006), 0.13 (2007) and 0.14 (2008), indicating no practically significant difference.

The data subsets (from 2005, 2006, 2007 and 2008, respectively) were categorised into a "metabolic syndrome" category (the study population) (refer to Table 3.4) and six "at risk" categories, namely: an antidiabetic category, an antihypertensive category, a hipolipidaemic category, an antidiabetic/antihypertensive category, an antihypertensives/hipolipidaemic-category and an antidiabetics/hipolipidaemics- category. The empirical investigation showed that nearly three-quarters of the "at risk"-category patients received antihypertensives over the study period (monotherapy and in combination with either antidiabetics or hipolipidaemics). This observation fits well within the context of the South African population, for example, estimates from the 2003-Demographic and Health Survey showed that the prevalence of individuals taking antihypertensives was 71.9% (Department of Health, 2007). Approximately 20-23% of these patients on antihypertensives received hipolipidaemic agents concurrently, which is more than twice the rate of patients receiving antihypertensives concomitantly with antidiabetics (i.e. 9-11%).

In contrast to the 2003-SADHS that estimated a higher antidiabetic utilisation rate by males, the findings from this study also showed that more than half of the number of patients that received either antidiabetics or antihypertensives, or a combination of these two agents, were female. The mean prevalent age of patients receiving these medicines, however, only appeared earlier in females than males (by an average of 6 years) in those patients receiving only antidiabetics. The mean prevalent age for receiving antihypertensives appeared earlier in males than in

females by 2 years, whereas those receiving both antidiabetics and antihypertensives were approximately of the same age. Subsequently, more than half of the number of patients that received hipolipidaemic agents, or a combination of antihypertensives and hipolipidaemic agents, or a combination of antidiabetics and hipolipidaemic agents, were male. The mean prevalent age for the prescribing of these latter medicine items (with the exception of the combination of antidiabetics and hipolipidaemic agents), appeared earlier in males than in females by about 3 to 4 years. The demographic data thus indicate that the use of antidiabetics in females and hipolipidaemic agents in males should be considered possible “risk flags for disease burden” for patients in the private South African Health care environment. The national estimate for the prevalence of antidiabetic use in 2003 was 18.9% (Department of Health, 2007), whereas in this empirical investigation a lower prevalence of 14.3% ($n = 261\ 036$) and 15.4% ($n = 214\ 109$) in 2005 and 2008, respectively was determined. The use of hipolipidaemic agents were more than 20% higher than the national estimate of 5%, at 27.1% ($n = 261\ 036$) in 2005 and 26.1% ($n = 214\ 109$) in 2008. Ratio wise, these results therefore indicate a 1-in-5 usage of hipolipidaemics compared with the national estimate of 1-in-20 patients.

The majority of patients from the different at risk-categories were in age group 4, which are patients between the ages of 46 and 60 years (with the exception of the majority of patients that received a combination of antihypertensive and hipolipidaemic agents that were aged $>60, \leq 75$ years). These are patients between the stages of still being economically active and retirement.

As can be expected, concomitant medicine uses adds to a higher resource utilisation. The findings showed that a maximum of four hipolipidaemic medicine items, 6 antidiabetics and 8-10 antihypertensives were claimed as monotherapy per prescription per year for patients from the data subset over the study period. With concomitant use of these medicine items, however, the maximum number of items claimed, increased to 10-16 for those receiving a combination of antidiabetics and antihypertensives, 11-12 items for those receiving a combination of antihypertensives and hipolipidaemic agents and 6-8 items for those receiving the combination of antidiabetics and hipolipidaemic agents.

The direct annual medicine treatment cost per patient was lowest for patients receiving antihypertensives monotherapy and highest for those patients receiving a combination of antihypertensives and hipolipidaemics over the study period. The total direct costs of medicine treatment for this latter group were approximately triple the cost for a patient receiving just an antihypertensive. Based on Cohen's *d*-value (refer to Table C.6, Annexure C), the differences in average annual direct medicine treatment cost for a patient receiving the combination of antihypertensives and antidiabetics were practically significantly more than for a patient

receiving antihypertensive monotherapy in 2007 ($d = 0.9$). The difference in average annual direct medicine treatment cost for patients receiving the combination of antihypertensives and hipolipidaemics was furthermore practically significantly more compared with cost for patients receiving antidiabetics monotherapy during 2005 and 2006 (Cohen's d for both = 0.8), antihypertensive monotherapy for 2005-2008 ($0.9 \leq d \leq 1.0$) and hipolipidaemic monotherapy 2005-2008 ($0.8 \leq d \leq 0.9$) (Table C.6, Annexure C).

Putting these results in perspective: the criteria for the diagnosis of the metabolic syndrome in adults require three criteria to be present (refer to paragraphs 2.4.1 and 3.4.1). In this empirical investigation, there were another 60 683 (4.0%, $n = 1\,509\,621$) of patients from the 2005-dataset meeting two criteria for the metabolic syndrome. This number of patients increased to reach 63 835 (4.1%, $n = 1\,558\,090$) in 2006, thereafter decreasing to 57 992 (4.9%, $n = 1\,178\,596$) in 2007 and 57 220 (5.9%, $n = 974\,497$) in 2008 (refer to Tables 4.1 and 4.8). Many of these patients would probably fall into the category of metabolic syndrome if all five criteria for diagnosis had been available. Without any intervention, they may very well advance to fulfil all the diagnostic criteria in the presence of increasing weight and/or decreasing levels of physical activity. These “at risk” patients furthermore carry a higher risk for cardiovascular disease and mortality. For example, based on the findings from the Framingham Heart Study, two combinations of risk factors more than doubled the risk for cardiovascular disease and mortality (Franco *et al.*, 2009:1948). In their study, Franco and colleagues showed that patients with central obesity, high blood pressure and hyperglycaemia had the highest risk of incident cardiovascular disease (2.36-fold) and mortality (3-fold), followed by those with dyslipidaemia (increased triglycerides, decreased HDL-cholesterol) and elevated blood pressure (1.94-fold risk of cardiovascular disease; 2.73-fold risk for mortality). This empirical investigation identified 18 312 patients from 2005, 20 710 from 2006, 18 128 from 2007 and 18 027 from 2008 respectively, that were treated concurrently with antidiabetics and antihypertensives (Table 4.16). A further 39 594 from 2005, 39 999 from 2006, 36 930 from 2007 and 36 253 from 2008 were treated concurrently with antihypertensives and hipolipidaemics (Table 4.18). Early detection and management of these “at risk” patients are thus critical not only from a cost perspective, but also from a clinical perspective.

In conclusion, this analysis was conducted to position patients with one or more risk factor for the development of metabolic syndrome [as defined by the definitions of the American Heart Association/National Heart, Lung and Blood Institute, and the joint interim statement (refer to paragraph 3.4.1)] with regard to all patients from the respective datasets. The analysis was further conducted to establish baseline utilisation information with regard to medicine claims patterns (prescriptions and medicine items) and associated direct treatment cost for patients “at risk” for development of metabolic syndrome.

- **Specific empirical objectives 7-12: Study population**

Review the prevalence and demographic profile, the nature of prescriptions and medicine items claimed and associated cost of medicine claims of metabolic syndrome patients for the period January 1, 2005 to December 31, 2008, stratified by age and gender.

Medicine claims were used as a proxy for diagnosis for the metabolic syndrome, defined as “An individual on the medicine claims database with a claim for at least one medicine item(s) per year from each of the pharmacological drug classes of antihypertensives (including diuretics) (based on the MIMS classification 7.3 and 16.1), hipolipidaemics (MIMS classification 7.7) and antidiabetics (MIMS classification system for medicines 19.1)”. Although these medicines can be used for a number of other conditions, the conceptual importance for the purpose of this empirical investigation lies in the chance that they are prescribed concurrently to a particular patient.

The empirical investigation showed that the prevalence of metabolic syndrome as identified based on the criteria of the American Heart Association/National Heart, Lung and Blood Institute, and the joint interim statement (refer to paragraph 3.4.1), increased from 1.0% (n = 1 509 621) in 2005, to 1.1% in 2006 (n = 1 558 090), 1.5% in 2007 (n = 1 178 596) and 1.8% in 2008 (n = 974 497) (refer to Tables 4.1 and 4.22). These patients therefore represented 0.22% of all beneficiaries covered by medical schemes registered in terms of the Medical Schemes Act, (Act 131/1998), in South Africa (N = 6 835 621) in 2005 (CMS, 2006:47) increasing to 0.23% in 2008 (N = 7 874 826) (CMS, 2009:123). Because this diagnosis was based on surrogate markers, this “prevalence rate” is likely to be a conservative estimate.

In keeping with general epidemiological studies (refer to paragraph 2.5.1), more than half of the patients from the metabolic syndrome category over the study period were male. The mean prevalent age for receiving medication furthermore appeared earlier in males by 2 years. The prevalence of the syndrome was furthermore age-dependent, increasing from a relatively low prevalence in patients' ≤30 years, to peak at around 40% in those aged >60,≤75 years, subsequently lowering to approximately 20% for mature patients older than 75 years. Patients >75 years, however, represented approximately 4% of the total number of patients in the corresponding age group from the 2005-dataset increasing to more than 6.2% in 2008.

Since the metabolic syndrome is associated with several co-morbidities, it is conceivable that it can lead to higher health care utilisation (refer to paragraph 2.5). In accordance, the findings from this empirical investigation showed that patients from the metabolic syndrome subset had, on average, a higher medicine item per prescription claim rate than patients from the respective

datasets (refer to paragraphs 4.3.2 and 4.5.2). Prescriptions and medicine items claimed from the metabolic syndrome category furthermore both increased from 2005 to 2008 – indicating a higher resource utilisation rate over time. As expected, prescriptions and medicine items claimed also increased with age, peaking in adults aged 61-75 years. These findings were in accordance with general drug utilisation patterns found in older persons with multiple chronic conditions (e.g. Hivert, 2009; Lehnert *et al.*, 2011:417). In contrast to the different datasets and data subsets, however, patients from the metabolic syndrome subset were more likely to be male. Males from the metabolic syndrome subset also showed a higher prescription and medicine item claim rate than their female counterparts.

The analysis of the specific medicine items claimed based on age revealed that the oral antidiabetics, metformin and gliclazide were the most claimed medicine items in patients from all age groups from the metabolic syndrome category (with the exception of children and adolescents in whom insulin was mostly claimed) (paragraph 4.5.2.2). Based on gender stratification, males received less oral antidiabetics, but more insulin than their female counterparts (paragraph 4.5.2.1).

Males and females received an equal number of hipolipidaemic medicine items over the study period. Simvastatin (as single substance or in combination with ascorbic acid, citric acid monohydrate and butylated hydroxyanisole), followed by atorvastatin were also the most notable claimed hipolipidaemic agents for both male and female patients. Among the fibrates, bezafibrate was claimed most. Simvastatin (single substance or in combination with ascorbic acid, citric acid monohydrate and butylated hydroxyanisole) was also the most significantly claimed hipolipidaemic in patients older than 15 years, followed by atorvastatin in the second place. The reverse was true for children younger than 15 years of age in this empirical investigation. Females were more often treated with antihypertensives than male patients. The majority of antihypertensives claimed for adolescents and adults up to the age of 75 years were from the classes of ACE inhibitors, followed by diuretics, with males receiving more ACE inhibitors and females receiving more diuretics. Patients older than 75 years received mostly diuretics (refer to paragraphs 4.5.2.1-4.5.2.3). The majority of claims for 2005 and 2007 for children from the metabolic syndrome category were from the class of ACE inhibitors. The majority of claims from 2006 and 2008, however, were from the class of diuretics – in particular spironolactone and hydrochlorothiazide. The rationale for the prescribing of these medicine items based on gender and age stratification, was presented in paragraph 4.5.2.3.

Similar to findings among adult Americans published by Medco Health Solutions Inc. (2005), the total direct medicine treatment cost associated with the metabolic syndrome-subset costs were substantial. The total direct medicine treatment cost from the metabolic syndrome category

increased by 32% over the study period, representing between 4% and 5% of the total cost of the datasets over the study period (refer to Tables 4.1 and 4.24). These costs subsequently represented approximately 1% of benefits paid for medicines dispensed by pharmacists and providers other than hospitals in the private health care industry in South Africa over the study period (CMS, 2006:49; CMS, 2007:51; CMS, 2008:64; CMS, 2009:126). Medical aid schemes carried approximately 87-90% of these direct medicine treatment costs.

The average annual direct medicine treatment cost for a patient from the metabolic syndrome category summed to R4 809.20 ± 4 057.46 (median R3 850.67) in 2005, increasing to R5 300.03 ± 4 433.93 (median R4 100.06) in 2008. These costs were 3 to 4 times higher than that of all patients from the respective datasets (refer to paragraph 4.3.3), and also more than double that estimated by Boudreau *et al.* (2009:310) for patients with metabolic syndrome (i.e. 1.6) (refer to paragraph 2.6.2). The estimates of direct costs reviewed here may generally be conservative – they rely on the cost of antihypertensive, antidiabetic and hipolipidaemic agents prescribed concomitantly. These cost estimates further underestimate the true cost of metabolic syndrome to society, as higher use of health care services and prevalence of chronic conditions such as cardiovascular disease are associated with increases in missed workdays and lower productivity. Indirect costs associated with the treatment of patients with metabolic syndrome are further estimated to be 13 to 17 times higher than direct pharmacotherapeutic costs (Turek *et al.*, 2010:538). Health problems associated with the metabolic syndrome may further result in intangible costs such as a reduced quality of life (refer to paragraph 2.5.2).

The direct costs of medicine items claimed for males were higher than for their female counterparts, coinciding with the higher male prevalence, and higher health care service utilisation rate (i.e. higher prescribing volume) among men from the metabolic syndrome-subset. Stratification of the direct medicine treatment cost claimed per age group (Table 4.24) furthermore showed that the total cost of medicine item claims was the highest for patients in age group 5 (i.e. those aged 61-75 years) over the study period at approximately 44-45% of total costs incurred by patients from the metabolic syndrome-subset. This also coincides with the larger number of patients in this age group as well as the higher total number of medicine items claimed for this group.

The top 20 medicine items prescribed, based on prescribing volume and cost were established as a prescribing index for metabolic syndrome patients. The top 20 medicine items prescribed based on prescribing volume, represented more than 76% of all items claimed over the study period, and an associated direct treatment cost representing more than 71% of the total cost of all items claimed over the study period (refer to paragraph 4.5.4). The five foremost medicine items identified, based on prescribing volume over the 4-year study period were metformin,

simvastatin, atorvastatin, insulin and gliclazide. Insulin (4th ranked based on prevalence) was the most expensive antidiabetic and the most expensive medicine item claimed over the study period for patients from the metabolic syndrome subset (Refer to Tables C.15-D.18, Annexure C). The (median) cost per item for insulin was approximately 8 to 10 times that of the median cost of all items from the respective datasets. This cost difference was also practically significant ($1.0 \geq d \leq 1.9$).

The oral antidiabetic, glimepiride, was also relatively expensive, at an average cost more than double that of all items from the respective datasets. Other cost-driving items on this top 20 prescribing index included atorvastatin, the fixed dose combination of perindopril with indapamide and ramipril. Hydrochlorothiazide and the fixed dose combination of amiloride and hydrochlorothiazide were the least expensive items on the top 20 prescribing index, at approximately one-eighth to one-fifth of the cost of all items from the respective datasets (refer to Tables 4.4 and D.15-18, Annexure C). Prescribing indexes serve to represent products with the largest budget impacts in terms of prescribing volume and/or costs. These indexes may be of benefit to inform decisions-makers on managing chronic diseases. There are, however, numerous factors that can influence the prescribing of a product or active substance, for example, physicians targeted promotions, provider preference, medical aid scheme composition and formularies, therapeutic committees compiling drug formularies, generic substitution, the prescribed minimum benefits, the availability of alternative treatments and the cost of the product (Krishnamurthi, 2007). These factors were not taken into consideration with the compilation of the index in this empirical investigation.

The cluster of components and risk factors associated with the metabolic syndrome warrants the prescribing of multiple active substances in the majority of cases (Hanefeld & Schaper, 2005:397). The treatment regimens (active substances prescribed per single prescription) identified for patients from the 2008-metabolic syndrome category consisted of 17 716 different combinations. These treatment regimens contained from one to a maximum of 12 different active substances per regimen.

The majority (90.7%, $n = 17\ 716$) of treatment regimens for patients from the metabolic syndrome subset contained between 3-7 different active substances per prescription; a further 3.3% of prescriptions containing eight or more active substances each. Based on the ratio of cost- to prevalence percentage (CPI) calculation, treatment regimens containing between one and three active substances per regimen during 2008 were relatively inexpensive ($CPIs \leq 0.9$). The cost of all prescriptions containing more than three medicine items per prescription represented 78.4% ($n = R94\ 690\ 393.54$) of all prescription costs for 2008. Based on Serfontein's CPI values, though, these regimen groups were all relatively expensive ($CPI > 1$).

Overall, the combination of indapamide and perindopril with amlodipine, or simvastatin and/or metformin had the highest prevalence among treatment regimens containing three or more active substances. This combination provides additive actions in high risk patients such as those with metabolic syndrome in that it affects the same pharmacodynamic end-point/accepted marker/surrogates effect to reduce risk of major vascular events by more than half. It is furthermore suitable for a large number of patients (refer to paragraphs 2.9.2.5.2 and 4.5.5.2).

As was expected, the direct cost associated with the different treatment regimens (active ingredients prescribed simultaneously per prescription) further increased with the addition of an active substance or medicine item to treatment regimens. The treatment regimen with the highest weighted average cost was a 10-medicine items treatment regimen consisting of pioglitazone, candesartan, carvedilol, metformin, glibenclamide, hydrochlorothiazide, insulin, furosemide, atorvastatin and spironolactone. The weighted cost of this regimen summed to R8 371.35 ($n = 1$) which was approximately 32 times higher than the average cost per prescription from the 2008 dataset (i.e. $R263.56 \pm 789.01$, median R151.56) (refer to paragraph 4.3.3.1).

The metabolic syndrome relates to an amplified risk for a variety of disease outcomes (refer to paragraph 2.6.1). A total of 7 050 patients (39.5%, $n = 17\ 866$) or approximately every third patient from the metabolic syndrome category had at least one other chronic condition during 2008. An average chronic disease count of 1.4 ± 0.63 (median 1) (range: 1-5) per patient was calculated. In accordance to general comorbidity studies among metabolic syndrome patients, the present study showed that diseases that co-occurred the most, were hypothyroidism (22.7%, $n = 7\ 050$), coronary artery disease (13.6%), cardiac failure (10.7%), asthma (7.3%) and glaucoma (4.5%).

In conclusion, medicine claims data and using an arbitrary definition for the identification of metabolic syndrome both have their confines; however, in combination they form a remarkable tool to identify patients and populations at risk. Identification of at-risk individuals could be useful to reduce health care cost and resource utilisation associated with risk factor clustering (Hivert *et al.*, 2009). Knowledge of existing prescribing patterns in the treatment of metabolic syndrome can likewise provide useful information for improving clinical practice in this field, whereas medicine claims data provide an opportunity to assess real practice patterns of therapy. Economic evaluations about cost attributable to the metabolic syndrome in South Africa, especially in the private health care sector, highlight the potential value to health care systems of metabolic syndrome detection. These data can provide health care decision-makers with valuable information, allowing optimal distribution of scarce resources.

5.3 STUDY STRENGTHS AND WEAKNESSES

The strength of the empirical investigation phase of the study centres mainly on the use of the medicine claims database employed during the empirical investigation phase of the study. These types of database are recognised resources for drug utilisation reviews, pharmacoepidemiological and health economics studies, and other types of health services research (Andrade *et al.*, 2012:166) (refer to Section 3.9). The database employed in the present study is updated regularly, providing for current, valid denominator data. The database furthermore contains information on a large number of prescription medication use in South Africa, by patients from all provinces in the country. The PBM administering the database has various built-in audit and eligibility checks to ascertain the data quality (refer to paragraph 3.9.1 and Table B.5, Annexure B). Observational studies employing medicine claims data furthermore allow for the study of real-world populations, unlike randomised controlled trials that focus on a highly selected number of patients. All patients from the database were initially included in the study (refer to Section 4.3), with no age or gender restrictions. Furthermore, only paid claims were included (refer to paragraph 3.9.2).

The present study, however, has some limitations that may limit the scope thereof, such as the use of surrogate measures in determining patient prevalence, a lack of validation for this technique, the complexity of data programming needed in order to utilise the data, and the potential of confounding in determining comorbidity. Firstly, surrogate estimates of elevated blood pressure, hyperglycaemia and dyslipidaemia as part of an arbitrary definition of the metabolic syndrome were used to identify patients (refer to paragraph 3.4.2). This was done because of a lack of clinical data on the database and/or incomplete ICD-10 coding fields on the database over the study period. The sensitivity and specificity of this method for determining prevalence in the South African private health care sector have not yet been determined because of the difficulty in establishing a gold standard in the absence of a definite diagnosis or clinical data. The lack of clinical data furthermore reduces the ability to estimate prevalence rates accurately, as many of the patients in the “at risk” for metabolic syndrome category would probably reside in the metabolic syndrome category if all diagnostic criteria or clinical data had been available on the database. On the other hand, the presence of a prescription for a specific medicine item does not necessarily mean that the agent was taken for the indication it was originally designed for – many medications are taken off-label for other conditions. This may lead to both under- and over-ascertainment of prevalence in claims data. However, the identification of these patients presents an opportunity to rationalise health services to deliver coordinated care to patients with one or more risk factors for the metabolic syndrome within a managed care environment (refer to paragraph 2.6.1).

The literature study furthermore established that the prevalence of the syndrome is highly age-dependent and affects more males, and occurs more frequently in the general adult population of developed countries, or urban areas of developing countries where lifestyle changes towards a western urbanised pattern (refer to paragraph 2.5.1). Moreover, the risk of chronic diseases and co-morbidity also increases with age (4.3.2.2). Prevalence rates estimated in this empirical investigation were higher among males and older patients (i.e. more than 90% of patients from the metabolic syndrome category were ≥ 45 years). A potential for confounding therefore existed between certain variables, e.g. age, gender, co-morbidity, economic status and the prevalence of metabolic syndrome and concurrent chronic conditions. Lack of information on patients' genetic background, ethnicity, lifestyle factors such as diet, levels of physical activity, obesity, use of alcohol and smoking status, levels of over- and under-nutrition, birth weight, co-morbidity, social status, level of education, place of residence, and medical aid scheme choice, though, limit adjustments for prevalence calculations. These confounding factors could also have influenced the direct cost associated with the treatment of patients from this patient category. Despite these limitations, statistical results from several studies (Bayliss *et al.*, 2005; De Coster *et al.*, 2006; Hivert, 2009; Powell *et al.*, 2001:692) support the use of administrative data for measuring comorbidity and chronic disease counts. Wild and Byrne (2011:11) state that whether or not adjustment is applied, a potential for residual confounding will always remain.

The central database of the PBM is furthermore situated in the private health care sector of South Africa where the majority of patients live in "first world" conditions with a relative higher income. This limits the external validity of the study in that results cannot be generalised to the total South African population. Patients from the medicine claims database furthermore represented 22.1% of all beneficiaries covered by medical aid schemes registered in South Africa during 2005, decreasing to 12.4% in 2008. The patient distribution on the database emulates a left-skewed distribution, indicating that the PBM most likely provided fewer services to medical aid schemes members below the age of 25 years, with the majority of patients in the 40-80 years age bracket during the study period. In comparison, the percentage age distribution of the total number of all beneficiaries covered by medical schemes registered in South Africa from 2005 to 2008 emulated a bimodal distribution with coverage in the 20-29 year age group lower compared with the age groups on either side (CMS, 2006:48; CMS, 2007b:50; CMS, 2008:63; CMS, 2009:123). The demographic profile of patients from the database though, reflects that of beneficiaries covered by medical aid schemes registered in South Africa from 2005 to 2008 (refer to paragraph 4.3.1).

Because of the rather complex data programming needed to determine the prescribing patterns of medicine items in patients (refer to comment iv, chapter 3), it was not possible to determine the specific treatment regimen prescribed per patient. The different combinations "per prescription"

were therefore used as a proxy measure, recognizing, however, that patients might have received more than one prescription containing different active ingredients simultaneously.

A final limitation that could limit the scope of the empirical investigation phase of the study included that only direct treatment costs were analysed.

5.4 RECOMMENDATIONS FOR FUTURE RESEARCH

The study raised some questions relating to the use of arbitrary definitions of the metabolic syndrome suitable for research in a managed care environment often plagued by an absence of clinical data. Suggestions of future research therefore include:

- To determine the sensitivity and specificity of the method used in this empirical investigation for a diagnosis of metabolic syndrome and to use these data to estimate the likely number of patients with the condition in the total private South African health care sector.
- To determine which other risk factors have to be considered for a risk stratification of patients with metabolic syndrome within a medicine claims database.
- To re-evaluate the prevalence and prescribing trends of the metabolic syndrome in South Africa in comparison with the estimates for 2005-2008 presented here.
- To analyse the cost and outcomes associated with patients “at risk” for the development of metabolic syndrome and those with the syndrome, in terms of active substances/products and dosages prescribed.
- To investigate the possible use of a chronic disease risk score developed based on the 27-Chronic Conditions List (CDL) for use in a research context within the private South African health care sector.
- To determine the potential impact of metabolic syndrome on a future National Health Insurance system for South Africa.

5.5 CHAPTER SUMMARY

This final chapter concludes the study by linking the specific study objectives to what has been achieved. In addition, the strength and weaknesses of the study was described, and recommendations for future research were made.

Hereby the objectives of this study were met.

ANNEXURE A

Supplement to Chapter 2

This supplement contains information documents and figures pertaining to the literature review phase of the research project (refer to Chapter 2).

Table A.1: Risk scoring totals for the treatment of obesity in adults in South Africa
[Copyright Prof M.-T. Van der Merwe. Reproduced with permission.]

RISK SCORING		
HISTORY SCORE		RESULT
Family history	Score 1	
Childhood obesity	Score 1	
Weight gain since 18yr >10kg	Score 1	
Post-partum weight gain >5%	Score 1	
Infertility/PCOD/menopause	Score 1	
Cessation of smoking	Score 1	
Depression or treatment of depression	Score 1	
Endocrinopathies – related to obesity	Score 1	
Epilepsy or treatment of epilepsy	Score 1	
History of eating disorders	Score 1	
Failure of obesity pharmacotherapy	Score 1	
Mediation resulting in obesity	Score 1	
Total Score: (12)		
CLINICAL SCORE		RESULT
Waist circumference	Score 2*	
Male: >102; Female: >88		
BMI: 35 & Comorbid disease (surgery)	Score 1	
BMI: 30 & Comorbid disease (pharmacotherapy)		
BP: >130/80	Score 2*	
Neck circumference: >41.5 cm	Score 1	
Cardiomegaly/vascular disease	Score 1	
Hepatomegaly/gallstones	Score 1	
Sleep disordered breathing/aspiration	Score 1	
Arthropathy/chronic back pain	Score 1	
Total Score: (10)		
SPECIAL INVESTIGATIONS		RESULT
Fasting glucose > 5.6 mmol/L	Score 2*	
Fasting TG > 1.7mmol/L	Score 2*	
HDL-cholesterol Females: <1.3; Males: <1.0 mmol/L	Score 2*	
LDL-cholesterol >3.5 mmol/L		

Table A.1: Risk scoring totals for the treatment of obesity in adults in South Africa
[Copyright Prof M.-T. Van der Merwe. Reproduced with permission.] (continued)

RISK SCORING		
Elevated Alanine transaminase/Glutamine transferase	Score 1	
HISTORY SCORE		RESULT
Elevated pro-BNP	Score 1	
Total Score: (8)		
SPECIALIST LEVEL INVESTIGATIONS		RESULT
C-reactive protein	Score 1	
Growth hormone: stimulated <3µg/L	Score 1	
Oesophageal erosions or related	Score 1	
Dexa %fat Females >35%; Males >20%	Score 1	
MRI L4/5 >30% expected	Score 1	
Total Score: (5)		
RISK FACTOR SCORE	Total Score 35	
*IDF criteria for metabolic syndrome have been weighted as 2		

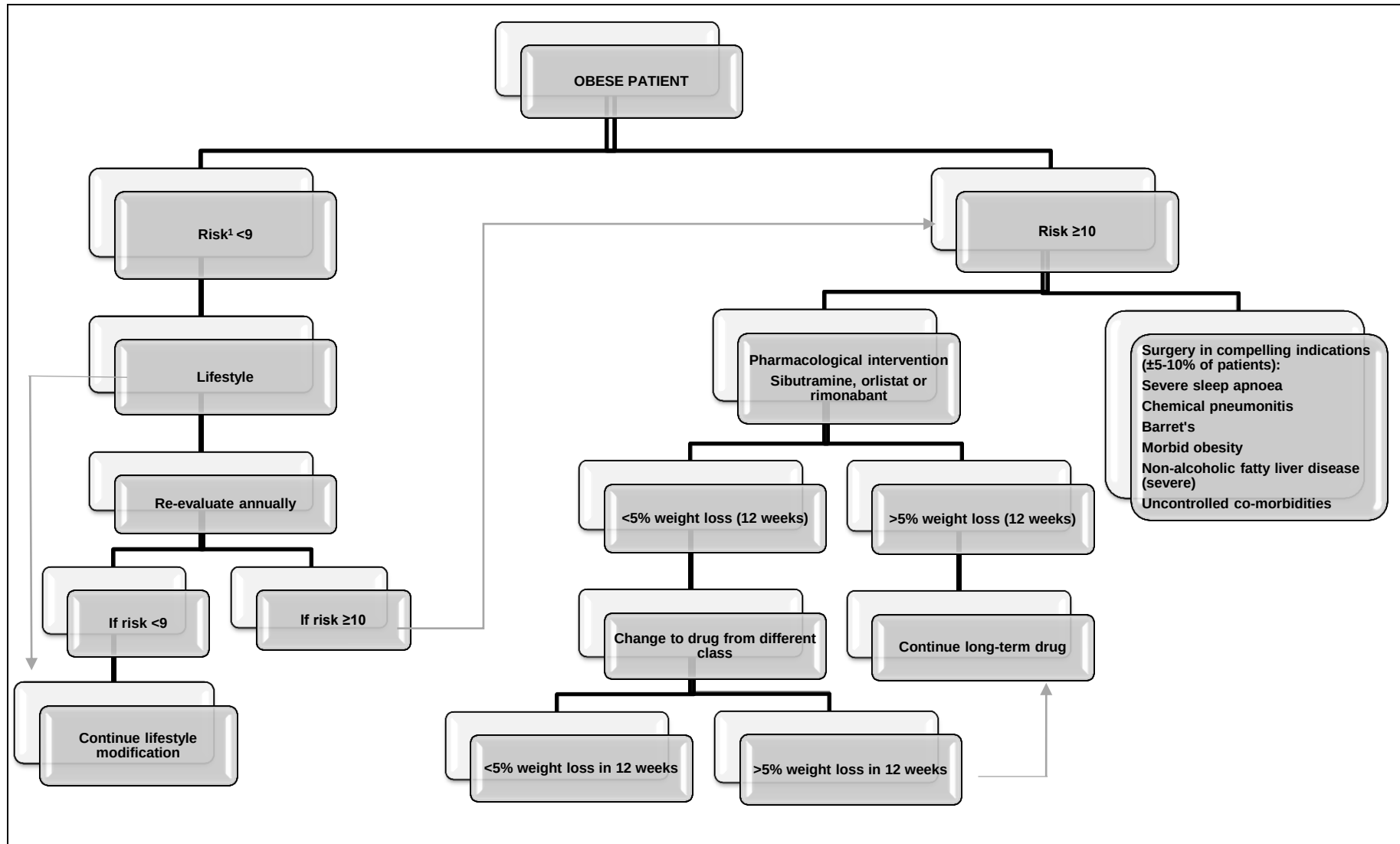


Figure A.1: Algorithm for the treatment of obesity in adults in South Africa [Copyright Prof M.-T. Van der Merwe. Reproduced with permission.]

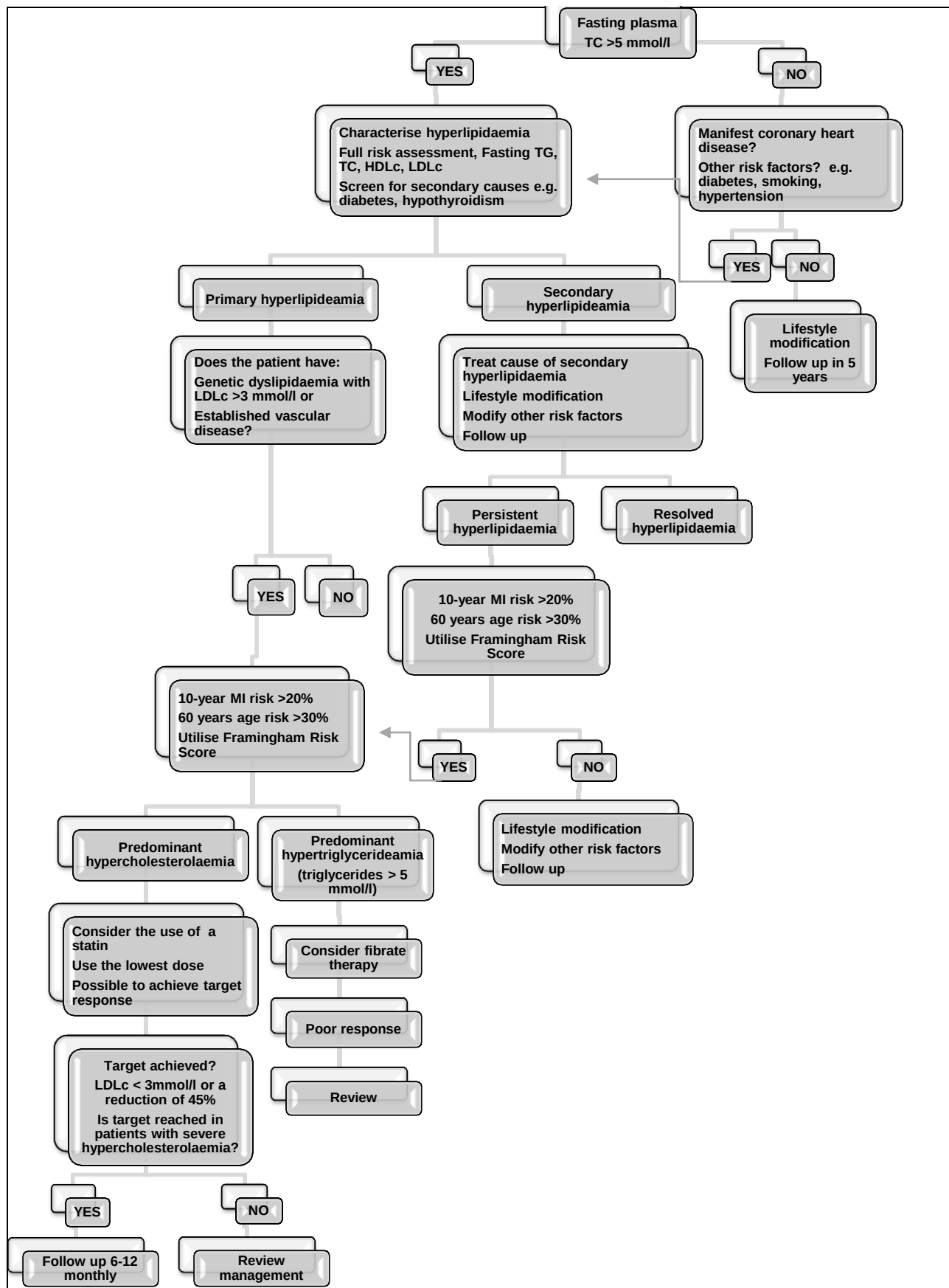


Figure A.2: Council for Medical Schemes 2003 guideline for the treatment of hyperlipidaemia (CMS, 2003)

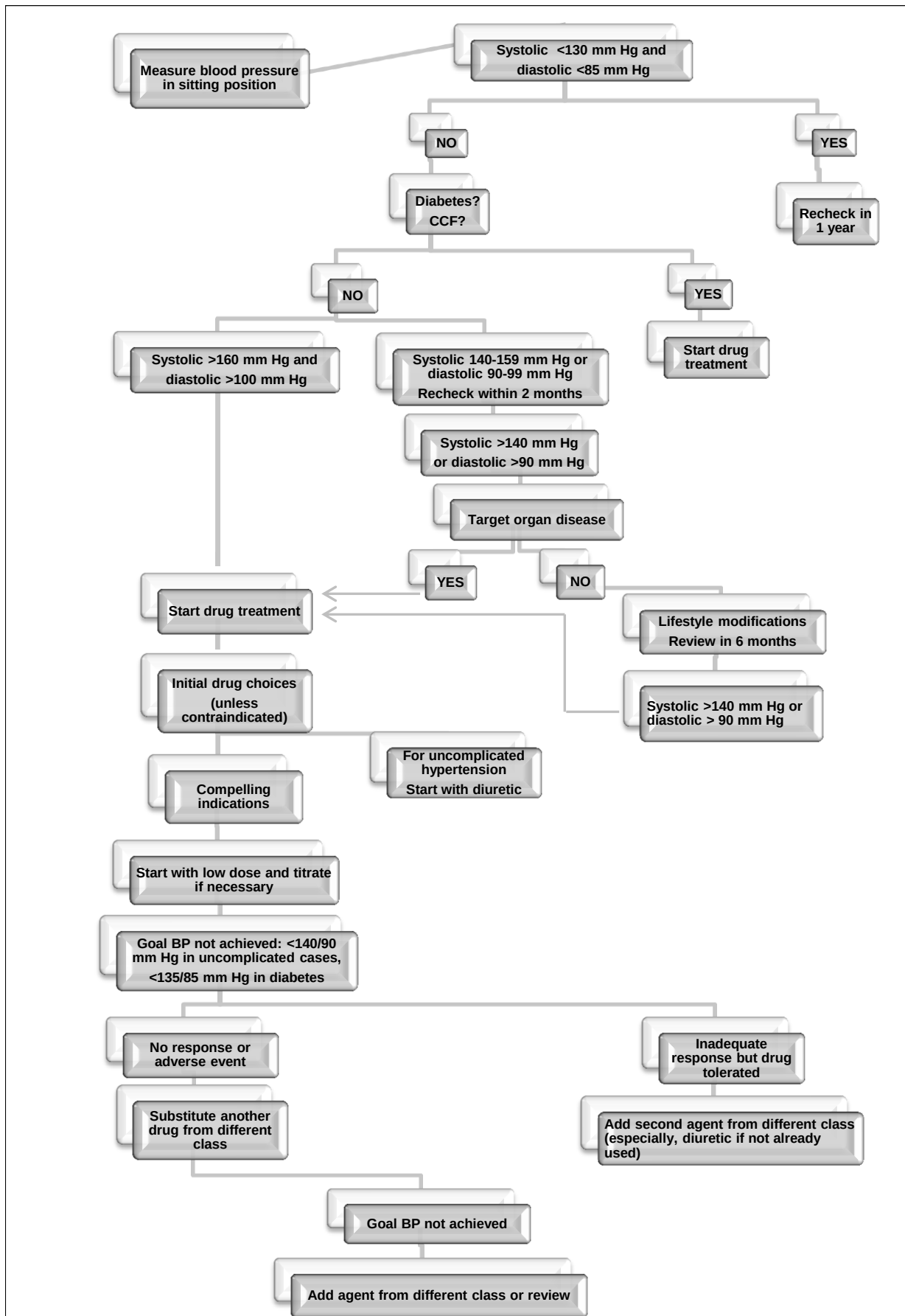


Figure A.3: Council for Medical Schemes 2003 guideline for the treatment of hypertension (CMS, 2003)

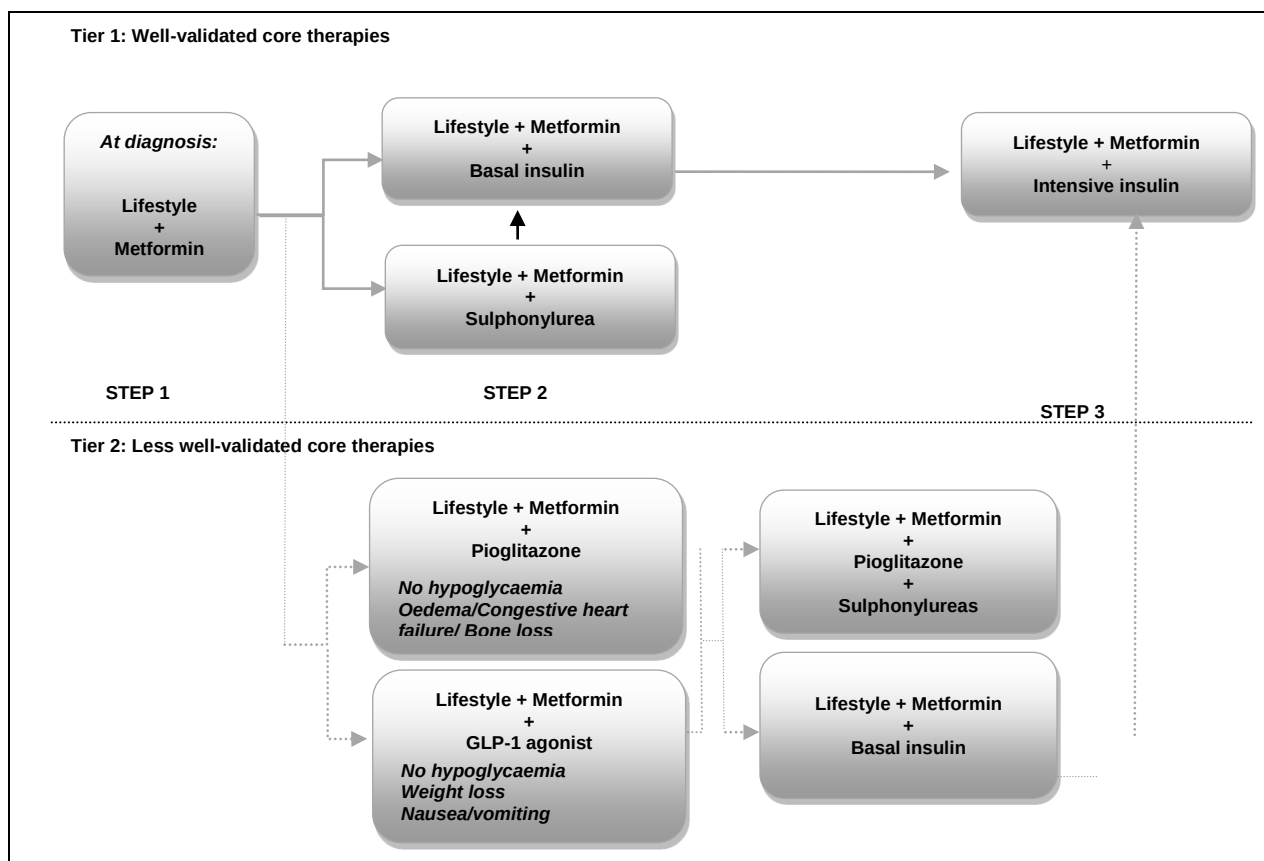


Figure A.4: Algorithm for the management of hyperglycaemia in type 2 diabetes (adapted from Nathan *et al.*, 2009:8)

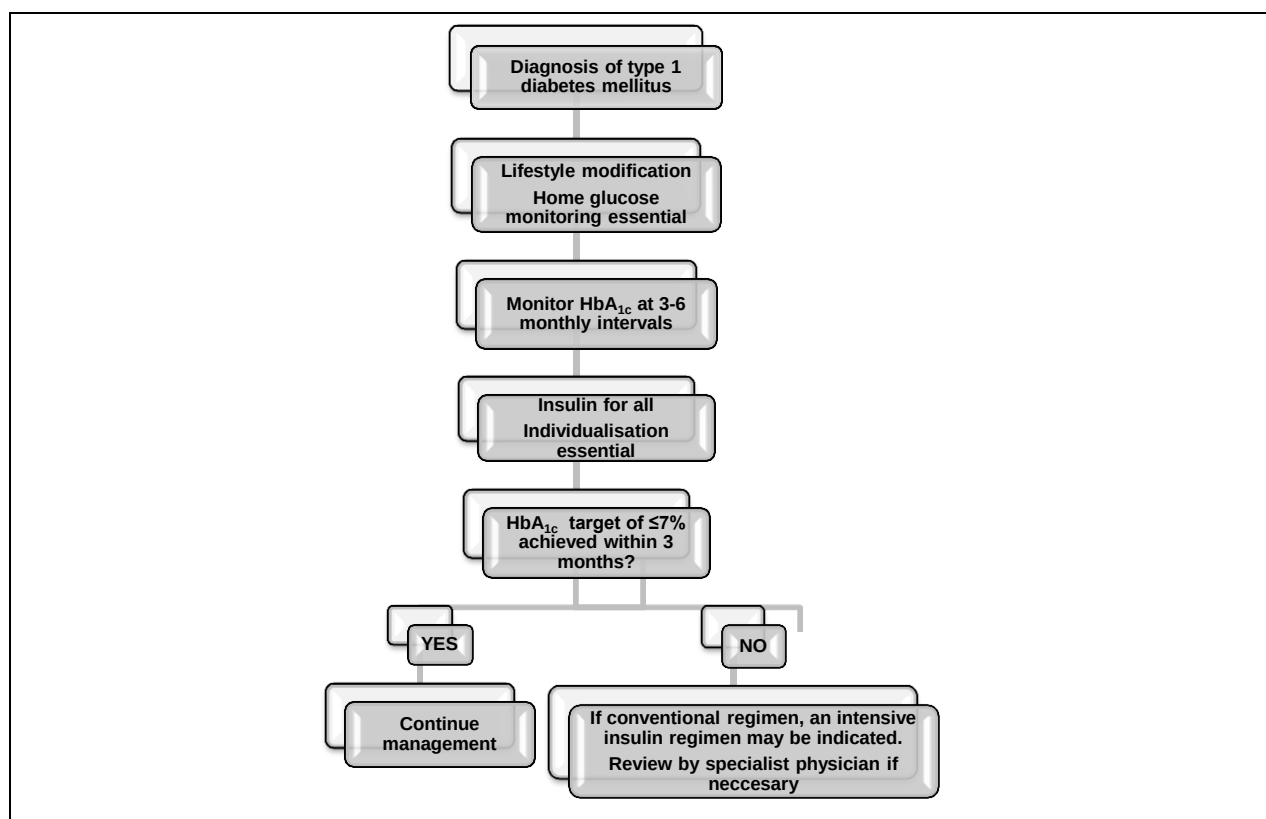


Figure A.5: Council for Medical Schemes 2003 guideline for the treatment of type 1 diabetes mellitus (CMS, 2003)

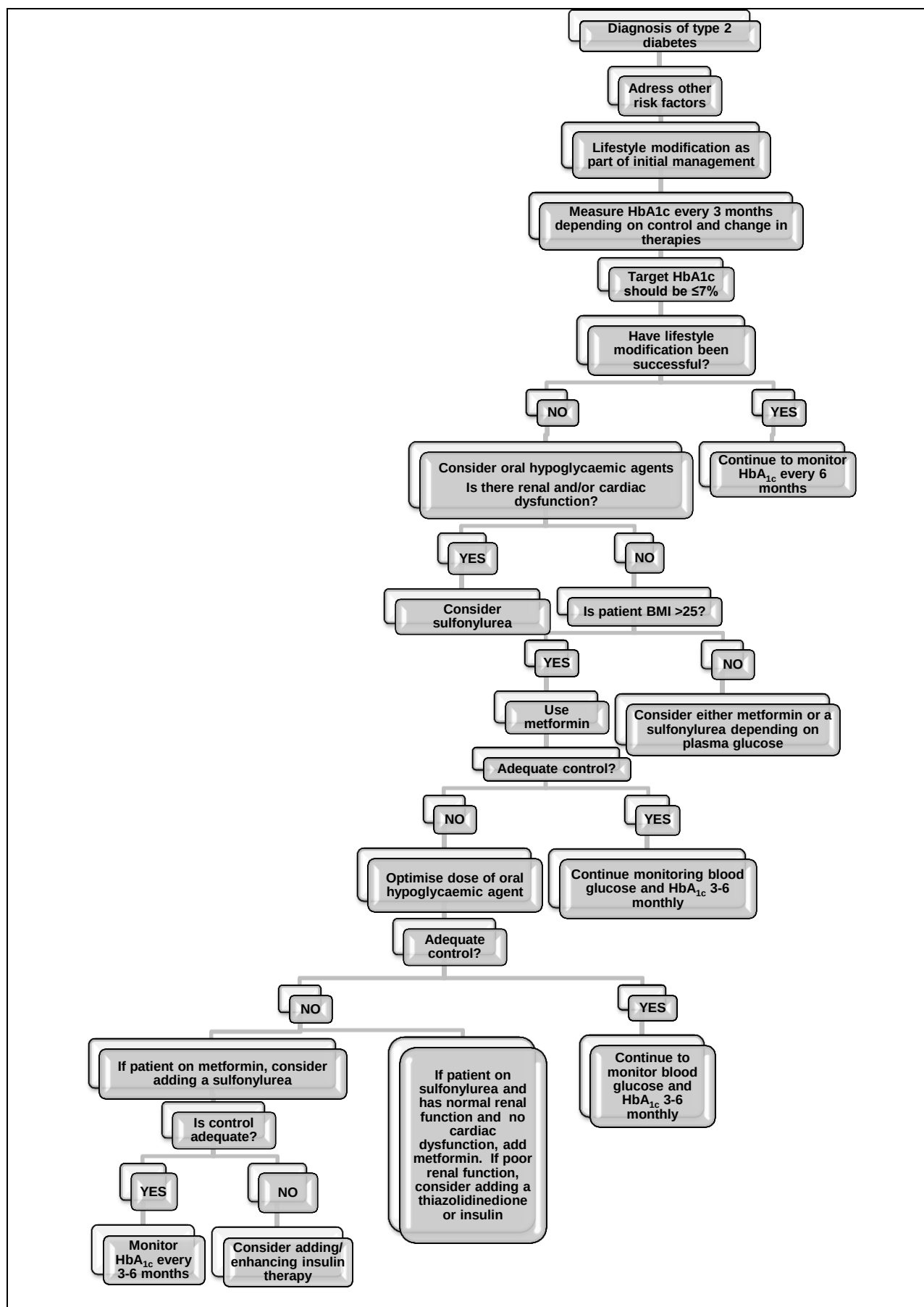


Figure A.6: Council for Medical Schemes 2003 guideline for the treatment of type 2 diabetes mellitus (CMS, 2003)

Estimate of 10-year risk for MEN: (Framingham point scores)						Estimate of 10-year risk for WOMEN: (Framingham point scores)					
AGE (yrs.)			Points			AGE (yrs.)			Points		
20-34			-9			20-34			-7		
35-39			-4			35-39			-3		
40-44			0			40-44			0		
45-49			3			45-49			3		
50-54			6			50-54			6		
55-59			8			55-59			8		
60-64			10			60-64			10		
65-69			11			65-69			12		
70-74			12			70-74			14		
75-79			13			75-79			16		

Total cholesterol (mmol/l)	Points (Age group)					Total cholesterol (mmol/l)	Points (Age group)				
	20-39	40-49	50-59	60-69	70-79		20-39	40-49	50-59	60-69	70-79
<4	0	0	0	0	0	<4	0	0	0	0	0
4.10-5.00	4	3	2	1	0	4.10-5.00	4	3	2	1	1
5.10-6.20	7	5	3	1	0	5.10-6.20	8	6	4	2	1
6.21-7.20	9	6	4	2	1	6.21-7.20	11	8	5	3	2
≥7.2	11	8	5	3	1	≥7.2	13	10	7	4	2

Age	Points					Age	points				
	20-39	40-49	50-59	60-69	70-79		20-39	40-49	50-59	60-69	70-79
Non-smoker	0	0	0	0	0	Non-smoker	0	0	0	0	0
Smoker	8	5	3	1	1	Smoker	9	7	4	2	1

HDL (mmol/l)		Points		HDL (mmol/l)		Points	
≥1.6		-1		≥1.6		-1	
1.30-1.59		0		1.30-1.59		0	
1.00-1.29		1		1.00-1.29		1	
<1		2		<1		2	

Systolic BP (mm Hg)	Points		Systolic BP (mm Hg)	Points	
	If untreated	If treated		If untreated	If treated
<120	0	0	<120	0	0
120-129	0	1	120-129	1	
130-139	1	2	130-139	2	
140-159	1	2	140-159	3	
≥160	2	3	≥160	4	

Point total		10-year risk%		Point total		10-year risk%	
<0		<1		<9		<1	
0		1		9		1	
1		1		10		1	
2		1		11		1	
3		1		12		1	
4		1		13		2	
5		2		14		2	
6		2		15		3	
7		3		16		4	
8		4		17		5	
9		5		18		6	
10		6		19		8	
11		8		20		11	
12		10		21		14	
13		12		22		17	
14		16		23		22	
15		20		24		27	
16		25		≥25		≥30	
10-year risk %		≥17		10-year risk %			

Figure A.7: Framingham 10-year risk assessment chart (adapted from NIH, 2001:2497)

ANNEXURE B

Supplement to Chapter 3

This supplement contains tables pertaining to the empirical investigation phase of the research project (refer to Chapter 3).

Table B.1: Classification codes for active ingredients used for medicine item identification (Snyman, 2010)

MIMS code	Pharmacological classification	Active ingredient/substance
7	CARDIOVASCULAR AGENTS	
7.3	Antihypertensives (Single agents and combinations including diuretic combinations)	
7.3.1	Central acting sympathetic nervous system inhibitors	Moxonidine; Methyl dopa
7.3.2	Alpha-receptor blockers	Alfuzosin; Doxazosin; Prazosin; Terazosin
7.3.3	Beta-receptor blockers	Acebutolol; Atenolol; Bisoprolol; Metoprolol; Timolol; Sotalol
7.3.4	Alpha- and beta-receptor blockers	Carvedilol; Labetalol
7.3.5	Sympathetic nervous system inhibitors	Reserpine; Dihydroergocristine/clopramine/reserpine
7.3.6	Direct-acting vasodilators	Hydralazine; Sodium nitroprusside; Minoxidil
7.3.7	Calcium Channel blockers	Amlodipine; Felodipine; Isradipine; Lercanidipine; Nifedipine; Verapamil
7.3.8	ACE-inhibitors	Benazepril; Captopril; Cilazapril; Enalapril; Fosinopril; Lisinopril; Perindopril; Quinapril; Ramipril; Trandolapril
7.3.9	Angiotensin receptor antagonists	Candesartan; Eprosartan; Irbesartan; Losartan; Telmisartan; Valsartan
7.3.10	Other	Amlodipine/atorvastatin; Nebivolol
16	URINARY SYSTEM	
16.1	Diuretics	Furosemide; Hydrochlorothiazide; Indapamide; Piretanide; Spironolactone; Triamterene; Torasemide
7.7	HIPOLIPIDAEMIC AGENTS	
7.7.1	Fibrates	Bezafibrate; Fenofibrate; Gemfibrozil
7.7.2	HMG-CoA reductase inhibitors (Statins)	Atorvastatin; Fluvastatin; Lovastatin; Pravastatin; Rosuvastatin; Simvastatin
7.7.3	Cholesterol absorption inhibitors	Ezetimibe
7.7.4	Others	Acipimox; Cholestyramine
19	ENDOCRINE SYSTEM	
19.1	Antidiabetic agents	
19.1.1	Insulin	Biphasic biosynthetic human insulin comprising 30%soluble Insulin/70% isophane insulin; Insulin Aspart; Soluble insulin aspart/protamine insulin comprising 30/70 ratio; Insulin Detemir; Insulin Lispro; Biosynthetic isophane human insulin; Insulin Glargine; Insulin Glulisine; Protamine Insulin
19.1.2	Oral agents	Acarbose; Chlorpropamide; Glibenclamide; Gliclazide; Glimepiride; Glipizide; Metformin; Nateglinide; Repaglinide; Rosiglitazone; Pioglitazone

Table B.2: Beers Criteria list for potentially inappropriate medication use in older adults: independent of diagnoses or conditions (Fick et al., 2003:2719-2721)

Medication	Concern	Severity rating (high or low)
Alprazolam (>2 mg)	Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums.	High
Amiodarone	Associated with QT interval problems and risk of provoking <i>torsade's de pointes</i> . Lack of efficacy in older adults.	High
Amitriptyline	Because of its strong anticholinergic and sedation properties, amitriptyline is rarely the antidepressant of choice for elderly patients	High
Amphetamines	These drugs have potential for causing dependence, hypertension, angina, and myocardial infarction. Amphetamines (excluding methylphenidate hydrochloride and anorexics) have central nervous system stimulant adverse effects.	High
Anorexic agents	These drugs have potential for causing dependence, hypertension, angina, and myocardial infarction.	High
Barbiturates	All barbiturates (except phenobarbital) except when used to Control seizures are highly addictive and cause more adverse effects than most sedative or hypnotic drugs in elderly patients.	High
Belladonna alkaloids	Gastro-intestinal antispasmodic drugs are highly anticholinergic and have uncertain effectiveness. These drugs should be avoided (especially for long-term use).	High
Bisacodyl	May exacerbate bowel dysfunction.	High
Carisoprodol	Most muscle relaxants and antispasmodic drugs are poorly tolerated by elderly patients, since these cause anticholinergic adverse effects, sedation, and weakness. Additionally, their effectiveness at doses tolerated by elderly patients is questionable.	High
Cascara sagrada	May exacerbate bowel dysfunction.	High
Chlordiazepoxide	These drugs have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.	High
Chlordiazepoxide/amitriptyline	These drugs have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required. Because of its strong anticholinergic and sedation properties, amitriptyline is rarely the antidepressant of choice for elderly patients	High
Chlorpheniramine	All non-prescription and many prescription antihistamines may have potent anticholinergic properties. Non-anticholinergic antihistamines are preferred in elderly patients when treating allergic reactions.	High
Chlorpropamide	It has a prolonged half-life in elderly patients and could cause prolonged hypoglycaemia. Additionally, it is the only oral hypoglycaemic agent that causes syndrome of inappropriate antidiuretic hormone secretion.	High
Chlorzoxazone	Most muscle relaxants and antispasmodic drugs are poorly tolerated by elderly patients, since these cause anticholinergic adverse effects, sedation, and weakness. Additionally, their effectiveness at doses tolerated by elderly patients is questionable.	High
Cimetidine	Central nervous system adverse effects including confusion.	Low
Clidinium-chlordiazepoxide	Gastro-intestinal antispasmodic drugs are highly anticholinergic and have uncertain effectiveness. These drugs should be avoided (especially for long-term use). These drugs have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.	High
Clonidine	Potential for orthostatic hypotension and central nervous system adverse effects.	Low

Table B.2: Beers Criteria list for potentially inappropriate medication use in older adults: independent of diagnoses or conditions (*continued*)

Medication	Concern	Severity rating (high or low)
Clorazepate	These drugs have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.	High
Cyclandelate	Have not been shown to be effective in the doses studied.	Low
Cyclobenzaprine	Most muscle relaxants and antispasmodic drugs are poorly tolerated by elderly patients, since these cause anticholinergic adverse effects, sedation, and weakness. Additionally, their effectiveness at doses tolerated by elderly patients is questionable.	High
Cyproheptadine	All non-prescription and many prescription antihistamines may have potent anticholinergic properties. Non-anticholinergic antihistamines are preferred in elderly patients when treating allergic reactions.	High
Desiccated thyroid	Concerns about cardiac effects. Safer alternatives available.	High
Dexchlorpheniramine	All non-prescription and many prescription antihistamines may have potent anticholinergic properties. Non-anticholinergic antihistamines are preferred in elderly patients when treating allergic reactions.	High
Diazepam	These drugs have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.	High
Dicyclomine	Gastro-intestinal antispasmodic drugs are highly anticholinergic and have uncertain effectiveness. These drugs should be avoided (especially for long-term use).	High
Digoxin	Decreased renal clearance may lead to increased risk of toxic effects. (should not exceed >0.125 mg/d except when treating atrial arrhythmias)	Low
Diphenhydramine	All non-prescription and many prescription antihistamines may have potent anticholinergic properties. Non-anticholinergic antihistamines are preferred in elderly patients when treating allergic reactions. May cause confusion and sedation. Should not be used as a hypnotic, and when used to treat emergency allergic reactions, it should be used in the smallest possible dose.	High
Dipyridamole	May cause orthostatic hypotension. Do not consider the long-acting dipyridamole (which has better properties than the short-acting in older adults) except with patients with artificial heart valves	Low
Disopyramide	Of all antiarrhythmic drugs, this is the most potent negative inotrope and therefore may induce heart failure in elderly patients. It is also strongly anticholinergic. Other antiarrhythmic drugs should be used.	High
Doxazosin	Potential for hypotension, dry mouth, and urinary problems.	Low
Doxepin	Because of its strong anticholinergic and sedating properties, doxepin is rarely the antidepressant of choice for elderly patients	High
Ergot mesyloids	Have not been shown to be effective in the doses studied.	Low
Oestrogens	Evidence of the carcinogenic (breast and endometrial cancer) potential of these agents and lack of cardioprotective effect in older women.	Low
Ethacrynic acid	Potential for hypertension and fluid imbalances. Safer alternatives available.	Low
Ferrous sulphate	Doses >325 mg/d do not dramatically increase the amount absorbed but greatly increase the incidence of constipation.	Low
Fluoxetine	Long half-life of drug and risk of producing excessive central nervous system stimulation, sleep disturbances, and increasing agitation. Safer alternatives exist.	High
Flurazepam	This benzodiazepine hypnotic has an extremely long half-life in elderly patients (often days), producing prolonged sedation and increasing the incidence of falls and fracture. Medium- or short-acting benzodiazepines are preferable	High
Guanadrel	May cause orthostatic hypotension.	High

Table B.2: Beers Criteria list for potentially inappropriate medication use in older adults: independent of diagnoses or conditions (*continued*)

Medication	Concern	Severity rating (high or low)
Guanethidine	May cause orthostatic hypotension. Safer alternatives exist.	High
Halazepam	These drugs have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.	
Hydroxyzine	All non-prescription and many prescription antihistamines may have potent anticholinergic properties. Non-anticholinergic antihistamines are preferred in elderly patients when treating allergic reactions.	High
Hyoscyamine	Gastro-intestinal antispasmodic drugs are highly anticholinergic and have uncertain effectiveness. These drugs should be avoided (especially for long-term use).	High
Indomethacin	Of all available non-steroidal anti-inflammatory drugs, this drug produces the most central nervous system adverse effects.	High
Isoxsuprine	Lack of efficacy.	Low
Ketorolac	Immediate and long-term use should be avoided in older persons, since a significant number have asymptomatic GI pathologic conditions.	High
Lorazepam (> 3 mg)	Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums.	High
Meperidine	Not an effective oral analgesic in doses commonly used. May cause confusion and has many disadvantages to other narcotic drugs.	High
Meprobamate	This is a highly addictive and sedating anxiolytic. Those using meprobamate for prolonged periods may become addicted and may need to be withdrawn slowly.	High
Mesoridazine	Central nervous system and extrapyramidal adverse effects.	High
Metaxalone	Most muscle relaxants and antispasmodic drugs are poorly tolerated by elderly patients, since these cause anticholinergic adverse effects, sedation, and weakness. Additionally, their effectiveness at doses tolerated by elderly patients is questionable.	High
Methocarbamol	Most muscle relaxants and antispasmodic drugs are poorly tolerated by elderly patients, since these cause anticholinergic adverse effects, sedation, and weakness. Additionally, their effectiveness at doses tolerated by elderly patients is questionable.	High
Methyldopa plus/minus hydrochlorothiazide	May cause bradycardia and exacerbate depression in elderly patients.	High
Methyltestosterone	Potential for prostatic hypertrophy and cardiac problems.	High
Mineral oil	Potential for aspiration and adverse effects. Safer alternatives available.	High
Naproxen	Long-term use of full-dosage, longer half-life, non-cyclooxygenase-selective Nonsteroidal anti-inflammatory drugs have the potential to produce GI bleeding, renal failure, high blood pressure, and heart failure.	High
Neoloid	May exacerbate bowel dysfunction (except in the presence of opiate Analgesic use)	High
Nifedipine	Short acting nifedipine have potential for hypotension and constipation.	High
Nitrofurantoin	Potential for renal impairment. Safer alternatives available.	High
Orphenadrine	Causes more sedation and anticholinergic adverse effects than safer alternatives.	High
Oxaprozin	Long-term use of full-dosage, longer half-life, non-cyclooxygenase-selective Nonsteroidal anti-inflammatory drugs have the potential to produce GI bleeding, renal failure, high blood pressure, and heart failure.	High
Oxazepam (>60 mg)	Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums.	High
Oxybutynin	Most muscle relaxants and antispasmodic drugs are poorly tolerated by elderly patients, since these cause anticholinergic adverse effects, sedation, and weakness. Additionally, their	High

Table B.2: Beers Criteria list for potentially inappropriate medication use in older adults: independent of diagnoses or conditions (*continued*)

Medication	Concern	Severity rating (high or low)
Oxybutynin (<i>continued</i>)	effectiveness at doses tolerated by elderly patients is questionable.	
Pentazocine	Narcotic analgesic that causes more central nervous system adverse effects, including confusion and hallucinations, more commonly than other narcotic drugs. Additionally, it is a mixed agonist and antagonist.	High
Perphenazine-amitriptyline	Because of its strong anticholinergic and sedation properties, amitriptyline is rarely the antidepressant of choice for elderly patients	High
Piroxicam	Long-term use of full-dosage, longer half-life, non-cyclooxygenase-selective Nonsteroidal anti-inflammatory drugs have the potential to produce GI bleeding, renal failure, high blood pressure, and heart failure.	High
Promethazine	All non-prescription and many prescription antihistamines may have potent anticholinergic properties. Non-anticholinergic antihistamines are preferred in elderly patients when treating allergic reactions.	High
Propantheline	Gastro-intestinal antispasmodic drugs are highly anticholinergic and have uncertain effectiveness. These drugs should be avoided (especially for long-term use).	High
Propoxyphene and combination products	Offers few analgesic advantages over acetaminophen, yet has the adverse effects of other narcotic drugs.	Low
Quazepam (>60 mg)	These drugs have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.	High
Reserpine	May induce depression, impotence, sedation, and orthostatic hypotension at doses >0.25 mg.	Low
Temazepam (>15 mg)	Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums.	High
Thioridazine	Greater potential for central nervous system and extrapyramidal adverse effects.	High
Ticlopidine	Has been shown to be no better than aspirin in preventing clotting and may be considerably more toxic. Safer, more effective alternatives exist.	High
Triazolam (>0.25 mg)	Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums.	High
Trimethobenzamide	One of the least effective antiemetic drugs, yet it can cause extrapyramidal adverse effects.	High
Tripelennamine	All non-prescription and many prescription antihistamines may have potent anticholinergic properties. Non-anticholinergic antihistamines are preferred in elderly patients when treating allergic reactions.	High

Table B.3: Chronic Disease List (CDL) of South Africa and associated diagnosis code (CMS, 2003)

Chronic Disease	Diagnosis/ ICD code	Description
Addison's disease	E27.1	Primary adrenocortical insufficiency Disorder of adrenal gland, unspecified
Asthma	J45 J45.8	Asthma Mixed asthma
Bronchiectasis	J47 Q33.4	Bronchiectasis Congenital bronchiectasis
Cardiac failure	I50 I50.0 I50.1	Heart failure Congestive heart failure Left ventricular failure
Cardiomyopathy	I42 I42.0 I25.5	Cardiomyopathy Dilated cardiomyopathy Ischaemic cardiomyopathy
Chronic obstructive pulmonary disorder	J43 J44	Emphysema Other chronic obstructive pulmonary disease
Chronic renal disease	N03 N11 N18	Chronic nephritic syndrome Chronic tubulo- interstitial nephritis Chronic renal failure
Coronary artery disease	I20 I120.0 I25	Angina pectoris Unstable angina Chronic ischaemic heart disease
Crohn's disease	K50 K50.8	Crohn's disease (Regional enteritis) Other Crohn's disease
Diabetes insipidus	E23.2	Diabetes insipidus
Diabetes mellitus types 1	E10 E10.6 E10.9	Insulin-Dependent Diabetes Mellitus Insulin-Dependent Diabetes Mellitus with other specified complications Insulin-Dependent Diabetes Mellitus without complications
Diabetes mellitus type 2	E11 E11.8 E11.9	Non-Insulin-Dependent Diabetes Mellitus Non-Insulin-Dependent Diabetes Mellitus with other specified complications Non-Insulin-Dependent Diabetes Mellitus without complications
Dysrhythmias	I47 I47.2 I48	Other cardiac arrhythmias Ventricular tachycardia Atrial fibrillation and flutter
Epilepsy	G40 G40.8	Epilepsy Other Epilepsy
Glaucoma	H40 Q15.0	Glaucoma Congenital Glaucoma
Haemophilia	D66 D67	Hereditary Factor VIII Deficiency Hereditary Factor XI Deficiency
Hyperlipidaemia	E78.0 E78.8 E78.5	Pure Hypercholesterolaemia Mixed Hyperlipidaemia Hyperlipidaemia, unspecified
Hypertension	I10 I11 I15	Essential (primary) hypertension Hypertensive heart disease Secondary hypertension
Hypothyroidism	E02 E03 E03.8	Subclinical iodine-deficiency hypothyroidism Other hypothyroidism Other specified hypothyroidism
Multiple sclerosis	G35	Multiple sclerosis
Parkinson's disease	G20 G21	Parkinson's disease Secondary Parkinsonism
Rheumatoid arthritis	M05 M06 M08.0	Seropositive rheumatoid arthritis Other rheumatoid arthritis Juvenile rheumatoid arthritis
Schizophrenia	F20 F20.8	Schizophrenia Other schizophrenia
Systemic lupus erythematosus	M32 L93 L93.2	Systemic lupus erythematosus Lupus erythematosus Other local lupus erythematosus
Ulcerative colitis	K51 K51.9	Ulcerative Colitis Other ulcerative colitis, unspecified

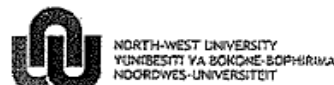
Table B.4: EQUATDUR-2 evaluation score sheet

Criterion	Study Score	Potential Score	Explanation
A. Sample Selection [Prescriptions selected]	3	3	All eligible prescriptions were assessed (refer to paragraph 3.4)
B. Data collection	2	2	Data collection was verified by double-checking (refer to Table 3.5)
C.1 Data analysis	2	2	≥2 sources from up-to-date, evidence-based, peer reviewed sources, current peer reviewed scientific evidence, and publications in peer reviewed sources were used to develop criteria for evaluating appropriateness
C.2 Determination of appropriateness of medication use	1	2	Computer generated appropriateness of medication use was not verified by a second source
C.3 Assessors of appropriateness	0	1	Appropriateness was determined by the researcher alone. Not blinded.
Total score for DUR (A + B + C)	8	10	Quality Rating Category: 8-10 High

Table B.5: Validation processes to insure the validity and reliability of data employed by the PBM

Validation processes	Examples
Data integrity validation & Eligibility management	- Claim field format checks - Provider validation checks - Member validation checks - Verify dependant code - Waiting period check - Duplicate check
Medicine utilisation management (checked at active ingredient level against patient history)	- Refill limits (e.g. 12 fills per year for chronic medication) - Fill limitations per period (e.g. 1 fill per 26 days) - Product quantity limits (e.g. 200 analgesics/365 days) - Products requiring pre-authorisation (e.g. immune-modulating agents) - Patient specific exclusions (e.g. for pre-existing conditions and general waiting periods) - Pre-existing conditions (e.g. patient specific as advised by scheme) - Drug to age range limitations (e.g. RitalinTM and generics will pay for patients 16 years and younger) - Drug to gender limitations (e.g. hormone replacement therapy in women) - Invalid prescriber specialty (e.g. DianeTM prescribed by dermatologists) - Broad category exclusions (e.g. soaps/shampoos excluded) - Specific products excluded (e.g. urinary antiseptics) - Waiting periods (e.g. patient specific as advised by scheme)
Clinical management	- Ingredient duplication - Maximum daily dose exceeded - Therapeutic duplication - Drug-drug interactions - Drug-allergy interactions - Drug-age interactions - Drug-gender interactions - Drug-disease interactions - Drug-inferred health state interactions
Pricing management	- Continuous price file maintenance - Apply reference pricing e.g. generic reference pricing and therapeutic reference pricing (i.e. formulary based pricing for chronic diseases)
Formulary management	- Management of Chronic disease List prescribed minimum benefits and non-chronic disease list conditions - Daily real-time benefit validation

Annex B.6: Permission to conduct the study



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28 August 2007

Dear Prof M S Lubbe (project leader)

ETHICS APPROVAL OF PROJECT

The North-West University Ethics Committee (NWU-EC) hereby approves your project as indicated below. This implies that the NWU-EC grants its permission that, provided the special conditions specified below are met and pending any other authorisation that may be necessary, the project may be initiated, using the ethics number below.

Project title: AHA/NHLBI defined metabolic syndrome in the private health care sector of South Africa: a pharmacoeconomic perspective.	
Ethics number:	2007-0-00000005-07-A5
Legend: 0 = Study/Research; P = Pre-approval; A = Approval; S = Submission	
Approval date: 30 July 2007	Expiry date: 30 July 2012

Special conditions of the approval (if any):

The following statement is made in the project proposal

"Individuals with predictable high future costs will be identified (only by number, refer to 4.2), that might be mitigated through a disease management plan. This will be to the benefit of the patient and the third party payer in terms of possible cost-savings. A treatment algorithm for the cost-effective treatment of the metabolic syndrome within the private health care sector of South Africa will be constructed. To date, no such algorithm exists within the private

health care sector of South Africa. Decision makers within the managed health care environment of South Africa will benefit from this exercise. Also, the results on prevalence and cost of treatment will provide a benchmark for the private health care sector of South Africa as there are currently a paucity of

information regarding the prevalence and associated treatment cost of the syndrome in South Africa."

Although the application has been approved, the committee had the following comments:

"Op watter wyse kan voorspel word dat daar in die toekoms hoë kostes gaan wees? Is dit korrek om h/d pt'e te identifiseer en gaan die pt hiervan in kennis gestel word? Is dit eties korrek om hierdie inligting aan die derde party bekend te maak? Verder is h/d studie tog retrospektief, m.a.w. sou die inligting nog relevant wees vir die pt en/of derde party? Ek stem saam dat die studie wel toekomstige voordele mag inhou vir die besluitnemers en die derde party, maar nie noodwendig vir die pasiënt wie se data gebruik is nie. Wat is die praktiese uitvoerbaarheid daarvan om hierdie pasiënte op te spoor en hulle hele behandelingsplan te verander?"

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:

- The project leader (principal investigator) must report in the prescribed format to the NWU-EC:
 - annually (or as otherwise requested) on the progress of the project,
 - without any delay in case of any adverse event (or any matter that interests sound ethical principles) during the course of the project.
- The approval applies strictly to the protocol as stipulated in the application form. Would any changes to the protocol be deemed necessary during the course of the project, the project leader must apply for approval of these changes at the NWU-EC. Would there be deviation from the project protocol without the necessary approval of such changes, the ethics approval is immediately and automatically forfeited.
- The date of approval indicates the first date that the project may be started. Would the project have to continue after the expiry date, a new application must be made to the NWU-EC and new approval received before or on the expiry date.
- In the interest of ethical responsibility the NWU-EC retains the right to:
 - request access to any information or data at any time during the course or after completion of the project;
 - withdraw or postpone approval if:
 - any unethical principles or practices of the project are revealed or suspected,
 - it becomes apparent that any relevant information was withheld from the NWU-EC or that information has been false or misrepresented,
 - the required annual report and reporting of adverse events was not done timely and accurately,
 - new institutional rules, national legislation or international conventions deem it necessary.

The Ethics Committee would like to remain at your service as scientist and researcher, and wishes you well with your project. Please do not hesitate to contact the Ethics Committee for any further enquiries or requests for assistance.

Yours sincerely

Prof M Lowes
(chair NWU Ethics Committee)

ANNEXURE C

Supplement to Chapter 4

This supplement contains frequency- and descriptive tables describing the data used for analysis during the empirical investigation phase of the research project (refer to Chapter 4).

Table C.1: Cohen's *d*-value for the differences in the average number of prescriptions and medicine items claimed, by study period

Age group	Dataset (study period)	Average number of prescriptions claimed per age group				Dataset (study period)	Average number of medicine items claimed per age group			
>0,≤15			2005	2006	2007			2005	2006	2007
			3.1±3.14	3.2±3.27	3.5±3.50			2.5±1.35	2.5±1.38	2.5±1.39
	2005	3.1±3.14	-	-	-	2005	2.5±1.35	-	-	-
	2006	3.2±3.27	0.03	-	-	2006	2.5±1.38	0	-	-
	2007	3.5±3.50	0.11	0.09	-	2007	2.5±1.39	0	0	-
>15,≤30	2008	3.4±3.52	0.09	0.06	0.03	2008	2.5±1.39	0	0	0
			2005	2006	2007			2005	2006	2007
			3.4±3.87	3.5±3.99	3.9±4.25			2.2±1.32	2.3±1.35	2.3±1.36
	2005	3.4±3.87	-	-	-	2005	2.2±1.32	-	-	-
	2006	3.5±3.99	0.03	-	-	2006	2.3±1.35	0.07	-	-
>30,≤45	2007	3.9±4.25	0.12	0.09	-	2007	2.3±1.36	0.07	0	-
	2008	3.9±4.39	0.11	0.02	0	2008	2.2±1.36	0	0.07	0.07
			2005	2006	2007			2005	2006	2007
			5.0±5.55	5.1±5.75	6.0±6.27			2.3±1.40	2.3±1.42	2.4±1.45
	2005	5.0±5.55	-	-	-	2005	2.3±1.40	-	-	-
>45,≤60	2006	5.1±5.75	0.02	-	-	2006	2.3±1.42	0	-	-
	2007	6.0±6.27	0.16	0.14	-	2007	2.4±1.45	0.07	0.07	-
	2008	6.0±6.38	0.16	0.14	0	2008	2.4±1.45	0.07	0.07	0
			2005	2006	2007			2005	2006	2007
			6.9±7.50	7.0±7.64	8.2±8.07			2.3±1.50	2.4±1.55	2.4±1.59
>60,≤75	2005	6.9±7.50	-	-	-	2005	2.3±1.50	-	-	-
	2006	7.0±7.64	0.01	-	-	2006	2.4±1.55	0.07	-	-
	2007	8.2±8.07	0.16	0.15	-	2007	2.4±1.59	0.06	0	-
	2008	8.1±8.07	0.15	0.14	0.01	2008	2.4±1.62	0.06	0	0
			2005	2006	2007			2005	2006	2007
>75			9.9±9.45	10.1±9.75	12.1±9.97			2.4±1.76	2.5±1.80	2.5±1.84
	2005	9.9±9.45	-	-	-	2005	2.4±1.76	-	-	-
	2006	10.1±9.75	0.02	-	-	2006	2.5±1.80	0.06	-	-
	2007	12.1±9.97	0.22	0.20	-	2007	2.5±1.84	0.05	0	-
	2008	11.9±10.03	0.20	0.18	0.02	2008	2.6±1.88	0.11	0.05	0.05
>75			2005	2006	2007			2005	2006	2007
			12.1±10.84	12.6±11.25	15.1±11.32			2.5±1.87	2.5±1.91	2.6±1.95
	2005	12.1±10.84	-	-	-	2005	2.5±1.87	-	-	-
	2006	12.6±11.25	0.04	-	-	2006	2.5±1.91	0	-	-
	2007	15.1±11.32	0.27	0.22	-	2007	2.6±1.95	0.05	0.05	-
	2008	15.0±11.64	0.25	0.21	0.01	2008	2.6±1.99	0.05	0.05	0

Table C.2: Cohen's *d*-value for the difference in the average number of prescriptions claimed per year, by age group

Dataset (study period)	Age group	Average number of medicine items claimed per dataset (study period), by age group					
		Mean $\pm$ SD					
			3.1 $\pm$ 3.14 (>0, $\leq$ 15)	3.4 $\pm$ 3.87 (>15, $\leq$ 30)	5.0 $\pm$ 5.55 (>30, $\leq$ 45)	6.9 $\pm$ 7.50 (>45, $\leq$ 60)	9.9 $\pm$ 9.45 (>60, $\leq$ 75)
2005	>0, $\leq$ 15	3.1 $\pm$ 3.14	-	-	-	-	-
	>15, $\leq$ 30	3.4 $\pm$ 3.87	0.08	-	-	-	-
	>30, $\leq$ 45	5.0 $\pm$ 5.55	0.34	0.29	-	-	-
	>45, $\leq$ 60	6.9 $\pm$ 7.50	0.51	0.47	0.25	-	-
	>60, $\leq$ 75	9.9 $\pm$ 9.45	0.72	0.69	0.52	0.31	-
	>75	12.1 $\pm$ 10.84	0.83	0.80	0.65	0.47	0.20
			3.2 $\pm$ 3.27 (>0, $\leq$ 15)	3.5 $\pm$ 3.99 (>15, $\leq$ 30)	5.1 $\pm$ 5.75 (>30, $\leq$ 45)	7.0 $\pm$ 7.64 (>45, $\leq$ 60)	10.1 $\pm$ 9.75 (>60, $\leq$ 75)
2006	>0, $\leq$ 15	3.2 $\pm$ 3.27	-	-	-	-	-
	>15, $\leq$ 30	3.5 $\pm$ 3.99	0.08	-	-	-	-
	>30, $\leq$ 45	5.1 $\pm$ 5.75	0.33	0.28	-	-	-
	>45, $\leq$ 60	7.0 $\pm$ 7.64	0.50	0.46	0.25	-	-
	>60, $\leq$ 75	10.1 $\pm$ 9.75	0.71	0.68	0.51	0.32	-
	>75	12.6 $\pm$ 11.25	0.84	0.81	0.67	0.50	0.22
			3.5 $\pm$ 3.50 (>0, $\leq$ 15)	3.9 $\pm$ 4.25 (>15, $\leq$ 30)	6.0 $\pm$ 6.27 (>30, $\leq$ 45)	8.2 $\pm$ 8.07 (>45, $\leq$ 60)	12.1 $\pm$ 9.97 (>60, $\leq$ 75)
2007	>0, $\leq$ 15	3.5 $\pm$ 3.50	-	-	-	-	-
	>15, $\leq$ 30	3.9 $\pm$ 4.25	0.09	-	-	-	-
	>30, $\leq$ 45	6.0 $\pm$ 6.27	0.40	0.33	-	-	-
	>45, $\leq$ 60	8.2 $\pm$ 8.07	0.58	0.53	0.27	-	-
	>60, $\leq$ 75	12.1 $\pm$ 9.97	0.86	0.82	0.61	0.39	-
	>75	15.1 $\pm$ 11.32	1.02	0.99	0.80	0.61	0.27
			3.4 $\pm$ 3.52 (>0, $\leq$ 15)	3.9 $\pm$ 4.39 (>15, $\leq$ 30)	6.0 $\pm$ 6.38 (>30, $\leq$ 45)	8.1 $\pm$ 8.07 (>45, $\leq$ 60)	11.9 $\pm$ 10.03 (>60, $\leq$ 75)
2008	>0, $\leq$ 15	3.4 $\pm$ 3.52	-	-	-	-	-
	>15, $\leq$ 30	3.9 $\pm$ 4.39	0.1	-	-	-	-
	>30, $\leq$ 45	6.0 $\pm$ 6.38	0.4	0.3	-	-	-
	>45, $\leq$ 60	8.1 $\pm$ 8.07	0.6	0.5	0.3	-	-
	>60, $\leq$ 75	11.9 $\pm$ 10.03	0.9	0.8	0.6	0.4	-
	>75	15.0 $\pm$ 11.64	1.00	1.0	0.8	0.6	0.3

Table C.3: Cohen's *d*-value for the difference in the average number of medicine items claimed per year, by age group

Dataset (study period)	Age group	Average number of medicine items claimed per dataset (study period), by age group Mean $\pm$ SD					
			2.5 $\pm$ 1.35 (>0, $\leq$ 15)	2.2 $\pm$ 1.32 (>15, $\leq$ 30)	2.3 $\pm$ 1.40 (>30, $\leq$ 45)	2.3 $\pm$ 1.50 (>45, $\leq$ 60)	2.5 $\pm$ 1.87 (>60, $\leq$ 75)
2005	>0, $\leq$ 15	2.5 $\pm$ 1.35	-	-	-	-	-
	>15, $\leq$ 30	2.2 $\pm$ 1.32	0.2	-	-	-	-
	>30, $\leq$ 45	2.3 $\pm$ 1.40	0.14	0.07	-	-	-
	>45, $\leq$ 60	2.3 $\pm$ 1.50	0.13	0.07	0	-	-
	>60, $\leq$ 75	2.4 $\pm$ 1.76	0.06	0.11	0.06	0.06	-
	>75	2.5 $\pm$ 1.87	0	0.16	0.11	0.11	0
			2.5 $\pm$ 1.38 (>0, $\leq$ 15)	2.3 $\pm$ 1.35 (>15, $\leq$ 30)	2.3 $\pm$ 1.42 (>30, $\leq$ 45)	2.4 $\pm$ 1.55 (>45, $\leq$ 60)	2.5 $\pm$ 1.80 (>60, $\leq$ 75)
2006	>0, $\leq$ 15	2.5 $\pm$ 1.38	-	-	-	-	-
	>15, $\leq$ 30	2.3 $\pm$ 1.35	0.15	-	-	-	-
	>30, $\leq$ 45	2.3 $\pm$ 1.42	0.14	0	-	-	-
	>45, $\leq$ 60	2.4 $\pm$ 1.55	0.06	0.07	0.07	-	-
	>60, $\leq$ 75	2.5 $\pm$ 1.80	0	0.11	0.11	0.06	-
	>75	2.5 $\pm$ 1.91	0	0.11	0.11	0.05	0
			2.5 $\pm$ 1.39 (>0, $\leq$ 15)	2.3 $\pm$ 1.36 (>15, $\leq$ 30)	2.4 $\pm$ 1.45 (>30, $\leq$ 45)	2.4 $\pm$ 1.59 (>45, $\leq$ 60)	2.5 $\pm$ 1.84 (>60, $\leq$ 75)
2007	>0, $\leq$ 15	2.5 $\pm$ 1.39	-	-	-	-	-
	>15, $\leq$ 30	2.3 $\pm$ 1.36	0.14	-	-	-	-
	>30, $\leq$ 45	2.4 $\pm$ 1.45	0.07	0.07	-	-	-
	>45, $\leq$ 60	2.4 $\pm$ 1.59	0.06	0.05	0	-	-
	>60, $\leq$ 75	2.5 $\pm$ 1.84	0	0.11	0.05	0.05	-
	>75	2.6 $\pm$ 1.95	0.05	0.15	0.10	0.10	0.05
			2.5 $\pm$ 1.39 (>0, $\leq$ 15)	2.2 $\pm$ 1.36 (>15, $\leq$ 30)	2.4 $\pm$ 1.45 (>30, $\leq$ 45)	2.4 $\pm$ 1.62 (>45, $\leq$ 60)	2.6 $\pm$ 1.88 (>60, $\leq$ 75)
2008	>0, $\leq$ 15	2.5 $\pm$ 1.39	-	-	-	-	-
	>15, $\leq$ 30	2.2 $\pm$ 1.36	0.22	-	-	-	-
	>30, $\leq$ 45	2.4 $\pm$ 1.45	0.07	0.14	-	-	-
	>45, $\leq$ 60	2.4 $\pm$ 1.62	0.06	0.12	0	-	-
	>60, $\leq$ 75	2.6 $\pm$ 1.88	0.05	0.21	0.11	0.11	-
	>75	2.6 $\pm$ 1.99	0.05	0.20	0.10	0.10	0

Table C.4: Cohen's *d*-value for the difference in the average cost per medicine item claimed per age group, by study period

Age group	Dataset (Study period)	Average cost per medicine item (R) per age group, by study period Mean $\pm$ SD			
			58.49 $\pm$ 78.92 (2005)	58.28 $\pm$ 88.79 (2006)	61.28 $\pm$ 111.59 (2007)
>0, $\leq$ 15	2005	58.49 $\pm$ 78.92	-	-	-
	2006	58.28 $\pm$ 88.79	0.00	-	-
	2007	61.28 $\pm$ 111.59	0.03	0.03	-
	2008	67.51 $\pm$ 129.42	0.07	0.07	0.05
>15, $\leq$ 30			77.35 $\pm$ 136.15 (2005)	75.43 $\pm$ 153.12 (2006)	79.12 $\pm$ 226.16 (2007)
	2005	77.35 $\pm$ 136.15	-	-	-
	2006	75.43 $\pm$ 153.12	0.01	-	-
	2007	79.12 $\pm$ 226.16	0.01	0.02	-
	2008	86.86 $\pm$ 321.24	0.03	0.04	0.02
>30, $\leq$ 45			79.34 $\pm$ 151.90 (2005)	78.48 $\pm$ 170.16 (2006)	84.64 $\pm$ 268.96 (2007)
	2005	79.34 $\pm$ 151.90	-	-	-
	2006	78.48 $\pm$ 170.16	0.01	-	-
	2007	84.64 $\pm$ 268.96	0.02	0.02	-
	2008	91.98 $\pm$ 342.99	0.04	0.04	0.02
>45, $\leq$ 60			99.15 $\pm$ 179.21 (2005)	97.96 $\pm$ 212.75 (2006)	104.56 $\pm$ 356.93 (2007)
	2005	99.15 $\pm$ 179.21	-	-	-
	2006	97.96 $\pm$ 212.75	0.01	-	-
	2007	104.56 $\pm$ 356.93	0.02	0.02	-
	2008	110.44 $\pm$ 486.93	0.02	0.02	0.01
>60, $\leq$ 75			118.84 $\pm$ 200.67 (2005)	119.72 $\pm$ 251.35 (2006)	129.34 $\pm$ 416.10 (2007)
	2005	118.84 $\pm$ 200.67	-	-	-
	2006	119.72 $\pm$ 251.35	0.00	-	-
	2007	129.34 $\pm$ 416.1	0.03	0.02	-
	2008	133.55 $\pm$ 563.02	0.03	0.02	0.01
>75			117.46 $\pm$ 180.26 (2005)	116.53 $\pm$ 202.80 (2006)	125.33 $\pm$ 346.32 (2007)
	2005	117.46 $\pm$ 180.26	-	-	-
	2006	116.53 $\pm$ 202.80	0.00	-	-
	2007	125.33 $\pm$ 346.32	0.02	0.03	-
	2008	128.43 $\pm$ 375.98	0.03	0.03	0.01

Table C.5: Cohen's *d*-value for the difference in average cost per item claimed, by study period

Dataset (Study period)	Age group	Average cost per medicine item (R) per dataset (study period), by age group Mean $\pm$ SD					
			(>0,≤15)	(>15,≤30)	(>30,≤45)	(>45,≤60)	(>60,≤75)
			58.49±78.92	77.35±136.15	79.34±151.90	99.15±179.21	118.84±200.67
2005	>0,≤15	58.49±78.92	-	-	-	-	-
	>15,≤30	77.35±136.15	0.14	-	-	-	-
	>30,≤45	79.34±151.90	0.14	0.01	-	-	-
	>45,≤60	99.15±179.21	0.23	0.12	0.11	-	-
	>60,≤75	118.84±200.67	0.30	0.21	0.20	0.10	-
	>75	117.46±180.26	0.33	0.22	0.21	0.10	0.01
			58.28±88.79	75.43±153.12	78.48±170.16	97.96±212.75	119.72±251.35
2006	>0,≤15	58.28±88.79	-	-	-	-	-
	>15,≤30	75.43±153.12	0.11	-	-	-	-
	>30,≤45	78.48±170.16	0.12	0.02	-	-	-
	>45,≤60	97.96±212.75	0.19	0.11	0.09	-	-
	>60,≤75	119.72±251.35	0.24	0.18	0.16	0.09	-
	>75	116.53±202.80	0.29	0.20	0.19	0.09	0.01
			61.28±111.59	79.12±226.16	84.64±268.96	104.56±356.93	129.34±416.10
2007	>0,≤15	61.28±111.59	-	-	-	-	-
	>15,≤30	79.12±226.16	0.08	-	-	-	-
	>30,≤45	84.64±268.96	0.09	0.02	-	-	-
	>45,≤60	104.56±356.93	0.12	0.07	0.06	-	-
	>60,≤75	129.34±416.1	0.16	0.12	0.11	0.06	-
	>75	125.33±346.32	0.18	0.13	0.12	0.06	0.01
			67.51±129.42	86.86±321.24	91.98±342.99	110.44±486.93	133.55±563.02
2008	>0,≤15	67.51±129.42	-	-	-	-	-
	>15,≤30	86.86±321.24	0.06	-	-	-	-
	>30,≤45	91.98±342.99	0.07	0.01	-	-	-
	>45,≤60	110.44±486.93	0.09	0.05	0.04	-	-
	>60,≤75	133.55±563.02	0.12	0.08	0.07	0.04	-
	>75	128.43±375.98	0.16	0.11	0.10	0.04	0.01

Table C.6: Cohen's *d*-value for differences in the average direct medicine treatment cost associated with "at risk" categories

Study period	Category		Average direct medicine treatment cost per year (R) Mean ± SD				
			Antidiabetics	Antihypertensives	Hipolipidaemics	Antidiabetics /Antihypertensive	Antihypertensive/ Hipolipidaemics
			1 009.99 ± 1 990.48	871.22 ± 1 141.96	1 044.78 ± 973.28	2 258.17 ± 2 719.75	2 677.79 ± 2 001.35
2005	Antidiabetics	1 009.99 ± 1 990.48	-	-	-	-	-
	Antihypertensives	871.22 ± 1 141.96	0.07	-	-	-	-
	Hipolipidaemics	1 044.78 ± 973.28	0.02	0.15	-	-	-
	Antidiabetics /Antihypertensive	2 258.17 ± 2 719.75	0.5	0.5	0.5	-	-
	Antihypertensive/ Hipolipidaemics	2 677.79 ± 2 001.35	0.8	0.9	0.8	0.15	-
	Antidiabetic-/Hipolipidaemics	2 437.66 ± 2 874.53	0.5	0.6	0.5	0.06	0.08
			1 100.88 ± 2 149.40	866.20 ± 1 117.54	1 077.55 ± 1 026.15	2 528.45 ± 2 958.78	2 785.06 ± 1 956.51
2006	Antidiabetics	1 100.88 ± 2 149.40	-	-	-	-	-
	Antihypertensives	866.20 ± 1 117.54	0.11	-	-	-	-
	Hipolipidaemics	1 077.55 ± 1 026.15	0.01	0.19	-	-	-
	Antidiabetics /Antihypertensive	2 528.45 ± 2 958.78	0.5	0.6	0.5	-	-
	Antihypertensive/ Hipolipidaemics	2 785.06 ± 1 956.51	0.8	1.0	0.9	0.09	-
	Antidiabetic-/Hipolipidaemics	2 514.73 ± 2 879.23	0.5	0.6	0.5	0.005	0.09
			1 277.86 ± 2 427.12	1 008.17 ± 1 201.51	1 189.12 ± 1 028.23	2 784.38 ± 3 131.45	2 966.28 ± 1 956.51
2007	Antidiabetics	1 277.86 ± 2 427.12	-	-	-	-	-
	Antihypertensives	1 008.17 ± 1 201.51	0.11	-	-	-	-
	Hipolipidaemics	1 189.12 ± 1 028.23	0.04	0.15	-	-	-
	Antidiabetics /Antihypertensive	2 784.38 ± 3 131.45	0.5	0.9	0.5	-	-
	Antihypertensive/ Hipolipidaemics	2 966.28 ± 1 956.51	0.7	1.0	0.9	0.06	-
	Antidiabetic-/Hipolipidaemics	2 865.56 ± 3 163.88	0.5	0.6	0.5	0.03	0.03
			1 281.27 ± 2 400.81	984.69 ± 1 173.20	1 112.33 ± 997.14	2 807.14 ± 3 190.56	2 856.10 ± 1 906.39
2008	Antidiabetics	1 281.27 ± 2 400.81	-	-	-	-	-
	Antihypertensives	984.69 ± 1 173.20	0.12	-	-	-	-
	Hipolipidaemics	1 112.33 ± 997.14	0.07	0.11	-	-	-
	Antidiabetics /Antihypertensive	2 807.14 ± 3 190.56	0.5	0.6	0.5	-	-
	Antihypertensive/ Hipolipidaemics	2 856.10 ± 1 906.39	0.7	1.0	0.9	0.02	-
	Antidiabetic-/Hipolipidaemics	2 770.39 ± 3 093.52	0.5	0.6	0.5	0.01	0.03

Table C.7: Medicine items claimed for female patients from the metabolic syndrome category

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Insulin	Insulin	10 871 (5.0)	12 678 (4.6)	15 565 (5.3)	14 618 (4.9)	-0.1
	Insulin glulisine	-	125 (0.05)	252 (0.09)	221 (0.07)	+0.07
	Insulin isophane/regular insulin	23 (0.01)	104 (0.04)	133 (0.05)	133 (0.04)	+0.03
	Insulin lispro	-	49 (0.02)	106 (0.04)	155 (0.05)	+0.05
	Biphasic isophane insulin	-	-	-	3 (0.001)	+0.001
Oral antidiabetics	Acarbose	190 (0.09)	141 (0.05)	134 (0.05)	109 (0.04)	-0.05
	Chlorpropamide	13 (0.006)	5 (0.002)	1 (0.0003)	-	-0.006
	Glibenclamide	2 542 (1.16)	2 928 (1.1)	3 044 (1.0)	2 574 (0.9)	-0.26
	Gliclazide	9 118 (4.2)	9 826 (3.6)	11 576 (4.0)	10 971 (3.7)	-0.5
	Glimepiride	3 421 (1.6)	3 624 (1.3)	3 671 (1.3)	3 144 (1.1)	-0.5
	Glipizide	172 (0.08)	108 (0.04)	92 (0.03)	73 (0.02)	-0.06
	Metformin	26 223 (12.0)	31 275 (11.4)	38 632 (13.2)	37 535 (12.7)	+0.7
	Metformin/Glibenclamide	1 179 (0.5)	1 807 (0.7)	2 311 (0.8)	2129 (0.7)	+0.2
	Nateglinide	48 (0.02)	58 (0.02)	47 (0.02)	20 (0.01)	-0.01
	Pioglitazone	442 (0.2)	633 (0.2)	920 (0.3)	1 207 (0.4)	+0.2
	Repaglinide	199 (0.09)	218 (0.08)	208 (0.07)	185 (0.06)	-0.03
	Rosiglitazone	1 194 (0.5)	1 264 (0.5)	1 205 (0.4)	659 (0.2)	-0.3
Statins	Atorvastatin	19 041 (8.7)	23 325 (8.5)	19 649 (6.7)	21 773 (7.4)	-1.3
	Fluvastatin	2 027 (0.9)	2 092 (0.8)	1 509 (0.5)	1 427 (0.5)	-0.4
	Lovastatin	180 (0.08)	686 (0.3)	639 (0.2)	632 (0.2)	+0.12
	Simvastatin	26 300 (12.0)	36 046 (13.1)	36 187 (12.4)	38 446 (13.0)	+1.0
	Simvastatin /Ascorbic acid/Citric acid monohydrate/Butylated hydroxyanisole	153 (0.07)	1 475 (0.5)	83 (0.03)	5 (0.002)	-0.068
	Pravastatin	2 537 (1.2)	3 060 (1.1)	2 471 (0.9)	2 192 (0.7)	-0.5
	Rosuvastatin	-	1 123 (0.4)	4 331 (1.5)	6 741 (2.3)	+2.3
	Bezafibrate	1 354 (0.6)	1 962 (0.7)	1 722 (0.6)	1 993 (0.7)	+0.1
Fibrates	Fenofibrate	184 (0.08)	38 (0.01)	5 (0.002)	138 (0.05)	-0.03
	Gemfibrozil	33 (0.02)	61 (0.02)	37 (0.01)	61 (0.02)	-
Cholesterol absorption inhibitor	Ezetimibe	159 (0.07)	857 (0.3)	818 (0.3)	749 (0.3)	+0.23
Other hipolipidaemics	Cholestyramine	205 (0.09)	220 (0.08)	-	221 (0.07)	-0.02
	Acipimox	33 (0.02)	63 (0.02)	-	15 (0.01)	-0.01

Table C.7: Medicine items claimed for female patients from the metabolic syndrome category (*continued*)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Other (<i>continued</i>)	Nicotinic acid	29 (0.01)	63 (0.02)	46 (0.02)	42 (0.01)	-
ACE-inhibitors	Benazepril	34 (0.02)	24 (0.009)	-	-	-0.02
	Benazepril/Hydrochlorothiazide	9 (0.004)	18 (0.007)	6 (0.002)	4 (0.001)	-0.003
	Captopril	1 241 (0.6)	1 166 (0.4)	1 134 (0.4)	1 064 (0.4)	-0.2
	Captopril/Hydrochlorothiazide	129 (0.06)	119 (0.04)	133 (0.05)	150 (0.05)	-0.01
	Cilazapril	103 (0.05)	94 (0.03)	123 (0.04)	87 (0.03)	-0.02
	Cilazapril/Hydrochlorothiazide	52 (0.02)	40 (0.02)	32 (0.01)	36 (0.01)	-0.01
	Enalapril	5 594 (2.6)	6 724 (2.5)	6 125 (2.1)	6 178 (2.1)	-0.5
	Enalapril/Hydrochlorothiazide	2 647 (1.2)	3 223 (1.2)	3 457 (1.2)	3 522 (1.2)	-
	Fosinopril	135 (0.06)	222 (0.08)	173 (0.06)	116 (0.04)	-0.02
	Fosinopril/Hydrochlorothiazide	120 (0.06)	62 (0.02)	22 (0.008)	35 (0.01)	-0.05
	Lisinopril	4 993 (2.3)	6 067 (2.2)	5 978 (2.1)	6 453 (2.2)	-0.1
	Lisinopril/Hydrochlorothiazide	1 104 (0.5)	1 574 (0.6)	1 842 (0.6)	1 894 (0.6)	+0.1
	Perindopril	6 933 (3.2)	8 936 (3.3)	9 518 (3.3)	8 631 (2.9)	-0.3
	Perindopril/Indapamide	3 490 (1.6)	6 050 (2.2)	7 445 (2.6)	7 921 (2.7)	+1.1
	Quinapril	616 (0.3)	554 (0.2)	575 (0.2)	575 (0.19)	-0.11
	Quinapril/Hydrochlorothiazide	1 003 (0.5)	1 033 (0.4)	1 059 (0.4)	939 (0.3)	-0.2
	Ramipril	2 203 (1.0)	2 219 (0.8)	2 318 (0.8)	2 088 (0.7)	-0.3
	Ramipril/Felodipine	1 115 (0.5)	1 144 (0.4)	1 192 (0.4)	1 117 (0.4)	-0.1
	Trandolapril	219 (0.10)	378 (0.14)	345 (0.12)	290 (0.10)	-
	Verapamil/Trandolapril	706 (0.3)	718 (0.3)	675 (0.2)	561 (0.19)	-0.11
Calcium channel blockers	Amlodipine	5 800 (2.6)	8 437 (3.1)	11 184 (3.8)	12 021 (4.1)	+1.5
	Felodipine	1 759 (0.8)	1 825 (0.7)	1 900 (0.7)	2 018 (0.7)	+0.1
	Isradipine	538 (0.3)	397 (0.15)	395 (0.14)	371 (0.13)	-0.17
	Lercanidipine	113 (0.05)	573 (0.21)	799 (0.3)	937 (0.3)	-0.25
	Nifedipine	794 (0.4)	882 (0.3)	1 124 (0.4)	923 (0.3)	-0.1
	Verapamil	129 (0.06)	253 (0.09)	245 (0.08)	245 (0.08)	-0.02
Angiotensin II receptor blockers	Candesartan	3 916 (1.8)	4 407 (1.6)	4 108 (1.4)	3 953 (1.3)	-0.5
	Eprosartan	68 (0.03)	75 (0.03)	596 (0.2)	1 462 (0.5)	+0.47
	Irbesartan	914 (0.4)	1 370 (0.5)	1 358 (0.5)	1 134 (0.4)	-
	Irbesartan/Hydrochlorothiazide	1 045 (0.5)	1 409 (0.5)	1 562 (0.5)	1 502 (0.5)	-
	Losartan	1 180 (0.5)	1 276 (0.5)	1 179 (0.4)	1 951 (0.7)	+0.2

Table C.7: Medicine items claimed for female patients from the metabolic syndrome category (*continued*)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Angiotensin II receptor blockers (<i>continued</i>)	Losartan/Hydrochlorothiazide	2 702 (1.2)	2 940 (1.1)	3 094 (1.1)	3 145 (1.1)	-0.1
	Telmisartan	1 142 (0.5)	1 570 (0.6)	1 933 (0.7)	1 833 (0.6)	+0.1
	Telmisartan/Hydrochlorothiazide	1 077 (0.5)	1 450 (0.5)	1 802 (0.6)	1 694 (0.6)	+0.1
	Valsartan	1 666 (0.8)	2 051 (0.8)	2 368 (0.8)	2 217 (0.8)	-
	Valsartan/Hydrochlorothiazide	2 473 (1.1)	3 346 (1.2)	3 862 (1.3)	4 568 (1.5)	+0.4
α-receptor blockers	Alfuzosin	7 (0.003)	3 (0.001)	6 (0.002)	4 (0.001)	-0.002
	Doxazosin	977 (0.5)	1 035 (0.4)	1 188 (0.4)	1 101 (0.4)	-0.1
	Prazosin	428 (0.20)	466 (0.17)	395 (0.14)	362 (0.12)	-0.08
	Terazosin	2 (0.001)	6 (0.002)	2 (0.001)	3 (0.001)	-
β-blockers	Acebutolol	764 (0.4)	761 (0.3)	442 (0.15)	477 (0.16)	-0.24
	Atenolol	-	-	33 (0.01)	8 (0.003)	+0.003
	Atenolol/Chlorthalidone	1 693 (0.8)	1 953 (0.7)	1 695 (0.6)	1 723 (0.6)	-0.2
	Bisoprolol	4 850 (2.2)	7 528 (2.7)	8 992 (3.1)	9 725 (3.3)	+1.1
	Bisoprolol/Hydrochlorothiazide	2 983 (1.4)	3 546 (1.3)	3 891 (1.3)	3 572 (1.2)	-0.2
	Metoprolol	25 (0.01)	5 (0.002)	6 (0.002)	11 (0.004)	-0.006
	Nadolol	37 (0.02)	50 (0.02)	19 (0.007)	-	-0.02
	Nadolol/Bendroflumethiazide	24 (0.01)	12 (0.004)	-	-	-0.01
	Nebivolol	221 (0.10)	188 (0.07)	229 (0.08)	287 (0.10)	-
	Propranolol	116 (0.05)	150 (0.06)	105 (0.04)	21 (0.01)	-0.04
	Sotalol	540 (0.3)	684 (0.3)	546 (0.19)	702 (0.2)	-0.1
	Timolol/Amiloride	139 (0.06)	202 (0.07)	101 (0.04)	55 (0.02)	-0.04
α/ β receptor blockers	Carvedilol	4 531 (2.1)	5 778 (2.1)	6 753 (2.3)	6 637 (2.2)	-0.1
	Labetalol	10 (0.005)	27 (0.01)	35 (0.01)	3 (0.001)	-0.004
Diuretics	Acetazolamide	103 (0.05)	129 (0.05)	111 (0.04)	115 (0.04)	-0.01
	Chlorthalidone	15 (0.007)	14 (0.005)	-	3 (0.001)	-0.006
	Chlorthalidone/Reserpine	6 (0.003)	1 (0.0004)	-	-	-0.003
	Amiloride/Hydrochlorothiazide	5 868 (2.7)	7 336 (2.7)	6 392 (2.2)	6 491 (2.2)	-0.5
	Bumetanide	82 (0.04)	65 (0.02)	65 (0.02)	90 (0.03)	-0.01
	Bumetanide/KCL	1 631 (0.7)	1 662 (0.6)	1 706 (0.6)	1 446 (0.5)	-0.2
	Furosemide	7 743 (3.5)	8 823 (3.2)	10 003 (3.4)	9 172 (3.1)	-0.4
	Hydroflumethiazide/Reserpine/ Hydrochlorothiazide	58 (0.03)	79 (0.03)	-	2 (0.001)	-0.029

Table C.7: Medicine items claimed for female patients from the metabolic syndrome category (*continued*)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Diuretics (<i>continued</i>)	Hydrochlorothiazide	4 523 (2.1)	5 001 (1.8)	4 839 (1.7)	5218 (1.8)	-0.3
	Indapamide	8 296 (3.8)	10 243 (3.7)	9 844 (3.4)	9 469 (3.2)	-0.6
	Hydrochlorothiazide/Triamterene	357 (0.16)	409 (0.15)	342 (0.12)	281 (0.09)	-0.07
	Piretanide	266 (0.12)	228 (0.08)	223 (0.08)	151 (0.05)	-0.07
	Spironolactone	3 828 (1.8)	5 009 (1.8)	5 439 (1.9)	5 714 (1.9)	+0.1
	Spironolactone/Isobutyl hydrochlorothiazide	30 (0.01)	72 (0.03)	27 (0.009)	61 (0.02)	+0.01
	Torsemide	1 423 (0.7)	1 624 (0.6)	1 340 (0.5)	1 050 (0.4)	-0.3
	Xipamide	2 (0.001)	-	-	-	-0.001
Central acting sympathetic nervous system inhibitors	Methyldopa	958 (0.4)	1 122 (0.4)	983 (0.3)	1 082 (0.4)	-
	Moxonidine	600 (0.3)	717 (0.3)	827 (0.3)	753 (0.3)	-
Peripheral sympatholytic agents	Dihydroergocristine/Clopamide/ Reserpine	251 (0.11)	218 (0.08)	169 (0.06)	163 (0.06)	-0.05
	Reserpine	180 (0.08)	266 (0.10)	226 (0.08)	216 (0.07)	-0.01
Direct acting vasodilators	Hydralazine	122 (0.06)	176 (0.06)	196 (0.07)	156 (0.05)	-0.01
	Minoxidil	11 (0.005)	11 (0.004)	28 (0.01)	2 (0.001)	-0.004
TOTAL		219 332 (100)	274 139 (100)	292 253 (100)	296 132 (100)	

Table C.8: Medicine items claimed for male patients from the metabolic syndrome category

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Insulin	Insulin	16 550 (6.1)	19 767 (5.8)	23 390 (6.3)	22 833 (6.2)	-0.1
	Insulin glulisine	-	196 (0.06)	474 (0.13)	421 (0.1)	+0.1
	Insulin isophane/Regular insulin	27 (0.01)	139 (0.04)	205 (0.06)	210 (0.06)	+0.05
	Insulin lispro	-	60 (0.02)	122 (0.03)	144 (0.04)	+0.04
	Biphasic isophane insulin	-	-	-	8 (0.002)	+0.002
Oral antidiabetics	Acarbose	267 (0.10)	209 (0.06)	202 (0.05)	122 (0.03)	-0.07
	Chlorpropamide	2 (0.001)	2 (0.001)	-	-	-0.001
	Glibenclamide	4 453 (1.6)	4 711 (1.4)	4 795 (1.3)	4 630 (1.3)	-0.3
	Gliclazide	13 561 (5.0)	15 872 (4.6)	17 758 (4.8)	16 703 (4.5)	-0.5
	Glimepiride	6 270 (2.3)	6 898 (2.0)	6 887 (1.9)	5 879 (1.6)	+0.7
	Glipizide	227 (0.08)	213 (0.06)	192 (0.05)	128 (0.03)	-0.05
	Metformin	35 940 (13.2)	44 697 (13.1)	52 496 (14.2)	52 486 (14.2)	+1.0
	Metformin/Glibenclamide	2 092 (0.8)	2 923 (0.9)	3 976 (1.1)	3 757 (1.0)	+0.2
	Nateglinide	73 (0.03)	39 (0.01)	-	59 (0.02)	-0.01
	Pioglitazone	933 (0.3)	1 088 (0.3)	1 607 (0.4)	1 994 (0.5)	+0.2
	Repaglinide	565 (0.2)	474 (0.14)	384 (0.1)	266 (0.07)	-0.13
	Rosiglitazone	1 661 (0.6)	1 798 (0.5)	1 685 (0.5)	839 (0.2)	-0.4
Statins	Atorvastatin	25 755 (9.4)	30 429 (8.9)	27 075 (7.3)	27 156 (7.4)	-2.0
	Fluvastatin	1 966 (0.7)	2 002 (0.6)	1 455 (0.4)	1 304 (0.4)	-0.3
	Lovastatin	167 (0.06)	536 (0.16)	600 (0.16)	468 (0.13)	+0.07
	Simvastatin	30 709 (11.3)	41 877 (12.2)	42 291 (11.4)	43 305 (11.7)	+0.4
	Simvastatin/Ascorbic acid/Citric acid monohydrate/Butylated hydroxyanisole	230 (0.08)	1 458 (0.4)	88 (0.02)	13 (0.004)	-0.076
	Pravastatin	2 729 (1.0)	3 206 (0.9)	2 700 (0.7)	2 199 (0.6)	-0.4
	Rosuvastatin	-	1 426 (0.4)	6 199 (1.7)	9 535 (2.6)	+2.6
	Bezafibrate	2 412 (0.9)	3 522 (1.0)	3 655 (1.0)	3 608 (1.0)	+0.1
Fibrates	Fenofibrate	266 (0.10)	37 (0.01)	85 (0.02)	361 (0.1)	-
	Gemfibrozil	245 (0.09)	242 (0.07)	241 (0.07)	241 (0.07)	-0.02
Cholesterol absorption inhibitor	Ezetimibe	215 (0.08)	1 069 (0.3)	1142 (0.3)	1 268 (0.3)	+0.22
Other hipolipidaemics	Cholestyramine	149 (0.06)	155 (0.05)	-	160 (0.04)	-0.02
	Acipimox	24 (0.009)	13 (0.004)	-	23 (0.01)	+0.001

Table C.8: Medicine items claimed for male patients from the metabolic syndrome category (*continued*)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Other hipolipidaemics (continued)	Nicotinic acid	42 (0.02)	56 (0.02)	50 (0.01)	40 (0.01)	-0.01
	Phospholipids	5 (0.002)	-	-	-	-0.002
ACE-inhibitors	Benazepril/Hydrochlorothiazide	12 (0.004)	11 (0.003)	12 (0.003)	12 (0.003)	-0.001
	Benazepril	37 (0.01)	32 (0.009)	44 (0.01)	54 (0.01)	-
	Captopril	1 627 (0.6)	1 682 (0.5)	1 238 (0.3)	1 275 (0.4)	-0.2
	Captopril/Hydrochlorothiazide	110 (0.04)	132 (0.04)	117 (0.03)	117 (0.03)	-0.01
	Cilazapril	173 (0.06)	108 (0.03)	167 (0.05)	59 (0.02)	-0.04
	Cilazapril/Hydrochlorothiazide	146 (0.05)	66 (0.02)	83 (0.02)	35 (0.01)	-0.04
	Enalapril	7 528 (2.8)	8 711 (2.5)	7 951 (2.1)	8 299 (2.3)	-0.5
	Enalapril/Hydrochlorothiazide	3 050 (1.12)	3 669 (1.1)	3 749 (1.0)	3 634 (1.0)	-0.12
	Fosinopril	245 (0.09)	289 (0.08)	216 (0.06)	144 (0.04)	-0.05
	Fosinopril/Hydrochlorothiazide	72 (0.03)	46 (0.01)	36 (0.01)	40 (0.01)	-0.02
	Lisinopril	6 892 (2.5)	8 592 (2.5)	8 393 (2.3)	8 727 (2.4)	-0.1
	Lisinopril/Hydrochlorothiazide	1 133 (0.4)	1 751 (0.5)	2 074 (0.6)	2 239 (0.6)	+0.2
	Perindopril	10 437 (3.8)	13 957 (4.1)	15 085 (4.1)	13 911 (3.8)	-
	Perindopril/Indapamide	4 030 (1.5)	6 656 (2.0)	8 482 (2.3)	9 740 (2.6)	+1.1
	Quinapril	1 127 (0.4)	915 (0.3)	1 061 (0.3)	1 115 (0.3)	-0.1
	Quinapril/Hydrochlorothiazide	1 382 (0.5)	1 394 (0.4)	1 378 (0.4)	1 019 (0.3)	-0.2
	Ramipril	4 166 (1.5)	4 567 (1.3)	4 527 (1.2)	4 087 (1.1)	-0.4
	Ramipril/Felodipine	1 556 (0.6)	1 920 (0.6)	1 814 (0.5)	1 471 (0.4)	-0.2
	Trandolapril	179 (0.07)	512 (0.15)	354 (0.10)	360 (0.10)	+0.03
	Verapamil/Trandolapril	783 (0.3)	924 (0.3)	821 (0.2)	695 (0.19)	-0.11
Calcium channel blockers	Amlodipine	5 932 (2.2)	9 191 (2.7)	12 683 (3.4)	13 658 (3.7)	+1.5
	Felodipine	1 727 (0.6)	2 133 (0.6)	1 901 (0.5)	1 832 (0.5)	-0.1
	Isradipine	385 (0.14)	299 (0.09)	272 (0.07)	221 (0.06)	-0.08
	Lercanidipine	126 (0.05)	441 (0.13)	824 (0.2)	1 020 (0.3)	+0.25
	Nifedipine	1 106 (0.4)	1 531 (0.5)	1 834 (0.5)	1 619 (0.4)	-
	Verapamil	199 (0.07)	217 (0.06)	215 (0.06)	265 (0.07)	-
Angiotensin II receptor blockers	Candesartan	4 408 (1.6)	4 972 (1.5)	4 702 (1.3)	3 936 (1.1)	-0.5
	Eprosartan	80 (0.03)	165 (0.05)	606 (0.16)	1 282 (0.4)	+0.37
	Irbesartan	1 402 (0.5)	1 807 (0.5)	1 658 (0.5)	1 549 (0.4)	-0.1
	Irbesartan/Hydrochlorothiazide	951 (0.4)	1 445 (0.4)	1 659 (0.5)	1 483 (0.4)	-

Table C.8: Medicine items claimed for male patients from the metabolic syndrome category (*continued*)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Angiotensin II receptor blockers (continued)	Losartan	1 523 (0.6)	1 598 (0.5)	1 508 (0.4)	2 321 (0.6)	-
	Losartan/Hydrochlorothiazide	2 493 (0.9)	2 973 (0.9)	3 170 (0.9)	3 115 (0.8)	-0.1
	Telmisartan	1 232 (0.5)	1 706 (0.5)	2 268 (0.6)	2 242 (0.6)	+0.1
	Telmisartan/Hydrochlorothiazide	774 (0.3)	1 175 (0.3)	1 474 (0.4)	1 687 (0.5)	+0.2
	Valsartan	1 773 (0.7)	2 189 (0.6)	2 575 (0.7)	2 173 (0.6)	-0.1
	Valsartan/Hydrochlorothiazide	3 309 (1.2)	3 409 (1.0)	3 945 (1.1)	4 307 (1.2)	-
α-receptor blockers	Alfuzosin	442 (0.16)	753 (0.2)	965 (0.3)	866 (0.23)	+0.07
	Doxazosin	2 472 (0.9)	3 158 (0.9)	3 529 (1.0)	3 248 (0.9)	-
	Prazosin	318 (0.12)	347 (0.10)	466 (0.13)	403 (0.11)	-0.01
	Terazosin	420 (0.15)	424 (0.12)	391 (0.1)	251 (0.07)	-0.08
β-blockers	Acebutolol	827 (0.3)	806 (0.2)	680 (0.18)	470 (0.13)	-0.17
	Atenolol	-	-	27 (0.007)	51 (0.01)	+0.01
	Atenolol/Chlorthalidone	1 365 (0.5)	1 403 (0.4)	1339 (0.4)	1 195 (0.3)	-0.2
	Bisoprolol	5 779 (2.1)	8 699 (2.5)	11 237 (3.0)	12 749 (3.5)	+1.4
	Bisoprolol/Hydrochlorothiazide	2 651 (1.10)	2 975 (0.9)	2 973 (0.8)	2 862 (0.8)	-0.3
	Metoprolol	12 (0.004)	36 (0.01)	28 (0.008)	42 (0.01)	+0.006
	Nadolol	48 (0.02)	43 (0.01)	10 (0.003)	-	-0.02
	Nadolol/Bendroflumethiazide	25 (0.009)	27 (0.008)	3 (0.001)	-	-0.009
	Nebivolol	158 (0.06)	184 (0.05)	238 (0.06)	202 (0.05)	-0.01
	Propranolol	81 (0.03)	97 (0.03)	39 (0.01)	9 (0.002)	-0.028
	Sotalol	538 (0.20)	682 (0.2)	787 (0.2)	724 (0.2)	-
	Timolol/Amiloride	39 (0.01)	32 (0.009)	25 (0.007)	35 (0.01)	-
α/ β receptor blockers	Carvedilol	7 262 (2.7)	9 228 (2.7)	10 452 (2.8)	10 202 (2.8)	+0.1
	Labetalol	-	-	1 (0.0003)	-	-
Diuretics	Acetazolamide	68 (0.03)	106 (0.03)	118 (0.03)	107 (0.03)	-
	Chlorthalidone	12 (0.004)	13 (0.004)	12 (0.003)	28 (0.01)	+0.006
	Chlorthalidone/Reserpine	16 (0.006)	-	-	-	-0.006
	Amiloride/Hydrochlorothiazide	3 389 (1.2)	3 840 (1.1)	3 441 (0.9)	3 063 (0.8)	-0.4
	Bumetanide	57 (0.02)	84 (0.03)	89 (0.02)	61 (0.02)	-
	Bumetanide/KCL	720 (0.3)	718 (0.2)	661 (0.18)	557 (0.15)	-0.15
	Furosemide	8 238 (3.0)	9 605 (2.8)	11 706 (3.2)	10 381 (2.8)	-0.2
	Hydrochlorothiazide	3 714 (1.4)	4 711 (1.4)	4 081 (1.1)	4 213 (1.1)	-0.3

Table C.8: Medicine items claimed for male patients from the metabolic syndrome category (*continued*)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Diuretics (<i>continued</i>)	Hydroflumethiazide/Reserpine/ Hydrochlorothiazide	40 (0.02)	32 (0.009)	-		-
	Indapamide	7 442 (2.7)	8 677 (2.5)	8 280 (2.2)	7 879 (2.1)	-0.6
	Hydrochlorothiazide/Triamterene	178 (0.07)	236 (0.07)	242 (0.07)	199 (0.05)	-0.02
	Piretanide	156 (0.06)	167 (0.05)	119 (0.03)	78 (0.02)	-0.04
	Spironolactone	4 756 (1.7)	5 599 (1.6)	6 696 (1.8)	6 348 (1.7)	-
	Spironolactone/Isobutyl hydrochlorothiazide	38 (0.01)	40 (0.01)	27 (0.007)	26 (0.01)	-
	Torsemide	1 342 (0.5)	1 489 (0.4)	1 516 (0.4)	1 104 (0.3)	-0.2
	Xipamide	1 (0.0004)	-	-	-	-0.0004
Central acting sympathetic nervous system inhibitors	Methyldopa	526 (0.19)	526 (0.15)	669 (0.18)	501 (0.14)	-0.05
	Moxonidine	366 (0.13)	466 (0.14)	649 (0.18)	671 (0.18)	+0.05
Peripheral sympatholytic agents	Dihydroergocristine/ Clopamide/Reserpine	231 (0.09)	147 (0.04)	164 (0.04)	204 (0.06)	-0.03
	Reserpine	104 (0.04)	121 (0.04)	118 (0.03)	104 (0.03)	-0.01
Direct acting vasodilators	Hydralazine	151 (0.06)	164 (0.05)	203 (0.06)	196 (0.05)	-0.01
	Minoxidil	78 (0.03)	102 (0.03)	132 (0.0)	112 (0.03)	-
TOTAL			342 036 (100)	37 0799 (100)	368 837 (100)	

Table C.9: Medicine items claimed for patients with unknown gender from the metabolic syndrome category

Pharmacological class	Active substance	Number of medicine items claimed, n (%)	
		2005	2006
Insulin	Insulin	-	26 (14.1)
Oral antidiabetics	Glibenclamide	19 (8.1)	-
	Gliclazide	31 (13.2)	8 (4.3)
	Glimepiride	12 (5.1)	12 (6.5)
	Metformin	31 (13.2)	25 (13.6)
Statins	Fluvastatin	12 (5.1)	12 (6.5)
	Simvastatin	38 (16.2)	27 (14.7)
ACE-inhibitors	Captopril	2 (0.9)	1 (0.5)
	Enalapril	23 (9.8)	-
	Enalapril/Hydrochlorothiazide	1 (0.4)	-
	Lisinopril	18 (7.7)	12 (6.5)
	Lisinopril/Hydrochlorothiazide	-	12 (6.5)
	Perindopril	9 (3.8)	12 (6.5)
Calcium channel blockers	Amlodipine	10 (4.3)	-
Angiotensin II receptor blockers	Telmisartan/Hydrochlorothiazide	3 (1.3)	-
Diuretics	Amiloride/Hydrochlorothiazide	11 (4.7)	-
	Furosemide	-	8 (4.3)
	Hydrochlorothiazide	-	13 (7.1)
	Indapamide	4 (1.7)	11 (6.0)
	Torasemide	11 (4.7)	5 (2.7)
TOTAL		235 (100)	184 (100)

Table C.10: Medicine items claimed for patients aged >0,≤15 years (age group 1)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Insulin	Insulin	11 (17.7)	2 (6.9)	-	3 (12.0)	-5.7
	Insulin glulisine	-	-	-	1 (4.0)	+4.0
Oral antidiabetics	Glibenclamide	1 (1.6)	-	-	-	-1.6
	Metformin	4 (6.4)	1 (3.5)	3 (5.9)	2 (8.0)	+1.6
	Metformin/Glibenclamide	-	1 (3.5)	-	-	-
Statins	Atorvastatin	10 (16.1)	4 (13.8)	3 (5.9)	2 (8.0)	-8.1
	Simvastatin	4 (6.5)	4 (13.8)	12 (23.5)	6 (24.0)	+17.5
ACE-inhibitors	Captopril	-	-	4 (7.8)	-	-
	Enalapril	-	-	13 (25.5)	2 (8.0)	+8.0
	Lisinopril	-	1 (3.5)	-	-	-
	Perindopril	8 (12.9)	2 (6.9)	1 (2.0)	2 (8.0)	-4.9
	Perindopril/Indapamide	-	-	2 (3.9)	-	-
	Ramipril	6 (9.7)	1 (3.5)	-	-	-9.7
Calcium channel blockers	Amlodipine	5 (8.1)	-	-	-	-8.1
	Felodipine	3 (4.8)	-	-	-	-4.8
Angiotensin II receptor blockers	Losartan	5 (8.1)	-	-	-	-8.1
	Valsartan	-	1 (3.5)	-	-	-
α-receptor blockers	Doxazosin	3 (4.8)	-	-	-	-4.8
β-blockers	Bisoprolol	1 (1.6)	1 (3.5)	1 (2.0)	-	-1.6
	Bisoprolol/Hydrochlorothiazide	1 (1.6)	-	-	-	-1.6
Diuretics	Furosemide	-	-	2 (3.9)	-	-
	Hydrochlorothiazide	-	-	4 (7.8)	3 (12.0)	+12.0
	Spironolactone	-	11 (37.9)	6 (11.8)	4 (16.0)	+16.0
TOTAL		62 (100)	29 (100)	51 (100)	25 (100)	

Table C.11: Medicine items claimed for patients aged >15,≤30 years (age group 2)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Insulin	Insulin	263 (23.4)	250 (18.5)	265 (20.2)	234 (17.0)	-6.4
	Insulin glulisine	-	8 (0.6)	21 (1.6)	16 (1.2)	+1.2
Oral antidiabetics	Glibenclamide	11 (1.0)	-	2 (0.15)	-	-1.0
	Gliclazide	23 (2.1)	37 (2.7)	26 (2.0)	73 (5.3)	+3.2
	Glimepiride	1 (0.09)	1 (0.07)	-	1 (0.07)	-0.02
	Glipizide	-	1 (0.07)	-	-	-
	Metformin	126 (11.2)	179 (13.2)	164 (12.5)	179 (13.0)	+1.8
	Metformin/Glibenclamide	-	4 (0.3)	24 (1.8)	16 (1.2)	+1.2
	Pioglitazone	-	17 (1.3)	2 (0.15)	1 (0.07)	+0.07
	Repaglinide	4 (0.4)	-	-	-	-0.4
	Rosiglitazone	-	2 (0.2)	-	20 (1.5)	+1.5
Statins	Atorvastatin	92 (8.2)	131 (9.7)	73 (5.6)	101 (7.4)	-0.8
	Fluvastatin	3 (0.3)	-	4 (0.3)	16 (1.2)	+0.9
	Lovastatin	-	12 (0.9)	1 (0.08)	-	-
	Simvastatin	147 (13.1)	188 (13.9)	219 (16.7)	174 (12.7)	-0.4
	Simvastatin/Ascorbic acid/Citric acid monohydrate/Butylated hydroxyanisole	-	14 (1.0)	-	-	-
	Pravastatin	-	-	-	6 (0.4)	+0.4
	Rosuvastatin	-	7 (0.5)	10 (0.8)	44 (3.2)	+3.2
Fibrates	Bezafibrate	-	9 (0.7)	3 (0.2)	4 (0.3)	+0.3
	Fenofibrate	-	-	-	11 (0.8)	+0.8
Other hipolipidaemics	Cholestyramine	3 (0.3)	1 (0.07)	-	4 (0.3)	-
ACE-inhibitors	Captopril	3 (0.3)	12 (0.9)	2 (0.15)	3 (0.2)	-0.1
	Enalapril	63 (5.6)	26 (1.9)	11 (0.8)	21 (1.5)	-4.1
	Enalapril/Hydrochlorothiazide	27 (2.4)	13 (1.0)	-	-	-2.4
	Fosinopril	1 (0.09)	-	-	3 (0.2)	+0.11
	Lisinopril	37 (3.3)	29 (2.1)	28 (2.1)	22 (1.6)	-1.7

Table C.11: Medicine items claimed for patients aged >15,≤30 years (age group 2) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
ACE-inhibitors (continued)	Lisinopril/Hydrochlorothiazide	2 (0.18)	-	8 (0.6)	3 (0.15)	-0.03
	Perindopril	27 (2.4)	113 (8.4)	86 (6.6)	86 (6.3)	+3.9
	Perindopril/Indapamide	17 (1.5)	40 (3.0)	43 (3.3)	72 (5.2)	+3.7
	Quinapril	3 (0.3)	5 (0.4)	7 (0.5)	15 (1.1)	+0.8
	Quinapril/Hydrochlorothiazide	3 (0.3)	-	3 (0.2)	-	-0.3
	Ramipril	14 (1.3)	11 (0.8)	11 (0.8)	24 (1.7)	+0.4
	Ramipril/Felodipine	6 (0.5)	5 (0.4)	-	-	-0.5
	Trandolapril	-	4 (0.3)	5 (0.4)	1 (0.07)	+0.07
	Verapamil/Trandolapril	13 (1.2)	-	-	-	-1.2
Calcium channel blockers	Amlodipine	15 (1.3)	43 (3.2)	36 (2.8)	46 (3.3)	+2.0
	Felodipine	25 (2.2)	1 (0.07)	3 (0.2)	1 (0.07)	-2.13
	Lercanidipine	-	-	14 (1.1)	4 (0.3)	+0.3
	Nifedipine	2 (0.18)	-	-	-	-0.18
	Verapamil	-	1 (0.07)	-	-	-
Angiotensin II receptor blockers	Candesartan	15 (1.3)	26 (1.9)	13 (1.0)	5 (0.4)	-0.9
	Eprosartan	-	-	4 (0.3)	1 (0.07)	+0.07
	Irbesartan/Hydrochlorothiazide	9 (0.8)	28 (2.1)	27 (2.1)	18 (1.3)	+0.5
	Losartan	1 (0.09)	-	2 (0.15)	8 (0.6)	+0.5
	Losartan/Hydrochlorothiazide	6 (0.5)	6 (0.4)	-	1 (0.07)	-0.43
	Telmisartan/Hydrochlorothiazide	-	-	2 (0.15)	-	-
	Valsartan	12 (1.1)	9 (0.7)	6 (0.5)	13 (0.9)	-0.2
	Valsartan/Hydrochlorothiazide	12 (1.1)	7 (0.5)	38 (2.9)	12 (0.9)	-0.2
α-receptor blockers	Alfuzosin	-	2 (0.15)	-	-	-
	Doxazosin	3 (0.3)	2 (0.15)	11 (0.8)	-	-0.3
	Prazosin	1 (0.09)	-	9 (0.7)	-	-0.09
β-blockers	Atenolol/Chlorthalidone	-	-	-	11 (0.8)	+0.8
	Bisoprolol	16 (1.4)	8 (0.6)	30 (2.3)	14 (1.0)	-0.4
	Bisoprolol/Hydrochlorothiazide	14 (1.3)	9 (0.7)	8 (0.6)	1 (0.07)	-1.23

Table C.11: Medicine items claimed for patients aged >15,≤30 years (age group 2) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
β-blockers (continued)	Propranolol	2 (0.18)	-	-	-	-0.18
	Nebivolol	-	-	1 (0.08)	-	-
α/ β receptor blockers	Carvedilol	25 (2.2)	7 (0.5)	3 (0.2)	1 (0.07)	-2.13
Diuretics	Acetazolamide	-	1 (0.07)	-	-	-
	Amiloride/Hydrochlorothiazide	5 (0.4)	14 (1.0)	10 (0.8)	1 (0.1)	-0.3
	Bumetanide/KCL	3 (0.3)	19 (1.4)	-	9 (0.7)	+0.4
	Furosemide	18 (1.6)	5 (0.4)	46 (3.5)	22 (1.6)	-
	Hydrochlorothiazide	3 (0.3)	2 (0.15)	-	18 (1.3)	+1.0
	Indapamide	34 (3.0)	23 (1.7)	1 (0.08)	28 (2.0)	-1.0
	Spironolactone	2 (0.18)	3 (0.2)	1 (0.08)	10 (0.7)	+0.52
	Torasemide	1 (0.09)	1 (0.07)	-	-	-0.09
Central acting sympathetic nervous system inhibitors	Methyldopa	5 (0.4)	6 (0.4)	-	1 (0.07)	-0.33
	Moxonidine	3 (0.3)	10 (0.7)	17 (1.3)	-	-0.3
Direct acting vasodilators	Minoxidil	3 (0.3)	-	11 (0.8)	-	-0.3
TOTAL		1 124 (100)	1 352 (100)	1 311 (100)	1 374 (100)	

Table C.12: Medicine items claimed for patients aged >30, ≤45 years (age group 3)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Insulin	Insulin	2 789 (10.4)	3 265 (10.1)	3 154 (9.3)	2 661 (8.8)	-1.6
	Insulin glulisine	-	71 (0.2)	125 (0.4)	72 (0.2)	+0.2
	Insulin isophane/Regular insulin	6 (0.02)	18 (0.06)	22 (0.06)	44 (0.15)	+0.13
	Insulin lispro	-	-	4 (0.01)	32 (0.11)	+0.11
Oral antidiabetics	Acarbose	2 (0.01)	1 (0.003)	6 (0.02)	-	-0.01
	Glibenclamide	352 (1.3)	319 (1.0)	308 (0.9)	195 (0.7)	-0.6
	Gliclazide	931 (3.5)	1 118 (3.4)	1 377 (4.1)	1 154 (3.8)	+0.3
	Glimepiride	524 (2.0)	500 (1.5)	514 (1.5)	332 (1.1)	-0.9
	Glipizide	-	1 (0.003)	-	-	-
	Metformin	4 166 (15.5)	5 114 (15.8)	5 460 (16.0)	4 861 (16.1)	+0.6
	Metformin/Glibenclamide	209 (0.8)	346 (1.1)	463 (1.4)	387 (1.3)	+0.5
	Nateglinide	2 (0.01)	-	-	-	-0.01
	Pioglitazone	144 (0.5)	140 (0.4)	188 (0.6)	166 (0.6)	+0.1
	Repaglinide	29 (0.11)	32 (0.11)	12 (0.04)	8 (0.03)	-0.08
	Rosiglitazone	158 (0.6)	181 (0.6)	177 (0.5)	102 (0.3)	-0.3
Statins	Atorvastatin	2 620 (9.8)	2 850 (8.8)	2 527 (7.4)	2 138 (7.1)	-2.7
	Fluvastatin	255 (1.0)	205 (0.6)	104 (0.3)	65 (0.2)	-0.8
	Lovastatin	29 (0.11)	72 (0.2)	67 (0.2)	84 (0.3)	+0.19
	Simvastatin	2 900 (10.8)	3 985 (12.3)	3 854 (11.3)	3 371 (11.2)	+0.4
	Simvastatin/Ascorbic Acid/Citric Acid Monohydrate/Butylated Hydroxyanisole	7 (0.03)	68 (0.2)	4 (0.01)	2 (0.007)	-0.02
	Pravastatin	262 (1.0)	279 (0.9)	194 (0.6)	101 (0.3)	-0.7
	Rosuvastatin	-	169 (0.5)	775 (2.3)	1 074 (3.6)	+3.6
Fibrates	Bezafibrate	304 (1.1)	402 (1.2)	395 (1.2)	415 (1.4)	+0.3
	Fenofibrate	20 (0.07)	-	8 (0.02)	72 (0.2)	+0.13
	Gemfibrozil	57 (0.2)	47 (0.14)	60 (0.18)	37 (0.12)	-0.08
Cholesterol absorption inhibitor	Ezetimibe	43 (0.16)	99 (0.3)	132 (0.4)	81 (0.3)	+0.14
Other hipolipidaemics	Cholestyramine	23 (0.09)	26 (0.1)	-	34 (0.11)	+0.02

Table C.12: Medicine items claimed for patients aged >30, ≤45 years (age group 3) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Other hipolipidaemics (continued)	Acipimox	12 (0.04)	12 (0.04)	-	11 (0.04)	-
	Nicotinic acid	3 (0.01)	-	1 (0.003)	3 (0.01)	-
ACE-inhibitors	Benazepril/Hydrochlorothiazide	9 (0.03)	9 (0.02)	-	-	-0.03
	Captopril	170 (0.6)	79 (0.2)	84 (0.3)	88 (0.3)	-0.3
	Captopril/Hydrochlorothiazide	20 (0.07)	1 (0.003)	16 (0.04)	40 (0.13)	+0.06
	Cilazapril	1 (0.004)	-	1 (0.003)	-	-0.004
	Cilazapril/Hydrochlorothiazide	26 (0.1)	13 (0.04)	-	-	-0.1
	Enalapril	737 (2.8)	748 (2.3)	826 (2.4)	689 (2.3)	-0.5
	Enalapril/Hydrochlorothiazide	203 (0.8)	311 (1.0)	317 (0.9)	265 (0.9)	+0.1
	Fosinopril	21 (0.08)	19 (0.06)	14 (0.04)	9 (0.03)	-0.05
	Fosinopril/Hydrochlorothiazide	-	1 (0.003)	-	-	-
	Lisinopril	624 (2.3)	667 (2.1)	666 (2.0)	619 (2.1)	-0.2
	Lisinopril/Hydrochlorothiazide	109 (0.4)	136 (0.4)	212 (0.6)	210 (0.7)	+0.3
	Perindopril	1 028 (3.8)	1 333 (4.1)	1 669 (4.9)	1 394 (4.6)	+0.8
	Perindopril/Indapamide	581 (2.2)	803 (2.5)	1 025 (3.0)	1 234 (4.1)	+1.9
	Quinapril	98 (0.4)	54 (0.17)	62 (0.18)	79 (0.3)	-0.1
	Quinapril/Hydrochlorothiazide	129 (0.5)	119 (0.4)	123 (0.4)	52 (0.2)	-0.3
	Ramipril	440 (1.6)	388 (1.2)	373 (1.1)	202 (0.7)	-0.9
	Ramipril/Felodipine	131 (0.5)	193 (0.6)	161 (0.5)	124 (0.4)	-0.1
	Trandolapril	19 (0.07)	102 (0.3)	47 (0.14)	25 (0.08)	+0.01
	Verapamil/Trandolapril	44 (0.16)	89 (0.3)	55 (0.16)	32 (0.11)	-0.05
Calcium channel blockers	Amlodipine	457 (1.7)	687 (2.1)	1 073 (3.2)	1 112 (3.7)	+2.0
	Felodipine	72 (0.3)	99 (0.3)	103 (0.3)	56 (0.19)	-0.11
	Isradipine	12 (0.04)	18 (0.06)	24 (0.07)	2 (0.007)	-0.03
	Lercanidipine	12 (0.04)	35 (0.1)	70 (0.2)	71 (0.2)	+0.16
	Nifedipine	126 (0.5)	120 (0.4)	97 (0.3)	114 (0.4)	-0.1
	Verapamil	10 (0.04)	13 (0.04)	23 (0.07)	6 (0.02)	-0.02
Angiotensin II receptor blockers	Candesartan	513 (1.9)	268 (1.6)	427 (1.3)	372 (1.2)	-0.7

Table C.12: Medicine items claimed for patients aged >30, ≤45 years (age group 3) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Angiotensin II receptor blockers (continued)	Eprosartan	12 (0.04)	11 (0.03)	85 (0.3)	61 (0.2)	+0.16
	Irbesartan	198 (0.7)	276 (0.8)	258 (0.8)	184 (0.6)	-0.1
	Irbesartan/Hydrochlorothiazide	119 (0.4)	152 (0.5)	135 (0.4)	132 (0.4)	-
	Losartan	144 (0.5)	154 (0.5)	130 (0.4)	225 (0.8)	+0.3
	Losartan/Hydrochlorothiazide	240 (0.9)	241 (0.7)	274 (0.8)	224 (0.7)	-0.2
	Telmisartan	140 (0.5)	186 (0.6)	228 (0.7)	196 (0.7)	+0.2
	Telmisartan/Hydrochlorothiazide	95 (0.4)	96 (0.3)	142 (0.4)	150 (0.5)	+0.1
	Valsartan	204 (0.8)	242 (0.8)	213 (0.6)	151 (0.5)	-0.3
	Valsartan/Hydrochlorothiazide	303 (1.1)	428 (1.3)	499 (1.5)	496 (1.6)	+0.5
α-receptor blockers	Alfuzosin	7 (0.03)	12 (0.04)	-	16 (0.05)	+0.02
	Doxazosin	144 (0.5)	125 (0.4)	111 (0.3)	96 (0.3)	-0.2
	Prazosin	25 (0.09)	19 (0.06)	30 (0.09)	48 (0.16)	+0.07
	Terazosin	12 (0.04)	12 (0.04)	-	1 (0.003)	-0.037
β-blockers	Acebutolol	12 (0.04)	4 (0.01)	-	-	-0.04
	Atenolol	-	-	2 (0.01)	1 (0.003)	+0.003
	Atenolol/Chlorthalidone	96 (0.4)	96 (0.3)	79 (0.2)	58 (0.19)	-0.21
	Bisoprolol	455 (1.7)	583 (1.8)	683 (2.0)	808 (2.7)	+1.0
	Bisoprolol/Hydrochlorothiazide	424 (1.6)	434 (1.3)	440 (1.3)	263 (0.9)	-0.26
	Propranolol	19 (0.07)	10 (0.03)	13 (0.04)	1 (0.003)	-0.067
	Nebivolol	15 (0.06)	30 (0.09)	32 (0.09)	13 (0.04)	-0.02
	Sotalol	-	1 (0.003)	1 (0.003)	15 (0.05)	+0.05
α/ β receptor blockers	Carvedilol	321 (1.2)	548 (1.7)	485 (1.4)	448 (1.5)	+0.3
Diuretics	Acetazolamide	18 (0.07)	25 (0.06)	15 (0.04)	6 (0.02)	-0.05
	Amiloride/Hydrochlorothiazide	349 (1.3)	478 (1.5)	466 (1.4)	269 (0.9)	-0.4
	Bumetanide	1 (0.004)	-	12 (0.04)	1 (0.003)	-0.001
	Bumetanide/KCL	136 (0.5)	106 (0.3)	100 (0.3)	89 (0.3)	-0.2
	Furosemide	443 (1.7)	514 (1.6)	506 (1.5)	368 (1.2)	-0.5
	Hydrochlorothiazide	390 (1.5)	446 (1.4)	344 (1.0)	395 (1.3)	-0.2

Table C.12: Medicine items claimed for patients aged >30,≤45 years (age group 3) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Diuretics (continued)	Indapamide	670 (2.5)	775 (2.4)	810 (2.4)	618 (2.1)	-0.4
	Triamterene/Hydrochlorothiazide	16 (0.06)	10 (0.03)	2 (0.01)	1 (0.003)	-0.057
	Piretanide	4 (0.01)	11 (0.03)	-	1 (0.003)	-0.007
	Spironolactone	166 (0.6)	267 (0.8)	278 (0.8)	242 (0.8)	+0.2
	Spironolactone/isobutyl hydrochlorothiazide	19 (0.07)	26 (0.08)	-	-	-0.07
	Torsemide	26 (0.1)	54 (0.17)	60 (0.18)	57 (0.19)	+0.09
Central acting sympathetic nervous system inhibitors	Methyldopa	53 (0.2)	106 (0.3)	81 (0.2)	113 (0.4)	+0.2
	Moxonidine	41 (0.15)	37 (0.11)	51 (0.15)	49 (0.16)	+0.01
Peripheral sympatholytic agents	Dihydroergocristine/Clopamide/ Reserpine	9 (0.03)	17 (0.05)	21 (0.06)	28 (0.09)	+0.06
	Reserpine	17 (0.06)	21 (0.06)	1 (0.003)	11 (0.04)	-0.02
Direct acting vasodilators	Hydralazine	4 (0.01)	13 (0.04)	18 (0.05)	15 (0.1)	+0.09
	Minoxidil	18 (0.07)	28 (0.09)	29 (0.09)	21 (0.07)	-
TOTAL		26 802 (100)	32 473 (100)	34 033 (100)	30 168 (100)	

Table C.13: Medicine items claimed for patients aged >45,≤60 ears (age group 4)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Insulin	Insulin	10 886 (6.9)	13 314 (6.7)	16 358 (7.6)	15 161 (7.3)	+0.4
	Insulin glulisine	-	102 (0.05)	303 (0.14)	249 (0.12)	+0.12
	Insulin isophane/Regular insulin	10 (0.01)	94 (0.05)	131 (0.06)	108 (0.05)	+0.04
	Insulin lispro	-	63 (0.03)	117 (0.05)	118 (0.06)	+0.06
	Biphasic isophane				5 (0.002)	+0.002
Oral antidiabetics	Acarbose	141 (0.09)	121 (0.06)	125 (0.06)	78 (0.04)	-0.05
	Chlorpropamide	-	2 (0.001)	-	-	-
	Glibenclamide	2 415 (1.5)	2 773 (1.4)	2 822 (1.3)	2 632 (1.3)	-0.2
	Gliclazide	6 979 (4.4)	8 341 (4.2)	9 118 (4.2)	8 781 (4.2)	-0.2
	Glimepiride	3 284 (2.1)	3 677 (1.9)	3 387 (1.6)	2 792 (1.3)	-0.8
	Glipizide	73 (0.1)	60 (0.03)	34 (0.02)	27 (0.01)	-0.09
	Metformin	22 605 (14.4)	28 634 (14.4)	33 686 (15.7)	32 556 (15.7)	+1.3
	Metformin/Glibenclamide	1 207 (0.8)	1 842 (0.9)	2 382 (1.1)	2 211 (1.1)	+0.3
	Nateglinide	22 (0.01)	-	1 (0.001)	15 (0.007)	-0.003
	Pioglitazone	513 (0.3)	628 (0.3)	967 (0.5)	1 266 (0.6)	+0.3
	Repaglinide	206 (0.13)	165 (0.08)	152 (0.07)	88 (0.04)	-0.09
	Rosiglitazone	1 090 (0.7)	1 130 (0.6)	1 105 (0.5)	623 (0.3)	-0.4
Statins	Atorvastatin	15 170 (9.6)	18 212 (9.2)	15 813 (7.4)	15 346 (7.4)	-2.2
	Fluvastatin	1 118 (0.7)	1 073 (0.5)	619 (0.3)	565 (0.3)	-0.4
	Lovastatin	179 (0.11)	486 (0.2)	481 (0.2)	372 (0.18)	+0.07
	Simvastatin	17 444 (11.1)	23 200 (11.7)	23 654 (11.0)	23 574 (11.3)	+0.2
	Simvastatin/Ascorbic Acid/Citric Acid Monohydrate/Butylated Hydroxyanisole	103 (0.07)	811 (0.4)	65 (0.03)	4 (0.002)	-0.068
	Pravastatin	1 407 (0.9)	1 746 (0.9)	1 454 (0.7)	1 075 (0.5)	-0.4
	Rosuvastatin	-	1 040 (0.5)	4 291 (2.0)	6 211 (3.0)	+3.0
Fibrates	Bezafibrate	1 467 (0.9)	2 099 (1.1)	2 200 (1.0)	2 208 (1.1)	+0.2
	Fenofibrate	186 (0.12)	36 (0.02)	26 (0.01)	221 (0.11)	-0.01
	Gemfibrozil	59 (0.04)	78 (0.04)	91 (0.04)	108 (0.1)	+0.06

Table C.13: Medicine items claimed for patients aged >45,≤60 ears (age group 4) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Cholesterol absorption inhibitor	Ezetimibe	130 (0.08)	693 (0.4)	869 (0.4)	689 (0.3)	+0.22
Other hipolipidaemics	Acipimox	18 (0.01)	22 (0.01)	-	5 (0.002)	-0.008
	Cholestyramine	73 (0.05)	53 (0.03)	-	95 (0.05)	-
	Nicotinic acid	25 (0.02)	45 (0.02)	26 (0.01)	11 (0.01)	-0.01
	Phospholipids	5 (0.003)	-	-	-	-0.003
ACE-inhibitors	Benazepril	49 (0.03)	28 (0.01)	22 (0.01)	14 (0.007)	-0.023
	Benazepril/Hydrochlorothiazide	9 (0.01)	6 (0.003)	-	-	-0.01
	Captopril	981 (0.6)	1 104 (0.6)	916 (0.4)	765 (0.4)	-0.2
	Captopril/Hydrochlorothiazide	72 (0.05)	119 (0.06)	140 (0.07)	89 (0.04)	-0.01
	Cilazapril	104 (0.07)	56 (0.03)	46 (0.02)	21 (0.01)	-0.06
	Cilazapril/Hydrochlorothiazide	81 (0.05)	41 (0.02)	45 (0.02)	39 (0.02)	-0.03
	Enalapril	4 200 (2.7)	4 868 (2.5)	4 273 (2.0)	4 460 (2.1)	-0.6
	Enalapril/Hydrochlorothiazide	2 049 (1.3)	2 248 (1.1)	2 231 (1.0)	2 165 (1.0)	-0.3
	Fosinopril	109 (0.07)	107 (0.05)	94 (0.04)	56 (0.03)	-0.04
	Fosinopril/Hydrochlorothiazide	68 (0.04)	30 (0.02)	40 (0.024)	39 (0.02)	-0.02
	Lisinopril	3 875 (2.5)	4 940 (2.5)	4 849 (2.3)	4 636 (2.2)	-0.3
	Lisinopril/Hydrochlorothiazide	713 (0.5)	1 169 (0.6)	1 406 (0.7)	1 380 (0.7)	+0.2
	Perindopril	5 390 (3.4)	7 148 (3.6)	7 872 (3.7)	7 025 (3.4)	-
	Perindopril/Indapamide	2 674 (1.7)	4 641 (2.3)	5 948 (2.8)	6 150 (3.0)	+1.3
	Quinapril	624 (0.4)	506 (0.3)	540 (0.3)	591 (0.3)	-0.1
	Quinapril/Hydrochlorothiazide	946 (0.6)	911 (0.5)	804(0.4)	617 (0.3)	-0.3
	Ramipril	2 059 (1.3)	2 141 (1.1)	2 185 (1.0)	1 747 (0.8)	-0.5
	Ramipril/Felodipine	756 (0.5)	905 (0.5)	898 (0.4)	782 (0.4)	-0.1
	Trandolapril	133 (0.08)	270 (0.14)	227 (0.11)	182 (0.09)	+0.01
	Verapamil/Trandolapril	588 (0.4)	572 (0.3)	502 (0.2)	377 (0.18)	-0.22
Calcium channel blockers	Amlodipine	3 888 (2.5)	5 623 (2.8)	7 690 (3.6)	7 915 (3.8)	+1.3
	Felodipine	667 (0.4)	893 (0.5)	735 (0.3)	765 (0.4)	-
	Isradipine	131 (0.08)	61 (0.03)	58 (0.03)	72 (0.04)	-0.04
	Lercanidipine	74 (0.05)	201 (0.1)	404 (0.19)	553 (0.3)	+0.25

Table C.13: Medicine items claimed for patients aged >45,≤60 ears (age group 4) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Calcium channel blockers (continued)	Nifedipine	663 (0.4)	940 (0.5)	1 158 (0.5)	917 (0.4)	-
	Verapamil	104 (0.07)	171 (0.09)	136 (0.06)	144 (0.07)	-
Angiotensin II receptor blockers (continued)	Candesartan	2 285 (1.5)	2 617 (1.3)	2 542 (1.2)	2 061 (1.0)	-0.5
	Eprosartan	66 (0.04)	93 (0.05)	311 (0.14)	844 (0.4)	+0.36
	Irbesartan	803 (0.5)	1 086 (0.6)	986 (0.5)	872 (0.4)	-0.1
	Irbesartan/Hydrochlorothiazide	782 (0.5)	1 072 (0.5)	1 137 (0.5)	1 052 (0.5)	-
	Losartan	772 (0.5)	727 (0.4)	825 (0.4)	1 306 (0.6)	-0.1
	Losartan/Hydrochlorothiazide	1 786 (1.1)	2 071 (1.0)	2 158 (1.0)	2 063 (1.0)	-0.1
	Telmisartan	759 (0.5)	1 029 (0.5)	1 325 (0.6)	1 249 (0.6)	+0.1
	Telmisartan/Hydrochlorothiazide	793 (0.5)	979 (0.5)	1 219 (0.6)	1 249 (0.6)	+0.1
	Valsartan	942 (0.6)	1 188 (0.6)	1 403 (0.7)	1 183 (0.6)	-
	Valsartan/Hydrochlorothiazide	1 565 (1.0)	2 244 (1.1)	2 560 (1.2)	2 883 (1.4)	+0.4
α-receptor blockers	Alfuzosin	84 (0.05)	105 (0.05)	136 (0.06)	99 (0.05)	-
	Doxazosin	956 (0.6)	1 171 (0.6)	1 202 (0.6)	1 040 (0.5)	-0.1
	Prazosin	259 (0.16)	203 (0.1)	224 (0.1)	206 (0.1)	-0.06
	Terazosin	68 (0.04)	105 (0.05)	81 (0.04)	38 (0.02)	-0.02
β-blockers	Acebutolol	349 (0.2)	316 (0.16)	183 (0.09)	119 (0.06)	-0.14
	Atenolol	-	-	6 (0.003)	10 (0.005)	+0.005
	Atenolol/Chlorthalidone	961 (0.6)	1 026 (0.5)	817 (0.4)	649 (0.3)	-0.3
	Bisoprolol	3 403 (2.2)	5 079 (2.6)	5 919 (2.8)	6 217 (3.0)	+0.8
	Bisoprolol/Hydrochlorothiazide	1 767 (1.1)	2 008 (1.0)	2 297 (1.1)	2 237 (1.1)	-
	Metoprolol	-	20 (0.01)	4 (0.002)	15 (0.007)	+0.007
	Nadolol	11 (0.01)	-	3 (0.001)	-	-0.01
	Nadolol/Bendroflumethiazide	14 (0.01)	16 (0.01)	2 (0.001)	-	-0.01
	Nebivolol	163 (0.10)	132 (0.07)	136 (0.06)	169 (0.08)	-0.02
	Propranolol	69 (0.04)	94 (0.05)	36 (0.02)	26 (0.01)	-0.03
	Sotalol	149 (0.09)	277 (0.14)	269 (0.13)	229 (0.11)	+0.02
	Timolol/Amiloride	37 (0.02)	52 (0.03)	39 (0.02)	24 (0.01)	-0.01
α/ β receptor blockers	Carvedilol	3 116 (2.0)	3 971 (2.0)	4 695 (2.2)	4 556 (2.2)	+0.2

Table C.13: Medicine items claimed for patients aged >45,≤60 ears (age group 4) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
α/ β receptor blockers	Labetalol	10 (0.01)	5 (0.003)	1 (0.001)	1 (0.001)	-0.009
Diuretics	Acetazolamide	30 (0.02)	60 (0.03)	57 (0.03)	55 (0.03)	+0.01
	Amiloride/Hydrochlorothiazide	2 507 (1.6)	3 100 (1.6)	2 892 (1.4)	2 831 (1.4)	-0.2
	Bumetanide	12 (0.01)	1 (0.001)	33 (0.02)	32 (0.02)	+0.01
	Bumetanide/KCL	770 (0.5)	599 (0.3)	670 (0.3)	574 (0.3)	-0.2
	Chlorthalidone	-	-	-	1 (0.001)	+0.001
	Chlorthalidone/Reserpine	6 (0.004)	-	-	-	-0.004
	Furosemide	3 164 (2.0)	3 812 (1.9)	4 345 (2.0)	3 953 (1.9)	-0.1
	Hydrochlorothiazide	2 334 (1.5)	2 568 (1.3)	2 396 (1.1)	2 369 (1.1)	-0.4
	Hydroflumethiazide/Reserpine/ Hydrochlorothiazide	29 (0.02)	15 (0.01)	-	-	-0.02
	Indapamide	4 944 (3.1)	5 569 (2.8)	5 523 (2.6)	4 980 (2.4)	-0.7
	Triamterene/Hydrochlorothiazide	170 (0.11)	224 (0.11)	144 (0.07)	118 (0.06)	-0.05
	Piretanide	140 (0.09)	108 (0.05)	110 (0.05)	61 (0.03)	-0.06
	Spirolactone	1 966 (1.3)	2 365 (1.2)	2 738 (1.3)	2 613 (1.3)	-
	Spirolactone/isobutyl Hydrochlorothiazide	5 (0.003)	13 (0.01)	2 (0.001)	13 (0.006)	+0.003
	Toraseamide	675 (0.4)	761 (0.4)	576 (0.3)	401 (0.19)	-0.21
	Xipamide	3 (0.002)	-	-	-	-0.002
Central acting sympathetic nervous system inhibitors	Methyldopa	313 (0.2)	449 (0.2)	478 (0.2)	372 (0.18)	-0.21
	Moxonidine	301 (0.19)	376 (0.19)	430 (0.2)	309 (0.15)	-0.04
Peripheral sympatholytic agents	Dihydroergocristine/Clopamide/ Reserpine	140 (0.09)	122 (0.06)	104 (0.05)	78 (0.04)	-0.05
	Reserpine	148 (0.09)	152 (0.08)	134 (0.06)	88 (0.04)	-0.05
Direct acting vasodilators	Hydralazine	94 (0.06)	136 (0.07)	103 (0.05)	61 (0.03)	-0.03
	Minoxidil	28 (0.02)	36 (0.02)	32 (0.01)	14 (0.007)	-0.013
TOTAL		157 570 (100)	198 388 (100)	214 779 (100)	208 011 (100)	

Table C.14: Medicine items claimed for patients aged >60, ≤75 years (age group 5)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Insulin	Insulin	10 984 (4.9)	13 207 (4.7)	15 573 (5.3)	15 903 (5.3)	+0.4
	Insulin glulisine	-	120 (0.04)	252 (0.09)	273 (0.09)	+0.09
	Insulin isophane/Regular insulin	34 (0.02)	107 (0.04)	147 (0.05)	159 (0.05)	-0.03
	Insulin lispro	-	36 (0.01)	94 (0.03)	131 (0.04)	+0.04
	Biphasic isophane insulin	-	-	-	5 (0.002)	+0.002
Oral antidiabetics	Acarbose	223 (0.10)	119 (0.04)	86 (0.03)	78 (0.03)	-0.07
	Chlorpropamide	13 (0.01)	4 (0.001)	-	-	-0.01
	Glibenclamide	3 252 (1.5)	3 590 (1.3)	3 595 (1.2)	3 399 (1.1)	-0.4
	Gliclazide	10 873 (4.9)	12 071 (4.3)	13 220 (4.5)	12 723 (4.2)	-0.7
	Glimepiride	4 421 (2.0)	4 826 (1.7)	4 745 (1.6)	4 037 (1.4)	-0.6
	Glipizide	140 (0.06)	108 (0.04)	85 (0.03)	64 (0.02)	-0.04
	Metformin	28 049 (12.2)	33 785 (12.1)	40 071 (13.7)	41 011 (13.7)	+1.5
	Metformin/Glibenclamide	1 362 (0.6)	1 947 (0.7)	2 605 (0.9)	2 582 (0.9)	+0.3
	Nateglinide	71 (0.03)	54 (0.02)	39 (0.01)	24 (0.008)	-0.022
	Pioglitazone	583 (0.3)	777 (0.3)	1 065 (0.4)	1 474 (0.5)	+0.2
	Repaglinide	441 (0.2)	393 (0.14)	292 (0.1)	212 (0.07)	-0.13
	Rosiglitazone	1 325 (0.6)	1 462 (0.5)	1 243 (0.4)	634 (0.2)	-0.4
Statins	Atorvastatin	19 559 (8.7)	23 386 (8.4)	20 179 (6.9)	21 946 (7.3)	-1.4
	Fluvastatin	1 905 (0.9)	1 823 (0.7)	1 507 (0.5)	1 327 (0.4)	-0.5
	Lovastatin	121 (0.05)	511 (0.18)	525 (0.18)	429 (0.14)	+0.09
	Simvastatin	26 878 (12.0)	36 295 (13.0)	35 447 (12.1)	37 238 (12.4)	+0.4
	Simvastatin/ascorbic acid/citric acid monohydrate/butylated hydroxyanisole	199 (0.09)	1 489 (0.5)	76 (0.03)	12 (0.004)	-0.086
	Pravastatin	2 432 (1.1)	2 798 (1.0)	2 311 (0.8)	1 883 (0.6)	-0.5
	Rosuvastatin	-	1 040 (0.4)	4 335 (1.5)	6 800 (2.3)	+2.3
Fibrates	Bezafibrate	1 672 (0.8)	2 449 (0.9)	2 278 (0.8)	2 383 (0.8)	-
	Fenofibrate	177 (0.08)	26 (0.01)	44 (0.02)	162 (0.05)	-0.03
	Gemfibrozil	144 (0.06)	171 (0.06)	127 (0.04)	134 (0.05)	-0.01

Table C.14: Medicine items claimed for patients aged >60, ≤75 years (age group 5) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Cholesterol absorption inhibitor	Ezetimibe	178 (0.08)	998 (0.4)	749 (0.3)	1 021 (0.3)	+0.22
Other hipolipidaemics	Cholestyramine	166 (0.07)	203 (0.07)	-	129 (0.04)	-0.03
	Acipimox	27 (0.01)	36 (0.01)	-	22 (0.007)	-0.003
	Nicotinic acid	10 (0.005)	25 (0.01)	24 (0.01)	39 (0.01)	+0.005
ACE-inhibitors	Benazepril	22 (0.01)	12 (0.004)	12 (0.004)	20 (0.007)	-0.003
	Benazepril/Hydrochlorothiazide	3 (0.002)	14 (0.005)	18 (0.006)	16 (0.005)	-0.003
	Captopril	1 297 (0.6)	1 234 (0.4)	929 (0.3)	1 033 (0.3)	-0.3
	Captopril/Hydrochlorothiazide	92 (0.04)	69 (0.02)	49 (0.02)	104 (0.04)	-
	Cilazapril	145 (0.06)	95 (0.03)	166 (0.06)	82 (0.03)	-0.03
	Cilazapril/Hydrochlorothiazide	70 (0.03)	48 (0.02)	49 (0.02)	16 (0.005)	-0.025
	Enalapril	6 172 (2.8)	7 269 (2.6)	6 589 (2.3)	6 718 (2.2)	-0.6
	Enalapril/Hydrochlorothiazide	2 772 (1.2)	3 394 (1.2)	3 640 (1.2)	3 699 (1.2)	-
	Fosinopril	147 (0.07)	216 (0.08)	201 (0.07)	110 (0.04)	-0.03
	Fosinopril/Hydrochlorothiazide	95 (0.04)	47 (0.02)	-	24 (0.008)	-0.072
	Lisinopril	5 643 (2.5)	7 030 (2.5)	6 395 (2.2)	7 365 (2.5)	-
	Lisinopril/Hydrochlorothiazide	1 027 (0.5)	1 603 (0.6)	1 766 (0.6)	1 878 (0.6)	+0.1
	Perindopril	7 309 (3.3)	9 780 (3.5)	10 165 (3.5)	9 390 (3.1)	-0.2
	Perindopril/Indapamide	3 028 (1.4)	5 187 (1.9)	6 487 (2.2)	6 856 (2.3)	+0.9
	Quinapril	740 (0.3)	585 (0.2)	649 (0.2)	677 (0.2)	-0.1
	Quinapril/Hydrochlorothiazide	943 (0.4)	983 (0.4)	976 (0.3)	915 (0.3)	-0.1
	Ramipril	2 663 (1.2)	2 876 (1.0)	3 000 (1.0)	2 923 (1.0)	-0.2
	Ramipril/Felodipine	1 262 (0.6)	1 419 (0.5)	1 316 (0.5)	1 106 (0.4)	-0.2
	Trandolapril	151 (0.07)	387 (0.14)	310 (0.11)	279 (0.09)	+0.02
	Verapamil/Trandolapril	640 (0.3)	747 (0.3)	746 (0.3)	618 (0.2)	-0.1
Calcium channel blockers	Amlodipine	5 288 (2.4)	7 779 (2.8)	10 392 (3.6)	11 527 (3.8)	+1.4
	Felodipine	1 735 (0.8)	1 808 (0.7)	1 958 (0.7)	1 961 (0.7)	-0.1
	Isradipine	553 (0.3)	383 (0.14)	363 (0.12)	317 (0.11)	-0.19
	Lercanidipine	104 (0.05)	508 (0.18)	719 (0.3)	803 (0.3)	+0.25
	Nifedipine	826 (0.4)	1 030 (0.4)	1 258 (0.4)	1 149 (0.4)	-

Table C.14: Medicine items claimed for patients aged >60, ≤75 years (age group 5) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Calcium channel blockers	Verapamil	156 (0.07)	208 (0.07)	211 (0.07)	241 (0.08)	+0.01
Angiotensin II receptor blockers	Candesartan	3 998 (1.8)	4 457 (1.6)	3 985 (1.4)	3 449 (1.2)	-0.6
	Eprosartan	67 (0.03)	131 (0.05)	603 (0.2)	1 291 (0.4)	+0.37
	Irbesartan	943 (0.4)	1 306 (0.5)	1 228 (0.4)	1 144 (0.4)	-
	Irbesartan/Hydrochlorothiazide	885 (0.4)	1 265 (0.5)	1 521 (0.5)	1 275 (0.4)	-
	Losartan	1 081 (0.5)	1 334 (0.5)	1 155 (0.4)	1 773 (0.6)	+0.1
	Losartan/Hydrochlorothiazide	2 357 (1.0)	2 633 (0.9)	2 708 (0.9)	2 815 (0.9)	-0.1
	Telmisartan	1 078 (0.5)	1 454 (0.5)	1 972 (0.7)	1 849 (0.6)	+0.1
	Telmisartan/Hydrochlorothiazide	770 (0.3)	1 213 (0.4)	1 498 (0.5)	1 469 (0.5)	+0.2
	Valsartan	1 537 (0.7)	1 867 (0.7)	2 116 (0.7)	1 945 (0.7)	-
	Valsartan/Hydrochlorothiazide	2 216 (1.1)	3 083 (1.1)	3 338 (1.1)	4 063 (1.4)	+0.3
α-receptor blockers	Alfuzosin	235 (0.10)	408 (0.15)	583 (0.2)	496 (0.17)	+0.07
	Doxazosin	1 826 (0.8)	2 109 (0.8)	2 447 (0.8)	2 280 (0.8)	-
	Prazosin	310 (0.14)	363 (0.13)	391 (0.13)	359 (0.12)	-0.02
	Terazosin	291 (0.13)	236 (0.08)	230 (0.08)	170 (0.06)	-0.07
β-blockers	Acebutolol	863 (0.4)	858 (0.3)	623 (0.2)	501 (0.17)	-0.23
	Atenolol	-	-	27 (0.01)	30 (0.01)	+0.01
	Atenolol/Chlorthalidone	1 535 (0.7)	1 749 (0.6)	1 685 (0.6)	1 690 (0.6)	-0.1
	Bisoprolol	4 912 (2.2)	7 616 (2.7)	9 395 (3.2)	10 497 (3.5)	+1.3
	Bisoprolol/Hydrochlorothiazide	2 330 (1.0)	3 100 (1.1)	2 938 (1.0)	2 843 (1.0)	-
	Metoprolol	12 (0.01)	12 (0.003)	18 (0.01)	22 (0.007)	-0.003
	Nadolol	25 (0.01)	53 (0.02)	17 (0.01)	-	-0.01
	Nadolol/Bendroflumethiazide	34 (0.02)	12 (0.004)	1 (0.0003)	-	-0.02
	Nebivolol	119 (0.05)	142 (0.05)	241 (0.08)	212 (0.07)	+0.02
	Propranolol	67 (0.03)	92 (0.03)	67 (0.02)	2 (0.001)	-0.029
	Sotalol	657 (0.3)	760 (0.3)	757 (0.3)	753 (0.3)	-
	Timolol/amiloride	92 (0.04)	136 (0.05)	74 (0.03)	33 (0.01)	-0.03
α/ β receptor blockers	Carvedilol	5 790 (2.6)	7 201 (2.6)	7 814 (2.7)	7 910 (2.6)	-
	Labetalol	-	12 (0.004)	23 (0.01)	2 (0.001)	+0.001

Table C.14: Medicine items claimed for patients aged >60, ≤75 years (age group 5) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Diuretics	Acetazolamide	82 (0.04)	98 (0.04)	110 (0.04)	101 (0.03)	-0.01
	Amiloride/Hydrochlorothiazide	4 659 (2.1)	5 222 (1.9)	4 480 (1.5)	4 406 (1.5)	-0.6
	Bumetanide	90 (0.04)	82 (0.03)	80 (0.03)	64 (0.02)	-0.02
	Bumetanide/KCL	903 (0.4)	1 082 (0.4)	980 (0.3)	780 (0.3)	-0.1
	Chlorthalidone	21 (0.01)	23 (0.01)	12 (0.004)	25 (0.008)	-0.002
	Chlorthalidone/Reserpine	12 (0.01)	-	-	-	-0.01
	Furosemide	7 396 (3.3)	8 299 (3.0)	9 511 (3.3)	8 547 (2.8)	-0.5
	Hydroflumethiazide/Reserpine/ Hydrochlorothiazide	57 (0.03)	48 (0.02)	-	-	-0.03
	Hydrochlorothiazide	4 000 (1.8)	4 699 (1.7)	4 240 (1.5)	4 581 (1.5)	-0.3
	Indapamide	7 120 (3.2)	9 000 (3.2)	8 313 (2.8)	8 132 (2.7)	-0.5
	Triamterene/Hydrochlorothiazide	219 (0.10)	285 (0.10)	269 (0.09)	244 (0.08)	-0.02
	Piretanide	137 (0.06)	100 (0.04)	155 (0.05)	97 (0.03)	-0.03
	Spirolactone	4 214 (1.9)	5 019 (1.8)	5 206 (1.8)	5 332 (1.8)	-0.1
	Spirolactone/isobutyl hydrochlorothiazide	44 (0.02)	72 (0.03)	52 (0.02)	47 (0.02)	-
	Torsemide	1 096 (0.5)	1 276 (0.5)	1 027 (0.4)	826 (0.3)	-0.2
Central acting sympathetic nervous system inhibitors	Methyldopa	853 (0.4)	758 (0.3)	708 (0.2)	737 (0.3)	-0.1
	Moxonidine	473 (0.2)	581 (0.2)	736 (0.3)	782 (0.3)	+0.1
Peripheral sympatholytic agents	Dihydroergocristine/ Clopamide/Reserpine	253 (0.11)	148 (0.05)	112 (0.04)	148 (0.05)	-0.06
	Reserpine	116 (0.05)	139 (0.05)	162 (0.06)	160 (0.05)	-
Direct acting vasodilators	Hydralazine	112 (0.05)	148 (0.05)	208 (0.07)	191 (0.06)	+0.01
	Minoxidil	39 (0.02)	38 (0.01)	72 (0.02)	66 (0.02)	-
TOTAL		224 048 (100)	279 283 (100)	292 986 (100)	300 200 (100)	

Table C.15: Medicine items claimed for patients aged >75 years (age group 6)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Insulin	Insulin	2 488 (3.0)	2 433 (2.3)	3 605 (3.0)	3 489 (2.8)	-0.2
	Insulin glulisine	-	20 (0.02)	28 (0.02)	31 (0.03)	+0.03
	Insulin isophane/Regular insulin	-	24 (0.02)	38 (0.03)	32 (0.03)	+0.03
	Insulin lispro	-	10 (0.01)	13 (0.01)	18 (0.01)	+0.01
	Biphasic isophane insulin	-	-	-	1 (0.001)	+0.001
Oral antidiabetics	Acarbose	91 (0.11)	109 (0.1)	119 (0.10)	75 (0.06)	-0.05
	Chlorpropamide	3 (0.004)	1 (0.001)	1 (0.001)	-	-0.004
	Glibenclamide	983 (1.2)	957 (0.9)	1 112 (0.9)	978 (0.8)	-0.4
	Gliclazide	3 904 (4.7)	4 139 (4.0)	5 593 (4.7)	4 943 (4.0)	-0.7
	Glimepiride	1 473 (1.8)	1 530 (1.5)	1 912 (1.6)	1 861 (1.5)	-0.3
	Glipizide	186 (0.2)	151 (0.14)	165 (0.14)	110 (0.09)	-0.11
	Metformin	7 244 (8.8)	8 284 (7.9)	11 744 (9.8)	11 412 (9.1)	+0.3
	Metformin/Glibenclamide	493 (0.6)	590 (0.6)	813 (0.7)	690 (0.6)	-
	Nateglinide	26 (0.03)	43 (0.04)	43 (0.04)	40 (0.03)	-
	Pioglitazone	135 (0.16)	159 (0.15)	305 (0.3)	294 (0.2)	+0.04
	Repaglinide	84 (0.10)	102 (0.1)	136 (0.11)	143 (0.11)	+0.01
	Rosiglitazone	-	287 (0.3)	365 (0.3)	119 (0.1)	+0.1
Statins	Atorvastatin	7 345 (8.9)	9 171 (8.8)	8 129 (6.8)	9 396 (7.5)	-1.4
	Fluvastatin	724 (0.9)	1 005 (1.0)	730 (0.6)	758 (0.6)	-0.3
	Lovastatin	18 (0.02)	141 (0.13)	165 (0.14)	215 (0.17)	+0.15
	Simvastatin	9 674 (11.7)	14 278 (13.6)	15 292 (12.8)	17 388 (13.9)	+2.2
	Simvastatin/Ascorbic Acid/Citric Acid Monohydrate/Butylated Hydroxyanisole	74 (0.09)	551 (0.5)	26 (0.02)	-	-0.09
	Pravastatin	1 165 (1.4)	1 443 (1.4)	1 212 (1.0)	1 326 (1.1)	-0.3
	Rosuvastatin	282 (0.3)	293 (0.3)	1 119 (0.9)	2 147 (1.7)	+1.4
Fibrates	Bezafibrate	323 (0.4)	525 (0.5)	501 (0.4)	591 (0.5)	+0.1
	Fenofibrate	67 (0.08)	13 (0.01)	12 (0.01)	33 (0.03)	-0.05
	Gemfibrozil	18 (0.02)	7 (0.01)	-	23 (0.02)	-

Table C.15: Medicine items claimed for patients aged >75 years (age group 6) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Other hipolipidaemics	Cholestyramine	89 (0.11)	92 (0.09)	-	119 (0.1)	-0.01
	Ezetimibe	23 (0.03)	136 (0.13)	210 (0.18)	226 (0.18)	+0.15
	Acipimox	-	6 (0.01)	-	-	-
	Nicotinic acid	33 (0.04)	49 (0.05)	45 (0.04)	29 (0.02)	-0.02
ACE-inhibitors	Benazepril	-	16 (0.02)	10 (0.01)	20 (0.02)	+0.02
	Captopril	419 (0.5)	420 (0.4)	437 (0.4)	450 (0.4)	-0.1
	Captopril/Hydrochlorothiazide	55 (0.07)	62 (0.06)	45 (0.04)	34 (0.03)	-0.04
	Cilazapril	26 (0.03)	51 (0.05)	77 (0.06)	43 (0.03)	-
	Cilazapril/Hydrochlorothiazide	21 (0.03)	4 (0.004)	21 (0.02)	16 (0.01)	-0.02
	Enalapril	1 973 (2.4)	2 524 (2.4)	2 364 (2.0)	2 587 (2.1)	-0.3
	Enalapril/Hydrochlorothiazide	647 (0.8)	926 (0.9)	1 018 (0.9)	1 027 (0.8)	-
	Fosinopril	102 (0.12)	169 (0.16)	77 (0.06)	82 (0.07)	-0.05
	Fosinopril/Hydrochlorothiazide	29 (0.04)	30 (0.03)	1 (0.001)	12 (0.01)	-0.03
	Lisinopril	1 724 (2.1)	2 004 (1.9)	2 433 (2.0)	2 538 (2.0)	-0.1
	Lisinopril/Hydrochlorothiazide	386 (0.5)	429 (0.4)	524 (0.4)	663 (0.5)	-
	Perindopril	3 617 (4.4)	4 529 (4.3)	4 810 (4.0)	4 645 (3.7)	-0.7
	Perindopril/Indapamide	1 220 (1.5)	2 035 (1.9)	2 422 (2.0)	3 079 (2.5)	+1.0
	Quinapril	278 (0.3)	319 (0.3)	375 (0.3)	328 (0.3)	-
	Quinapril/Hydrochlorothiazide	364 (0.4)	414 (0.4)	531 (0.4)	374 (0.3)	-0.1
	Ramipril	1 187 (1.4)	1 369 (1.3)	1 276 (1.1)	1 279 (1.0)	-0.4
	Ramipril/Felodipine	516 (0.6)	542 (0.5)	631 (0.5)	576 (0.5)	-0.1
	Trandolapril	95 (0.11)	127 (0.12)	110 (0.09)	163 (0.13)	+0.02
	Verapamil/Trandolapril	204 (0.3)	234 (0.2)	193 (0.16)	229 (0.18)	-0.12
Calcium channel blockers	Amlodipine	2 089 (2.5)	3 496 (3.3)	4 676 (3.9)	5 079 (4.1)	+1.6
	Felodipine	984 (1.2)	1 157 (1.1)	1 002 (0.8)	1 067 (0.9)	-0.3
	Isradipine	227 (0.3)	234 (0.2)	222 (0.19)	201 (0.16)	-0.14
	Lercanidipine	49 (0.06)	270 (0.3)	416 (0.4)	526 (0.4)	+0.34
	Nifedipine	293 (0.4)	323 (0.3)	445 (0.4)	362 (0.3)	-0.1
	Verapamil	58 (0.07)	77 (0.07)	90 (0.08)	119 (0.1)	+0.03

Table C.15: Medicine items claimed for patients aged >75 years (age group 6) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Angiotensin II receptor blockers	Candesartan	1 513 (1.8)	1 757 (1.7)	1 843 (1.5)	2 002 (1.6)	-0.2
	Eprosartan	4 (0.004)	5 (0.005)	199 (0.17)	547 (0.4)	+0.396
	Irbesartan	372 (0.5)	509 (0.5)	544 (0.5)	483 (0.4)	-0.1
	Irbesartan/Hydrochlorothiazide	201 (0.2)	337 (0.3)	401 (0.3)	508 (0.4)	+0.2
	Losartan	700 (0.9)	659 (0.6)	575 (0.5)	960 (0.8)	-0.1
	Losartan/Hydrochlorothiazide	806 (1.0)	962 (0.9)	1 124 (0.9)	1 157 (0.9)	-0.1
	Telmisartan	397 (0.5)	607 (0.6)	676 (0.6)	781 (0.6)	+0.1
	Telmisartan/Hydrochlorothiazide	196 (0.2)	337 (0.3)	415 (0.4)	513 (0.4)	+0.2
	Valsartan	744 (0.9)	933 (0.9)	1 205 (1.0)	1 098 (0.9)	-
	Valsartan/Hydrochlorothiazide	731 (0.9)	993 (1.0)	1 372 (1.1)	1 484 (1.2)	+0.7
α-receptor blockers	Alfuzosin	124 (0.15)	229 (0.2)	252 (0.2)	259 (0.2)	+0.05
	Doxazosin	517 (0.6)	786 (0.8)	946 (0.8)	933 (0.8)	+0.2
	Prazosin	151 (0.18)	228 (0.2)	207 (0.17)	152 (0.12)	-0.06
	Terazosin	51 (0.06)	77 (0.07)	82 (0.07)	45 (0.04)	-0.02
β-blockers	Acebutolol	367 (0.4)	389 (0.4)	316 (0.3)	327 (0.3)	-0.1
	Atenolol	-	-	25 (0.02)	18 (0.01)	+0.01
	Atenolol/Chlorthalidone	466 (0.6)	487 (0.5)	453 (0.4)	510 (0.4)	-0.2
	Bisoprolol	1 842 (2.2)	2 943 (2.8)	4 201 (3.5)	4 938 (3.9)	+1.7
	Bisoprolol/Hydrochlorothiazide	1 098 (1.3)	970 (0.9)	1 181 (1.0)	1 090 (0.9)	-0.4
	Metoprolol	25 (0.03)	12 (0.01)	12 (0.01)	16 (0.01)	-0.02
	Nadolol	49 (0.06)	40 (0.04)	9 (0.01)	-	-0.06
	Nadolol/Bendroflumethiazide	1 (0.001)	11 (0.01)	-	-	-0.001
	Nebivolol	82 (0.10)	68 (0.06)	57 (0.05)	95 (0.09)	-0.01
	Propranolol	40 (0.05)	51 (0.05)	28 (0.02)	1 (0.001)	-0.049
	Sotalol	272 (0.3)	328 (0.3)	306 (0.3)	429 (0.3)	-
	Timolol/amiloride	49 (0.06)	46 (0.04)	13 (0.01)	33 (0.03)	-0.03
α/ β receptor blockers	Carvedilol	2 541 (3.1)	3 279 (3.1)	4 208 (3.5)	3 924 (3.1)	-
	Labetalol	-	10 (0.01)	12 (0.01)	-	-
Diuretics	Acetazolamide	41 (0.05)	51 (0.05)	47 (0.04)	60 (0.05)	-

Table C.15: Medicine items claimed for patients aged >75 years (age group 6) (continued)

Pharmacological class	Active substance	Number of medicine items claimed, n (%)				Relative change 2005 vs. 2008 (%)
		2005	2006	2007	2008	
Diuretics (continued)	Amiloride/Hydrochlorothiazide	1 748 (2.1)	2 360 (2.3)	1 985 (1.7)	2 047 (1.6)	-0.5
	Bumetanide	36 (0.04)	66 (0.06)	29 (0.02)	54 (0.04)	-
	Bumetanide/KCL	539 (0.7)	574 (0.6)	617 (0.5)	551 (0.4)	-0.3
	Chlorthalidone	6 (0.01)	4 (0.004)	-	5 (0.004)	-0.006
	Chlorthalidone/Reserpine	4 (0.005)	1 (0.001)	-	-	-0.005
	Furosemide	4 960 (6.0)	5 806 (5.5)	7 299 (6.1)	6 663 (5.3)	-0.7
	Hydrochlorothiazide	1 521 (1.8)	2 010 (1.9)	1 936 (1.6)	2 065 (1.7)	-0.1
	Hydroflumethiazide/Reserpine/ Hydrochlorothiazide	12 (0.01)	48 (0.05)	-	2 (0.001)	-0.009
	Indapamide	2 974 (3.6)	3 564 (3.4)	3 477 (2.9)	3 590 (2.9)	-0.7
	Triamterene/Hydrochlorothiazide	130 (0.16)	126 (0.12)	169 (0.14)	117 (0.09)	-0.07
	Piretanide	141 (0.17)	176 (0.17)	77 (0.06)	70 (0.06)	-0.11
	Spirolactone	2 236 (2.7)	2 943 (2.8)	3 906 (3.3)	3 861 (3.1)	+0.4
	Spirolactone/isobutyl hydrochlorothiazide	-	1 (0.001)	-	27(0.02)	+0.02
	Torsemide	978 (1.2)	1 026 (1.0)	1 193 (1.0)	870 (0.7)	-0.5
Central acting sympathetic nervous system inhibitors	Methyldopa	260 (0.3)	329 (0.3)	385 (0.3)	360 (0.3)	-
	Moxonidine	148 (0.18)	179 (0.17)	242 (0.2)	284 (0.2)	+0.02
Peripheral sympatholytic agents	Dihydroergocristine/ Clopamide/Reserpine	81 (0.10)	78 (0.07)	96 (0.08)	113 (0.09)	-0.01
	Reserpine	3 (0.004)	75 (0.07)	47 (0.04)	65 (0.05)	+0.049
Direct acting vasodilators	Hydralazine	63 (0.08)	43 (0.04)	70 (0.06)	85 (0.07)	-0.01
	Minoxidil	1 (0.001)	11 (0.01)	16 (0.01)	13 (0.01)	+0.009
TOTAL		82 727 (100)	104 834 (100)	119 892 (100)	125 191 (100)	

Table C.16: Direct medicine treatment cost associated with the 2005 prescribing index

Active substance	Frequency (n; %)*	Mean $\pm$ SD (R)	Median (R)	Total Cost** (R) (n; %)	CPI
Metformin	62 194 (12.6)	47.18 $\pm$ 19.83	51.22	2 934 480.74 (4.1)	0.3
Simvastatin	57 047 (11.6)	116.93 $\pm$ 27.56	115.38	6 670 223.45 (9.3)	0.8
Atorvastatin	44 796 (9.1)	219.38 $\pm$ 57.14	190.28	9 827 138.97 (13.7)	1.5
Insulin	24 504 (5.6)	568.22 $\pm$ 244.93	480.41	15 293 053.52 (21.3)	3.8
Gliclazide	22 710 (4.6)	77.21 $\pm$ 42.91	69.02	1 753 510.45 (2.4)	0.5
Perindopril	17 379 (3.5)	132.40 $\pm$ 32.58	130.54	2 301 031.54 (3.2)	0.9
Furosemide	15 981 (3.2)	93.71 $\pm$ 111.16	54.41	1 497 552.16 (2.1)	0.6
Indapamide	15 742 (3.2)	41.95 $\pm$ 30.99	28.45	660 408.12 (0.9)	0.3
Enalapril	13 145 (2.7)	60.97 $\pm$ 27.32	62.06	801 469.28 (1.1)	0.4
Lisinopril	11 903 (2.4)	67.82 $\pm$ 28.47	66.66	807 298.89 (1.1)	0.5
Carvedilol	11 793 (2.4)	125.20 $\pm$ 58.71	124.11	1 476 429.37 (2.1)	0.9
Amlodipine	11 742 (2.4)	143.63 $\pm$ 38.12	138.08	1 686 553.12 (2.4)	1
Bisoprolol	10 629 (2.2)	76.31 $\pm$ 29.92	81.98	811 065.13 (1.1)	0.5
Glimepiride	9 703 (2.0)	163.39 $\pm$ 81.08	144.43	1 585 352.64 (2.2)	1.1
Amiloride/Hydrochlorothiazide	8 966 (1.9)	10.40 $\pm$ 8.83	6.74	122 478.31 (0.2)	0.1
Spironolactone	8 584 (1.7)	59.22 $\pm$ 59.89	31.01	508 307.42 (0.7)	0.4
Hydrochlorothiazide	8 248 (1.7)	12.78 $\pm$ 7.83	10.27	105 433.39 (0.1)	0.1
Indapamide/Perindopril	7 520 (1.5)	182.09 $\pm$ 20.40	179.09	1 369 320.77 (1.9)	1.2
Glibenclamide	7 014 (1.4)	44.22 $\pm$ 49.06	27.69	310 169.93 (0.4)	0.3
Ramipril	6 369 (1.3)	203.85 $\pm$ 65.62	220.97	1 298 324.00 (1.8)	1.4
TOTAL	375 969 (76.4)			51 819 601.20 (72.2)	

*n = 492 333; **n = R71 724 445.88; CPI = Cost prevalence Index (refer to paragraph 3.6.5).

Table C.17: Direct medicine treatment cost associated with the 2006 prescribing index

Active substance	Frequency (n; %)*	Mean $\pm$ SD (R)	Median (R)	Total Cost** (R) (n; %)	CPI
Metformin	77 950 (12.3)	46.37 $\pm$ 19.42	50.98	3 524 288.24 (4.0)	0.3
Simvastatin	75 997 (12.6)	114.17 $\pm$ 24.04	115.28	8 899 581.02 (10.1)	0.8
Atorvastatin	53 754 (8.7)	223.75 $\pm$ 57.22	190.14	12 027 385.43 (13.7)	1.6
Insulin	29 302 (5.3)	575.25 $\pm$ 237.83	488.41	18 341 524.43 (20.9)	4.0
Gliclazide	25 706 (4.2)	75.33 $\pm$ 44.52	63.56	1 936 495.79 (2.2)	0.5
Perindopril	22 905 (3.7)	132.87 $\pm$ 33.21	130.54	3 043 325.37 (3.5)	0.9
Furosemide	18 436 (3.0)	89.97 $\pm$ 107.87	54.41	1 658 679.24 (1.9)	0.6
Indapamide	18 931 (3.1)	39.49 $\pm$ 29.52	28.45	747 676.57 (0.9)	0.3
Enalapril	15 435 (2.5)	59.36 $\pm$ 25.82	62.06	916 282.13 (1.0)	0.4
Lisinopril	14 671 (2.4)	65.52 $\pm$ 24.04	66.07	961 215.05 (1.1)	0.5
Carvedilol	15 006 (2.4)	116.74 $\pm$ 52.79	97.22	1 751 777.94 (2.0)	0.8
Amlodipine	17 628 (2.9)	131.74 $\pm$ 36.97	132.64	2 322 317.66 (2.6)	0.9
Bisoprolol	16 227 (2.6)	63.97 $\pm$ 28.56	55.43	1 037 987.38 (1.2)	0.4
Glimepiride	10 534 (1.7)	153.51 $\pm$ 77.43	144.43	1 617 024.48 (1.8)	1.1
Amiloride/Hydrochlorothiazide	10 952 (1.8)	10.13 $\pm$ 8.82	6.74	136 021.32 (0.2)	0.1
Spironolactone	10 608 (1.7)	53.32 $\pm$ 48.37	29.56	565 591.43 (0.6)	0.4
Hydrochlorothiazide	9 725 (1.6)	13.08 $\pm$ 8.35	10.27	127 212.05 (0.1)	0.1
Indapamide/Perindopril	12 706 (2.1)	164.70 $\pm$ 26.62	157.09	2 092 741.49 (2.4)	1.2
Glibenclamide	7 639 (1.2)	43.15 $\pm$ 47.21	27.69	329 630.69 (0.4)	0.3
Enalapril/Hydrochlorothiazide	6 892 (1.1)	82.42 $\pm$ 15.82	77.33	568 068.79 (0.6)	0.6
TOTAL	471 004 (76.4)			62 604 826.50 (71.3)	

*n = 616 359; **n = R87 786 565.60; CPI = Cost prevalence Index (refer to paragraph 3.6.5).

Table C.18: Direct medicine treatment cost associated with the 2007 prescribing index

Active substance	Frequency (n; %)*	Mean $\pm$ SD (R)	Median (R)	Total Cost** (R) (n; %)	CPI
Metformin	91 128 (13.7)	47.20 $\pm$ 19.89	49.88	4 301 156.24 (4.5)	0.3
Simvastatin	78 478 (11.8)	115.43 $\pm$ 25.94	111.62	9 058 692.46 (9.4)	0.8
Atorvastatin	46 724 (7.0)	206.10 $\pm$ 66.73	188.10	9 629 781.64 (10.0)	1.4
Insulin	35 729 (5.9)	588.03 $\pm$ 243.31	499.96	22 563 821.12 (23.5)	4.0
Gliclazide	29 334 (4.4)	81.80 $\pm$ 46.32	68.71	2 399 534.86 (2.5)	0.6
Perindopril	24 603 (3.7)	136.04 $\pm$ 37.65	130.54	3 347 088.43 (3.5)	0.9
Furosemide	21 709 (3.3)	96.60 $\pm$ 122.35	45.90	2 097 068.43 (2.2)	0.7
Indapamide	18 124 (2.7)	39.18 $\pm$ 30.00	29.12	710 018.97 (0.7)	0.3
Enalapril	14 076 (2.1)	62.97 $\pm$ 27.74	65.47	886 296.64 (0.9)	0.4
Lisinopril	14 371 (2.2)	70.47 $\pm$ 27.05	70.29	1 012 702.18 (1.1)	0.5
Carvedilol	17 205 (2.6)	118.09 $\pm$ 50.40	108.60	2 031 798.56 (2.1)	0.8
Amlodipine	23 867 (3.6)	131.68 $\pm$ 41.63	132.93	3 142 764.30 (3.3)	0.9
Bisoprolol	20 229 (3.1)	63.27 $\pm$ 28.20	55.61	1 279 789.39 (1.3)	0.4
Glimepiride	10 558 (1.6)	156.82 $\pm$ 80.04	144.43	1 655 743.45 (1.7)	1.1
Amiloride / Hydrochlorothiazide	9 833 (1.5)	10.48 $\pm$ 8.16	7.09	120 459.27 (0.1)	0.1
Spironolactone	12 135 (1.8)	54.02 $\pm$ 45.85	37.54	655 564.49 (0.7)	0.4
Hydrochlorothiazide	8 920 (1.3)	14.31 $\pm$ 8.39	10.81	127 667.91 (0.1)	0.1
Rosuvastatin	10 530 (1.6)	210.62 $\pm$ 60.45	199.63	2 217 807.11 (2.3)	1.5
Indapamide / Perindopril	15 927 (2.4)	159.08 $\pm$ 25.30	156.39	2 533 625.39 (2.6)	1.1
Glibenclamide	7 839 (1.2)	45.62 $\pm$ 45.84	29.21	357 652.58 (0.4)	0.3
TOTAL	511 319 (77.1)			70 129 033.42 (72.9)	

*n = 663 052; **n = R96 142 661.22; CPI = Cost prevalence Index (refer to paragraph 3.6.5)

Table C.19: Direct medicine treatment cost associated with the 2008 prescribing index

Active substance	Frequency (n; %)*	Mean $\pm$ SD (R)	Median (R)	Total Cost** (R) (n; %)	CPI
Metformin	90 021 (13.5)	47.29 $\pm$ 20.26	49.20	4 256 854.78 (4.5)	0.3
Simvastatin	81 751 (12.3)	113.06 $\pm$ 26.30	110.88	9 242 412.10 (9.8)	0.8
Atorvastatin	48 929 (7.4)	181.29 $\pm$ 60.33	179.03	8 870 275.07 (9.4)	1.3
Insulin	34 724 (5.6)	608.84 $\pm$ 267.53	533.21	22 508 802.74 (23.8)	4.2
Gliclazide	27 674 (4.2)	87.06 $\pm$ 50.11	72.40	2 407 823.53 (2.5)	0.6
Perindopril	22 542 (3.4)	137.97 $\pm$ 39.13	133.95	3 110 199.64 (3.3)	1.0
Furosemide	19 553 (2.9)	90.27 $\pm$ 123.39	37.30	1 765 070.90 (1.9)	0.6
Indapamide	17 348 (2.6)	41.25 $\pm$ 30.79	30.89	715 551.61 (0.8)	0.3
Enalapril	14 477 (2.2)	65.84 $\pm$ 26.86	69.00	953 096.14 (1.0)	0.5
Lisinopril	15 180 (2.3)	70.63 $\pm$ 25.16	69.73	1 072 140.18 (1.1)	0.5
Carvedilol	16 839 (2.5)	118.98 $\pm$ 49.12	115.57	2 003 484.65 (2.1)	0.8
Amlodipine	25 679 (3.9)	115.97 $\pm$ 40.51	107.76	2 977 967.57 (3.1)	0.8
Bisoprolol	22 474 (3.4)	65.11 $\pm$ 29.10	55.72	1 463 238.04 (1.5)	0.5
Glimepiride	9 023 (1.4)	159.27 $\pm$ 85.89	131.56	1 437 086.52 (1.5)	1.1
Amiloride / Hydrochlorothiazide	9 554 (1.4)	11.37 $\pm$ 8.70	7.55	118 105.77 (0.1)	0.1
Spironolactone	12 062 (1.8)	53.38 $\pm$ 46.25	37.54	643 873.38 (0.7)	0.4
Hydrochlorothiazide	9 431 (1.4)	15.37 $\pm$ 9.10	11.50	144 994.20 (0.2)	0.1
Rosuvastatin	16 276 (2.4)	220.54 $\pm$ 61.10	199.63	3 589 449.61 (3.8)	1.5
Indapamide / Perindopril	16 682 (2.6)	157.21 $\pm$ 24.53	153.90	2 729 595.15 (2.9)	1.1
Candesartan	7 889 (1.2)	201.69 $\pm$ 49.41	206.68	1 636 749.62 (1.7)	1.5
TOTAL	518 108 (77.9)			71 646 771.20 (75.7)	

*n = 664 969; **n = R94 690 393.54; CPI = Cost prevalence Index (refer to paragraph 3.6.5).

Table C.20: Top 20* “one active substance” treatment regimens for 2008

Active substance	Prevalence (n, %)	Average cost per regimen (mean $\pm$ SD)	Total treatment cost (R) (n, %)
Simvastatin	8 934 (16.7)	112.74 $\pm$ 5.06	1 007 251.79 (11.7)
Metformin	7 286 (13.6)	43.41 $\pm$ 0.34	316 255.04 (3.7)
Atorvastatin	6 067 (11.3)	179.62 $\pm$ 11.15	1 089 727.73 (12.6)
Insulin	5 494 (10.3)	639.65 $\pm$ 161.25	3 514 234.42 (40.8)
Furosemide	2 861 (5.3)	92.58 $\pm$ 15.64	26 4868.1 (3.1)
Perindopril	2 617 (4.9)	134.97 $\pm$ 7.58	353 205.86 (4.1)
Bisoprolol	2 508 (4.7)	63.18 $\pm$ 3.65	158 455.94 (1.8)
Amlodipine	2 429 (4.5)	115.32 $\pm$ 4.53	280 100.00 (3.2)
Rosuvastatin	2 303 (4.3)	214.42 $\pm$ 13.72	493 809.66 (5.7)
Indapamide	1 961 (3.7)	45.09 $\pm$ 1.14	88 414.68 (1.0)
Gliclazide	1 721 (3.2)	94.84 $\pm$ 2.10	163 219.48 (1.9)
Carvedilol	1 549 (2.9)	115.88 $\pm$ 5.75	179 501.05 (2.1)
Spironolactone	1 373 (2.6)	51.98 $\pm$ 10.50	71 367.20 (0.8)
Enalapril	1 342 (2.5)	63.51 $\pm$ 3.02	85 227.84 (1.0)
Lisinopril	1 237 (2.3)	70.33 $\pm$ 2.59	86 994.38 (1.0)
Hydrochlorothiazide	1 128 (2.1)	15.75 $\pm$ 0.20	17 770.17 (0.2)
Valsartan	762 (1.4)	186.39 $\pm$ 10.92	142 031.13 (1.6)
Ramipril	724 (1.4)	161.19 $\pm$ 4.01	116 692.98 (1.4)
Pravastatin	643 (1.2)	193.71 $\pm$ 52.44	124 554.64 (1.4)
Losartan	625 (1.2)	105.97 $\pm$ 12.32	66 233.03 (0.8)
TOTAL	53 564 (100)		8 619 915.12 (100)

*The top 20 active substances were determined based on prescribing volume.

Table C.21: Top 20* “two active substances” treatment regimens for 2008

Active substance	Prevalence (n, %)	Average cost per regimen (mean $\pm$ SD)	Total treatment cost (R) (n, %)
Indapamide / Perindopril	2 313 (12.5)	160.24 $\pm$ 21.06	370 635.19 (12.6)
Simvastatin / Metformin	1 798 (9.7)	154.14 $\pm$ 9.68	277 134.59 (9.4)
Amiloride / Hydrochlorothiazide	1 390 (7.5)	14.19 $\pm$ 0.11	19 722.75 (0.7)
Valsartan / Hydrochlorothiazide	1 182 (6.4)	179.80 $\pm$ 21.43	212 518.04 (7.2)
Atorvastatin / Metformin	1 054 (5.7)	213.36 $\pm$ 36.19	224 881.07 (7.6)
Metformin / Glibenclamide	1 005 (5.4)	117.00 $\pm$ 14.87	117 582.88 (4.0)
Bisoprolol / Hydrochlorothiazide	925 (5.0)	123.21 $\pm$ 13.19	113 966.25 (3.9)
Simvastatin / Perindopril	885 (4.8)	245.04 $\pm$ 8.01	216 863.30 (7.3)
Gliclazide / Metformin	836 (4.5)	146.25 $\pm$ 10.35	122 261.63 (4.1)
Simvastatin / Lisinopril	808 (4.4)	182.47 $\pm$ 11.34	147 436.71 (5.0)
Losartan / Hydrochlorothiazide	741 (4.0)	121.01 $\pm$ 11.17	89 668.71 (3.0)
Atorvastatin / Perindopril	740 (4.0)	316.75 $\pm$ 31.44	234 396.76 (7.9)
Simvastatin / Enalapril	727 (3.9)	180.25 $\pm$ 9.77	131 038.78 (4.4)
Simvastatin / Indapamide	727 (3.9)	149.72 $\pm$ 4.98	108 844.37 (3.7)
Enalapril / Hydrochlorothiazide	722 (3.9)	89.11 $\pm$ 11.40	64 340.30 (2.2)
Lisinopril / Hydrochlorothiazide	590 (3.2)	97.62 $\pm$ 14.00	57 594.43 (2.0)
Simvastatin / Bisoprolol	587 (3.2)	173.35 $\pm$ 6.56	101 754.64 (3.4)
Bisoprolol / Atorvastatin	531 (2.9)	255.70 $\pm$ 38.28	135 774.09 (4.6)
Simvastatin / Amlodipine	526 (2.8)	227.57 $\pm$ 15.66	119 699.81 (4.1)
Simvastatin / Furosemide	484 (2.6)	179.30 $\pm$ 23.28	86 781.66 (2.9)
TOTAL	18 571 (100)		2 952 895.96 (100)

*The top 20 active substances were determined based on prescribing volume.

Table C.22: Top 20* “three active substances” treatment regimens for 2008

Active substance	Prevalence (n, %)	Average cost per regimen (mean $\pm$ SD)	Total treatment cost (R) (n, %)
Amlodipine / Indapamide / Perindopril	2 681 (21.2)	221.02 $\pm$ 11.48	592 562.81 (19.4)
Simvastatin / Indapamide / Perindopril	1 051 (8.3)	275.19 $\pm$ 20.59	289 229.52 (9.5)
Simvastatin / Metformin / Perindopril	857 (6.8)	284.41 $\pm$ 10.08	243 739.85 (8.0)
Simvastatin / Lisinopril / Metformin	840 (6.6)	217.71 $\pm$ 15.59	182 880.52 (6.0)
Simvastatin / Enalapril / Hydrochlorothiazide	804 (6.4)	198.26 $\pm$ 15.62	159 404.19 (5.2)
Simvastatin / Enalapril / Metformin	706 (5.6)	210.26 $\pm$ 16.87	148 441.42 (4.9)
Atorvastatin / Indapamide / Perindopril	639 (5.1)	344.95 $\pm$ 28.37	220 425.54 (7.2)
Amiloride / Hydrochlorothiazide / Simvastatin	532 (4.2)	123.10 $\pm$ 5.93	65 489.89 (2.1)
Metformin / Indapamide / Perindopril	498 (3.9)	209.48 $\pm$ 15.30	104 323.01 (3.4)
Atorvastatin / Metformin / Perindopril	467 (3.7)	348.08 $\pm$ 15.31	162 555.63 (5.3)
Simvastatin / Gliclazide / Metformin	458 (3.6)	245.38 $\pm$ 18.12	112 382.20 (3.7)
Simvastatin / Lisinopril / Hydrochlorothiazide	448 (3.5)	206.88 $\pm$ 19.13	92 680.95 (3.0)
Simvastatin / Valsartan / Hydrochlorothiazide	420 (3.3)	290.46 $\pm$ 10.06	121 991.67 (4.0)
Simvastatin / Bisoprolol / Hydrochlorothiazide	338 (2.7)	232.84 $\pm$ 25.22	78 698.82 (2.6)
Atorvastatin / Valsartan / Hydrochlorothiazide	337 (2.7)	366.72 $\pm$ 36.39	123 583.35 (4.1)
Atorvastatin / Bisoprolol / Hydrochlorothiazide	335 (2.7)	294.54 $\pm$ 18.10	98 670.92 (3.2)
Simvastatin / Metformin / Indapamide	334 (2.6)	175.09 $\pm$ 11.76	58 481.45 (1.9)
Simvastatin / Metformin / Glibenclamide	301 (2.4)	241.79 $\pm$ 38.63	72 779.34 (2.4)
Simvastatin / Losartan / Hydrochlorothiazide	298 (2.4)	233.06 $\pm$ 10.83	69 451.48 (2.3)
Simvastatin / Atenolol / Chlorthalidone	293 (2.3)	179.07 $\pm$ 3.39	52 466.65 (1.7)
TOTAL	12 637 (100)		3 050 239.21 (100)

*The top 20 active substances were determined based on prescribing volume.

Table C.23: Top 20* “four active substances” treatment regimens for 2008

Active substance	Prevalence (n, %)	Average cost per regimen (mean $\pm$ SD)	Total treatment cost (R) (n, %)
Simvastatin / Metformin / Indapamide / Perindopril	1 042 (14.8)	316.53 $\pm$ 25.36	329 825.39 (13.0)
Simvastatin / Enalapril / Hydrochlorothiazide / Metformin	622 (8.8)	244.01 $\pm$ 17.65	151 776.87 (6.0)
Atorvastatin / Metformin / Indapamide / Perindopril	539 (7.7)	368.68 $\pm$ 43.35	198 717.85 (7.9)
Simvastatin / Gliclazide / Metformin / Lisinopril	491 (7.0)	319.05 $\pm$ 23.50	156 654.59 (6.2)
Simvastatin / Lisinopril / Hydrochlorothiazide / Metformin	424 (6.0)	236.81 $\pm$ 22.66	100 407.38 (4.0)
Simvastatin / Gliclazide / Metformin / Perindopril	367 (5.2)	376.28 $\pm$ 23.96	138 095.17 (5.5)
Simvastatin / Losartan / Hydrochlorothiazide / Metformin	329 (4.7)	270.62 $\pm$ 18.27	89 034.94 (3.5)
Simvastatin / Valsartan / Hydrochlorothiazide / Insulin	327 (4.6)	827.24 $\pm$ 408.14	270 509.03 (10.7)
Simvastatin / Gliclazide / Metformin / Enalapril	321 (4.6)	314.32 $\pm$ 31.94	100 897.83 (4.0)
Amiloride / Hydrochlorothiazide / Simvastatin / Metformin	287 (4.1)	162.97 $\pm$ 13.55	46 773.38 (1.8)
Atorvastatin / Valsartan / Hydrochlorothiazide / Metformin	247 (3.5)	401.39 $\pm$ 52.16	99 142.45 (3.9)
Simvastatin / Gliclazide / Indapamide / Perindopril	247 (3.5)	359.45 $\pm$ 32.40	88 785.18 (3.5)
Atorvastatin / Losartan / Hydrochlorothiazide / Metformin	241 (3.4)	310.74 $\pm$ 27.21	74 888.41 (3.0)
Simvastatin / Valsartan / Hydrochlorothiazide / Metformin	241 (3.4)	329.97 $\pm$ 21.13	79 521.83 (3.1)
Enalapril / Insulin / Metformin / Simvastatin	234 (3.3)	915.36 $\pm$ 237.79	214 193.82 (8.5)
Simvastatin / Metformin / Bisoprolol / Hydrochlorothiazide	228 (3.2)	276.56 $\pm$ 22.82	63 054.65 (2.5)
Atorvastatin / Gliclazide / Metformin / Perindopril	221 (3.1)	460.51 $\pm$ 45.07	101 773.52 (4.0)
Simvastatin / Irbesartan / Hydrochlorothiazide / Metformin	214 (3.0)	403.90 $\pm$ 9.78	85 626.76 (3.4)
Atorvastatin / Metformin / Lisinopril / Hydrochlorothiazide	208 (3.0)	292.81 $\pm$ 25.59	60 904.09 (2.4)
Simvastatin / Amlodipine / Indapamide / Perindopril	208 (3.0)	381.14 $\pm$ 27.07	79 276.75 (3.1)
TOTAL	7 038 (100)		2 529 859.89 (100)

*The top 20 active substances were determined based on prescribing volume.

Table C.24: Top 20* “five active substances” treatment regimens for 2008

Active substance	Prevalence (n, %)	Average cost per regimen (mean $\pm$ SD)	Total treatment cost (R) (n, %)
Simvastatin / Gliclazide / Metformin / Indapamide / Perindopril	509 (14.2)	423.63 $\pm$ 34.22	215 626.34 (12.1)
Simvastatin / Gliclazide / Metformin / Enalapril / Hydrochlorothiazide	401 (11.2)	317.09 $\pm$ 22.42	127 154.38 (7.1)
Atorvastatin / Gliclazide / Metformin / Indapamide / Perindopril	245 (6.8)	479.07 $\pm$ 58.15	117 372.04 (6.6)
Simvastatin / Gliclazide / Metformin / Lisinopril / Hydrochlorothiazide	207 (5.8)	346.88 $\pm$ 55.88	71 804.45 (4.0)
Simvastatin / Metformin / Glibenclamide / Indapamide / Perindopril	199 (5.6)	386.14 $\pm$ 63.07	76 841.50 (4.3)
Enalapril / Hydrochlorothiazide / Glibenclamide / Metformin / Simvastatin	187 (5.2)	298.05 $\pm$ 36.47	55 734.74 (3.1)
Simvastatin / Metformin / Insulin / Indapamide / Perindopril	187 (5.2)	1 082.53 $\pm$ 221.61	202 434.00 (11.4)
Simvastatin / Metformin / Insulin / Enalapril / Hydrochlorothiazide	169 (4.7)	976.32 $\pm$ 306.48	164 998.72 (9.3)
Simvastatin / Amlodipine / Metformin / Indapamide / Perindopril	167 (4.7)	429.16 $\pm$ 53.35	71 669.26 (4.0)
Simvastatin / Amlodipine / Metformin / Enalapril / Hydrochlorothiazide	159 (4.4)	367.44 $\pm$ 37.71	58 423.08 (3.3)
Amiloride / Hydrochlorothiazide / Simvastatin / Metformin / Enalapril	154 (4.3)	243.14 $\pm$ 28.77	37 443.66 (2.1)
Simvastatin / Bisoprolol / Metformin / Enalapril / Hydrochlorothiazide	148 (4.1)	319.06 $\pm$ 48.65	47 221.57 (2.7)
Atorvastatin / Metformin / Insulin / Indapamide / Perindopril	138 (3.9)	1 071.91 $\pm$ 217.98	147 923.52 (8.3)
Simvastatin / Losartan / Hydrochlorothiazide / Metformin / Insulin	120 (3.4)	987.07 $\pm$ 165.25	118 448.51 (6.6)
Losartan / Hydrochlorothiazide / Gliclazide / Metformin / Simvastatin	114 (3.2)	355.20 $\pm$ 36.97	40 493.34 (2.3)
Amlodipine / Metformin / Atorvastatin / Indapamide / Perindopril	114 (3.2)	500.09 $\pm$ 34.01	57 010.51 (3.2)
Atorvastatin / Valsartan / Hydrochlorothiazide / Gliclazide / Metformin	112 (3.1)	549.33 $\pm$ 60.07	61 525.42 (3.5)
Bisoprolol / Lisinopril / Hydrochlorothiazide / Metformin / Simvastatin	89 (2.5)	358.62 $\pm$ 36.38	31 916.79 (1.8)
Atorvastatin / Glimepiride / Metformin / Indapamide / Perindopril	85 (2.4)	660.98 $\pm$ 52.51	56 183.71 (3.2)
Simvastatin / Metformin / Glibenclamide / Lisinopril / Hydrochlorothiazide	78 (2.2)	274.32 $\pm$ 47.68	21 397.04 (1.2)
TOTAL	3 582 (100)		1 781 622.58 (100)

*The top 20 active substances were determined based on prescribing volume.

Table C.25: Top 20* “six active substances” treatment regimens for 2008

Active substance	Prevalence (n, %)	Average cost per regimen (mean $\pm$ SD)	Total treatment cost (R) (n, %)
Simvastatin / Amlodipine / Gliclazide / Metformin / Indapamide / Perindopril	87 (8.8)	516.50 $\pm$ 53.43	44 935.10 (7.4)
Simvastatin / Amlodipine / Indapamide / Perindopril / Metformin / Insulin	81 (8.2)	1056.84 $\pm$ 160.82	85 604.39 (14.2)
Simvastatin / Amlodipine / Valsartan / Hydrochlorothiazide / Gliclazide / Metformin	67 (6.8)	518.98 $\pm$ 61.34	34 771.55 (5.8)
Amlodipine / Atorvastatin / Gliclazide / Metformin / Indapamide / Perindopril	60 (6.1)	592.29 $\pm$ 90.38	35 537.16 (5.9)
Simvastatin / Gliclazide / Metformin / Amlodipine / Lisinopril / Hydrochlorothiazide	59 (6.0)	444.83 $\pm$ 138.21	26 244.75 (4.3)
Simvastatin / Amlodipine / Metformin / Glibenclamide / Indapamide / Perindopril	58 (5.9)	465.63 $\pm$ 59.03	27 006.76 (4.5)
Bisoprolol / Simvastatin / Indapamide / Perindopril / Gliclazide / Metformin	57 (5.8)	493.38 $\pm$ 82.38	28 122.68 (4.7)
Bisoprolol / Indapamide / Perindopril / Gliclazide / Metformin / Atorvastatin	47 (4.8)	581.09 $\pm$ 167.32	27 311.09 (4.5)
Carvedilol / Gliclazide / Metformin / Atorvastatin / Indapamide / Perindopril	45 (4.6)	649.26 $\pm$ 87.14	29 216.72 (4.8)
Gliclazide / Lisinopril / Atenolol / Chlorthalidone / Metformin / Simvastatin	44 (4.5)	396.31 $\pm$ 51.32	17 437.81 (2.9)
Simvastatin / Amlodipine / Bisoprolol / Indapamide / Perindopril / Metformin	44 (4.5)	439.43 $\pm$ 35.33	19 335.07 (3.2)
Simvastatin / Gliclazide / Metformin / Enalapril / Bisoprolol / Hydrochlorothiazide	44 (4.5)	401.87 $\pm$ 89.40	17 682.14 (2.9)
Atorvastatin / Metformin / Bisoprolol / Amlodipine / Indapamide / Perindopril	41 (4.1)	542.64 $\pm$ 72.91	22 248.22 (3.7)
Atorvastatin / Bisoprolol / Metformin / Insulin / Indapamide / Perindopril	39 (3.9)	1 152.47 $\pm$ 183.98	44 946.49 (7.4)
Carvedilol / Gliclazide / Losartan / Hydrochlorothiazide / Metformin / Simvastatin	38 (3.8)	487.23 $\pm$ 65.94	18 514.91 (3.1)
Simvastatin / Bisoprolol / Insulin / Perindopril / Indapamide / Metformin	36 (3.6)	1 150.98 $\pm$ 178.26	41 435.17 (6.9)
Simvastatin / Bisoprolol / Metformin / Glibenclamide / Indapamide / Perindopril	36 (3.6)	468.82 $\pm$ 79.89	16 877.45 (2.8)
Amlodipine / Metformin / Simvastatin / Indapamide / Insulin / Perindopril	35 (3.5)	1 147.54 $\pm$ 190.22	40 163.93 (6.7)
Amiloride / Hydrochlorothiazide / Gliclazide / Metformin / Enalapril / Simvastatin	35 (3.5)	332.99 $\pm$ 50.87	11 654.52 (1.9)
Gliclazide / Metformin / Atorvastatin / Enalapril / Bisoprolol / Hydrochlorothiazide	35 (3.5)	418.75 $\pm$ 60.53	14 656.24 (2.4)
TOTAL	988 (100)		603 702.15 (100)

*The top 20 active substances were determined based on prescribing volume.

Table C.26: Top 20* “7-active substances” treatment regimens for 2008

Active substance	Prevalence (n, %)	Average cost per regimen (mean $\pm$ SD)	Total treatment cost (R) (n, %)
Amlodipine / Gliclazide / Metformin / Insulin / Atorvastatin / Indapamide / Perindopril	20 (6.3)	1 174.92 $\pm$ 176.79	23 498.39 (7.2)
Lisinopril / Metformin / Insulin / Atorvastatin / Amlodipine / Bisoprolol / Hydrochlorothiazide	19 (6.0)	1 931.88 $\pm$ 141.05	36 705.75 (11.2)
Simvastatin / Carvedilol / Gliclazide / Metformin / Furosemide / Perindopril / Spironolactone	18 (5.7)	751.57 $\pm$ 154.46	13 528.32 (4.1)
Simvastatin / Lisinopril / Metformin / Glibenclamide / Amlodipine / Bisoprolol / Hydrochlorothiazide	18 (5.7)	616.75 $\pm$ 109.52	11 101.57 (3.4)
Simvastatin / Bisoprolol / Valsartan / Hydrochlorothiazide / Metformin / Furosemide / Gliclazide	17 (5.4)	530.42 $\pm$ 29.67	9 017.07 (2.8)
Atorvastatin / Carvedilol / Metformin / Glibenclamide / Furosemide / Ramipril / Spironolactone	16 (5.1)	1 154.06 $\pm$ 20.10	18 464.90 (5.6)
Quinapril / Hydrochlorothiazide / Glimepiride / Carvedilol / Metformin / Atorvastatin / Felodipine	16 (5.1)	1 012.00 $\pm$ 110.46	16 192.01 (4.9)
Bisoprolol / Amlodipine / Indapamide / Perindopril / Gliclazide / Metformin / Simvastatin	16 (5.1)	477.44 $\pm$ 44.26	7 639.01 (2.3)
Simvastatin / Amlodipine / Gliclazide / Metformin / Insulin / Indapamide / Perindopril	16 (5.1)	1 227.28 $\pm$ 95.18	19 636.46 (6.0)
Simvastatin / Amlodipine / Metformin / Insulin / Perindopril / Bisoprolol / Hydrochlorothiazide	16 (5.1)	1 297.30 $\pm$ 30.79	20 756.84 (6.3)
Atorvastatin / Metformin / Glibenclamide / Felodipine / Ramipril / Bisoprolol / Hydrochlorothiazide	15 (4.8)	808.35 $\pm$ 105.40	12 125.28 (3.7)
Atorvastatin / Telmisartan / Hydrochlorothiazide / Gliclazide / Metformin / Atenolol / Chlorthalidone	15 (4.8)	642.14 $\pm$ 4.14	9 632.06 (2.9)
Simvastatin / Insulin / Furosemide / Gliclazide / Metformin / Losartan / Hydrochlorothiazide	15 (4.8)	772.12 $\pm$ 35.73	11 581.87 (3.5)
Candesartan / Hydrochlorothiazide / Carvedilol / Insulin / Atorvastatin / Enalapril / Metformin	14 (4.4)	1 970.72 $\pm$ 341.16	27 590.09 (8.4)
Furosemide / Metformin / Simvastatin / Carvedilol / Enalapril / Insulin / Spironolactone	14 (4.4)	1 070.76 $\pm$ 150.62	14 990.71 (4.6)
Simvastatin / Carvedilol / Metformin / Glibenclamide / Hydrochlorothiazide / Telmisartan / Ramipril	14 (4.4)	724.08 $\pm$ 12.10	10 137.11 (3.1)
Metformin / Atorvastatin / Indapamide / Perindopril / Gliclazide / Bisoprolol / Hydrochlorothiazide	14 (4.4)	556.90 $\pm$ 4.85	7 796.61 (2.4)
Amiloride / Hydrochlorothiazide / Candesartan / Rosuvastatin / Glibenclamide / Insulin / Metformin	14 (4.4)	1 111.57 $\pm$ 135.31	15 561.91 (4.8)
Amlodipine / Enalapril / Hydrochlorothiazide / Bisoprolol / Metformin / Insulin / Atorvastatin	14 (4.4)	1 293.95 $\pm$ 143.17	18 115.32 (5.5)
Nifedipine / Atorvastatin / Carvedilol / Losartan / Hydrochlorothiazide / Metformin / Insulin	14 (4.4)	1 654.23 $\pm$ 27.04	23 159.20 (7.1)
TOTAL	315 (100)		327 230.48 (100)

*The top 20 active substances were determined based on prescribing volume.

Table C.27: Top 20* “8-active substances” treatment regimens for 2008

Active substance	Prevalence (n, %)	Average cost per regimen (mean $\pm$ SD)	Total treatment cost (R) (n, %)
Doxazosin / Glimepiride / Bisoprolol / Gliclazide / Atorvastatin / Perindopril / Furosemide / Metformin	13 (5.4)	1 061.65 $\pm$ 91.51	13 801.43 (4.8)
Amlodipine / Simvastatin / Glimepiride / Indapamide / Perindopril / Furosemide / Metformin / Spironolactone	13 (5.4)	6 28.72 $\pm$ 3.44	8 173.38 (2.8)
Simvastatin / Carvedilol / Felodipine / Gliclazide / Enalapril / Hydrochlorothiazide / Metformin / Spironolactone	13 (5.4)	531.31 $\pm$ 161.52	6 907.09 (2.4)
Doxazosin / Simvastatin / Minoxidil / Reserpine / Metformin / Spironolactone / Felodipine / Ramipril	13 (5.4)	732.72 $\pm$ 21.14	9 525.30 (3.3)
Nifedipine / Simvastatin / Pioglitazone / Glimepiride / Metformin / Insulin / Indapamide / Perindopril	13 (5.4)	1 386.24 $\pm$ 150.54	18 021.12 (6.2)
Amlodipine / Doxazosin / Lisinopril / Insulin / Atorvastatin / Furosemide / Atenolol / Chlorthalidone	12 (5.0)	2 047.01 $\pm$ 133.37	24 564.17 (8.5)
Nifedipine / Simvastatin / Pioglitazone / Glimepiride / Metformin / Insulin / Indapamide / Perindopril	13 (5.4)	1386.24 $\pm$ 150.54	18021.12 (6.2)
Nifedipine / Valsartan / Hydrochlorothiazide / Indapamide / Perindopril / Metformin / Insulin / Atorvastatin	12 (5.0)	1 545.92 $\pm$ 32.39	18 551.01 (6.4)
Irbesartan / Rosiglitazone / Amlodipine / Carvedilol / Indapamide / Perindopril / Atorvastatin	12 (5.0)	1 183.78 $\pm$ 197.70	14 205.36 (4.9)
Amiloride / Hydrochlorothiazide / Simvastatin / Gliclazide / Metformin / Moxonidine / Bezafibrate / Lisinopril	12 (5.0)	756.30 $\pm$ 21.27	9 075.63 (3.1)
Losartan / Hydrochlorothiazide / Metformin / Glibenclamide / Insulin / Atorvastatin / Amlodipine	12 (5.0)	1 102.73 $\pm$ 160.13	13 232.74 (4.6)
Quinapril / Hydrochlorothiazide / Simvastatin / Glimepiride / Amlodipine / Doxazosin / Bisoprolol / Metformin	12 (5.0)	902.52 $\pm$ 181.14	10 830.26 (3.8)
Bezafibrate / Losartan / Hydrochlorothiazide / Gliclazide / Metformin / Indapamide / Bisoprolol / Simvastatin	12 (5.0)	947.85 $\pm$ 24.74	11 374.14 (3.9)
Nifedipine / Amiloride / Hydrochlorothiazide / Bisoprolol / Insulin / Atorvastatin / Metformin / Ramipril	12 (5.0)	1 646.94 $\pm$ 65.58	19 763.27 (6.9)
Simvastatin / Pioglitazone / Valsartan / Hydrochlorothiazide / Gliclazide / Metformin / Amlodipine / Nebivolol	12 (5.0)	929.83 $\pm$ 18.70	11 157.97 (3.9)
Carvedilol / Pioglitazone / Gliclazide / Atorvastatin / Indapamide / Perindopril / Furosemide / Metformin	12 (5.0)	703.70 $\pm$ 2.91	8 444.42 (2.9)
Atorvastatin / Bisoprolol / Irbesartan / Hydrochlorothiazide / Felodipine / Insulin / Furosemide / Moxonidine	11 (4.5)	3 356.81 $\pm$ 47.70	36 924.87 (12.8)
Bisoprolol / Bezafibrate / Ezetimibe / Glimepiride / Metformin / Atorvastatin / Captopril / Spironolactone	11 (4.5)	1 256.83 $\pm$ 18.66	13 825.1 (4.8)
Doxazosin / Bisoprolol / Indapamide / Metformin / Glibenclamide / Atorvastatin / Amlodipine / Ramipril	11 (4.5)	1 223.30 $\pm$ 268.17	13 456.29 (4.7)
Quinapril / Hydrochlorothiazide / Glimepiride / Bisoprolol / Metformin / Glibenclamide / Atorvastatin / Amlodipine	11 (4.5)	782.49 $\pm$ 149.37	8 607.39 (3.0)
TOTAL	242 (100)		288 462.06 (100)

*The top 20 active substances were determined based on prescribing volume.

Table C.28: Top 20* “9-active substances” treatment regimens for 2008

Active substance	Prevalence (n, %)	Average cost per regimen (mean ±SD)	Total treatment cost (R) (n, %)
Simvastatin / Felodipine / Losartan / Hydrochlorothiazide / Insulin / Metformin / Furosemide / Bezafibrate / Bisoprolol	12 (7.4)	3 397.05 ± 214.23	40 764.60 (14.4)
Doxazosin / Felodipine / Losartan / Hydrochlorothiazide / Metformin / Glibenclamide / Atorvastatin / Atenolol / Chlorthalidone	12 (7.4)	1 271.69 ± 97.65	15 260.24 (5.4)
Quinapril / Hydrochlorothiazide / Irbesartan / Doxazosin / Bisoprolol / Metformin / Insulin / Atorvastatin / Amlodipine	12 (7.4)	2 001.57 ± 34.92	24 018.81 (8.5)
Nifedipine / Bisoprolol / Irbesartan / Simvastatin / Metformin / Glibenclamide / Methyldopa / Furosemide / Enalapril	12 (7.4)	1 669.18 ± 242.73	20 030.14 (7.1)
Candesartan / Hydrochlorothiazide / Dihydroergocristine / Clopamide / Reserpine / Rosuvastatin / Metformin / Fenofibrate / Amlodipine	12 (7.4)	1 100.33 ± 24.09	13 203.94 (4.7)
Nifedipine / Metformin / Simvastatin / Bisoprolol / Valsartan / Hydrochlorothiazide / Glimepiride / Furosemide / Spironolactone	11 (6.8)	879.03 ± 96.29	9 669.38 (3.4)
Bisoprolol / Simvastatin / Metformin / Hydrochlorothiazide / Insulin / Furosemide / Perindopril / Glibenclamide / Eprosartan	9 (5.6)	1 978.06 ± 64.58	17 802.58 (6.3)
Glimepiride / Candesartan / Hydrochlorothiazide / Carvedilol / Metformin / Insulin / Amlodipine / Pravastatin / Spironolactone	8 (4.9)	2 234.93 ± 170.48	17 879.46 (6.3)
Atorvastatin / Carvedilol / Valsartan / Hydrochlorothiazide / Metformin / Methyldopa / Insulin / Furosemide / Prazosin	8 (4.9)	1 767.70 ± 78.03	14 141.58 (5.0)
Metformin / Carvedilol / Amlodipine / Hydralazine / Insulin / Lisinopril / Hydrochlorothiazide / Furosemide / Simvastatin	8 (4.9)	1 898.00 ± 179.35	15 184.01 (5.4)
Bisoprolol / Amiloride / Hydrochlorothiazide / Atorvastatin / Pioglitazone / Amlodipine / Gliclazide / Metformin / Losartan	7 (4.3)	560.77 ± 25.88	3 925.37 (1.4)
Amlodipine / Atorvastatin / Carvedilol / Valsartan / Hydrochlorothiazide / Insulin / Furosemide / Metformin / Spironolactone	7 (4.3)	1 748.57 ± 3.95	12 240.02 (4.3)
Amlodipine / Insulin glulisine / Simvastatin / Rosiglitazone / Doxazosin / Metformin / Insulin / Enalapril / Hydrochlorothiazide	7 (4.3)	1 665.66 ± 110.63	11 659.63 (4.1)
Simvastatin / Amlodipine / Carvedilol / Telmisartan / Hydrochlorothiazide / Glimepiride / Insulin / Furosemide / Metformin	6 (3.7)	1 548.09 ± 195.11	9 288.56 (3.3)
Rosiglitazone / Insulin / Furosemide / Atorvastatin / Indapamide / Nebivolol / Amlodipine / Lisinopril / Hydrochlorothiazide	6 (3.7)	1 983.23 ± 286.83	11 899.39 (4.2)
Nifedipine / Atorvastatin / Doxazosin / Carvedilol / Valsartan / Hydrochlorothiazide / Metformin / Insulin / Spironolactone	5 (3.1)	2 462.56 ± 15.00	12 312.82 (4.4)
Simvastatin / Irbesartan / Pioglitazone / Felodipine / Metformin / Methyldopa / Insulin / Bisoprolol / Hydrochlorothiazide	5 (3.1)	2 032.96 ± 65.76	10 164.80 (3.6)
Nifedipine / Atorvastatin / Valsartan / Hydrochlorothiazide / Bisoprolol / Metformin / Glibenclamide / Insulin / Bezafibrate	5 (3.1)	1 590.68 ± 11.17	7 953.40 (2.8)
Irbesartan / Hydrochlorothiazide / Bisoprolol / Gliclazide / Metformin / Amlodipine / Simvastatin / Eprosartan / Torasemide	5 (3.1)	1 014.75 ± 22.46	5 073.77 (1.8)
Amlodipine / Simvastatin / Carvedilol / Enalapril / Hydrochlorothiazide / Metformin / Glibenclamide / Insulin / Spironolactone	5 (3.1)	2029.32 ± 224.42	10146.61 (3.6)
TOTAL	162 (100)		282 619.11 (100)

*The top 20 active substances were determined based on prescribing volume.

Table C.29: Top 20* “10-active substances” treatment regimens for 2008

Active substance	Prevalence (n, %)	Average cost per regimen (mean $\pm$ SD)	Total treatment cost (R) (n, %)
Bisoprolol / Rosiglitazone / Gliclazide / Atorvastatin / Metformin / Indapamide / Perindopril / Furosemide / Bezafibrate / Spironolactone	10 (13.5)	1 263.91 $\pm$ 42.63	12 639.10 (10.0)
Amlodipine / Candesartan / Hydrochlorothiazide / Rosiglitazone / Doxazosin / Atorvastatin / Moxonidine / Bezafibrate / Gliclazide / Metformin	7 (9.5)	1 813.58 $\pm$ 41.08	12 695.08 (10.0)
Dihydroergocristine / Clopamide / Reserpine / Bisoprolol / Losartan / Hydrochlorothiazide / Metformin / Glibenclamide / Fluvastatin / Lercanidipine	7 (9.5)	1 133.53 $\pm$ 12.67	7 934.69 (6.3)
Glimepiride / Rosiglitazone / Captopril / Metformin / Insulin / Furosemide / Minoxidil / Moxonidine / Spironolactone / Simvastatin	6 (8.1)	2 257.27 $\pm$ 300.13	13 543.59 (10.7)
Bisoprolol / Bumetanide / Doxazosin / Amlodipine / Telmisartan / Hydrochlorothiazide / Methyldopa / Insulin / Metformin / Simvastatin	6 (8.1)	1 685.52 $\pm$ 59.19	10 113.13 (8.0)
Pioglitazone / Gliclazide / Carvedilol / Valsartan / Metformin / Insulin / Furosemide / Sotalol / Spironolactone / Simvastatin	5 (6.8)	2 419.75 $\pm$ 172.25	12 098.73 (9.5)
Simvastatin / Amiloride / Hydrochlorothiazide / Carvedilol / Amlodipine / Metformin / Insulin / Spironolactone / Trandolapril / Verapamil	4 (5.4)	1 190.81 $\pm$ 4.29	4 763.23 (3.8)
Amiloride / Hydrochlorothiazide / Simvastatin / Carvedilol / Glimepiride / Metformin / Repaglinide / Indapamide / Perindopril / Bezafibrate	3 (4.1)	1 414.80 $\pm$ 84.30	4 244.39 (3.3)
Simvastatin / Candesartan / Hydrochlorothiazide / Gliclazide / Indapamide / Perindopril / Furosemide / Hydralazine / Metformin / Lercanidipine	3 (4.1)	1 025.32 $\pm$ 0.00	3 075.96 (2.4)
Doxazosin / Glibenclamide / Insulin / Nebivolol / Amlodipine / Moxonidine / Perindopril / Metformin / Bisoprolol / Hydrochlorothiazide	3 (4.1)	1 496.22 $\pm$ 329.54	4 488.65 (3.5)
Pravastatin / Rosiglitazone / Carvedilol / Telmisartan / Hydrochlorothiazide / Ezetimibe / Gliclazide / Insulin / Amlodipine / Torasemide	3 (4.1)	2 085.60 $\pm$ 50.99	6 256.79 (4.9)
Simvastatin / Insulin glulisine / Irbesartan / Pioglitazone / Felodipine / Metformin / Methyldopa / Insulin / Bisoprolol / Hydrochlorothiazide	3 (4.1)	2 028.88 $\pm$ 35.06	6 086.65 (4.8)
Nifedipine / Simvastatin / Carvedilol / Valsartan / Metformin / Insulin / Furosemide / Perindopril / Spironolactone / Torasemide	2 (2.7)	2 456.83 $\pm$ 0.00	4 913.66 (3.9)
Simvastatin / Carvedilol / Amlodipine / Telmisartan / Hydrochlorothiazide / Insulin / Furosemide / Metformin / Indapamide / Perindopril	2 (2.7)	2 102.42 $\pm$ 0.00	4 204.84 (3.3)
Bisoprolol / Insulin / Pioglitazone / Valsartan / Hydrochlorothiazide / Gliclazide / Metformin / Insulin / Atorvastatin / Furosemide	2 (2.7)	2 521.22 $\pm$ 15.40	5 042.44 (4.0)
Insulin glulisine / Candesartan / Metformin / Pioglitazone / Amlodipine / Insulin / Perindopril / Bezafibrate / Bisoprolol / Hydrochlorothiazide	2 (2.7)	1 713.96 $\pm$ 0.79	3 427.92 (2.7)
Nifedipine / Carvedilol / Valsartan / Hydrochlorothiazide / Rosuvastatin / Ezetimibe / Metformin / Insulin / Trandolapril / Spironolactone	2 (2.7)	2 116.05 $\pm$ 5.12	4 232.10 (3.3)
Simvastatin / Amlodipine / Carvedilol / Telmisartan / Hydrochlorothiazide / Glimepiride / Insulin / Furosemide / Metformin / Spironolactone	2 (2.7)	1 669.63 $\pm$ 0.00	3 339.26 (2.6)
Bisoprolol / Pioglitazone / Perindopril / Metformin / Hydrochlorothiazide / Gemfibrozil / Amlodipine / Furosemide / Glibenclamide / Pravastatin	1 (1.4)	1 086.36	1 086.36 (0.9)

Table C.29: Top 20* “10-active substances” treatment regimens for 2008 (continued)

Active substance	Prevalence (n, %)	Average cost per regimen (mean ±SD)	Total treatment cost (R) (n, %)
Pioglitazone / Candesartan / Carvedilol / Metformin / Glibenclamide / Hydrochlorothiazide / Insulin / Furosemide / Atorvastatin / Spironolactone	1 (1.4)	2 729.31	2 729.31 (2.2)
TOTAL	74 (100)		126 915.88 (100)

*The top 20 active substances were determined based on prescribing volume.

Table C.30: Treatment regimens for 2008 containing 11 active substances

Active substance	Prevalence (n, %)	Average cost per regimen (mean ±SD)	Total treatment cost (R) (n, %)
Doxazosin / Perindopril / Rosuvastatin / Glibenclamide / Insulin / Nebivolol / Amlodipine / Moxonidine / Metformin / Hydrochlorothiazide / Bisoprolol	4 (28.6)	2 076.69 ±152.67	8 306.77 (27.6)
Insulin / Rosiglitazone / Carvedilol / Ezetimibe / Gliclazide / Metformin / Insulin / Atorvastatin / Indapamide / Perindopril / Bezafibrate	4 (28.6)	2 526.18 ± 338.36	10 104.72 (33.5)
Simvastatin / Doxazosin / Glibenclamide / Insulin / Nebivolol / Amlodipine / Moxonidine / Perindopril / Metformin / Hydrochlorothiazide / Bisoprolol	3 (21.4)	1 912.97 ±32.03	5 738.92 (19.0)
Atorvastatin / Amlodipine / Losartan / Hydrochlorothiazide / Metformin / Insulin / Glipizide / Amlodipine / Enalapril / Furosemide / Simvastatin	1 (7.1)	1 552.65	1 552.65 (5.2)
Bezafibrate / Atenolol / Chlorthalidone / Amiloride / Hydrochlorothiazide / Rosiglitazone / Metformin / Insulin / Nebivolol / Amlodipine / Prazosin	1 (7.1)	2 355.69	2 355.69 (7.8)
Doxazosin / Rosuvastatin / Glibenclamide / Insulin / Nebivolol / Amlodipine / Moxonidine / Perindopril / Metformin / Hydrochlorothiazide / Bisoprolol	1 (7.1)	2 076.05	2 076.05 (6.9)
TOTAL	14 (100)		30 134.80 (100)

Table C.31: Treatment regimen for 2008 containing 12 active substances

Active substance	Prevalence (n, %)	Average cost per regimen (mean ±SD)	Total treatment cost (R) (n, %)
Dihydroergocristine / Clopamide / Reserpine / Amlodipine / Telmisartan / Hydrochlorothiazide / Rosuvastatin / Gliclazide / Metformin / Insulin / Indapamide / Perindopril	1	1 456.93	1 456.93

Table C.32: Cohen's *d*-value for the difference in weighted average cost per treatment regimen groups

Treatment regimen group	1	2	3	4	5	6	7	8	9	10	11
Weighted average cost	163.70 ± 161.58	232.55 ± 161.72	341.74 ± 215.28	460.04 ± 272.28	610.26 ± 344.25	804.55 ± 434.54	1 033.14 ± 470.39	1 272.66 ± 530.45	1 710.44 ± 647.83	1 849.94 ± 913.77	2 152.49 ± 298.79
1	163.70 ± 161.58	-	-	-	-						
2	232.55 ± 161.72	0.4									
3	341.74 ± 215.28	0.8	0.5								
4	460.04 ± 272.28	1.1	0.8	0.4							
5	610.26 ± 344.25	1.3	1.1	0.8	0.4						
6	804.55 ± 434.54	1.5	1.3	1.1	0.8	0.5					
7	1 033.14 ± 470.39	1.9	1.7	1.5	1.2	0.9	0.5				
8	1 272.66 ± 530.45	2.1	2.0	1.8	1.5	1.3	1.8	0.5			
9	1 710.44 ± 647.83	2.4	2.3	2.1	1.9	1.7	1.4	1.1	0.7		
10	1 849.94 ± 913.77	1.9	1.8	1.7	1.5	1.4	1.1	0.9	0.6	0.15	
11	2 152.49 ± 298.79	6.7	6.4	6.1	5.7	4.5	3.1	2.4	1.7	0.7	0.3
12	1 456.93 ± 0.00	8.0	7.6	5.2	3.7	2.5	1.5	0.9	0.4	0.4	0.4

Table C.33: Prevalence of the top 10 one-chronic disease list conditions (n = 5 061)

Chronic Disease List condition	Frequency n (%)
Hypothyroidism	1 597 (32.0)
Coronary Artery Disease	956 (19.2)
Cardiac Failure	755 (15.1)
Asthma	516 (10.4)
Glaucoma	318 (6.4)
Dysrhythmias	313 (6.3)
Cardiomyopathy	261 (5.2)
Epilepsy	152 (3.0)
Chronic obstructive pulmonary disease (COPD)	59 (1.2)
Parkinson's disease	57 (1.1)
Top 10 Total	4 984 (98.5)

Table C.34: Prevalence of the top 10 combinations containing two Chronic Disease List conditions (n = 1 627)

Chronic Disease List conditions	Frequency n (%)
Cardiac Failure / Coronary Artery Disease	152 (9.3)
Cardiac Failure / Hypothyroidism	149 (9.2)
Dysrhythmias / Hypothyroidism	144 (8.9)
Coronary Artery Disease / Hypothyroidism	132 (8.1)
Asthma / Hypothyroidism	125 (7.7)
Cardiac Failure / Dysrhythmias	118 (7.3)
Cardiomyopathy / Coronary Artery Disease	78 (4.8)
Asthma / Cardiac Failure	67 (4.1)
Cardiomyopathy / Hypothyroidism	58 (3.6)
Glaucoma / Hypothyroidism	52 (3.2)
Top 10 Total	1 075 (66.1)

Table C.35: Prevalence of the top 10 combinations containing three Chronic Disease List conditions (n = 300)

Chronic Disease List conditions	Frequency n (%)
Asthma / Cardiac Failure / Hypothyroidism	24 (8.0)
Cardiac Failure / Coronary Artery Disease / Hypothyroidism	24 (8.0)
Cardiac Failure / Coronary Artery Disease / Dysrhythmia	20 (6.7)
Cardiomyopathy / Coronary Artery Disease / Dysrhythmia	15 (5.0)
Cardiac Failure / Cardiomyopathy / Coronary Artery Disease	11 (3.7)
Cardiac Failure / Glaucoma / Hypothyroidism	11 (3.7)
Cardiac Failure / Coronary Artery Disease / Asthma	10 (3.4)
Coronary Artery Disease / Cardiomyopathy / Hypothyroidism	9 (3.3)
Cardiomyopathy / Coronary Artery Disease / Asthma	8 (2.7)
Cardiac Failure / Dysrhythmia / Glaucoma	8 (2.7)
Top 10 Total	140 (46.7)

Table C.36: Prevalence of the top 10 combinations containing four Chronic Disease List conditions (n = 56)

Chronic Disease List conditions	Frequency n (%)
Cardiac Failure / Coronary Artery Disease / Dysrhythmia / Hypothyroidism	6 (10.7)
Asthma / Cardiac Failure / Dysrhythmia / Hypothyroidism	5 (8.9)
Asthma / Cardiac Failure / Dysrhythmia / Coronary Artery Disease	4 (7.1)
Cardiomyopathy / Cardiac Failure / Coronary Artery Disease / Dysrhythmia	4 (7.1)
Cardiomyopathy / Coronary Artery Disease / Dysrhythmia / Hypothyroidism	4 (7.1)
Dysrhythmia / Cardiac Failure / Hypothyroidism / Chronic Obstructive Pulmonary Disease	3 (5.4)
Cardiomyopathy / Coronary Artery Disease / Cardiac Failure / Chronic Obstructive Pulmonary Disease	2 (3.6)
Addison's Disease / Coronary Artery Disease / Epilepsy / Hypothyroidism	2 (3.6)
Asthma / Dysrhythmia / Hypothyroidism / Parkinson's Disease	2 (3.6)
Asthma / Coronary Artery Disease / Cardiomyopathy / Hypothyroidism	2 (3.6)
Top 10 Total	34 (60.7)

Table C.37: Prevalence of the top combinations containing five Chronic Disease List conditions (n = 6)

Chronic Disease List conditions	Frequency n (%)
Asthma / Cardiac failure / Dysrhythmia / Glaucoma / Hypothyroidism	1 (16.7)
Asthma / Cardiac Failure / Cardiomyopathy / Chronic Obstructive Pulmonary Disease / Dysrhythmias	1 (16.7)
Asthma / Cardiac Failure / Dysrhythmias / Glaucoma / Systemic Lupus Erythematosus	1 (16.7)
Coronary Artery Disease / Asthma / Cardiac Failure / Cardiomyopathy / Chronic Obstructive Pulmonary Disease	1 (16.7)
Coronary Artery Disease / Asthma / Cardiomyopathy / Chronic Obstructive Pulmonary Disease / Hypothyroidism	1 (16.7)
Coronary Artery Disease / Cardiac Failure / Chronic Obstructive Pulmonary Disease / Dysrhythmias / Hypothyroidism	1 (16.7)

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