Usage patterns and cost analysis of antihypertensive drugs reimbursed by the national health insurance in Gabon

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ABSTRACT

Background: The 'Caisse Nationale d'Assurance Maladie et de Garantie Sociale' (CNAMGS), the national health insurance fund was implemented since 2007, so that every Gabonese citizen has access to quality healthcare. Currently, in Gabon, little has been done regarding a drug utilisation review and its impact on drug cost and prescribing patterns.

Objective: The study aimed to review the usage patterns, and analyse the cost of antihypertensive drugs reimbursed by the CNAMGS fund.

Methods: A retrospective drug utilisation review was conducted over a 12-month period (1 June 2013 – 31 May 2014) on prescription claims data, obtained from a community pharmacy in Gabon. The study population consisted of all prescriptions (N = 51 838) containing one or more antihypertensive drugs received at the pharmacy during the period of study. Information on the prescriptions and on the costs of drugs were then reported on a data capturing form and analysed using SPSS for Windows (SPSS IBM Corp., 2013). The defined daily dose (DDD), DDDs/1000 inhabitants/day and cost/DDD were used as drug utilisation metrics. Antihypertensive drugs were classified as plain formulation for those with a single active ingredient and as fixed-dose combinations for those with two or more active substances in a single drug. Drug cost was given in Central African CFA francs (ISO 4217 code: XAF).

Results: 2 504 (1.2%) prescriptions for 1 586 patients containing 3 360 antihypertensive drugs were analysed. The majority of hypertensive patients were females (n = 1 097; 69.2%). The mean patient age was 56.53 ± 14.77 years (95% CI 55.80 - 57.26), and the majority of patients (51.4%) were between the ages 45 to 65 years old.

Most antihypertensives were prescribed by general practitioners (n = 1108, 44.2%) and specialists (n = 1 049, 41.9%) ($p < 0.0001$, Cramér's $V = 0.42$).

Plain formulations were mostly prescribed (61.7%) as compared to fixed-dose combinations (38.3%). Calcium channel blockers were the most frequently prescribed plain formulations (22.2%), followed by diuretics and potassium sparing agents (15.4%), angiotensin converting enzyme inhibitors (8.6%), beta-blockers (6.7%), central acting agents (4.0%) and angiotensin receptor blockers (3.0%). Generic equivalents represented only 6.8% (n = 228) of all antihypertensives claimed.

Antihypertensives were prescribed at 8.35 DDDs/1000 inhabitants/day for plain formulations and 4.90 DDDs/1000 inhabitants/day for fixed-dose combinations. The total cost of antihypertensive drugs amounted to 46 576 511 XAF, of which 27 217 870 XAF (58.4%) was reimbursed by

CNAMGS and the remaining 19 358 641 XAF (41.6%) was the patients' co-payments. The total cost of generic equivalents amounted to 2 117 003 XAF (4.6% of the total cost). The mean cost for a prescription for an antihypertensive drug reimbursed by CNAMGS was 10 870 ± 7 617 XAF (95% CI, 10 571 – 11 168); in which angiotensin receptor blockers appeared to be the most expensive (cost/DDD = 476.9).

Diuretics and beta-blockers as plain formulations had the lowest cost/DDD ratios, at 199.8 and 191.7, respectively. These drugs were, therefore, less expensive than other antihypertensives in the study, such as angiotensin converting enzyme inhibitors (cost/DDD = 302.9), angiotensin receptor blockers (cost/DDD = 476.9), calcium channel blockers (cost/DDD = 301.8), central acting agents (cost/DDD = 315.9) and even fixed-dose combinations (cost/DDD = 439.3). It was deducted that generic substitution of captopril and amlodipine could have led to a potential saving of 0.9% and 4.5% of the total cost of angiotensin converting enzyme inhibitors and calcium channel blockers, respectively. The overall substitution where generic equivalents were available could have led to a potential saving of 4.8%, the total cost of all antihypertensives claimed during the period of study (2 246 594 XAF), or 1 313 009 XAF would have been saved by CNAMGS.

Conclusion and recommendations: Diuretics as first-line therapy are less expensive for the treatment of hypertension. The CNAMGS fund has the potential to decrease medicine cost through promotion of generic prescribing and dispensing.

Key terms: Caisse Nationale d'Assurance Maladie et de Garantie Sociale (CNAMGS), Gabon, antihypertensive drugs, Defined daily dose (DDD), DDD/1000 inhabitants/day, cost/DDD, drug utilisation review, generic substitution

UITTREKSEL

Agtergrond: Die "Caisse Nationale d'Assurance Maladie et de Garantie Sociale" (CNAMGS), die nasionale gesondheidsversekeringfonds is sedert 2007 geïmplementeer, sodat elke inwoner van Gaboen tot kwaliteit gesondheidsorg toegang het. Tans is daar weinig in Gaboen gedoen met betrekking tot medisyneverbruiksevaluering en die impak daarvan op geneesmiddelkoste en voorskryfpatrone.

Doelwit: Die studie het ten doel om die verbruikspatrone te evalueer en die koste van antihipertensiewe middels wat deur die CNAMGS fonds vergoed word, te ontleed.

Metodes: 'n Retrospektiewe medisyneverbruiksevaluering is uitgevoer op voorskrif-eisedata, van 'n 12-maande tydperk (1 Junie 2013 tot 31 Mei 2014), verkry uit 'n gemeenskapsapteek in Gaboen. Die studiepopulasie het bestaan uit alle voorskrifte (N = 51 838) wat een of meer antihipertensiewe geneesmiddels bevat, wat gedurende die studietydperk by die apteek ingedien is. Voorskrifinligting en geneesmiddelkoste is met behulp van 'n data-opname-vorm versamel en met behulp van ”SPSS for Windows” program (SPSS IBM Corp., 2013) ontleed. Die gedefinieerde daaglikse dosis (DDD), DDD/1000 inwoners/dag en koste/DDD is gebruik as medisyneverbruiksmaatstawwe. Antihipertensiewe middels met 'n enkele aktiewe bestanddeel is geklassifiseer as eenvoudige formulerings en dié met twee of meer aktiewe bestanddele in 'n enkele produk as ’n vaste dosis kombinasie. Geneesmiddelkoste is gegee in Sentraal-Afrikaanse CFA-frank (ISO 4217-kode: XAF).

Resultate: 'n Totaal van 2 504 (1.2%) voorskrifte vir 1 586 pasiënte wat 3 360 antihipertensiewe middels bevat het, is ontleed. Die meerderheid hipertensiewe pasiënte was vroue (n = 1 097; 69.2%). Die gemiddelde ouderdom van pasiënte was 56.53 ± 14.77 jaar (95% VI, 55.80 – 57.26), en die meeste pasiënte (51.4%) was tussen die ouderdomme 45 tot 65 jaar oud. Die meerderheid antihipertensiewe middels is deur algemene praktisyns (n = 1108, 44.2%) en spesialiste voorgeskryf (n = 1 049, 41.9%) ($p < 0.0001$, Cramér's $V = 0.42$).

Eenvoudige formulerings is die meeste voorgeskryf (61.7%) in vergelyking met vaste dosis kombinasies (38.3%). Kalsiumkanaalblokkeerders was die mees voorgeskrewe eenvoudige formulerings (22.2%), gevolg deur diuretika en kaliumsparende middels (15.4%), angiotensien-omskakelingsensiem-inhibeerders (8.6%), beta-blokkeerders (6.7%), sentraalwerkende middels (4.0%), en angiotensien-reseptoreblokkeerders (3.0%). Generiese ekwivalente het slegs 6.8% (n = 228) van alle antihipertensiewe middels wat geëis was, verteenwoordig.

Antihipertensiewe middels is voorgeskryf teen 8.35 DDDs/1000 inwoners/dag vir eenvoudige formulerings en 4.90 DDDs/1000 inwoners/dag vir vaste dosis kombinasies. Die totale koste van

antihipertensiewe middels het 46 576 511 Sentraal-Afrikaanse franke CFA XAF beloop, waarin 27 217 870 XAF (58.4%) deur CNAMGS vergoed is en die oorblywende 19 358 641 XAF (41.6%) bybetalings van die pasiënte was. Die totale koste van generiese ekwivalente het 2 117 003 XAF (4.6% van die totale koste) beloop. Die gemiddelde koste van 'n voorskrif vir antihipertensiewe middels wat deur CNAMGS terugbetaal is, was 10 870 ± 7 617 XAF (95% VI, 10 571 – 11 168); waarvan angiotensien-reseptorblokkeerders die duurste items was (koste/DDD = 476.9 XAF).

Diuretika en beta-blokkeerders as eenvoudige formulerings het die laagste koste/DDD verhoudings gehad, onderskeidelik 199.8 en 191.7. Hierdie geneesmiddels was dus goedkoper as ander antihipertensiewe geneesmiddels in die studie, soos angiotensien-omskakelingsensiem-inhibeerders (koste/DDD = 302.9), angiotensien-reseptorblokkeerders (koste/DDD = 476.9), kalsiumkanaalblokkeerderss (koste/DDD = 301.8), sentraalwerkende middels (koste/DDD = 315.9) en ook vaste dosis kombinasies (koste/DDD = 439.3). Daar is tot die gevolgtrekking gekom dat generiese vervanging van kaptopril en amlodipien tot 'n potensiële besparing van 0.9% en 4.5% van die totale koste van onderskeidelik angiotensien-omskakelingsensiem-inhibeerders en kalsiumkanaalblokkeerderss kon lei. Die algehele vervanging met generiese ekwivalente kon tot 'n moontlike besparing van 4.8% (n = 2 246 594 XAF) van die totale koste van alle antihipertensiewe middels wat gedurende die studietydperk geëis is, gelei het, of dan 1 313 009 XAF betaalbaar deur die CNAMGS fonds.

Gevolgtrekking en aanbevelings: Diuretika as eerste linie terapie is goedkoper vir die behandeling van hipertensie. Die CNAMGS fonds het die potensiaal om medisynekoste te verminder deur die bevordering van generiese voorskryf en reseptering.

Sleutelterme: Caisse Nationale d'Assurance Maladie et de Garantie Sociale (CNAMGS), Gaboen, antihipertensiewe middels, gedefinieerde daaglikse dosis (DDD), DDD/1000 inwoners/dag, koste/DDD, medisyneverbruiksevaluering, generiese vervanging

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LIST OF ABBREVIATIONS

ASMR	Amélioration du service médicale rendu (Improvement in actual benefit)
CDR	Common Drug Review
CEDAC	Canadian Expert Drug Advisory Committee
CMS	Center of Medicare and Medicaid service
CNAMGS	Caisse Nationale d'Assurance Maladie et de Garantie Sociale (Health Insurance and Social Guarantee Fund)
CNSS	Caisse National de Sécurité Social (National Social Security Fund)
CT	Commission of Transparency
GEF	Gabonais Economiquement Faible (Gabonese with low Income)
GNDP	Ghana National Drug Policy
HAS	Haute Autorité de Santé (French National Authority for Health)
HPFB	Health Products and Food Branch
IMF	International Monetary Fund
MMA	Medicare Modernization Act
MOH	Ministry of Health
MOHPH	Ministry of Health and Public Hygiene
MOHPH	Ministry of Health and Public Hygiene
MSH	Management Science for Health
MSHP	Ministère de la Sante et de l'Hygiène Public
NDP	National Drug Policy
NEDLC	National Essential Drug List Committee
NHI	National Health Insurance
NHIP	National Health Insurance Program
NOC	Notice of Compliance
NOC/c	Notice of compliance with condition

OHSC	Office of Health and Standards Compliances
PNDS	Plan National de Développement Sanitaire, (Gabon National Health Developement Plan)
PTC	Pharmacy and Therapeutic Committee
ROAM	Redevance Obligatoire à l'Assurance Maladie (Compulsory Health Insurance Levy)
SMR	Service medicale rendu (Actual benefit)
UHC	Universal Health Coverage
UN	United Nations
WDI	World Development Indices
WHO	World Health Organization
XAF	Communauté Financière Africaine franc (Currency for the Central African franc (CFA))

CHAPTER 1 STUDY OVERVIEW

1.1 Background

Located on the equator, the Republic of Gabon (hereafter referred to as 'Gabon') is a west central African country with an area of 267 667 square kilometres. The largest city, Libreville, is Gabon's capital. The Gabonese population is estimated at about 1.881 million citizens (IMF, 2017), with 37.6% (707 000 inhabitants) of the population residing in Libreville (Musango & Inoua, 2010; UN, 2017). Gabon has nine provinces, divided into 49 departments; the country has 10 Regional Health Directorates (Directions Régionales de Santé, DRS) and the Estuary Department is split into two DRS, namely Libreville-Owendo and Ouest (Saleh *et al*., 2014).

Gabon is an upper-middle-income country. The economy is mostly dependent on the extraction of primary materials such as oil, logging and manganese. Extraction of oil represents more than half of the Gabonese government's revenue; the recent decline in oil prices, therefore, presents a major challenge for the country's economy (IMF, 2016). Consequently, poverty and unemployment remain an issue in Gabon (IMF, 2016). In order to increase fiscal saving and make its economy less vulnerable to oil price volatility, Gabon's authorities have established several reforms and a public investment plan (i.e. the "Gabon emergent" strategic plan or the Plan Stratégique Gabon Emergent) so that by 2025, its economy will be diversified with more employment opportunities (IMF, 2016).

The Ministry of Health and Public Hygiene of Gabon (MOHPH) has prepared a National Health Development Plan (2011-15) (MOHPH, 2010) that is committed to achieve universal health coverage for everyone who needs health services at affordable prices, no matter their socioeconomic status. In 2007, the Gabonese government expanded health coverage through the National Insurance and Social Welfare fund called "Caisse Nationale d'Assurance Maladie ET de Garantie Sociale" (CNAMGS), to the economically challenged citizens of Gabon (Musango & Inoua, 2010). The national health insurance (NHI) coverage includes normal consultations, laboratory tests, hospitalisations and medicines (Musango & Inoua, 2010). The NHI has a mandate to provide public funds for both public and private healthcare, meaning that CNAMGS purchases services covered by its benefits package from accredited public and private health providers, clinics, hospitals and selected drugs from accredited pharmacies, therefore, 92% of public and 80% of private facilities in Libreville are working with the NHI (Saleh *et al*., 2014).

Pharmaceutical spending in Gabon has grown since the inception of the National Health Insurance Program (NHIP) (Saleh *et al.,* 2014). According to Saleh *et al*. (2014), this increase may be due to the introduction of the NHI because more people utilise hospitals, more frequently, subsequently causing a huge demand of health services and medicine. According to Article 7 by

Gabon Ministerial Order No 00021 (Decree no 0079 of October 2008), a list of drugs that are supposed to be reimbursed by the NHI was established (CNAMGS, 2016). This list of drugs is revised every two years. In 2012, 60% of the list consisted of generic equivalents (Inoua & Musango, 2013:18). Public and private healthcare institutions working with the NHI should, prioritise drugs that are on the list for any medical condition before using other drugs that are available in the market.

To date, cardiovascular diseases have caused about 17 million (~31%) of global deaths a year, of which 9.4 million were due to complications of high blood pressure (Mendis, 2013:1; World Health Organization ([WHO], 2013:9). In Gabon, 36% of the leading cause of deaths is due to non-communicable diseases (NCDs), in which cardiovascular diseases represent 16%, compared to diabetes (2%), chronic respiratory diseases (4%) and other NCDs (11%) (such as non-malignant neoplasms, endocrine, blood and immune disorders; sense organ, genito-urinary and skin diseases; oral conditions and congenital digestive anomalies) (WHO, 2014a).

According to the WHO (2013:10), in 2008, about 40% of adults around 25 years old were affected by hypertension; subsequently, 1 billion people in 2008 were diagnosed with uncontrolled blood pressure, compared to 600 million in 1980. The prevalence of hypertension in Africa is estimated at 35% in some communities, in which the number of people with elevated blood pressure is estimated between 10 to 20 million, with over 650 million people in Sub-Saharan Africa (Guwatudde *et al.,* 2015:2). It was estimated that in the year 2000, more than 80 million people suffered from hypertension in sub-Saharan Africa and it is predicted that more than 150 million Africans will have hypertension by 2025 (Cappuccio & Miller, 2016:300; Van de Vijver *et al.,* 2013). To date, the prevalence of hypertension is increasing (Siawaya *et al.,* 2014) and is the leading cause of cardiovascular diseases in Gabon (with 37% of the population affected) (Oxford Business Group*,* 2014). According to Miller *et al*. (1962) (quoted by Bukhman and Kidder, 2008:50), hypertension or hypertensive heart disease accounted for 7% of the prevalence of cardiovascular diseases in Lambaréné, Gabon, during the early 1960s. More recently, Mipinda *et al.* (2013:137) determined a prevalence rate of 51.8% for males and 48.2% for females in a study conducted at the Centre Hospitalier de Libreville in 2011. Based on this, hypertension is becoming a major public issue.

Hypertension, defined as a "*systolic pressure of about 140 mmHg at rest and a diastolic pressure of 90 mmHg or more*" (WHO, 2013:20), is a major risk factor for the development of cardiac and renal failure, cerebrovascular diseases, ischemic heart diseases and stroke, which may lead to organ damage (e.g. brain and kidney disease) (Drozdz & Kawecka-Jaszez, 2014:1507; WHO, 2003:21). The higher the blood pressure, the greater the risks (Beers *et al*., 2006:144). Malignant hypertension or a hypertensive crisis may also develop as a result of persistently severe raised high blood pressure and may cause progressive organ damage (Vaidya & Ouellette, 2007:43).

About 1 in 200 people with hypertension may suffer from a hypertensive emergency; this is more common among Africans (80%) than Caucasian patients (~20%), among men than women, and among people in lower socio-economic groups (Beers *et al*., 2006:145; Vaidya & Ouellette, 2007:44). This can be due to urbanisation; according to Steyn (2006:83-84), urbanisation independently predicted the presence of hypertension and is related to an increase in blood pressure. The THUSA study (Van Rooyen *et al*., 2000:779) that particularly paid attention to the factors related to high blood pressure in a black community in South Africa undergoing transition, found that factors related to urbanisation were positively associated with elevated blood pressure. The most important of these included bad eating habits (with the intake of high quantities of fat, animal proteins and salt) and obesity (Van Rooyen *et al*., 2000:779). Age is also associated with elevated blood pressure because of an increase in vascular resistance and stiffness sometimes occurring in elderly, characterised by a drastic decrease of nitric oxide and an increased activity in endothelin-1 (Camici *et al*., 2009:134; Foëx & Sear, 2004:72). Hypertension is thus very common in older people (Schwinghammer, 2011:104).

Based on the 2003 World Health Organization and International Society of Hypertension (WHO/ISH) guidelines (Whitworth, 2003:1983); managing hypertension involves lifestyle modifications and drug therapy. Lifestyle modifications consist of reducing body weight if overweight, exercising, reducing alcohol intake, smoking cessation and having a healthy diet with fresh fruits, vegetables, reduced fat and salt (WHO, 2013:32). Studies have shown a positive impact of physical activity, healthy diet and smoking cessation on lowering blood pressure and enhancing longevity; as illustrated by Buttar *et al.* (2005:244); smoking cessation reduces coronary arterial disease by 50% and daily exercise reduces systolic blood pressure by 8 mmHg. Furthermore, modest weight loss may prevent risk of hypertension by 20% in overweight people; decreasing weight by 5 kg may further reduce systolic blood pressure by 4.4 to 5.8 mmHg and diastolic blood pressure by 3.6-15.9 mmHg (Appel *et al*., 2006:297; Hollis *et al*., 2008:124). Adhering to effective lifestyle modifications is optimal, and then will reduce systolic blood pressure by 10 mmHg (Whitworth, 2003:1984). Drug treatment is needed though for the great majority of patients with essential hypertension, patients with comorbidities and other risk factors, and for those in whom blood pressure does not fall to normal after correction of any identifiable cause. The purpose of drug therapy is to maintain the level of blood pressure to below 140/90 mmHg (Seedat *et al*., 2014:290).

Most drugs used to treat hypertension have also been evaluated for a number of specific indications in patients with concomitant diseases such as diabetes, nephropathy, coronary and cerebrovascular disease, heart failure and left ventricular hypertrophy (Schwinghammer, 2011:104). For example, it has been proven through several clinical trials and essays that treating hypertension reduces the risk of developing a stroke by ~40%, myocardial infarction by ~20% and

heart failure by ~50% (Antonakoudis *et al.,* 2007:114; Karnes & Cooper-DeHoff, 2009:2; Whitworth, 2003:1986; WHO, 2003:21).

Although drug therapy has brought benefits in treating hypertension over the world, hypertension and other cardiovascular conditions remain a major threat to the global economy (Narayan *et al*., 2010:1198). The cost of treating hypertension may be enormous if complications such as stroke and heart failure occur, along with comorbidities when taken into account; even though these conditions are preventable, uncontrolled blood pressure, inadequately treated blood pressure and lower compliance will have a major impact on the cost of treating blood pressure (Elliot, 2003:S6).

The World Health Organization recommends that countries should spend no more than 5% of its gross domestic product (GDP) on health (Savedoff, 2007). In terms of this recommendation, Gabon performs well, compared to other upper middle-income countries within the African region concerning its health spending as part of its GDP. For example, according to the World Bank (2017), Gabon spent ~3.5% of its GDP (healthcare spent as percentage of GDP) in 2014 on health, compared to Algeria at 7.2%; Botswana at 5.4%; Lesotho at 10.6%, Libya at 5.0%; Namibia at 8.9%, South Africa at 8.8% and Tunisia at 7.0%. However, in 2013 pharmaceutical spending was estimated at XAF 71.85 billion ($147 million); drugs in Gabon thus represented 24% of total health spending in 2013 (Saleh *et al*., 2014:56). Gaziano *et al.* (2009:1472) reported that the cost of hypertension was estimated at US$ 370 billion in 2001 worldwide, this amount represented 10% of the healthcare expenditure; subsequently it was deducted that over a ten-year period, the cost would grow to US$ 1 trillion. Gaziano *et al.* (2009:1472) further emphasized that if measures were not taken to control the development of high blood pressure, the indirect cost could reach US$ 3.6 trillion each year. Hypertension care expenditure reached $42.9 billion in United States of America in 2010 for instance, in which prescription drugs accounted for $20.4 billion (Davis, 2012). Scarcity of health facilities and the cost of elevated blood pressure medications in some developing countries, particularly in Sub-Saharan Africa, make the treatment and management of hypertension difficult to control (Cappuccio & Miller, 2016:303). As a result, strategies should be implemented to limit the impact of blood pressure among the population. Therefore, in order to develop a good strategy for hypertension management, pharmacoeconomic analyses may be a useful tool for deciding on the appropriate drug therapy and its cost (Elliot, 2003:S3).

High blood pressure has become an important societal issue, it is the major cause of disability and premature death and patient's compliance to hypertension remains poor, therefore, and awareness should be improved among healthcare providers, the public and individuals with hypertension (Chockalingam *et al*., 2006:554). For a more efficient use of limited healthcare resources, drug utilisation review (DUR) studies are recommended (AMCP, 2009). A retrospective drug utilisation review (rDUR) is conducted when patient prescriptions and

medications data are reviewed after receiving treatment. Therefore, this type of review is used for interpreting data, understanding and improving drug prescribing, administration and usage (Navarro, 2008:215). Retrospective DUR programs may be useful in improving drug therapy for chronic conditions such as hypertension (Navarro, 2008:215). Using rDUR for this study will assist the National Health Insurance and Social Welfare Fund (i.e. CNAMGS) to improve prescribing patterns among antihypertensive drugs and to raise awareness on the use, administration and cost of these medicines.

Pharmacists, as members of healthcare teams, have more knowledge in drug therapy management and are aware of trends that occur in drug prescribing regarding disease conditions such as hypertension; therefore, to improve drug therapy pharmacists should work with prescribers (Navarro, 2008:217). The NHI provides a comprehensive benefits package that has a list of included and excluded services, therefore the NHI favours clinical care, promotes the use of generic equivalents (or brand name drugs if generic equivalents are not available) and the use of medicines from the National Essential Medicine list (Saleh *et al*., 2014). However, a list of covered drugs includes different classes of available antihypertensive drugs (brand name and generic equivalents). Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, vasodilators, diuretics and alpha-blockers are among these drugs (CNAMGS, 2016).

1.2 Problem statement

Although treating hypertension has also been shown to enhance life, it remains inadequately managed (WHO, 2003:21). According to Taty *et al*. (2001:1), hypertension is the leading cause of cardiovascular diseases in Gabon, affecting one in six individuals over the age of 40 years and there is an increase in the burden of the disease (Ngoungou *et al.*, 2012:77).

Drug treatment for elevated blood pressure, as stated previously, has been related to a reduction in the development of stroke and myocardial infarction, but still the cost and the ease of adhering to treatment should also be considered (Cappuccio & Miller, 2016:303). High blood pressure and its complications are major issues for the African economy and will cost the continent a lot of money in the next ten years; despite the presence of less, expensive and effective drug therapy on the market. Prescribing trends such as combination therapy and the development of newer drugs still make the treatment of hypertension expensive (Van de Vijver *et al.,* 2013:38). Therefore, the following questions were formulated for the study:

- What criteria do NHI use in the selection of drugs for hypertension?
- What are the usage patterns of antihypertensive drugs reimbursed by the NHI?

- What is the cost of antihypertensive drugs reimbursed by the NHI?

1.3 Research aim and objectives

The research project has a general aim and specific objectives.

1.3.1 General research aim

The primary aim of this research was to review the usage patterns, and analyse the cost of antihypertensive drugs reimbursed by the National Health Insurance and the Social Welfare Fund (Caisse Nationale d'Assurance, de Maladie et Garantie Sociale or CNAMGS), over a 12-month period, from June 2013 to 01 June 2014.

1.3.2 Specific research objectives

The study consisted of a literature review and an empirical investigation. The specific research objectives for the study included the following:

- To review the background and history of the CNAMGS.
- To compare drug selection criteria of the CNAMGS to that of other Social Health Insurance plans in other international countries.
- To conceptualise the classification, use and management of hypertension.
- To analyse the prescribing patterns of antihypertensive drugs stratified according to age, gender and prescribing health professional, using prescriptions in a private pharmacy situated in Libreville, Gabon.
- To determine the cost of all antihypertensive drugs prescribed from the CNAMGS prescriptions in a private pharmacy situated in Libreville, Gabon.
- To determine potential cost savings through generic substitution for antihypertensive drugs, using prescriptions in a private pharmacy situated in Libreville, Gabon.

1.4 Research methodology

1.4.1 Literature review

The literature review is all the written sources relevant to the topic of interest; a literature review involves finding, reading, understanding and forming a conclusion about the published research and theory as well as presenting it in an organised manner (Brink *et al.,* 2012:71). Rocco and Plakhotnik (2009:125) emphasised that a literature review's main purpose is to establish the

importance of the current study; therefore, new ideas are brought into the problem statement and explored. The literature review is part one of the research process. Relevant articles identified during the Boolean search for this study will be reviewed by a standard narrative review.

Resources identified for this literature review, include databases available through the North-West University (Potchefstroom Campus) Library system such as ScienceDirect® and Scopus®. Sources such as the internet (Google Scholar®), MedLine, books and handbooks from the World Bank Group, the World Health Organization's website, articles from the newspaper, and articles from the Minister in charge of Health and Social Security of Gabon, through the internet. Keywords that were used separately and in combination, included Caisse National d'Assurance, de Maladie et Garantie Sociale or CNAMGS; Social or National Health Insurance; hypertension; antihypertensive(s); hypertension and management or treatment; hypertension and gender; hypertension and age; medicine claims data; prevalence; drug utilisation; and medicine(s) review.

1.4.2 Empirical investigation

Brink *et al*. (2012:56) defines the empirical investigation as a process that relies on the type of study design and the population sample, therefore, involving setting, target population, data source, data collection source, study population and data analysis plan.

In this study, a quantitative, retrospective drug utilisation review of antihypertensive drugs prescribed for people on the CNAMGS over a 12-month period (1 June 2013 to 31 May 2014), was performed. The empirical investigation took place in a private pharmacy situated in Libreville, Gabon. The empirical investigation is discussed in detail in Chapter 3 of this dissertation.

1.5 Ethical considerations

A researcher is responsible for conducting research in an ethical manner from the conceptualisation and planning phases, through the implementation phase, to the dissemination phase (Brink *et al.,* 2012:32). This study was rigorously carried out and resources were managed with respect and integrity.

1.5.1 Permission

Permission to use the prescription claims data for this research was obtained from the pharmacy manager of the pharmacy where the dispensing of the medicine took place (refer to Annexure A). The research was further approved by the Health Research Ethics Committee (HREC) of the North-West University (Potchefstroom Campus) (Ethics number: NWU-00200 15-A1) (Annexure B).

1.5.2 Anonymity and confidentiality

Anonymity was assured by not capturing the patients' names, addresses or CNAMGS membership numbers. Each prescription analysed was given a number, and only this number was recorded on the data collection tool to ensure the privacy and confidentiality of the patient.

Data were captured electronically by the researcher only. Data analysis and report writing was based on the data collection tool only, which does not contain the link to individual patients. The pharmacy name was kept confidential.

1.5.3 Respect for research participants

Records serve as an economical source of information, they permit an examination of trends over time, and they eliminate the need for the researcher to seek cooperation from participants (Brink *et al*., 2012:161). Data were collected from CNAMGS prescriptions, sorted by hand and recorded on a data capturing form (excel sheet). Prescriptions were accessed retrospectively, with no direct contact with the study participants and no active intervention by the researcher.

1.5.4 Benefit-risk ratio analysis

Before beginning the study, the ratio between the benefits and the risks involved were reviewed. In this research project, the usage patterns of antihypertensive drugs, reimbursed through CNAMGS, using the drug utilisation review is a benefit for the healthcare system in Gabon, and the risk of doing the research does not exceed the potential benefits to be gained by the study since no harm is caused to the participants and the researcher. The research was categorised as minimal risk (refer to Annexure B).

1.6 Division of chapters

The division of chapters in this dissertation is as follows:

- Chapter 1: Study overview
- Chapter 2: Literature review
- Chapter 3: Research methodology
- Chapter 4: Results and Discussion
- Chapter 5: Conclusions and Recommendations

1.7 Chapter summary

This research project aimed to review the usage patterns and analyse the cost of antihypertensive drugs reimbursed by the National Health Insurance and the Social Welfare Fund of Gabon (Caisse Nationale d'Assurance Maladie et de Garantie Sociale or CNAMGS) over a 12-month period from 1 June 2013 to 31 May 2014. To conclude, Chapter 1 provided an overview, the problem statement and ethical considerations. The following chapter is a comprehensive literature review pertaining to the objectives of the literature phase of the study.

CHAPTER 2 LITERATURE REVIEW

2.1 Introduction

This chapter contains the background information gathered during the literature review. The specific objectives of the literature review were to review the background and history of the CNAMGS; to compare the CNAMGS to other Social Health Insurance systems in other international countries; and to conceptualise the classification, use and management of hypertension.

2.2 Background and history of the healthcare system in Gabon

The Gabonese Constitution of 1991 as consolidated to Law no 13/2003 of 19 August 2003, enshrines in Article 1 and paragraph 8, the right to health and social protection of Gabonese, guaranteed by the state (UN, 2014:31). Gabon's health strategy is centred on heavy investment by providing Universal Health Coverage (UHC). The Minister of Health and Public Hygiene (MOHPH), under the 'Plan National de Développement Sanitaire' (PNDS), 2010, has made an effort to improve service quality and expand hospital capacity (Oxford Business Group, 2014). For instance, the Ministry of Health (Ministère de la Santé, MS) of Gabon has carried out a renovation programme focused on Libreville, and more than 319 beds have already been added to two health facilities (Oxford Business Group, 2014). As a consequence, to date, hospital beds have increased from 1.3 hospitals beds per 1000 people in 2008 to 6.3 hospital beds per 1000 people in 2010 (World Bank, 2016). This will improve the health and welfare of the population; and has led to the construction and equipping of health facilities, training human resources and the mobilisation of financial resources for the health sector, therefore, the country aims to achieve universal health coverage as well as enhance the quality of care (Saleh *et al*., 2014).

Gabon's healthcare facilities are widely regarded as being generally good, compared to the rest of West Africa (KPMG, 2012). However, Gabon's health system has an average of 0.3 physicians per 1 000 citizens, with about 10% of residents not having easy access to medical facilities (Saleh *et al.,* 2014). The World Health Organization (2007:3) stated that, *"…a well-functioning health system ensures equitable access to essential medical products, and makes sure of quality, safety and cost effectiveness of medicines"*. In Gabon, more than 83 retail pharmacies are approved by CNAMGS (Mbeng Mendou, 2012). Medications and pharmaceutical products are generally mass produced in Libreville or imported (Saleh *et al.,* 2014; WHO, 2014a). In most central African countries, public, private and non-governmental organisations co-exist as a channel of distribution for medicines, since most of countries from this area have no local manufacturers (Yadav *et al.,* 2011). In Gabon for instance, for the public sector, most of the drugs are procured and distributed to public health facilities through a procurement agency called the 'Office Pharmaceutique

National' (OPN) (Saleh *et al.,* 2014). For the private sector, distribution and stockholding of drugs are carried out through two licensed wholesalers (i.e. Ubipharm and Pharma Gabon) and some licensed pharmacies, enabling retail pharmacies and other drug stores to be supplied with products that they require to meet their daily needs.

Pharmaceutical spending has grown significantly or has almost doubled in 2012 in Gabon since the implementation of CNAMGS (Saleh *et al.,* 2014); this could lead to a shortage of medicines due to high demands if there is a poorly designed distribution system and high prices. Medicines in Gabon are not widely available due to poor stock management and high prices, beside a national pharmaceutical plan and an available essential drug list (MOHPH, 2010). There are not enough qualified human resources to do drug procurement, management and distribution; furthermore, there is no quality control laboratory for medicines; as a consequence, there are many illicit and counterfeit drugs on the market (MOHPH, 2010). An ineffective or poorly designed distribution system is likely to cause stock-outs at health facilities, and make medicine system supply more complex (Yadav *et al*., 2011). Reforms brought to the pharmaceutical sector and the implementation of CNAMGS may, therefore, increase access to good medicines at reasonable prices (MOHPH, 2010). With the prevalence of high blood pressure and the aging population, health systems should implement reforms toward higher sustainability, such as maintaining the NHI (Gregório *et al*., 2017:13). Community pharmacy, because of its proximity and accessibility, plays a major role in primary healthcare, particularly for patients seeking health advice and information on minor ailments, the supply and the use of their medications. Therefore, with the large prescribing of antihypertensive drugs on NHI, keeping patients' records has become important, particularly for reimbursement. Evidence has shown that many low and middle-income countries keep on looking for different ways of financing their health system because of limited resources (Dalinjong & Laar, 2012). Since the implementation of CNAMGS in 2007, private pharmacies in Gabon have been faced with several challenges that have threatened their sustainability. Limited human and financial resources remain a huge problem for these pharmacies.

The average life expectancy for men and women was about 59.5 years in 2005, but has increased to 64 years in 2011 (World Bank, 2016). This increase can be explained by the improvement of health facilities and implemented health-related measures such as the NHI for instance (Novignon *et al.,* 2012:22).

The healthcare system in Gabon comprises a public and civil health sector (public hospitals), the military health sector (military hospital), a non-profit (such as Centre International de Recherche Medicales de Franceville "CIRMF," Albert Schweitzer, and Bongolo Hospitals, non-governmental organisation structures), a profit private health sector (polyclinics and clinics) and the traditional sector (e.g. traditional medicine and traditional healers) (Vaughan *et al.,* 2014).

The health sector in Gabon accounts for 5% of the state budget (MOPH, 2010b:19). Therefore, financing of healthcare was estimated at 3.5% of GDP in which health expenditure per capita was estimated at US$735 in 2013 (WHO, 2013). Before CNAMGS, the financing of healthcare was estimated at 6% of national funding; in which health expenditure per capita was estimated at US$127. This money was collected by the CNSS (National Social Security Fund) and was taken based on contributions representing the wage share (2.5%) on the one hand for employees and the employer's contribution (4.1%) on the other (Musango & Inoua, 2010). Depending on their socio-economic status, patients could be directed towards public health facilities where care was more or less free, and where access to medicines or generic equivalents was limited and other, more affluent patients were moving toward private health facilities.

In 2007, the Gabonese Government implemented an NHI fund to cover unemployed nationals, low resources citizens, farmers and those that were self-employed. The Government then expanded coverage to public sector workers in 2011, and private sector workers in 2013 (Humphreys, 2013:318-319).

2.2.1 The National Health Insurance

Following Gabon Law (13/2007 of July 2007), medical aid is compulsory for all citizens living in the country. As such, the President of the Republic, by order (0022 / PR / 2007 of 21 August 2007), introduced a compulsory medical scheme that management has entrusted to a fund, called ‘Caisse Nationale d’Assurance, de Maladie et de Garantie Sociale’ (CNAMGS, 2016).

The purpose of the National Health Insurance is to meet the challenges faced by the Gabonese people to access quality healthcare. This health insurance has a very broad scope as it covers: public sector employees, members of the constitutional institutions, the private sector employees, employees of the State or public administrations, self-employed, pensioners of private and public sector, ministers, pupils and students, economically disadvantaged Gabonese, foreign independents and refugees (Humphreys, 2013:318-319). Management of CNAMGS entitled a public autonomous organisation under the supervision of the Ministry of Health and Social Welfare. There is a board of directors and 16 representatives from private and public sectors. In addition to this, CNAMGS has an administrative department that controls and monitors: the management of funds, regulating of transactions and rate of health service consumption. An internal audit unit with a fraud department was put in place to check on facilities, practitioners and to control payment of invoices (Vaughan *et al.,* 2014).

2.2.2 Sources of financing for the National Health Insurance

Health financing as defined by the World Health Organization (2008), refers to three major discrete functions for the collection of revenues. This involves the mobilisation of money to cover

health needs; pooling of funds (accumulation of funds) and making it available across larger population groups; then purchasing services (allocation or use of funds) from public and private providers of health services so that all individuals have access to effective healthcare. Funding for the Gabonese health system comes from three main sources:

- the government budget;
- health insurance contributions by employers and employee (including the National Health Insurance and the Social Welfare Fund, i.e. “CNAMGS” and some private insurers); and
- Out-of-pocket expenditures by households (Saleh *et al.,* 2014).

The main objective of the CNAMGS is to provide all the insured people access to quality healthcare no matter their socio-economic status. Collecting funds for this structure is done on taxation-based financing. This actually means that the money made available for the social health insurance comes from taxes paid by the population (public workers, employees of private sectors and independent workers), government enterprises and private enterprises with a tax called the “Redevance Obligatoire à L’Assurance Maladie” (ROAM), such as mobile companies, Western Union and Money Gram (Humphreys, 2013:318-319).

CNAMGS coordinates over three funds:

- The private sector fund (taxes paid by the private sector workers and self-employed, depending on what they can afford).
- The public sector fund (taxes paid by the public sector worker), and
- The GEF fund (money collected by ROAM) (Humphreys, 2013:318-319).

Financing is done as follows:

- For employees in the public and private sector, 6.6% is the tax paid by the workers that is compulsory; 2.5% of this is from the salary of employees and the employer pays the remaining 4.1%. Retired people pay up to 1% of their income. Therefore, the medical aid will cover 80% of the fees related to a disease and the beneficiary will only pay 20% for a common disease and 10% for a chronic disease, pregnant women are exempted from user fees (CNAMGS, 2016; Musango & Inoua, 2010).
- Collecting taxes from independent workers or self-employed individuals is done according to what they can afford.

For the Gabonese that have low income, called 'Gabonais Economiquement Faible 'or 'GEF' (this group includes the poor, students, pupils and refugees), i.e. Gabonese with no incomes or less than 80 000 central Africa CFA (XAF) per month (thus R1 760[1] a month) (Saleh *et al*., 2014), financing is done according to a tax called ROAM. This money is collected from the four mobile companies installed in Gabon; 10% of their incomes and companies such as Western Union and Money Gram pay 1.5% of their revenues to finance CNAMGS. The other financial sources come from the government (Humphreys, 2013:318-319; Mbeng Mendou 2012).

2.2.3 Coverage under the National Health Insurance

Since its inception, the National Health Insurance covers everyone, no matter his or her socio-economic status. It started in 2009 with the GEF (Saleh *et al.,* 2014). In 2011, civil servants and public agents were covered under the health insurance for their medical conditions, this includes people working for the government and public institutions (Mbeng Mendou, 2012; Musango & Inoua, 2010); from 2014, private sector workers were also eligible for cover (CNAMGS, 2016).

To be enrolled as a 'GEF', one must be of Gabonese nationality, be 16 years of age and above and must earn less than 80 0000 CFA per month ($160). Therefore, a formulary must be drawn up and the agents of CNAMGS do a social investigation. Then a commission is set up to decide whether the person is eligible or not; if eligible, the person provides all the necessary documents to complete enrolment (CNAMGS, 2016). For public and private workers, self-employed and others, enrolment is done based on taxes paid, followed by presentation of the necessary documents requested by CNAMGS (2016).

Retail pharmacies provide prescribed medicines based on the three different funds — the agents of the public sector, the private sector and the GEF.

2.2.4 Services covered by the National Health Insurance

The purpose of CNAMGS is to deliver healthcare services that are efficient and equitable for everyone, so CNAMGS makes sure that everyone under the NHI, no matters their socio-economic rank or status have access to the same package of treatment and care within the health structures of the NHIS. CNAMGS purchases the services that are covered by its benefits package from accredited public and private health providers, clinics and hospitals, and selected drugs from accredited pharmacies (Saleh *et al.,* 2014). The package offered by the CNAMGS includes:

- External care, which implies normal consultations to doctors, nurses or dentists; medical analyses such as blood tests or x-rays; ambulatory and emergency care; any condition that requires a medical or paramedical intervention and pharmaceuticals; 100% of pregnancy, is

covered by the CNAMGS, including prenatal consultations, blood tests, x-rays and postnatal consultations.

- Hospitalisations, which include the cost of hospitalisation, with medical, surgical and technical interventions, transfer of patients between medical structures who require emergency interventions within the country, any cost related to maternity until delivery, and counselling on breastfeeding.

- Transfer of patients abroad for any condition that cannot be handled in the country, on the recommendation of the medical practitioner treating the patient. The NHI decide on an *ad hoc* basis whether to evacuate or not; in case of an emergency, a medical practitioner working for the NHI can decide alone to send the patient overseas. The accord of the NHI is required for transfer overseas. Some dental care, optometrist care, paramedic care physiotherapy and occupational health therapy are also included.

Plastic surgery, aesthetics, homeopathy, traditional medicine, expensive dental and eye surgery are excluded from the package (Musango & Inoua, 2010).

2.3 Pharmacy practice and the national health insurance system

The national health insurance system introduced the whole of Gabon to an innovative system of healthcare financing, which ensures that everyone has access to appropriate, efficient and quality health services. Therefore, it is improving equity in healthcare services. The question that now arises is what impact does CNAMGS have on pharmacy practice? As an answer, it is important to highlight or identify the mission and goals of pharmacy practice.

The mission of pharmacy according to Ordinance no 001PR/2011 of 27 January 2011 of the Gabonese Constitution (Gabon, 2011:195), is to serve society in a responsible way to ensure appropriate use of medication and devices, and to achieve the best possible therapeutic outcomes. The main goal is to provide a professional environment, where ideas can be exchanged between the customer and health professionals and to educate each patient about drug-related aspects, including dosages, possible side effects and contra-indications (FIP/WHO, 2012:6). Furthermore, in order to become part of the healthcare team, to make a unique contribution to high quality, cost-effective patient care and patient education; a pharmacy must always be conducted in a business-like manner to ensure success, not only for the pharmacist but for the community as well.

Gabon only has three pharmaceutical wholesale distributors implemented in Libreville, in which two are private independent suppliers. The OPN distributes pharmaceutical products to the public hospitals and dispensaries within Gabon. Independent community pharmacies only work with the

two private wholesalers; those accredited with CNAMGS. In the case of Gabon, the private sector is dominant regarding production, importation and distribution of medicines. Due to the scarcity of medicines within the public sector, people tend to obtain their medicines within the private sector, particularly in independent community pharmacies, even medicines for hospital use only.

Fewer pharmacies are accredited to CNAMGS (32.5% in Libreville), whereas 275 pharmacies and dispensaries were registered in Gabon by 2016 according to the Pharmacy Board of Gabon (ONPG, 2013). Therefore, one of the primary challenges of CNAMGS is medicine procurement by the population, the limited number of accredited pharmacies, particularly in the rural areas, and limited staff members to deal with issues regarding the national health insurance such as health promotion or collection of some medicines, particularly for chronic diseases. Community pharmacies represent 27.3% of all chemical stores registered with the Pharmacy Board in Gabon (ONPG, 2013); in the case of this study, beside counselling and blood pressure monitoring services, pharmacy workload is becoming too demanding; the pharmacy had to appoint certain staff members to deal with the CNAMGS prescription claims after dispensing. Therefore, before sending the prescription to the national health insurance for reimbursement, the prescriptions are first checked to see if they were filled according to the CNAMGS standards, that the prescriptions were in the correct fund (GEF, public agent or private fund) for reimbursement and whether the correct amount was filled in on the prescriptions, along with receipt. Adding to this, the pharmacy has to adjust with provision, huge demands, large consumption, and stock control and improve their services, particularly with the supply of chronic disease medication. Most customers collect their chronic medications (antihypertensive drugs) at the beginning of the month; this can be explained by the fact that some patients have a limited budget and rather get their medications during this period. Gregório *et al.* (2017:141) stated in his study, that in Portugal, customers rather buy their medicines early in the month because of small domestic budget. Furthermore, CNAMGS has limited the amount of chronic disease medication supply to three months on a single prescription. Patients can obtain their medicine supply in any accredited pharmacy as long as they have their CNAMGS prescriptions (CNAMGS, 2016).

The CNAMGS has a big impact on both patients and the pharmacy. For instance, CNAMGS has improved the access to quality care and provided the finances to protect the people against health-related risks, especially by eliminating the current situation where the people with the greatest need had the least access to healthcare and the outcome of service was usually poor (WHO, 2013). Therefore, it increases the use of services, and improves outpatient care (Wenjuan *et al.,* 2014).

By reducing the costs of healthcare, poverty can be alleviated. Individuals with national health insurance are likely to use healthcare facilities more regularly (Wenjuan *et al.,* 2014). The CNAMGS ensures that everyone has access to a comprehensive package of healthcare service;

these packages are provided by approved and accredited contracted healthcare professionals from both the public and private sector, with the main goal of providing quality healthcare and promoting health. Over the long-term, the country's evolving demographic profile may lead to domestic manufacturing capabilities and the success of the national health insurance scheme will provide momentum for pharmaceutical expenditure (pharmaceutical expenditure raised from XAF48.14bn [~R1.06 billion] in 2015 to XAF51.04bn [~R1.2 billion] in 2016) (Research and Markets, 2016). According to the WHO (2016:9), medicine pricing in Gabon is regulated by a decree that the Ministry of Economy set the margin to 1.58 in Libreville on all medicines. Although CNAMGS has increased the access and utilisation of medicines by reducing the cost with co-payment, particularly for chronic illness, people are still faced with challenges regarding the use of these medicines.

The fact that a pharmacy can qualify to work with the CNAMGS may lead to some changes in the scope of pharmacy practice; (for example, with increasing customers, quality of services could be affected) pharmacists should develop financial strategies to provide medicines to everyone, be able to avoid drug shortages and manage drug reimbursement. Drug information remains one of the main responsibilities of pharmacists (Ghaibi *et al*., 2015:394); subsequently pharmacists can assist the NHI with decision-making on medicine evaluation, drug cost analyses and drug utilisation for instance.

The CNAMGS has allowed community pharmacists to use their management skills in order to give advice on drug prices by proposing the therapeutic utility of certain drugs to the government and by establishing a drug formulary. Pharmacists are therefore more involved in the primary healthcare services and the management of chronic diseases by promoting the use of generic equivalents. According to the Oxford Business Group (2014), the use of generic equivalents should be promoted when establishing a list of reimbursed medicines. Stock shortages have been a problem for health centres in the past (MOHPH, 2010); with the NHI program, Gabon’s distribution network will need to be improved for the programme to function at full capacity, particularly in rural areas.

The negative effect of CNAMGS, however, is that community pharmacies have to accommodate the NHI to improve their services — this may include a delay in payment from the government for services rendered, which may lead to the closure of some small community pharmacies (Mbeng Mendou, 2012). Provider invoices are, therefore, due 30 days from the date of receipt if it is in accordance with the CNAMGS requirements (Vaughan *et al.,* 2014). Sufficient funds are needed to run and manage a community pharmacy; therefore, financial management is essential for the sustainability of the pharmacy (Kho *et al.,* 2017:5). Currently most accredited CNAMGS community pharmacies are private providers; besides stock procurement, they are faced with others expenses such as salaries, payment and maintenance of their facilities and even taxes.

Therefore, late reimbursement may cause a huge financial gap and stock-outs and may affect everyone in the chain, including the patients, the pharmacy and the suppliers. Because of this, some community pharmacies cannot work with the NHI. In the case of this study, it was reported that it took between three to six months to receive reimbursement from the CNAMGS. Several facilities in Ghana reported a 7- to 9-month delay payment from their NHI (Ashigbie *et al.*, 2016:8). In Gabon, because of stock shortage and financial problems, some community pharmacies even decided to limit their services to the CNAMGS clients if the payment was not on time. As a result, some patients with CNAMGS prescriptions were being denied medicines. For instance, it was reported in the national newspapers (L'union, 2017:7), that some pharmacies had to turn CNAMGS prescriptions away unless they were paid.

Pharmacists are entitled to drug selection and drug information and must be well trained to assure good management and distribution of medicines (FIP/WHO, 2011; Ghaibi *et al*., 2015:394). CNAMGS is already implemented and for the sake of the health of the nation and sustainability of the NHI and community pharmacy, it is better for the pharmacists to work with the government and other healthcare professionals for decision-making and drug selection for formularies.

2.4 Drug selection for reimbursement

The National Health Insurance program, according to the Ordonnance no 0022/PR/2007 of 21 August 2007, in its Articles 6, 7 and 8, stipulated that a list of reimbursed medicines was established. Following regulations of the Ministry of Health (MSHP, 2008). Prescribers and pharmacists must use this established list, which is revised on an annual basis according to the Gabon Essential Medicines List and WHO recommendations (MSHP, 2008).

The appropriate and rational use of an essential medicines list is one of the most profitable approaches that a country can rely on (The IMS Institute for Healthcare Informatics, 2015). The fact that CNAMGS had provided a list of reimbursement medicines, including antihypertensive drugs, makes the pharmacy decide which drugs to stock. Community pharmacies normally order their stock based on customer demands (Kho *et al.*, 2017). Therefore, a reimbursement list of medicines has become important for community pharmacies accredited with CNAMGS.

The increasing cost of medicines is a main concern to healthcare providers worldwide; as new drugs in particular are produced with an improved efficacy compared to the existing drugs, the cost remains a challenge for the healthcare providers (Pillay *et al.,* 2006:375). It is, therefore, difficult to choose which drugs should be available for patients or members. With the increase in expenditure of healthcare, many government, health insurance companies and health providers should develop strategies to manage the high cost of medication, including formulary management, the use of pharmacoeconomics (Alsultan, 2011:52) and a drug utilisation review

(Navarro, 2008; WHO, 2003). Medicines play a significant part in the healthcare system in such a way that they are always used in most of the therapeutic interventions (Kulkarni et al, 2009:362). However, as the cost of medicine is growing constantly and new medicines are marketed and are under patent law, preference of drug therapy and irrational drug prescriptions should be regarded as factors when selecting a drug (Kulkarni *et al.,* 2009:362).

Marketing of pharmaceuticals is a process that needs approval from national drug policy; therefore, the drug is evaluated according to criteria such as efficacy, quality, safety, cost and need (Chalker, 2012:27.2; Chase, 2010:68-69). The World Health Organization (Holloway & Green, 2003:15) defined a formulary list (essential medicines list) as the most cost-effective, safe, locally available drugs to assure quality healthcare needs of a population; this list can serve as a national formulary list, a provincial list, hospital list or a list that indicates products that are reimbursed by a health insurance program.

In some countries medicine selection is made by drug and therapeutic committees because that is the most appropriate body to develop drug policies; these committees can be composed of ministry of health representatives, medical and paramedical practitioners, hospital and districts pharmacists, hospital directors, pharmacologists and other specialists (Holloway & Green, 2003:7). In Gabon, a list of drugs was made available and some changes were made over time (CNAMGS, 2016; MSHP, 2008). The question that arises now is about how the drug selection process is done so that medicines can be reimbursed by CNAMGS; are criteria such as cost-effectiveness, utility, benefits and budget impact of drugs used when selecting the drugs that should be reimbursed?

In the next part of this literature review, the NHI that was developed and implemented in other countries is compared to the CNAMGS in terms of methods on drug selection for the benefit plans of these schemes.

2.5 Drug selection for drug benefit plans in other countries

A drug reimbursement formulary is an important tool in the healthcare system and to medical aid providers. The purpose of this section is to enlighten this process by reviewing how other countries such as the United States, Canada, France, South Africa and Ghana manage the formulary listing process based on the WHO model list of essential medicines. These countries were selected because of their reputation for being pioneers and one of the best in the world in the health insurance system such as France (LaPierre, 2012:1). Some of them were among the earliest countries to witness health system reforms and are highly industrialised (Canada and USA) and because some represent developing countries (Ghana and South Africa), there are

currently reforms in their health system (LaPierre, 2012:1; Ridic *et al.,* 2012:112-115; Saleh, 2013:15; Yoder, 2015:32).

2.5.1 Drug selection process in France

The healthcare system in France was ranked number one in terms of universal coverage by the WHO in 2000, and combines universal health coverage with a public-private mix of hospital and ambulatory care (Durand-Zaleski, 2015:53; Rodwin, 2005:31). Coverage is universal; it covers hospital care, ambulatory care and prescription drugs. Cost sharing involves co-payment, co-insurance and extra billing; it is applied to health services and drugs, and then depends on the type of care (hospital care, for instance is 20%, doctors visit and dental care are 30%). Prescriptions drugs are reimbursed from 100%, 65%, 35% to 0% (not reimbursed), depending on the therapeutic effect, (Durand-Zaleski, 2008:53).

For a drug to be commercialised, it must obtain an 'autorisation de mise sur le marché' (AMM, i.e. 'authorisation for market entry') from the ANSM (French Health Product Safety). Therefore, in order for the drug to be reimbursed, it has to appear in the positive list of the drugs reimbursed under social health insurance. The drug inclusion in the list is decided by the Ministry of Health and Social Insurance of France, with the advice of the Transparency Commission (CT) under the supervision of the Haute Autorité de Santé (High Authority of Health, HAS) (Nguyen-Kim *et al.,* 2005:47-49). The Commission evaluates the therapeutic value of drugs based on two criteria (Nguyen-Kim *et al.,* 2005:49). The first one is the 'Service Medicale Rendu' (SMR), defined as the effect of drugs on disease, and the second one is the improvement of the medical benefit (called 'Amelioration du Service Medical Rendu', ASMR) (Nguyen-Kim *et al.,* 2005:49). If these criteria are met, the commission recommends the drug to be included in the list and establishes the level of drug reimbursement (Nguyen-Kim *et al.,* 2005:49).

2.5.2 Drug selection process in Canada

The Canadian healthcare system coverage is funded by a provincial-federal cost-sharing formula; decisions on coverage of additional benefits such as outpatients' prescriptions drugs, dental care, vision care, mental care, hospice care and ambulance services are made by provincial and territorial governments (Allin & Radoler, 2015:21-22).

Pharmaceutical products must be approved by the Canadian Department of Health, through a Therapeutic Directorate of Health Products and Food Branch (HPFB), which is in charge of drug policy (i.e. safety, efficacy and quality) and reviewing new drugs for licensing and labelling (Paris & Docteur, 2007:10). Therefore, a committee of experts reviews drugs once the safety, efficacy and quality of the drugs have been assessed and have met the requirements. The Ministry of Health Canada may grant a marketing authorisation or notice of compliance (NOC) (Paris &

Doctor, 2007:21). Drugs for serious or life-threatening conditions may be granted a notice of compliance with conditions (NOC/C); meaning that additional studies should be done on the drugs before marketing (Paris & Docteur, 2007:21).

Drug coverage is a process done following the recommendations of common drug review. The common drug review is launched by the Canadian Expert Drug Advisory Committee (CEDAC); the committee evaluate therapeutic advantages and disadvantages, cost-effectiveness, safety, efficacy and quality-adjusted-life-years of drugs (QALY); once drugs have been evaluated, CEDAC may recommend them and send the decision to the Ministry of Health (Paris & Docteur, 2007:21). Following this, the drug insurance plan and the manufacturers make their formulary decisions based on the recommendation of the CEDAC (Paris & Docteur, 2007:22).

2.5.3 Drug selection process in the United States (US)

Health insurance in the US remains fragmented despite the Affordable Care Act of 2010 of Public Law number 111-148 (US, 2010:76) to establish cost-sharing between governments, employers and individuals so that everyone has access to affordable and quality healthcare (The Commonwealth Fund, 2015:153-154).

Health insurance coverage in the US includes private voluntary health insuring, employer provider insurance to public programs such as Medicare and Medicaid that covers various population groups. Usually, services covered are ambulance, hospital, emergency, maternity and new born, mental health, prescription drugs, chronic disease management and paediatric services (The Commonwealth Fund, 2015:154).

Private health insurance is funded on a cost-sharing formula depending on the health insurance plan (The Commonwealth Fund, 2015:155). Medicaid for instance, uses formularies to control the cost of drugs and appoint the percentage of tiered cost sharing of prescription drugs (The Commonwealth Fund, 2015:153). Formularies are provided by a body of medical experts known as a Pharmacy and Therapeutic Committee (PTC), composed of physicians and pharmacists. The committee then decides whether a drug should appear on formulary or not, according to drug information, on the basis of the effectiveness, safety, net cost and other clinical information such as monographs, therapeutic class, published studies, pharmacoeconomic studies, drug utilisation review, US Pharmacopeia and meta-analysis (Medpac, 2004). If the formulary of drug benefit plan complies with the Medicare Modernisation Act of 2003 of Public Law number 108-172 (2003:2072-2073), the formulary is then submitted to the centre of Medicare and Medicaid service (CMS) for validation by the PTC (Medpac, 2004).

2.5.4 Drug selection process in South Africa

The South African healthcare system is based on a large public sector funded by the state that delivers service to about 84% of the population (Biermann, 2007:4); a private sector funded by subscriptions of individuals to medical aid schemes where healthcare professionals provide their services to about 16% of the population (CMS, 2016:22); and non-governmental organisations (NGOs) focused on diseases such as human immunodeficiency virus (HIV) and tuberculosis (Biermann, 2007:4).

In 2007, the South African government had committed to establish a reform plan regarding implementation of a NHI so that all people within South Africa could have access to reasonable and better healthcare services (Ataguba & Akzili, 2010:75; Govender *et al.,* 2013). This was established through a white paper (Department of Health, 2015), in which implementation was described in three phases over 14 years. The first phase conducted over a 5-year period will focus on strengthening and improving quality healthcare in the public sector, therefore establishing an Office of Health Standards Compliances (OHSC) (Gray & Vawda, 2016:4). The second phase that will also run over a 5-year period will include the registration of the population and the creation of a NHI fund. Finally, the third phase will run over a 4-year period, and will ensure that the NHI fund is brought to full operation (Gray &Vawda, 2016:4).

As South Africa moves towards a NHI system, a National Essential Drugs List Committee (NEDLC), appointed by the South African Minister of Health, will be responsible for the selection of drugs to be used within the health care system (Department of Health, 2015). The drug selection process will be done according to WHO guidelines. The committee, composed of medical and pharmaceutical experts (clinical pharmacists, pharmacologists, medical specialists, paediatricians, professional nurses, medical practitioners, members of drug information centre and the Medicines Control Council will draw up a national list of essential drugs using generic equivalents; the list will be reviewed every two years (Department of Health, 2015).

Drug selection, following the South African National Drug Policy (NDP) set in 1996 will be based on criteria such as health needs, effectiveness, safety, risk/benefit ratio, pharmacological active ingredients, best cost advantages, pharmacokinetic properties and patient compliance (Department of Health, 2012). If drug selection requirements are met, the list will be used as a foundation for the national health system (NHS), for universal primary care, as model for medical schemes, drug donation, as a support for the national pharmaceutical industries, rational drug prescribing, procurement and drug usage (Department of Health, 2012).

2.5.5 Drug selection process in Ghana

The public healthcare system of Ghana is driven by the NHIS and was established in 2003 (Ashigbie *et al*., 2016:2). Its purpose was to remove barriers so that all residents have access to quality and equitable healthcare services (Ashigbie *et al*., 2016:2). It allows the operation of three types of insurance schemes, including district-wide (public) mutual health insurance schemes (DMHIS), which are the only insurance schemes to be financially supported by the NHIS, private mutual schemes and private commercial schemes (Blanchet *et al.,* 2012:77).

According to the NHIS, Ghanaians are required to pay an income-based premium and the government is responsible for covering the aged, older than 70 years, indigent (unemployed with no income, handicapped) and children under the age of 18 years whose parents are affiliated to the NHIS (Gajate-Garrido & Owasua, 2013; Gobah & Liang, 2011:92).

Ghana has adopted the national essential drugs list concept introduced by the WHO as a core component of drug selection and supply; this list serves as a basis for guiding the supply, prescription and dispensing of drugs (MOHNDP, 2010). However, under the NHIS, a medicine list, which includes more drugs than the national essential drug list, has been developed for reimbursement purposes (MOHNDP, 2010). The selection process of reimbursable drugs focuses on treatment indicated for priority health conditions in Ghana. Before evaluation, the drug should obtain a market approval from the Ghana Food and Drug Board. After approval, the NHI authority commissions an expert group composed of pharmacists and physicians to review the evidence for the management of major health problems (MOH, 2004).

2.5.6 Section summary

In order to assure quality healthcare services based on a drug selection program, and to assure cost-effectiveness treatment, CNAMGS should establish a drug selection program for their formulary following the WHO standard guidelines and essential medicine list, and should apply drug utilisation review as a core component of their national drug supply system. The present study focuses on the antihypertensive drugs reimbursed by CNAMGS. The question that needs to be answered is, “On what criteria are antihypertensive drugs selected by the NHI?” In order to answer this question, hypertension is discussed in the next part of the study, along with drugs used for the treatment of hypertension.

2.6 Hypertension

High blood pressure, an important risk factor for developing cardiovascular disease in Africa, represents a major threat for African countries’ economy and is a public health issue (Van de

Vijver *et al*., 2013). This part of the study aims to conceptualise the classification, management of hypertension and the use of antihypertensive drugs.

2.6.1 Definition of hypertension

Blood pressure is a continuous biological variable, measured in unit of millimetres of mercury (mmHg) and also referred to as the relationship between cardiac output (CO) and the total peripheral resistance (TPR) (Bakris, 2016a:1). Hypertension is then described as persistently raised pressure to the blood vessels and is defined as the systolic blood pressure and a diastolic blood pressure exceeding 140 mmHg and 90 mmHg, respectively (Weber *et al*., 2014:4). Meanwhile, children aged 17 years or younger are declared hypertensive if the blood pressure (systolic and diastolic) measurements are in the 95th percentile or above for age, gender and height (Alton, 2005:125).

2.6.2 Classification of hypertension

High blood pressure for adults aged 18 years or above is classified by the Seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC7) as follows (Chobanian *et al.,* 2003a:2561):

- Normal blood pressure defined at levels below 120 mmHg of systolic pressure and 90 mmHg of diastolic pressure (<120/90 mmHg).

- Prehypertension at systolic blood pressure (SBP) of 120-139 mmHg and/or diastolic blood pressure (DBP) of 80-89 mmHg. At these levels, the clinician and the patient should be aware of the risk of developing hypertension and early lifestyle modifications should be adopted to reduce BP. The patient is not a candidate for drug therapy except in the presence of others disease conditions such as diabetes.

- Hypertension defined as two stages in which stage 1 includes patients with blood pressure ranging from 140/90 mmHg to 159/99 mmHg; and stage 2 with a blood pressure equal to or higher than 160/100 mmHg (Chobanian *et al.,* 2003a:2561).

The European Society of Hypertension and the European Society of Cardiology (ESH/ESC, 2013) provide a more elaborate classification of blood pressure by adding to the following classification: isolated systolic hypertension at levels ≥140/<90 mmHg blood pressure; and a more severe case of hypertension (grade 3) with blood pressure ≥180/110 mmHg, defined as accelerated. Moreover, malignant elevated blood pressure where progressive damage or injury of target organ is present.

The World Health Organization (2003:1985) and International Society of Hypertension (Whitworth, 2003:1985), along with the Joint National Committee VII (JNC-7) (2013) and ESC/ESH (2013), classifies hypertension into several distinct categories, such as optimal, normal, high normal, Stage 1, Stage 2, Stage 3, and isolated systolic blood pressure. These are depicted in Table 2-1.

Table 2-1: Classification of hypertension

Blood pressure classification	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Comments
Optimal	<120	<80	
Normal	120-129	80-84	
High normal	130-139	85-89	
Grade 1 (mild)	140-159	90-99	No objective signs
Grade 2 (moderate)	160-179	100-109	Left ventricular hypertrophy based on examination
Grade 3 (severe)	≥ 180	≥ 110	HF, CVD, eye damage, aneurysm and CHD
Isolated systolic hypertension	≥ 140	<90	
HF: Heart Failure, CVD: Cardiovascular Diseases, CHD: Chronic heart disease			

The classification of blood pressure depends on the average of two or more accurate readings of blood pressure values from several clinical visits; therefore, four categories of hypertension are underlined: normal, prehypertension, stage 1 hypertension and stage 2 hypertension (WHO, 2011).

2.6.3 Prevalence and epidemiology

Elevated blood pressure is a potent precursor to the development of cardiovascular diseases and one of the major causes of death globally (Mendis, 2013:1). On the other hand, the cost-of-illness, comorbidity and mortality rate have increased significantly over the past decades; the number of people, for instance, with elevated blood pressure was estimated at 1 billion in 2008, compared to 600 million in 1980 (Mendis, 2013:1). This number increased by 7% in 2010 (Van de Vijver *et al.,* 2013:2). Hypertension has become a major public health challenge and about 9.4 million deaths occur each year due to raised blood pressure (Mendis, 2013:1; WHO, 2013:9).

Population ageing, high prevalence of obesity (especially in children and young adults), tobacco use and lifestyle can explain high prevalence of hypertension; however, the prevalence of elevated blood pressure differs significantly according to geographical region (Lacruz *et al.,* 2015). Currently, the highest prevalence of elevated blood pressure is recorded in sub-Saharan

African regions due to a low level of awareness, lack of effective treatment policies and scarcity of health resources in some regions (Cappuccio & Miller, 2016:299). More or less 46% of people aged 25 years and above, have been identified with raised blood pressure (Cappuccio & Miller, 2016:299; Van de Vijver *et al.,* 2013:2); whereas high income countries have the lowest prevalence of raised blood pressure (about 25%) due to the implementation of effective public health policy (WHO, 2013:9).

Blood pressure levels vary with gender, age, ethnicity and numerous other factors, including education, locality, awareness and income. For instance, data from MESA (a multi-ethnic study of atherosclerosis) (Carson *et al*., 2011:1101) showed that among American populations aged 25-34 years, the occurrence of elevated blood pressure in black men (27.3%) and women (23.6%) was two times greater than Caucasian men (11.9%) and women (8.1%) (Carson *et al*., 2011:1105) . However, from age 50 years and above, the prevalence of hypertension was similar (Carson *et al*., 2011:1105). Furthermore, a population-based cross-sectional study conducted in South Africa by Peltzer and Phaswana-Mafuya (2013:68) showed significant differences in terms of ethnicity regarding elevated blood pressure (Peltzer & Phaswana-Mafuya, 2013:68). In this study, elevated blood pressure was more prevalent in black Africans at 74% compared with other groups, 72.4% were overweight or obese and about 64.9% of study participants lived in urban areas (Peltzer & Phaswana-Mafuya, 2013:68).

The prevalence of raised blood pressure is increasing considerably in Africa; nearly 150 million people will have elevated blood pressure by 2025 compared to 80 million in 2000 (Van Vijver *et al.*, 2013:2); therefore, if effective measures are not taken, Africa will face a steady rise in poverty and health inequalities (Cappuccio & Miller, 2016:300). One in six individuals in Gabon were affected with raised blood pressure, of which 47.7% were males and 53.7% were females (Ngoungou *et al.*, 2012:77). The World Health Organization in 2010 estimated the prevalence of hypertension in Gabon at 41.3% for the population, with 43.9% for males and 38.7% for females.

According to Addo *et al*. (2007:1016), the incidence rate of hypertension in sub-Saharan Africa increases with age and is more prevalent in urban areas compared with populations living in rural areas. The prevalence of hypertension has emerged in urban areas of Africa and the economic burden of the disease between 2011 and 2025 is estimated to cost about US$3.76 trillion (WHO, 2013:45). Currently, the cost of elevated blood pressure represented 4.5% of the disease burden (Osibogun & Okwor, 2014:157). Because of economic development and epidemiological transitions, prevention, management and cost of the disease should be a priority for health policy makers, especially where poor availability and the cost of therapy is an obstacle for many people looking for quality healthcare services.

2.6.4 Risk and causes of hypertension

Risk factors that have been related to elevated blood pressure include the levels of systolic blood pressure (SBP), substantially normal SBP at rest is 120 mmHg; the higher the systolic blood pressure, the greater the risk, therefore, a reading of 140 mmHg is a sign of hypertension (Weber *et al.*, 2014:4). Along with SBP, high levels of diastolic blood pressure (>90 mmHg) have been regularly used as predictors of coronary disease and cerebrovascular diseases (Weber *et al.,* 2014:4). Furthermore, with readings of 115/75 mmHg, it has been reported that an increase in systolic blood pressure of 20 mmHg and in diastolic blood pressure of 10 mmHg may double the risk of developing cardiovascular diseases (Weber *et al.,* 2014:4).

Other predisposing factors associated with hypertension are age, tobacco use, high levels of cholesterol and dyslipidaemia, abnormal glucose tolerance and the level of fasting plasma glucose (Cappuccio & Campbell, 2016:300). A study has demonstrated that individuals are predisposed to developing high blood pressure from age 55 years and above for men and 65 years for women; a remarkable increase in systolic blood pressure between ages 30 to 84 years was observed during the Framingham Heart study (Pinto, 2007:111). Hence, systolic blood pressure and diastolic blood pressure tend to rise as people get older (about 50 years and above), age remains a non-modifiable risk factor due to the changes that occur in arteriolar stiffness caused by calcification, arteriosclerotic structural alterations and an increase in total peripheral resistance (TPR) in the small arteries (Pinto, 2007:111). The body undergoes significant strains and diseases such as renal diseases, where atherosclerotic renovascular diseases are more likely to develop (Buttar *et al.,* 2005:230; Pinto, 2007:111). Adding to this, other factors that can develop hypertension during ageing include an increase in responsiveness to sympathetic nervous system stimuli and a decrease in baroreceptor sensitivity, as noradrenaline is released, the blood pressure increases, along with this sodium metabolism and the renin aldosterone relationship may be altered (Foëx & Sear, 2004:72). Blood pressure in children increases with age and body size (Drozdz & Kawecka-Jaszez, 2014:1507); 10% of people between 10 and 25 years of age are affected by elevated blood pressure caused by obesity or type 2 diabetes mellitus (Seedat *et al.,* 2014:293).

Obesity, diabetes mellitus and other comorbidities are predisposing factors for developing CVD; about 80% of people with type 2 diabetes mellitus develop hypertension due to metabolic disorders (Khatib & El-Guindy, 2005:45). Abdominal obesity, impaired glucose tolerance and altered fat metabolism form the part of metabolic syndrome related to high blood pressure. Consequently, risk factors such as belly fat (waist circumference >102 cm for men and >80 cm for women), fasting glucose ≥6.105 mmol/l, triglycerides >8.325 mmol/l and HDL-cholesterol are the main precursors for the development of heart diseases and stroke (Khatib & El-Guindy, 2005:45). Study findings in Africa have shown a significant increase in prevalence of obese and

overweight people, especially in women living in urban areas (Van de Vijver *et al.*, 2013:4). Finally, elevated blood pressure is also associated with environmental and lifestyle factors; smoking for instance, is estimated to cause 10% of cardiovascular diseases (WHO, 2010:17). Hypertension remains the number one risk factor in developing cardiovascular diseases, heart failure, renal failure, ischemic heart diseases and aneurism (Pinto, 2007:109).

2.6.4.1 Causes of hypertension

Several factors contribute to the development of high blood pressure, from the environment, the socioeconomic situation or genetic and metabolic disorders (WHO, 2013:18). Table 2-2 (Khatib & EL-Guindy, 2005:17) lists the causes of hypertension.

Table 2-2: Causes of hypertension

Systolic and Diastolic Blood Pressure	Systolic Blood Pressure
Primary (Idiopathic)	Increase cardiac output
Secondary hypertension	Rigidity of aorta
Renal diseases cause (2.5-6% of hypertension)	Iatrogenic hypertension
Renal parenchymal: Polycystic kidneys disease Chronic kidney disease Pyelonephritis Acute glomerulonephritis Diabetic nephropathy	
Hormonal Disorders: Cushing Syndrome Primary aldosteronism Pheochromocytoma Congenital adrenal hyperplasia Acromegaly	
Drugs: Corticosteroids Oral contraceptives (oestrogen) NSAIDs* Erythropoietin Cocaine Decongestants with ephedrine Monoamine oxidase Cyclosporine and tacrolimus Liquorice	
Other: Pregnancy-induced hypertension Obstructive sleep apnoea Acute stress Alcohol	

Systolic and Diastolic Blood Pressure	Systolic Blood Pressure
Family history Unhealthy lifestyle habits Depression and stress	
*NSAIDs: nonsteroidal anti-inflammatory drugs	

According to Weber *et al.* (2014:5), 95% of people with hypertension have essential hypertension and the causes are multifactorial, poorly understood or unknown; the remaining 5% of adults with high blood pressure have known causes such as chronic kidney diseases, sleep apnoea and can be treated for some of these conditions (Weber *et al.,* 2014:5).

Social determinants such as urbanisation, globalisation, geolocality, poor education or low income can have adverse effects on blood pressure (WHO, 2013:18). Less developed countries, for instance, have limited access to medicines and quality healthcare services due to their high cost (Twagirumukiza *et al.,* 2010:355). Studies have demonstrated a significant change towards an increase in blood pressure between populations migrating from rural to urban areas (Bosu, 2010:11; Pinto, 2007:110). Elevated blood pressure in urban populations can be explained by behavioural risk factors such as unhealthy diet, high salt intake, more processed foods being consumed, minimal physical activity, stress, alcohol and tobacco consumption (Addo *et al.*, 2007:1016). Adding to this, behavioural factors can lead to the development of other disorders such as obesity, type 2 diabetes mellitus, glucose intolerance and high cholesterol levels (WHO, 2013:18).

Other causes of high blood pressure include, genetics, ageing, medicines, conditions such as pregnancy-induced hypertension and hormonal disorders (Khatib & El-Guindy, 2005:40-41). There is a relationship between the intrauterine exposure to hypertension, childhood period and the incidence of hypertension in adults; furthermore, children born into poorer families, with bad eating habits, tend to develop hypertension in their adulthood (Silva, 2006:1). According to Alton (2005:128), obese adolescents have an increase in flow rate and blood cell volume caused by insulin resistance; hence, high concentration of plasma insulin may cause sodium sensitivity in these adolescents.

High cardiac output and total peripheral resistance are often recorded in most hypertensive patients; increased cardiac output may be a consequence of increase in blood flow through the tissue and increase in vascular tone (Silva, 2006:2). Furthermore, the sympathetic nervous system induces vessel constriction and dilatation; therefore, if released, epinephrine's, responsiveness to stress stimuli might increase along with the decrease in baroreceptor sensitivity (Silva, 2006:4-5).

2.6.5 Prevention and treatment of hypertension

Prevention and treatment of hypertension is a major public health challenge; elevated, low or moderate blood pressure can be regulated throughout several processes, starting with a non-pharmacological approach such as lifestyle modifications (Chobanian *et al.*, 2003b:1213). If blood pressure is still greater or equal to 140 mmHg after three to six months of lifestyle modifications, antihypertensive therapy should be initiated.

Individuals with family history of hypertension or pre-hypertension, especially young adults and children, are advised to adopt strategies to prevent elevated blood pressure such as living a healthy lifestyle with good dietary habits, avoidance of substance use, maintaining a healthy body weight and promoting physical activity (Alton, 2005:133).

The main objective when treating hypertension is to keep blood pressure below 140/90 mmHg, even for individuals with comorbidities and other significant risk factors for cardiovascular diseases (Seedat *et al.*, 2014:290). For individuals aged 80 years or above with blood pressure greater than 160 mmHg, the main goal is to reach a blood pressure between 140-150/90 mmHg (Weber *et al.,* 2014:5) and for patients with renal diseases and diabetes, blood pressure levels should be controlled and kept at 130/80 mmHg (Goldstein *et al.*, 2011:527).

The following section of the study aims to identify the consequence of lifestyle modifications on hypertension and the pharmacological approach of treating blood pressure.

2.6.5.1 Lifestyle modifications for hypertension

The initial intervention used to delay or to slow the progression of hypertension is lifestyle counselling, which represents the cornerstone in the management of elevated blood pressure (Seedat *et al.,* 2014:290). Lifestyle modifications includes a reduction of excess weight, a normal body weight should indicate a body mass index between 18.5 to 25 kg/m^2 (Seedat *et al.*, 2014:290); furthermore, adopting the dietary approach to stop hypertension, increasing physical activity, promoting tobacco cessation and reduced alcohol consumption.

2.6.5.1.1 Weight reduction

Excess weight and elevated blood pressure are directly related; obesity leads to the development of major risk factors such as raised blood pressure, dyslipidaemia and type 2 diabetes mellitus (Hollis *et al.*, 2008:2). Chobanian *et al.* (2003b:1216) stated that even if the main goal when losing weight is to maintain weight within normal levels, modest weight loss of 4.5 kg reduces blood pressure in hypertensive patients and prevents raised blood pressure in normotensive people. Excess weight represents a great risk of developing others diseases and increased mortality, especially in people with a prior history of raised blood pressure (Buttar *et al.*, 2005:242).

According to Appel *et al*. (2006:297), a meta-analysis performed with the accumulation of 25 trials, found that a modest weight reduction of 5.1 kg on average significantly lowers blood pressure by 4.4/3.6 mmHg. Furthermore, additional trials demonstrated that a weight loss of approximately 20% reduces and prevents elevated blood pressure particularly in overweight patients (Butter *et al.,* 2005:242); consequently, efforts are needed to maintain a normal weight (BMI<25 kg/m^2) and prevent weight gain (Appel *et al.;* 2006:297). However, in order to maintain the healthy weight, a combination of factors such as physical activities, dietary approaches and reduction of salt intake are critically important.

2.6.5.1.2 Dietary approaches to stop hypertension (DASH)

Dietary modifications are effective strategies to lose weight and reduce blood pressure; a significant decrease in blood pressure has been noticed in individuals following the DASH diet, particularly in African Americans (Alton, 2005:130; Appel *et al.*, 2009:361).

The DASH diet recommends eating vegetables, fruits, whole grains, nuts, low fat dairy products, fish and poultry, a diet rich in calcium, potassium, magnesium and fibre, and a reduced intake of fats and cholesterols (Appel *et al.*, 2009:361). Furthermore, Appel *et al.* (2009:362) demonstrated in studies that the DASH diet was capable of lowering blood pressure by 5.5/3.0 mmHg, but the reduction was more significant in black participants, with 6.9/3.7 mmHg compared to 3.3/2.4 mmHg in Caucasians (Appel *et al.*, 2009:361). Additionally, the effects of DASH diet on blood pressure in some patients were even better at 11.6/5.3 mmHg compared to normotensive patients with 3.5/2.2 mmHg (Appel *et al.*, 2009:361). The DASH diet, when combined with reduced sodium intake is most effective in reducing blood pressure (Alton, 2005:130), but Appel *et al*. (2009:362) emphasises that the diet is not advised to patients with chronic kidney diseases as DASH diet has a high protein, potassium and phosphorus content. Currently, a well-balanced diet will decrease the risk of developing obesity and type 2 diabetes mellitus, hence, Buttar *et al.* (2005:233) recommends that type 2 diabetes mellitus patients reduce their caloric intake by 500 Kcal, to a maximum of 800 Kcal per day.

Maintaining a healthy weight involves a combination of factors such as physical activity, dietary approaches and reduction of salt intake. A study done by Hedayati *et al.* (2011:1064) shows that over a 6-month period, a 6.8 kg weight loss for patients with BMI greater than 25 kg decreases their blood pressure level by 4.3/2.6 mmHg, compared to the blood pressure of those who received advice, with only 3.7/1.7 mmHg. These were possible for people doing moderate exercise at least 3 hours/week, with a low sodium intake ≤100 mmol/day and less than 2 glasses of wine for men and 1 for women per day, in addition to a DASH diet (Hedayati *et al.,* 2011:1064). According to Appel *et al.* (2006:299), other dietary approaches such as potassium, magnesium, and calcium and fibre intake also have a positive effect on reducing blood pressure. For instance,

studies have documented a reduction of blood pressure levels by 4.4/2.5 mmHg in individuals with hypertension and 1.8/1.0 mmHg in normotensive individuals presenting high urinary potassium excretion of 50 mmol/day and it is more beneficial for blacks compared to Caucasians (Appel *et al.*, 2006:299; Stone *et al*., 2016:9). Furthermore, it was reported from meta-analysis studies that calcium supplementation reduced blood pressure by 0.9/1.4 mmHg and increased fibre intake (1.4 g/day) lowered blood pressure levels by 1.6/2.0 mmHg (Appel *et al.*, 2006:300).

2.6.5.1.3 Salt intake reduction

The daily amount of salt intake recommended by WHO (2013:31) is 2000 mg of sodium or 5 g of salt per day. Reducing salt intake will prevent hypertension and reduce the risk of developing other CVDs (He *et al.*, 2012:294). A meta-analysis by Appel *et al.* (2006:298), showed that a reduction in urinary sodium of about 1.8 g/day (78 mmol/day) led to a decrease in blood pressure of 2.0/1.0 mmHg in normotensive individuals and 5.0/2.7 mmHg for patients with elevated blood pressure. The higher the salt intake, the higher the blood pressure. A study performed in 20 individuals, in which sodium intake was lowered from 11.2 to 6.4 or 2.9 g/day, demonstrated a remarkable fall in blood pressure from 163/100 mmHg for those having 11.2g of salt/day, to 155/95 mmHg for those taking 6.4g of salt per day, and 147/91 mmHg for salt intake reduced to 2.9g/day (He *et al.*, 2012:294). Based on this study, He *et al.* (2012:294) suggested a further reduction of salt intake to 3g/day, for greater effects on blood pressure. Salt reduction is a cost-effective strategy and may reduce CV morbidity and mortality, as it lowers blood pressure by a mechanism similar to that of thiazide diuretics (He *et al.*, 2012:296).

2.6.5.1.4 Moderation of alcohol consumption and tobacco cessation

The link between blood pressure and alcohol intake is dose-dependent (Hedayati *et al*., 2011:1066). Small doses of alcohol (less than two portions a day) lead to a decrease in blood pressure, as small doses of alcohol cause dilations of peripheral veins (Mousa, 2005:77). A prolonged consumption and higher doses of alcohol may cause hypertension, because the chronic elevation of blood pressure increases calcium release into vascular smooth muscle, thus increasing cardiac output (Mousa, 2005:75). In a meta-analysis of 15 randomised controlled trials, Gupta and Guptha (2010:535) demonstrated that a 76% decrease in alcohol consumption lowered blood pressure levels by 3.3/2.0 mmHg in hypertensive and normotensive individuals. Moderation of alcohol consumption is adequate in reducing blood pressure; therefore, alcohol use should be limited to two drinks/day for men and one drink/day for women and individuals with a light weight (Appel *et al.,* 2006:299). Individuals tend to abuse alcohol consumption and because of the mortality and morbidity associated with excessive consumption of alcohol, moderation of alcohol should be recommended as an adequate strategy to lower blood pressure (Mousa, 2005:77).

Several studies have indicated tobacco as a particular risk factor for developing hypertension, atherosclerosis and other CVDs and respiratory diseases (Buttar *et al.,* 2005:246; Koene *et al.,* 2016:1108; U.S. Department of Health, 2010:355). Smoking cessation should be a priority for a hypertensive patient and should be promoted by global public health (Buttar *et al.,* 2005:245).

2.6.5.1.5 Increasing physical activity

Physical activity is a key factor in reducing high blood pressure and has a beneficial effect on hypertension (Monteiro & Filho, 2004:517). There is a strong positive relationship between physical activity and good health, as lipid profiles, blood pressure and cardiovascular health may be improved (Buttar *et al.*, 2005:233).

Physical activity is a useful approach for the management of blood pressure; it has a significant effect on weight loss and reducing blood pressure, 150 minutes per week of moderate exercise is recommended to manage blood pressure for adults aged 18 to 64 years (WHO, 2010:26). Exercising daily, or up to 3 to 5 times per week, will reduce blood pressure up to 8/6 mmHg, the amount of LDL cholesterol up to 0.555 mmol/l and may increase HDL up to 0.222 mmol/l (Buttar *et al.,* 2005:233). Even brisk walking for 30 minutes daily reduces blood pressure by 4/9 mmHg (Seedat *et al*., 2014:290). Aerobic exercise has been shown to reduce blood pressure by 3.84/2.58 mmHg in both normotensive and hypertensive people (Gupta & Guptha, 2010:567); further studies involving 105 study groups and 72 trials also demonstrated its effect on reducing blood pressure by 6.9/4.9 mmHg (Gupta & Guptha, 2010:567).

In summary, successful implementation of dietary lifestyle modifications by health professionals requires promotion through patient education, therefore, choosing the appropriate medicine, and for the treatment to be successful, multiple factors (such as environmental factors) in the patient's life should be addressed. Table 2-3 (Appel *et al*., 2009) shows the reduction of systolic and diastolic blood pressure according to lifestyle modifications.

Table 2-3: Effect of lifestyle modification interventions on blood pressure

Modifications	Reduction of systolic blood and diastolic blood pressure
Weight reduction by 5.1 kg	4.4 / 4.9 mmHg blood pressure
Potassium intake 2 g/d	4.4 mmHg/ 2.5 mmHg blood pressure on hypertensive patients 1.8/1.0 mmHg for normotensive individuals
Calcium supplement 400 mg/day	0.9/1.4 mmHg blood pressure
Fibre intake 1.4 g/day	1.6 / 2.0 mmHg blood pressure
DASH diet alone	5.5/3.0 mmHg reduction on blood pressure

Modifications	Reduction of systolic blood and diastolic blood pressure
DASH* diet	Reduces blood pressure by 11.6/5.3 mmHg in hypertensive patients
Reduction of sodium intake to 1.8 g/d	In hypertensive patients blood pressure is reduced by 5.0/2.7 mmHg
70% alcohol reduction	Reduces systolic blood pressure by 3.3 mmHg in hypertensive patients
30-45 minutes daily exercises	Blood pressure is reduced by 8/6 mmHg
Brisk walking effect on systolic blood pressure	Between 4-5 mmHg
*DASH: Dietary Approach to Stop Hypertension	

2.6.5.2 Pharmacological treatment of hypertension

The main objective when managing hypertension is to reduce blood pressure-associated morbidity and mortality so that cardiovascular diseases, heart failure and kidney diseases can be prevented (Cappuccio & Miller, 2016:301; Palmer & Fenves, 2010:240-241). Achieving a desired target blood pressure value may lower the risk of developing CVD; however, choosing hypertension medications depends on the degree of BP elevation and the presence of specific indications (Nguyen *et al.*, 2010:48).

Drug treatment is needed for a great majority of patients with essential hypertension and for those whose blood pressure does not fall to normal within 3 to 6 months after correction by lifestyle modification (Seedat *et al*., 2014:289). The purpose of drug therapy is to maintain blood pressure levels so that it remains below 140/90 mmHg for individuals with essential hypertension, and ≤130/80 mmHg for patients presenting with hypertension and concomitant diseases such as diabetes or renal disease (Chobanian *et al.,* 2003b:1216). For patients over 80 years, if systolic blood pressure is above 160 mmHg, treatment should be initiated and the target systolic blood pressure is 140 to 150 mmHg (Seedat *et al.,* 2014:290). The choice of hypertension medications is furthermore, influenced by factors such as age, race, concomitant diseases, availability and affordability of the drug (Weber *et al.,* 2014:7).

Currently, a large number of drugs for hypertension are available and can reduce BP through different mechanisms. Khatib and EL-Guindy (2005:55) defined three groups of antihypertensive drugs, i.e. diuretics, anti-adrenergics (working centrally, peripherally or as receptor blockers) and direct vasodilators (working via calcium channel blockade, angiotensin-converted enzyme inhibition or angiotensin II receptor blockade). In this section, the study focusses more on different classes of antihypertensive drugs.

2.6.5.2.1 Diuretics

Diuretics are first-line agents and are mostly used for the treatment of high blood pressure. They reduce blood pressure by promoting diuresis and natriuresis, hence decreased blood plasma volume, cardiac output and peripheral vascular resistance after long time use (Khatib & El-Guindy, 2005:56). Diuretics are mainly used for the treatment of hypertension with oedematous conditions, including heart failure, cirrhosis with ascites, nephrotic syndrome and chronic kidney diseases (Tamargo *et al.*, 2014b:605). A network meta-analysis confirmed the use of low dose diuretics as the drug of choice for the treatment of cardiovascular diseases (Unni, 2016:651). Three groups of diuretics are used for the treatment of high blood pressure; this includes thiazide like diuretics, loops diuretics and potassium sparing agents (Nguyen *et al*., 2010:49).

- **Loop diuretics**

Loop diuretics exert their actions on the thick ascending loop of Henle, where NaCl reabsorption is reduced and the luminal sodium-potassium-chloride (Na^+-K^+-$2Cl^-$) co-transporter is inhibited. Once the tubular Na^+ reabsorption is reduced, diuresis and natriuresis occur, which leads to a decreased extracellular fluid and plasma volume, a decreased cardiac output and systemic vascular resistance, then a reduced blood pressure (Nguyen *et al*., 2010:51-52).

Furosemide is the most commonly prescribed loop diuretic, as it exerts a more potent effect (Tamargo *et al.,* 2014b:607); other loop diuretics include torsemide, ethacrynic acid, bumetanide and piretanide. Loop diuretics might have lower efficacy than thiazide diuretics in reducing hypertension, but are more effective when used in the elderly, patients presenting signs of heart failure, chronic kidney diseases and black patients (Tamargo *et al.,* 2014b:607). Based on several studies, Musini *et al.* (2015:16) has demonstrated that the best lowering effect of loop diuretics on blood pressure over an 8-week period was estimated at 8/4 mmHg for both systolic and diastolic blood pressure.

Loop diuretics are primarily used in individuals with chronic kidney diseases (CKD) and renal insufficiency, or patients with a glomerular filtration rate (GFR) below 30 ml/min/1.73 m^2 (Munar & Singh, 2007:1488). Doses of furosemide below 80 mg have proven their efficacy in advanced CKD patients because of the renal dysfunction and should range between 80 to 160 mg (Oh & Han *al.*, 2015:17). Due to its high protein binding, no modification of the dose of furosemide in patients undergoing haemodialysis is necessary (Oh & Han*,* 2015:17-18).

Furosemide given twice daily for elevated blood pressure appears to be more effective than a single daily dose (Tamargo *et al.,* 2014b:607); once absorbed from the gastrointestinal tract, the diuretic effect of furosemide occurs between 1-1.5 hours after administrating it orally and between

10 and 30 min after I.V. injection (Oh & Han, 2015:17). The bioavailability of furosemide ranges from 10 to 90%, and may be disrupted by food, it should be administered before eating (Oh & Han, 2015:17), however, furosemide (>95%) binds to plasma proteins. Approximately 50% of furosemide remains unchanged in the urine when excreted and the rest is metabolised into glucuronide in the kidneys (Oh & Han, 2015:17). The other 50% is conjugated with glucuronic acid; patients with a decline in renal function for instance, have an increased plasma half-life of furosemide (Oh & Han, 2015:17).

Compared to furosemide, torsemide has 97% to 99% protein binding, and is metabolised by hepatic cytochrome P450 enzyme system (Vadivelan & Dabhi, 2013:386). Torsemide is eliminated through hepatic metabolism (73%) and through the urine (27%), with diuresis lasting 6 to 8 hours (Vadivelan & Dabhi, 2013:386). Torsemide's bioavailability is 90% to 100% and is not affected by chronic kidney diseases, conversely to furosemide where absorption is decreased by renal failure (Vasavada *et al.,* 2003:632).

According to Vasavada *et al*. (2003:637), torsemide and furosemide have similar effects on blood pressure; with torsemide significantly reducing systolic blood pressure by 9.7 ± 10 mmHg ($p = 0.007$) compared to 9.2 ± 12.6 mmHg for furosemide ($p = 0.021$) post-treatment. Adding to this, data obtained from randomised controlled clinical trial demonstrated that reducing systolic blood pressure by about 12 to 13 mmHg over a period of 4 years with loop diuretics might significantly reduce cardiovascular mortality rate by 25% and coronary heart diseases by 21% (Vasavada *et al.,* 2003:640).

Loop diuretics exhibit different side effects from excessive diuresis, electrolyte disturbances, hypersensitivity and ototoxicity (Tamargo *et al.,* 2014b:610-611). Electrolyte disturbances are characterised by dehydration, hypokalemia, hyponatremia, low levels of Ca^{2+} and $Mg^{2+,}$ and hypovolemia (Tamargo *et al.,* 2014b:610). Tamargo *et al.* (2014b:610) furthermore indicated that lowering the dose of diuretic can reduce hypovolemia, and serum potassium levels below 3.5 mEq/l (hypokalemia) and magnesium levels below1.4 mEq/l (hypomagnesia) may cause fatigue, constipation, anorexia and muscle cramps along with nausea and gastric irritation.

Otoxicity in loop diuretics is reversible and can cause vertigo, deafness, tinnitus and allergies (Tamargo *et al.,* 2014b:611). Furosemide, for instance, is a sulphonamide; taking the drug can cause a skin rash to develop or allergic interstitial nephritis (Oh & Han*,* 2015:19-20). Loop diuretics-induced hypokalemia increases the risk of developing arrhythmias, therefore, caution should be taken for patients receiving digoxin (Oh & Han*,* 2015:20). When used with other antihypertensive drugs, effects can be enhanced and concomitant use of opioids, baclofen, alcohol, antidepressants and barbiturates may cause postural hypotension (Tamargo *et al.,*

2014b:611).

Loop diuretics, (for example furosemide), when co-administered with non-steroidal anti-inflammatory drugs (NSAIDs) can cause sodium retention, azotemia and hyperkalemia because of reduced vasodilatation and natriuretic effects of NSAIDs (Oh & Han*;* 2015:19). Other drug-interactions include aminoglycosides, amphotericin B, cephalosporins and cisplatin, which may increase the risk of nephrotoxicity. Concomitant use with cyclosporine reduces renal urate excretion, therefore patients with gout should avoid taking loop diuretics, beta-agonists, xantines and corticosteroids, which may increase the risk of hypokalemia and finally, warfarin may not bind to blood proteins if used with loop diuretics (Tamargo *et al.,* 2014b:611).

Furosemide and torsemide should not be prescribed to patients who are allergic to sulphonamide or sulphonylureas; they can be replaced by ethacrynic acid and finally, to prevent dehydration and renal insufficiency, doses of loop diuretics should be adjusted according to the hepatic and renal function of the patient (Oh & Han*,* 2015:20).

Loop diuretics can be used in combination with other diuretics as they can inhibit Na^+ reabsorption at different sites of the nephron (Munar & Singh, 2007:1488) and are the preferred drugs for individuals with renal disease, heart failure and pulmonary oedema (Nguyen *et al.,* 2010:49).

- **Thiazide diuretics and thiazide-like diuretics**

Thiazide diuretics are the mainstay in the treatment of high blood pressure; compared to other antihypertensives, thiazide diuretics are largely considered by the JNC 7 (Joint National Commission for Detection, Evaluation and Treatment of Hypertension) and ESH/ESC guidelines (Salvetti & Ghiadoni, 2006:25; Shah *et al*., 2004:275; WHO, 2013) as first choice drugs for essential high blood pressure (Jennings & Cook, 2010:8). The use of these diuretics has been approved as essential for hypertension control due to their ability to reduce peripheral resistance and to sustain blood pressure reduction (Singh & Johnson, 2005:85).

Thiazide diuretics and thiazide-like diuretics exert their action mainly in the distal convoluted tubule (DCT) of the nephron; they inhibit Na^+/Cl^- reabsorption by blocking the apical Na^+/Cl^- symporter in the early segment of the DCT (Shah *et al.,* 2004:274). Subsequently, elimination of sodium, chloride, potassium and magnesium are increased in the urine and calcium reabsorption is enhanced (Tamargo *et al.,* 2014a:529). Consequently, moderate natriuretic effects are observed; diuresis occurs; plasma volume, venous return and cardiac output are reduced; resulting in hypotension (Tamargo *et al.,* 2014a:529-531). The natriuretic effect of thiazide diuretics can disappear if the glomerular filtration rate (GFR) is below 40 ml/min, except for

metazolone, which can be effective with a GFR of 20 ml/min (Shah *et al.*, 2004:271). The use of thiazide-type diuretics and thiazide-like diuretics may present different results on blood pressure because of their pharmacokinetic and pharmacodynamic properties (Olde Engberink *et al*., 2015:1033). Thiazide-like diuretics such as chlortalidone are mainly bound to plasma proteins (99% is bound to erythrocytes) and are orally well absorbed in the gastro-intestinal tract (Ernst & Moser, 2009:2153); however, due to their limited glomerular filtration, the drug is slowly excreted in the urine by the proximal tubular secretion in the kidneys (Tamargo *et al*., 2014a:532). Chlorthalidone, unlike hydrochlorothiazide, has strong inhibitory effects and a longer half-life of about 50 to 60 hours compared to 8 to 15 hours for hydrochlorothiazide after long-term dosing (Carter *et al.,* 2004:4-5). Chlorthalidone, therefore, results in better inhibition of blood pressure within a 24-hour period (Olde Engberink *et al*., 2015:1033).

Thiazide-like diuretics appear to have more beneficial effects and may decrease the risk of cardiovascular events by more than 12% ($p = 0.049$) and mortality by 21% ($p = 0.023$), compared to thiazide-type diuretics (Olde Engberink *et al.,* 2015:1037-1038). Low doses of hydrochlorothiazide (25-50 mg) or chlorthalidone (12.5-25 mg) may prevent stroke by 34%, chronic heart diseases by 28%, congestive heart failure by 42% and total mortality by 24%. For this reason, it remained the first-line drugs in the management of high blood pressure and have been recommended to prevent morbidity and mortality associated with elevated blood pressure (Tamargo *et al.*, 2014a:533). Overall, thiazide diuretics reduce blood pressure by 9/4 mmHg (Musini *et al.*, 2014:1). Therefore, thiazide diuretics, used as monotherapy at low doses such as 12.5 mg/day for hydrochlorothiazide, 1.5 mg/day for indapamide and 12.5 mg/day for chlorthalidone, induce a reduction of systolic BP of 10-12 mmHg and diastolic blood pressure of 5-10 mmHg (Tamargo *et al*., 2014a:533). Most type of thiazide diuretics have an onset of action of about 2 to 3 hours (Ernst & Moser, 2009:2153).

According to Musini *et al*., (2014:1) only hydrochlorothiazide has a dose-related hypertension lowering effect. Therefore, from doses 6.25 mg and 12.5 mg of this drug, blood pressure was reduced by 4/2 mmHg and 6/3 mmHg respectively; whereas other thiazide diuretics, such as chlorthalidone, decreases hypertension by 12.0/4.0 mmHg and indapamide (1.0-5.0 mg/day) by 9/4 mmHg, at doses 12.5 mg to 75 mg (Musini et al., 2014:1).

The main adverse effects of thiazide diuretics include electrolyte disturbances, metabolic disorders such as hyperglycaemia at higher doses, increased plasma triglycerides, nausea, gastric irritation, allergic reaction, increased uric acid reabsorption and sexual dysfunction (Magrini, 2008:18; Reilly *et al.*, 2010:1899).

Thiazide diuretics are first-line drugs for the management of hypertension, nephrolithiasis,

isolated high systolic blood pressure, hypertension in blacks, and are used to prevent cardiovascular events such as congestive heart failure (Catena *et al.*, 2012:67). Chlorthalidone appears to be the best option for first-line therapy, and combination with other drugs will enhance blood pressure reduction significantly.

- **Potassium-sparing diuretics**

Potassium-sparing agents are mostly used in combination with thiazide diuretics or loop diuretics to prevent potassium depletion (Shah *et al.*, 2004:275). These drugs exert their action through a different mechanism (Catena *et al.*, 2012:68), for example, spironolactone and eplerenone competitively prevent aldosterone binding to the mineralocorticoid receptor in the distal tubule and collecting duct of the nephron, whereas others such as amiloride and triamterene, block epithelial sodium channels in the distal tubule and collecting tubule (Tamargo *et al.*, 2014b:612).

Potassium sparing agents are not recommended as drugs of first choice in hypertension because of its weak effect on elevated blood pressure (Unni, 2016:652); however, their use has proven their efficacy in patients with resistant high blood pressure associated with excess mineralocorticoid and aldosterone-renin ratios (Shah *et al.*, 2004:275). Individuals with hyperaldosteronism often develop high blood pressure, cardiovascular events such as stroke and present with left ventricular hypertrophy (Aronova *et al.,* 2014:228, Milliez *et al.,* 2005:1246-1247).

Spironolactone is the drug of choice for elevated blood pressure and may decrease the overall blood pressure by 26/10 mmHg after one month of treatment (Tamargo *et al.*, 2014b:613). The meta-analysis by Catena *et al.* (2012:76) indicated that doses of 100 to 500 mg of spironolactone per day reduce blood pressure by 20/7 mmHg, but because of the high risk of hyperkalaemia, spironolactone should be used in combination with other drugs and diuretics. The addition of spironolactone (25 mg) to three other antihypertensive drugs in patients with uncontrolled elevated blood pressure, lowered blood pressure by 21.9/9.5 mmHg (Tamargo *et al.*, 2014b:613), thereby providing more hypotensive effects.

Conversely, eplerenone has a more selective inhibition of aldosterone receptors than for androgen or progesterone receptors; both drugs are well absorbed in the gastrointestinal tract, with an oral bioavailability of 65% for spironolactone and 95% for eplerenone (Catena *et al.*, 2012:75-79). They mainly bind to plasma proteins, approximately 90% and 50% for spironolactone and eplerenone, respectively.

Once administered, spironolactone undergoes hepatic first pass metabolism within 1.6 hours (Catena *et al.*, 2012:74), its active metabolite has a much longer half-life of about 20 hours (Ernst

& Moser, 2009:2157). Eplerenone half-life is short ~ 5 hours, is mainly metabolised in the liver via CYP3A4, and has no active metabolites. For epithelial sodium blockers such as amiloride, oral bioavailability is poor and the drug remains unchanged in the urine, while triamterene undergoes liver metabolism and 50% of its active metabolite is eliminated through the urine (Tamargo *et al.*, 2014b:614).

The main adverse effect of potassium sparing agents is hyperkalaemia, particularly in patients with kidney diseases and elderly or individuals with type 2 diabetes mellitus (Tamargo *et al.,* 2014b:614). Other side effects include sexual dysfunctions, gynecomastia, hypotension, diarrhoea, rashes, metabolic acidosis and chronic renal failure (Tamargo *et al.*, 2014b:614).

Overall, thiazide diuretics used as monotherapy reduce systolic blood pressure by 7.3 mmHg, compared to angiotensin converting enzyme inhibitors (6.8 mmHg), beta-blockers (9.3 mmHg) and calcium channel blockers (8.4 mmHg) (Tamargo *et al.*, 2014a:536).

2.6.5.2.2 Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme (ACE) inhibitors are the drugs of choice for most hypertensive patients with concomitant diseases such as heart failure, left ventricular dysfunction, myocardial infarction, ischaemic heart diseases (Ţânţu *et al*., 2014:452) and diabetes associated with proteinuria (Bhuyan & Mugesh, 2011:883; Michel & Hoffman, 2011:777). Angiotensin converting enzyme inhibitors are divided in three groups; (a) the sulphydryl-ACEI with captopril, (b) the dicarboxylic angiotensin converting enzyme inhibitors with benazepril, cilazapril, enalapril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril; and (c) the phosphorous-angiotensin converting enzyme inhibitors with fosinopril (Hilal-Dandan, 2011:731).

Angiotensin converting enzyme inhibitors have beneficial effects in various patients with hypertension. The renin angiotensin aldosterone system (RAAS) plays a significant part in regulating blood pressure in the long or short term; angiotensin detains high vasoconstrictor effects, then stimulates aldosterone secretion, which increases sodium and water retention (Willey, 2002:1); consequently, presenting increased angiotensin results in acute elevation of blood pressure (Silva, 2012:85). Elevated blood pressure is directly related to a reaction of RAAS (Ferrari, 2013:1). Angiotensin converting enzyme inhibitors prevents angiotensin converting enzyme from catalysing the conversion of inactive angiotensin I to angiotensin II (Bhuyan & Mugesh, 2011:881), thereby reducing blood pressure. In a more explicit way, angiotensin converting enzyme inhibitors enhance the biosynthesis of other vasodilating substances (prostaglandin E2 and prostacyclin) by antagonising the degradation of bradykinin, subsequently, increased bradykinin improves the blood pressure, lowering effects of angiotensin converting

enzyme inhibitors (Schwinghammer, 2009:119).

Vega (2009:3) reported that, with half of the maximum dose recommended, angiotensin converting enzyme inhibitors might reduce blood pressure by 6 to 9/ 4 to 5 mmHg. Adding to this, a meta-analysis study has revealed that using angiotensin converting enzyme-inhibitors reduce the risk of stroke by 28%, cardiovascular events by 11% (Ţânţu *et al.*, 2014:455) and mortality by 10% (Van Vark *et al.,* 2012:2094), therefore improving the quality-of-life of patients.

According to Ţânţu *et al*. (2014:455) and Schwinghammer (2009:119), the main side effects reported with the use of Ramipril, for instance, were headache (2.4%), dizziness (1.8%) and cough (3%). Furthermore, Matchar *et al*. (2008:16) indicated that the main adverse effects of angiotensin converting enzyme inhibitors were cough (5% to 20%) and angioedema (0.1% to 0.2%).

Most angiotensin converting enzyme inhibitors, except for fosinopril that is eliminated by the liver and the kidneys, undergo renal elimination and are usually well absorbed orally (Hilal-Dandan, 2011:732). Captopril for instance, has a bioavailability of ~75%, a half-life of ~2 hours and its absorption can be reduced to ~30% if administered with food. Therefore, it is recommended to be taken 1 hour before meals at oral doses of 6.25 to 150 mg, two to three times daily. Compared to captopril, enalapril is a prodrug, hydrolysed in the liver to an active metabolite. Enalapril has a bioavailability of 60%, and a half-life of 1.3 hours (Hilal-Dandan, 2011:732-734). Overall, angiotensin converting enzyme inhibitors are mainly prodrugs and are hydrolysed to active compounds in the liver (Ţânţu *et al.*, 2014:452).

Angiotensin converting enzyme inhibitors are not recommended during pregnancy due to severe foetal adverse effects and bilateral renal artery stenosis; besides a dry cough and angioedema as the main side effects. Other side effects include hypotension, hyperkalaemia, particularly for those taking a potassium supplement, K-sparing agents and NSAIDs (Michel & Hoffman, 2011:778), neutropenia, skin rash and nephrotic syndrome caused by the sulphydryl group of some angiotensin converting enzyme inhibitors (Hanif *et al*., 2010:16).

Angiotensin converting enzyme inhibitors are drugs of choice for hypertensive patients with diabetes associated with proteinuria, post-myocardial infarction, congestive heart failure and left ventricular hypertrophy (Hanif *et al*., 2010:13-14). It is more effective as monotherapy in Caucasian than in black patients, except when used with other antihypertensive drugs such as calcium channel blockers or diuretics (Weber *et al.*, 2014:10).

2.6.5.2.3 Angiotensin receptor blocking agents

Angiotensin receptor blocking agents should be first choice in the treatment of high blood pressure among young patients (<50 years) if angiotensin converting enzyme inhibitors are not tolerated (Poulter, 2010:7). This class of medication competitively blocks angiotensin II receptors (Barreras & Gurk-Turner, 2003:123). Blood pressure lowering effects occur as angiotensin receptor blockers directly block angiotensin type I receptors (AT1), they enhance smooth muscle vasodilatation, induce renal salt and water excretion, reduce catecholamine release, decrease plasma volume and cellular hypertrophy (Michel & Hoffman, 2011:778). Furthermore, angiotensin receptor blockers decrease peripheral vascular resistance, cardiac preload and afterload, causing a decrease in BP (Abraham *et al.,* 2015:34). Fuchs and DiNicolantonio (2015) indicated that angiotensin receptor blockers might decrease the risk of stroke, heart failure and development of type 2 diabetes mellitus. In addition, a meta-analysis study done by Savarese *et al.* (2013:139), demonstrated a significant decrease of stroke by 9.1% and new-onset of diabetes by 10.6% with angiotensin receptor blockers. Other randomised controlled trials of angiotensin receptor blockers showed a mean reduction of blood pressure around 7 to 21/ 6 to 10 mmHg (Abraham *et al*., 2015:27). The drugs include losartan, candesartan, irbesartan, valsartan, telmisartan, olmesartan and eprosartan and like angiotensin converting enzyme inhibitors; they benefit hypertensive patients with left ventricular hypertrophy, diabetes (Schwinghammer, 2009:120) and congestive heart failure (Dunlap & Peterson, 2002:436).

From Barreras and Gurk-Turner (2003:123), angiotensin receptor blockers' bioavailability appears to be low (<50%) except irbesartan (70%); protein binding is relatively high ~95% and they undergo hepatic and renal excretion. Candesartan cilexetil, a prodrug hydrolysed to its active metabolite candesartan, has a 67% elimination through the liver and 33% through the kidneys once administered, and a half-life of 9 hours (Hilal-Dandan, 2011:788).

Angiotensin receptor blockers are highly effective and well tolerated by most people; they do not produce any of the traditional side effects of other antihypertensive medications, and they are less likely than angiotensin converting enzyme inhibitors to cause a cough (Barreras & Gurk-Turner, 2003:124). In addition, angiotensin receptor blockers prevent the breakdown of bradykinin (Schwinghammer, 2009:119-120). Side effects of angiotensin receptor blockers include hyperkalaemia, rash and hypotension, and the drug is contraindicated in pregnancy due to harmful effects on the foetus (Barreras & Gurk-Turner, 2003:124).

2.6.5.2.4 Calcium channel blockers

Calcium channel blockers, combined with other drugs or used as monotherapy, are mostly recommended by ESH/ESC guidelines and JNC7 as the drugs of choice in the treatment of

essential high blood pressure and concomitant diseases such as diabetes, associated with hypertension (Sica, 2006:53-54; Nguyen *et al*., 2010:53). They are the preferred drugs for reducing blood pressure levels in individuals from African descent, advanced age patients with isolated systolic blood pressure and patients presenting a history of stroke, peripheral artery disease and left ventricular hypertrophy (Tocci *et al.*, 2014:2-3).

Calcium channel blockers are divided into three subgroups; (1) dihydropyridines (including nifedipine, nicardipine, felodipine, amlodipine, aranidipine, azelnidipine, clinidipine and efonidipine), which exert their action on peripheral blood vessels (Nguyen *et al.*, 2010:53); (2) phenylalkylamines (verapamil and gallopamil) and (3) benzothiazepines (diltiazem and clenazem), which act on cardiac muscles and peripheral blood vessels (Ozawa *et al*., 2006:104). Calcium channel blockers inhibit the entry of calcium across sensitive voltage calcium (α1-subunit L-type) channel, block calcium entry into the cell, lead to cardiac and vascular smooth muscle relaxation, weaken heart contractions and dilate blood vessels (Schwinghammer, 2009:120); consequently, total peripheral resistance decreases and blood pressure is lowered (Michel & Hoffman, 2011:777).

Only 50% of stage I or II hypertensive patients may respond to calcium channel blockers monotherapy (Sica, 2006:55). In a meta-analysis study, calcium channel blockers have demonstrated the same efficacy in lowering blood pressure and preventing cardiovascular events compared to other antihypertensive drugs (α-blockers, diuretics, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and beta-blockers); however, calcium channel blockers appeared to be more effective in reducing stroke (Jeffers *et al*., 2017:68). In addition, current meta-analysis confirmed that treatment of high blood pressure with Calcium channel blockers may reduce stroke by 7% conversely to diuretics or beta-blockers, and by 12% compared to angiotensin converting enzyme inhibitors (Sica, 2006:56), but are not beneficial for patients with heart failure as they deteriorate cardiac function (Ozawa *et al.,* 2006:105).

According to Michel and Hoffman (2011:758), the hemodynamic effects of calcium channel blockers are dependent on the route of administration. Dihydropyridines appear to be more potent than verapamil and diltiazem) (Michel & Hoffman, 2011:758). Furthermore, amlodipine, a dihydropyridine, has a slow absorption rate and a prolonged effect (half-life is 35-50 hours) (Michel & Hoffman, 2011:758). Verapamil has more direct negative chronotropic, dromotropic and inotropic effects (Ebadi, 2007:494), but is more potent than diltiazem (Seth, 2009:V.35). Calcium channel blockers are mainly used for angina, myocardial infarction, isolated blood pressure in elderly, cardiac arrhythmias and hypertension (Rosendorff *et al.*, 2007:2769-2780).

The main side effects reported with calcium channel blockers are polyuria, peripheral oedema,

tachycardia particularly with dihydropyridines and gastroesophageal reflux (Schwinghammer, 2009:120-121). Calcium channel blockers may increase the incidence of heart failure (Jeffers *et al*., 2017).

2.6.5.2.5 Direct vasodilators

The preferred direct vasodilators usually used to treat high blood pressure are, hydralazine and minoxidil for oral use (Nguyen *et al*., 2010:53), and nitroprusside, diazoxide and fenoldopam for parenteral use (Michel & Hoffman, 2011:781-783).

Minoxidil and hydralazine lower the blood pressure by causing a direct arteriolar smooth muscle relaxation (Schwinghammer, 2009:123). Blood pressure lowering effect by hydralazine is linked with selective decrease in vascular resistance in the renal, coronary and cerebral circulation; hence arteriolar smooth muscle relaxation occurs by inhibiting IP3-induced release of $Ca2^{+}$ from intracellular storage sites (Michel & Hoffman, 2011:783). Direct vasodilators are usually well absorbed and they undergo hepatic metabolism (Schwinghammer, 2009:123). Hydralazine has a half-life of 1 hour with a low bioavailability caused by first pass effect of liver metabolism (Rosendorff *et al*., 2007:2769). Hydralazine is the preferred drug for pre-eclampsia (Iqbal, 2011:12) and has been recommended for hypertensive emergency in pregnancy (Campbell *et al*., 2011:473); many practices worldwide use hydralazine as first choice in women with elevated blood pressure (Duley *et al.,* 2013). In addition, Campbell *et al.* (2011:475) indicated in their studies that parenteral administration of hydralazine was followed by a markedly reduced blood pressure of -24/9 ± -29/15 mmHg, and severe hypotension presented a significant decrease in systolic blood pressure, ranging from -27 to -10 mmHg.

Minoxidil, compared to hydralazine, has a plasma half-life of 3 to 4 hours and is effective in patients with refractory hypertension (Lee *et al.*, 2011:33). The hypotensive effects can last 72 hours; minoxidil alone may reduce blood pressure from 188/124 mmHg to 159/108 mmHg (29/16 mmHg) and concomitant use with other drugs such as beta-blockers may further reduce blood pressure (Sica, 2004:286). Adverse effects reported with the use of minoxidil, include reflex tachycardia, hypertrichosis, fluid retention, weight gain, pulmonary congestion and alteration of renal function (Lee *et al.,* 2011:35).

Nitroprusside is mainly used for hypertensive crisis (blood pressure 180/110 mmHg), heart failure, cardiac and aortic surgery (Hottinger *et al*., 2014:463). Nitroprusside produces vasodilation by releasing nitric oxide that in turn activates the guanylyl cyclase-cyclic GMP-PKG pathway (Hottinger *et al.,* 2104:463-466). The side effects of nitroprusside include accumulation of cyanide and methhemoglobinemia, nausea and vomiting (Udeh *et al*., 2015:1433).

Diazoxide and fenoldopam are also used in hypertensive crisis (Fenves & Ram, 2005:276-278). Fenoldopam is a dopamine-receptor agonist (DA1) that decreases total peripheral resistance, whereas diazoxide acts by opening of the potassium channel and inducing vasodilation, thereby lowering blood pressure (Fenves & Ram, 2005:276-278).

2.6.5.2.6 Sympatholytic agents

Alpha-methyldopa, clonidine, guanabenz and guanfacine are the principal centrally acting agents used in the treatment of elevated blood pressure (Sica, 2007:401-403). They act by stimulating α2-receptors in the brain, subsequently decreasing sympathetic flow and enhancing vagal tone; as a consequence, heart rate along with total peripheral resistance, cardiac output, baroreceptors reflex and plasma renin activity decrease (Schwinghammer, 2009:122). Clonidine is mainly used for hypertensive urgencies and to diagnose pheochromocytoma (Sica, 2007:402). Guanfacine appears to be a more selective α2-receptor agonist than clonidine (Sica, 2007:402).

Alpha-methyldopa is a prodrug with a half-life of ~2 hours and plasma peak concentration of 2-3 hours (Michel & Hoffman, 2009:773. The side effects of α-methyldopa include sedation, dry mouth, hyperprolactinemia, depression, decreased libido and a positive coombs test (Schwinghammer, 2009:122). Because of its effectiveness and safety for the child and the mother, α-methyldopa is the preferred drug for pregnancy, with an initial dose of 250 mg/day (Michel & Hoffman, 2009:773).

Guanethidine and reserpine both lower blood pressure by decreasing sympathetic tone (Griffith, 2003:14). Guanethidine is an orally active antihypertensive drug; once taken up into adrenergic neurons, guanethidine binds to the storage vesicles and prevents release of the neurotransmitter in response to a neuronal impulse, then sympathetic tone decreases (Griffith, 2003:14). Reserpine lowers blood pressure by inhibiting the effect of the sympathetic nerve terminals releasing norepinephrine; consequently, sympathetic tone is decreased, and a blood pressure lowering effect occurs (Schwinghammer, 2009:123).

2.6.5.2.7 Adrenoceptor blocking agents

Adrenoceptor blocking agents reduce the actions of endogenous neurotransmitters or other sympathomimetics (epinephrine or nor epinephrine) (Benowitz, 2007:159). These drugs include the alpha- and beta-blockers.

- Beta-blockers

Beta-blockers lower blood pressure through several mechanisms (Mehmood *et al.,* 2011:1031). As a result of a β-1 adrenergic receptor blockade, a decrease in blood pressure is observed (Nguyen *et al*., 2010:53). Furthermore, inhibition of renin secretion occurs, leading to a decrease in the production of angiotensin II (Michel & Hoffman, 2009:771), sympathetic outflow is diminished along with vasomotor tone and reduction of venous return and plasma volume, so baroreceptor reflexes occur (Mehmood *et al.*, 2011:1031). Beta-blockers include propranolol and metoprolol, undergo first-pass metabolism; moreover, atenolol, betaxolol, bisoprolol and metoprolol are cardio selective at lower doses; and acebutolol, carteolol, penbutolol and pindolol have intrinsic sympathomimetic activity (Schwinghammer, 2009:121).

Beta-blockers have proven their effectiveness in angina pectoris, and are the drugs of choice for hypertension associated with acute myocardial infarction and congestive heart failure (Mancia, 2009:A6; Nguyen *et al*., 2010:53). Beta-blockers are also effective in decreasing hypertension morbidity and mortality in young hypertensive people (Larochelle *et al.*, 2014:S20).

Labetalol is a non-selective beta-blocker; it lowers blood pressure within 2 hours when administered orally and within 5 minutes after intravenous administration; it presents minimal intrinsic sympathomimetic activity. Compared to carvedilol, which has no intrinsic sympathomimetic activity, the blood pressure lowering effect is dose-dependent (Ram, 2010:1821).

Nebivolol, a third generation β-blocker, has antioxidant properties and is a highly selective agent with vasodilating effects (Akbar & Alorainy, 2014:1310); Nebivolol enhances vasodilation, by reducing systemic vascular resistance and releasing nitric oxide (Ram, 2010:1821).

Podymow and August (2007:967) emphasises that atenolol use should be avoided in pregnancy, because it has been associated with lower birth weights and neonatal hypoglycaemia, but could be used in the postpartum period (Hall, 2014:73). Hence, compared to atenolol, labetalol can decrease blood pressure in pregnancy without compromising utero placental blood flow, birth weight or causing neonatal hypoglycaemia (Ghanem & Movahed, 2008:42). According to Quang Nguyen *et al.* (2010:50), drugs such as carvedilol are approved in cardiac heart failure.

Mancia (2009:A7) advised hypertensive patients to avoid concomitant use of beta-blockers and diuretics, particularly in patients that are subject to developing diabetes due to the consequences of beta-blockers on glucose metabolism. Beta-blockers may have lower efficacy in patients from African descent and advanced age, and the main adverse effects recorded are fatigue and

reduced libido (Weber *et al*., 2014:12).

- Alpha1-receptor blockers

Alpha1-receptor blockers include prazosin, terazosin, doxazosin and alfuzosin (Chapman *et al.,* 2010:1797). These drugs mostly produce their effects by selectively antagonizing α1-receptors, then reducing the amount of catecholamine in the smooth muscle cells; as a result, smooth muscle dilation occurs and blood pressure is lowered (Schwinghammer, 2009:122). According to Chapman *et al*. (2010:1797), effects on reducing blood pressure have reported to be the same for all α1-receptor blockers, reducing hypertension by up to 10% in some patients (Sica, 2005:758). Prazosin and doxazosin decrease hypertension in 70% of people who are suffering with hypertension; daily doses of 1 to 2 mg of doxazosin decreased blood pressure by 13.4/11.2 mmHg (Chapman *et al.*, 2010:1797). Doxazosin provides additional beneficial effects for men with benign prostatic hypertension, by influencing the smooth muscle dilation in the prostate (Mathur *et al.*, 2014:44). Other beneficial effects occur in lipid and glucose metabolism, these include reducing total cholesterol, LDL-cholesterol and increasing HDL-cholesterol (Chapman *et al*., 2010:1797).

Associated negative effects of α-1 receptors are dizziness, intra-operative floppy iris syndrome (Mathur *et al*., 2014:43), headache, asthenia, syncope, impotence (Chapman *et al.*, 2010:1798), hypotension, sodium and water retention and urinary incontinence in women (Sica, 2005:760).

Other antihypertensive agents such as direct renin inhibitors (aliskiren) antagonise the RAAS (Schwinghammer, 2009:122), displacing angiotensinogen in a competitive way (Duggan, 2009:1). Therefore, the first step in the RAAS is blocked; consequently, angiotensinogen is not converted to angiotensin I (Wal *et al.*, 2011:191). Musini *et al*. (2008:4) has shown in a meta-analysis that aliskiren presents a dose-related effect of reducing blood pressure; aliskiren doses of 75 mg, 150 mg, 300 mg and 600 mg decrease blood pressure by 2.9/2.3 mmHg, 5.5/3.0 mmHg, 8.7/5.0 mmHg and 11.4/6.6 mmHg, respectively.

Aliskiren is usually well absorbed and presents a poor oral bioavailability (~2.5%) with lower elimination (Wal *et al.,* 2011:193). The side effects recorded are dizziness, headache, fatigue, cough and hyperkalaemia (Wal *et al.*, 2011:193).

2.6.5.2.8 Combination therapy

Combination therapy is the preferred solution in patients taking antihypertensive therapy who do not reach their target blood pressure, particularly when the other drug improves the side effect of the first one (Gradman *et al.*, 2010:47).

Fixed dose combinations may be used as an alternative method of treating high blood pressure where monotherapy has failed or for patients with concurrent diseases. According to Wan *et al*. (2013:2), statistics have demonstrated that the majority of hypertensive patients need two or more antihypertensive drugs to lower their blood pressure effectively. Fixed-dose combinations appear to be a novel and underlying power in overcoming cardiovascular disease. Furthermore, clinical practices proved that fixed-dose combinations had many benefits compared to single drugs and separate agents in terms of effects, convenience, compliance, and costs to a certain extent (Wan *et al*., 2013:2-3).

Combination therapy is effective in reaching the desire blood pressure level because it improves compliance, is potentially cost saving (Mitkova *et al*., 2016:2, Schellack & Malan, 2014:208) and offers the possibility to use lower doses, limiting the possibility for adverse drug reactions (Del Pozo *et al*., 2004:248).

There are beneficial effects using combination therapy; according to Volpe and Tocci (2012:372), the different classes of antihypertensive drugs used in combination therapy through multiple and complementary mechanisms of action provide synergistic effects on blood pressure, therefore a higher antihypertensive efficacy. Furthermore, Wald and co-workers (2009:299) identified in a meta-analysis of 42 trials performed on 11 000 patients with elevated blood pressure, that combination therapy provided an additive effect that was about five times greater than doubling the dose of one of the components (i.e. angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics, angiotensin receptor blockers or beta-blockers). A meta-analysis of 11 studies for instance, has proven that a fixed combination of perindopril and indapamide, given as one tablet daily, is effective as first-line treatment for patients with essential hypertension (Thomson & Greenacre, 2007:78). Furthermore, targeting multiple mechanisms provides advantages in the control of hypertension, allowing for the use of lower dosages (Rayner, 2007:22). Combination therapy may also decrease adverse events because of lower doses used and should be considered for initial therapy (Rayner, 2007:30; Wald *et al*., 2009:299).

The principle of combination therapy according to Rayner (2007:22) is to use two antihypertensive agents that have different mechanisms of action in a smaller dose, so that the efficacy of the single agents along with tolerability are improved. Therefore, the combinations for antihypertensive drugs that are recommended include angiotensin converting enzyme inhibitors and low dose diuretics; and calcium channel blockers and angiotensin converting enzyme inhibitors or angiotensin receptor blockers (Rayner, 2007:22; Schultz, 2009:26).

Combination of angiotensin converting enzyme inhibitors with thiazide diuretics, for instance, improves blood pressure control, particularly in those of African descent and patients with diabetes and vascular diseases because of lower renin levels (Reboldi *et al.*, 2009:413-414,

Shultz, 2009:28). Furthermore, Mitkova *et al*. (2016:5) stated that combining angiotensin converting enzyme inhibitors and calcium channel blockers reduce many side effects of calcium channel blockers, such as legs oedema.

Two-drug combination therapy may have additive effects, but there is about 15%-20% of the patient population who still have difficulties in achieving their target blood pressure, thus requiring a combination of three or more antihypertensive drugs (Volpe & Tocci, 2012:376).

Schellack and Malan (2004:206) stated in their study that the use of fixed-dose combination might enhance compliance and reduce metabolic side effects. Other useful fixed-dose combinations used to control blood pressure, that are acceptable, include two diuretics, beta-blockers and diuretics, Calcium channel blockers and beta-blockers (Mallat *et al.,* 2013: 73-74, Schellack & Malan, 2004:208).

Some combination therapies produce more side effects when combined, and are, therefore, not generally recommended (Rayner, 2007:24). These include beta-blockers and non-dihydropyridine calcium channel blockers (long-term use may cause bradycardia and heart blockage) (Rayner, 2007:24), thiazide diuretics and beta-blockers (Schultz, 2009:24), beta-blockers plus centrally acting agents (Gradman *et al*., 2010:45-46), dihydropyridine calcium channel blockers and α-blockers or hydralazine (Rayner, 2007:32).

The rational use of fixed-dose combination of diuretics and renin angiotensin system (RAAS) blockers, particularly angiotensin converting enzyme inhibitors or angiotensin receptor blockers, is the number of beneficial effects such as greater reduction in elevated blood pressure (Kalra *et al*., 2010:3). With salt loss, thiazide diuretics stimulate the effect of RAAS; release of renin and subsequent production of angiotensin II leads to vasoconstriction, sodium retention and activation of the sympathetic nervous system (Reboldi *et al*., 2009:412). On the other side, the addition of a RAAS inhibitor (e.g. angiotensin converting enzyme inhibitors, angiotensin receptor blockers or direct renin inhibitor) will counteract the metabolic effects of thiazide diuretics such as hyperglycaemia and hypokalaemia. This combination appears to be favourable and effective in populations from African descent in whom angiotensin converting enzyme inhibitor or angiotensin receptor blocker monotherapy has shown to be less effective because of low plasma renin levels (Rayner, 2007:22).

Another rational use of fixed-dose combination is calcium channel blockers and RAAS blockers. Calcium channel blockers, in addition to having vasodilating activity, stimulate sympathetic activity and improve the effect of RAAS (angiotensin converting enzyme inhibitor or angiotensin receptor blockers) on blood pressure (Rayner, 2007:23, Wan *et al.,* 2014:5). Angiotensin converting enzyme inhibitors, inhibit the central sympathetic stimulation that may result from calcium

antagonist associated vasodilatation, furthermore buffering the calcium channel blocker-induced activation of the renin-angiotensin-aldosterone axis (Kalra *et al*., 2010:4). The use of angiotensin receptor blockers and calcium channel blockers (interacting in a synergistic way), therefore, reduces side effects such as peripheral oedema caused by calcium channel blockers alone (Schultz, 2009:26). Currently, some published short-term studies assessing the efficacy and tolerability of amlodipine combined to angiotensin receptor blockers in patients with mild to moderate elevated blood pressure, have shown promising results (Rubio-Guerra *et al*., 2009:55).

Fixed dose combination of potassium-sparing agents and thiazide diuretics are mainly used to reduce the risk of metabolic effects and might prevent thiazide-induced diabetes, thereby improving blood pressure control, particularly in the case of resistant hypertension (Anderson, 2012:50, Grossman *et al*., 2011:314).

Others combinations such as dual RAAS-blocker combination (angiotensin converting enzyme inhibitors with angiotensin receptor blockers or direct renin inhibitors) may provide a more complete RAAS-blockade (Kalra *et al*., 2010:5).

According to Reboldi *et al.* (2009:412-413), fixed-dose combination therapy may simplify the use of antihypertensive drugs by limiting failures caused by missed doses. The combination of two or more hypertension medications has proven to be more effective in reaching target blood pressure in most patients and may lead to cost saving and better compliance (Mitkova *et al*., 2016:2).

The use of combination therapy entitles co-administration of two or more drugs carefully selected so that the target blood pressure levels are reached, treatment remains effective and compliance is improved (Gradman *et al*., 2010:42-44). Table 2-4 (Gradman *et al.,* 2010:44) indicates the recommendations for combination therapy.

Table 2-4: Recommended combination therapy

Preferred combinations	Acceptable combinations	Less effective combinations
RAAS + Diuretics	β-Blocker + Diuretics	ACEI + ARB
ACEI + Diuretic	CCB + Beta-blocker	ACEI + Beta-blocker
ARB + Diuretic	CCB + Diuretic	ARB + Beta-blocker
RAAS + CCB	Direct renin inhibitor + ARB	CCB + Beta-blocker
ACEI + CCB	Thiazide diuretic + potassium sparing agents	Centrally acting agent + Beta-blocker
ARB + CCB		

ACEI: Angiotensin converting enzyme-inhibitors, ARB: Angiotensin receptor blockers, CCB: Calcium channel blockers

Several drugs are used for the treatment of hypertension with other conditions. Figure 2-1 shows the choice of antihypertensive drug therapy according to these specific conditions.

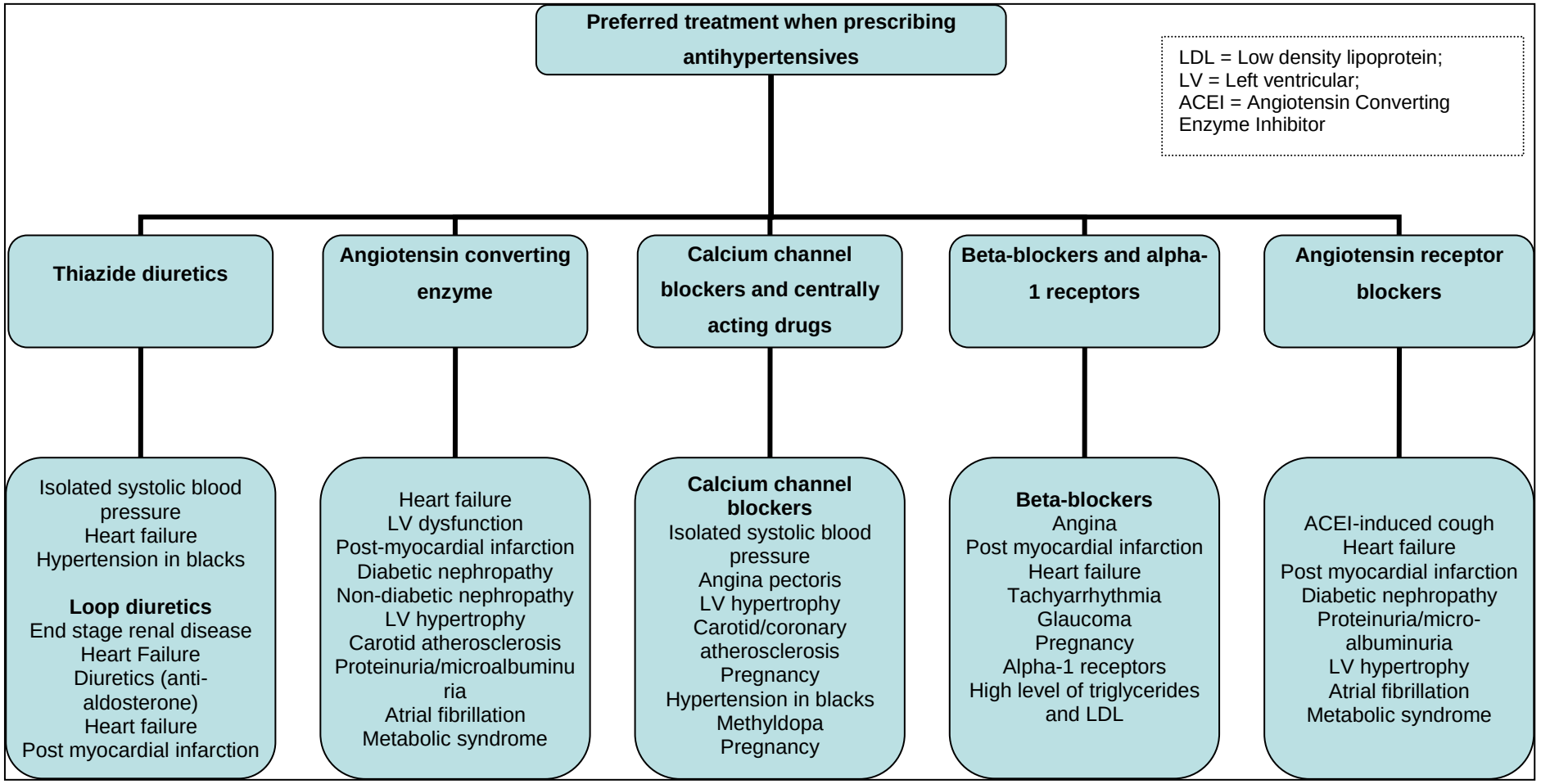

Figure 2-1: Choice of antihypertensive drug therapy according to some conditions

2.7 Conclusion

The blood pressure lowering effects of antihypertensive classes vary from one person to the next, for example, in African Americans, thiazide diuretics and calcium channel blockers are most effective at lowering blood pressure when used in combination with beta-blockers. Therefore, despite potential differences in antihypertensive effects, drug therapy selection should be based on compelling indications of what is recommended for the hypertensive population in general.

2.8 Chapter summary

This chapter (sections 2.2-2.5) provided an overview of CNAMGS. Therefore, its history, how the funding is collected and a comparison of drug selection programs within other health insurance systems in countries such as South Africa, Ghana, France, Canada and United States of America. Section 2.6 of this literature review focused on prevention, management and treatment of elevated blood pressure. To that end, Chapter 2 provided a comprehensive literature review related to the objectives of the literature phase of the study. The following chapter contains a description of the research method followed during the empirical investigation.

CHAPTER 3 RESEARCH METHODOLOGY

3.1 Introduction

This chapter contains the research methodology and gives insight into the study design including setting and data source, target and study population, and data collection tool and data collection process. Furthermore, data analysis is discussed along with study variables and the statistical analysis performed.

3.2 Research objectives and approach

The main objectives of the empirical investigation were to: (1) analyse the prescribing patterns of antihypertensive drugs stratified according to gender, age and prescribing health professionals, (2) determine the cost of all antihypertensive drugs prescribed within the period of the study in a pharmacy, and (3) determine the potential cost savings through generic substitution. In order to realise these objectives, a retrospective drug utilisation review (rDUR) of antihypertensive drugs reimbursed during the study period, was performed in a pharmacy. Certain steps are essential when conducting rDUR study (AMCP, 2009):

- Identify or determine optimal use: During this step, criteria for optimal use are identified depending on the relevant outcomes.
- Measure the actual use: In this step, data are collected and the actual use of the drug is determined.
- Evaluate: In this final step, appropriate and optimal use is compared. The application of these steps in the present study is described in subsequent paragraphs

3.2.1 Optimal use of antihypertensive drugs

The drugs should be identified and monitored for optimal use in advance. In this study, the appropriate use of antihypertensive drugs was identified through the literature review using the Joint National Committee (JNC) for Detection, Evaluation and Treatment of Hypertension (James *et al.,* 2014), the ESH/ESC guidelines for the treatment of hypertension (Mancia *et al.,* 2013a:1925-1938). The WHO/ISH statement on management of hypertension (Whitworth, 2003), the South African practice guidelines for hypertension (Seedat *et al.,* 2014) and the recommendations for prevention, diagnosis and management of hypertension and cardiovascular risk factors in Sub-Saharan Africa (Lemogoum *et al.,* 2003:1993-2000). Possible drug combinations and treatment regimens for treatment of hypertension were determined.

Antihypertensive drugs were classified according to the Anatomic Therapeutic Classification (ATC), classification of drugs obtained from the WHO Collaborating Centre for Drug Statistics and Methodology (2017), into the categories displayed in Table 3-1.

Table 3-1: Anatomical Therapeutic Classification (ATC) system for antihypertensive drugs

ATC-code	Drug class	Antihypertensive drug
C02	Antihypertensives	Alpha-methyldopa
C03	Diuretics	Indapamide, furosemide, spironolactone, hydrochlorothiazide
C07	Beta-blocking agents	Atenolol, bisoprolol, labetalol, propranolol, acebutolol, carvedilol
C08	Calcium channel blockers	Amlodipine, nicardipine, nifedipine, lercanidipine, diltiazem, verapamil
C09	Agents acting on renin-angiotensin system (angiotensin converting enzyme inhibitors or angiotensin receptor blockers)	Perindopril, captopril, enalapril, valsartan, candesartan

3.2.2 Measurement of the actual drug use

Data were gathered from claimed CNAMGS prescriptions and antihypertensive drugs were classified into plain formulations or fixed-dose combinations. Drugs were then categorised according to their active substances; strength and dosage form into pharmacological groups (such as angiotensin converting enzyme, angiotensin receptor blockers, calcium channel blockers, beta-blockers, central acting agents and diuretics). Finally, the prescribing of each drug according to total number of DDDs and DDDs/1000 inhabitants per day was determined and compared between the different classes of drugs used.

3.2.3 Evaluate: appropriate and optimal use are compared

In this part of the study, results of the study, such as the volume of the most prescribed drug and the cost of each drug were interpreted and compared according to criteria set in step one of the process (refer to paragraph 3.2.1).

3.3 Study design

This study followed a quantitative, cross-sectional design. Retrospective data of antihypertensive drugs prescribed for patients on the CNAMGS over a 12-month period (1 June 2013 to 31 May 2014) were employed. Retrospective designs measure variables that have occurred in the past (Brink *et al.,* 2012:10). In a quantitative, cross-sectional study, data are gathered at a specific

point in time, with focus on assessing measurable characteristics of human behaviour (Brink *et al.,* 2012:10).

3.4 Study setting and data source

The empirical investigation took place in a private pharmacy situated in Libreville, Gabon. This community pharmacy (one of the largest pharmacies in Libreville) was one of the first pharmacies working with the (CNAMGS) in Libreville. It is a community pharmacy composed of three pharmacists and one pharmacy manager, along with 30 staff members. The pharmacy, which is open every day to 22h00 in the evening, serves approximately a thousand people daily, providing pharmacy services such as the traditional dispensing of medicines, specialty compounding, smoking cessation support, nutritional support, health screening and disease management of malaria, hypertension and diabetes. In this study, CNAMGS prescription claims accounted for 34.2% of the total budget of the pharmacy.

The data source consisted of all prescriptions received from 1 June 2013 to 31 May 2014 in the pharmacy. Prescriptions from CNAMGS are made of three identical sheets called a “volet” (i.e. sheet); one is sent to CNAMGS for reimbursement, the second one goes to the patient as a receipt and the third is for the pharmacy. During the normal process of dispensing CNAMGS prescriptions in the pharmacy, drugs that are reimbursed by CNAMGS are dispensed and the patient pays the balance. Knowing that some drugs are reimbursed at 80% and other at 50% based on the CNAMGS list of selected medicines they reimburse, the till slip is attached to the sheet that is sent to CNAMGS for reimbursement, and a copy of the receipt is kept along with the sheet remaining at the pharmacy. Data fields available for research purposes included:

- Demographic information, such as patients’ age and gender.
- Drug prescribed (trade name, active ingredient and strength).
- Generic indicator (e.g. original drug or generic).
- The number of antihypertensive drugs prescribed per patient.
- Quantity of each drug prescribed.
- Dosing instruction.
- The cost of each drug per quantity dispensed including the drug price, patient levy cost and the cost paid by CNAMGS.
- Details on prescribers (such as the prescriber speciality).

- The Anatomic Therapeutic Classification (ATC) code of drugs.
- Date on which the prescription was issued.

3.5 Target and study population

The target population for this study included all the patients on CNAMGS with prescriptions filled for antihypertensives during the study period in Gabon. During this period, CNAMGS prescriptions represented 25.9% of the total prescriptions claimed, compared to other prescriptions at 4.5% (for private mutual and other medical aids). Overall, 28 289 patients with CNAMGS visited the study setting during the study period, claiming 51 838 prescriptions. The study population were defined as the set of patients who meet the inclusion criteria (Table 3-2). The data were filtered by means of the application of exclusion criteria.

Table 3-2: Inclusion and exclusion criteria for the study

Inclusion criteria	Exclusion criteria
All prescriptions containing at least one antihypertensive drug prescribed during the period 1 June 2013 to 31 May 2014.	Incomplete data with regards to prescriber-speciality. Unknown patient gender/date of birth.

A total of 1 586 (5.61%) patients claimed for antihypertensives at least once during the study period, thus forming the study population. There were no patients with unknown gender/date of birth and all data were complete with regard to prescriber-specialty.

3.6 Data-collection process

The process followed from obtaining permission to perform the study to the actual collection of data is described in subsequent paragraphs.

3.6.1 Permission to perform the study

After a prescription is claimed, the prescription remains the property of the pharmacy and the records are kept in the pharmacy for ten years. The researcher, as an employee of the pharmacy, had access to information required in the study on a daily basis as part of normal responsibilities as a pharmacist. Permission to use data for this research has been obtained from the pharmacy manager (refer to Annexure A).

3.6.2 Anonymity and confidentiality

Anonymity of data was assured by not capturing the patients' names, addresses or CNAMGS membership numbers. Each prescription analysed, was given a number, and only this number was recorded on the data collection tool to ensure the privacy and confidentiality of patients.

3.6.3 Development of the data-collection tool

In this study, the data-collection tool consisted of a data capture form developed in Microsoft Excel (2010) (refer to Annexure C). A blank CNAMGS prescription was used to develop the data capture form.

3.6.3.1 Validity of the data collection tool

Validity is determined as the extent to which conclusions made by the researcher reflect reality or as a tool used by the researcher to measure human experience (Brink *et al.,* 2012:127). The different types of measureable validity applicable to the present study are face and content validity.

3.6.3.1.1 Face validity

Face validity according to Oluwatayo (2012:392), is defined as a self-assessment or evaluation done by the researcher of its work and relevance to a questionnaire of whether the measuring instrument seems to be relevant, clear, unambiguous or reasonable. The criteria for evaluation may contain the structure of the instrument, unambiguity and clarity of the items, appropriateness, correct spelling, adequacy and reasonableness of items, attractiveness of the paper used and legibility of print out (Oluwatayo, 2012:392).

3.6.3.1.2 Content validity

Content validity of the data collection tool was ensured by sending it to other pharmacists in Libreville for validation. These pharmacists agreed that the survey form was clear and a true representation of the data source; the form was therefore regarded as valid. The supervisors of the project also assessed the data collection tool used for this study for face and content validity. Content validity focuses on the measuring instrument; therefore, analyses (if the measuring instrument has been made appropriately and the items analysed) should have a fair sample of the total potential content (Oluwatayo, 2012:392). Therefore, content validity requires good logic, intuitive skills and perseverance. Bowling (2014:174) defines content validity as the analysis brought forward to check if the measuring instrument can be logically examined and shows whether the measuring instrument contains the full characteristics of what it is supposed to be measure.

3.6.3.2 Reliability of the data-collection tool

Reliability of the research instrument is a further major concern of the researcher when collecting data (Brink *et al.,* 2012:169). Reliability in quantitative research can be regarded as the definition of dependability, consistency, reproducibility or replicability over time, of instruments and of groups of respondents (Oluwatayo, 2012:395). Reliability shows that if it were to be carried out on a similar group of respondents in a similar context, similar results would be obtained; therefore, it compares the data recorded by the researcher to that which occurs in the natural setting (Oluwatayo, 2012:395

In this study, reliability was mainly ensured by the researcher and involves completing the data collection; potential of inaccuracies/inconsistencies that may occur due to several data capturers was therefore be avoided. After data capturing, however, data were checked for outliers.

3.6.4 Data collection

After ethics approval was obtained, all prescriptions from CNAMGS received during the period of the study, (1 June 2013 to 31 May 2014) was sorted by hand, based on drugs prescribed. All prescriptions that complied with the inclusion criteria were then selected and exclusion criteria applied. Information on the prescriptions and on the costs of drugs (obtained from the till slip attached to each 'volet') was then transferred to the data capture form (Annexure C).

3.7 Data analysis

The procedures followed in the data analysis process is described in subsequent paragraphs.

3.7.1 Drug utilisation metrics

The drug utilisation metrics used in this study included the 90% drug utilisation (DU90%) segment, the total number of defined daily doses (DDDs), the DDD/1000 inhabitants/day, and cost per DDD.

3.7.1.1 The 90% drug utilisation (DU90%) segment

The drug utilisation 90% (DU90%) is defined as "the number of drugs accounting for 90% of drug use" (Bergman *et al.,* 1998:114). According to Bergman *et al*. (1998:115), the DU90% may serve as an indicator of the quality of drug prescribing. To determine the DU90%, drugs are ranked by volume of defined daily doses, and those contributing to 90% of the volume are then selected. In this study, the number of antihypertensive drugs using within DU90% was identified.

3.7.1.2 The total number of defined daily doses (DDDs)

The defined daily dose indicates the "*assumed average maintenance dose per day for a drug used for its main indication in adults*" (WHOCC, 2017). The number of DDDs is only calculated for drugs with an ATC-code; in this study, the number of DDDs for plain formulation was calculated using the following equation (Nachiya *et al.,* 2014:386):

$$Number\ of\ DDDs = \frac{Quantity\ of\ drug\ dispensed(g)}{DDD(g)}$$

Where:

Quantity of drug dispensed (g) = the overall quantity of the drug dispensed in gram (thus the number of items dispensed multiplied by the strength of drug in gram)

DDD= Defined Daily Dose as the World Health Organization assigned DDD for each drug, in gram.

The ATC-code and the DDDs for each drug were obtained through WHO Collaborating Centre for Drug Statistics and Methodology (WHOCC, 2017); DDD was given in milligrams (mg), then it was converted to grams (g). The DDD for combination products (fixed dose combinations) according to WHO Collaborating Centre for Drug Statistics and Methodology (2017) is calculated by using the combination as one (1) unit daily dose no matter the number of active substances present in the combination.

3.7.1.3 The DDD/1000 inhabitants per day

The DDDs/1000 inhabitant/day indicates the proportion of the study population treated daily with a particular drug or group of drugs. For instance, if the DDDs/1000 inhabitant/day is 10, it means that 1% of the population on average might receive a certain drug or group of drugs daily (WHO, 2003:38). DDDs/1000 inhabitant/day is used more for chronically used drugs, such as hypertension medications (WHO, 2003:38). The size of the population is useful when calculating DDDs/1000 inhabitant/day (WHO, 2003:38).

The DDDs/1000 inhabitant/day is calculated as follows (Salas, 2012):

$$DDD/1000\ inhabitants/day = \frac{Total\ Drug\ Consumption\ in\ 1\ year\ (mg) * 1000}{DDD(mg) * 365 * the\ number\ of\ inhabitants}$$

Where:

Total drug consumption in 1 year (mg) = the total dosage (strength) of a drug consumed in one year

DDD (mg) = Defined daily dose, is the World Health Organization assigned DDD for each drug

Number of inhabitants = Number of inhabitants under CNAMGS who visited the study setting during the study period (N = 28 289)

3.7.1.4 The cost per DDD

Drug utilisation can be interpreted in terms of cost (national currency) and can be used to identify drug expenditure (WHO, 2003:39). In this study, the cost/DDD was used to compare the costs of each pharmacological class of antihypertensive drugs. The cost/DDD was calculated in Central African Franc (XAF), using the total cost of each antihypertensive drug divided by the total number of DDDs within the study:

$$Cost\ per\ DDD = \frac{Total\ cost\ of\ the\ drug}{Total\ number\ of\ DDDs}$$

Where:

Cost of drug = Total cost of antihypertensive drug in Central African Franc (CFA), denoted by the ISO code 'XAF' XAF (). It is the currency used in six independent states in Central Africa, namely Cameroon, Central African Republic, Chad, Republic of the Congo, Equatorial Guinea and Gabon (one XAF was equal to R0.0223 for the period 1 June 2013 to 31 May 2014) (OANDA Corporation, 2017).DDD = Total number of defined daily doses for a specific antihypertensive drug or pharmacological class

3.7.2 Potential cost savings

According to Haas *et al.* (2005:891), generic substitution has the advantage of limiting drug expenditure, therefore, reducing the cost of some treatment such as hypertension. Potential cost savings by CNAMGS for drugs that have generic equivalents was calculated as followed:

$$Potential\ cost\ saving = \frac{\%\ Cost\ saving * \ Total\ cost\ reimbursed\ by\ CNAMGS\ of\ each\ drugs}{100}$$

With the percentage cost saving calculated as follows:

$$\%\ Cost\ saving = \frac{\left(\left(Mean\ cost_b - Mean\ cost_g\right) * \ 100\right)}{Mean\ cost_b}$$

Where:

Mean $cost_b$ = mean cost of brand name drug b

Mean $cost_g$ = mean cost of the generic equivalent

3.7.3 Study variables

The drug utilisation metrics used in this study was described in paragraph 3.7.1. Other dependent and independent variables included in the data analysis is depicted in Table 3-3.

Table 3-3: Dependent and independent variables

Variables	Description
Prevalence	In this study, prevalence were used to indicate the prevalence of hypertension by gender and age groups, and the number of antihypertensive prescribed, stratified according to age, gender and prescriber speciality.
Age group	Patients were categorised into four age groups below 30 years, between 30-44 years, 45-65 years, above 65 years.
Gender	The prevalence of hypertension among male and female patients was differentiated.
Drug prescribed (trade name)	The prevalence of drugs prescribed according to the different antihypertensive classes and trade names were determined.
Generic indicator (e.g. original drug or generic)	Antihypertensives were classified as either generic or innovators.
Drug strength	Drug strength represents the proportion of the active substance prescribed.
Prescriber speciality	Used to identify prescribing trends among different health professionals, categorised as general practitioners, specialists, nurses and interns.
Drug cost	The cost of per class and active substance of antihypertensive drugs was determined and expressed as the cost/DDD.

3.7.4 Statistical analysis

Data were analysed using SPSS for Windows version 23.0 (IBM Corp., 2013).

Statistical analysis is an important tool in medical research used to summarise the contents of a data set or to identify changes in a data set (Chernick & Friis, 2003:2). In this research project, descriptive, inferential statistics and effect sizes were used to determine the prescribing patterns and analyse the cost of antihypertensive drugs reimbursed by the CNAMGS.

3.7.4.1 Descriptive statistics

Descriptive statistics (explanatory data analysis) describes the content and summarises the data or makes a picture based on data by tabulating, organising and graphing the data (Chernick & Friis, 2003:2). Descriptive statistics employ numbers to describe a known data set (Heffner, 2014). The descriptive statistics used in the study, included frequencies (n) interpreted as percentage (%) values, arithmetic means, medians, standard deviations and 95% confidence intervals (CI).

3.7.4.2 Inferential statistics

Inferential statistics, instead, has two goals (estimate and predict); first it determines what is happening in a population based on a sample of the population and secondly, determines what will happen in future (Heffner, 2014); inferential statistics uses data to draw conclusions about the sample population. The inferential statistics employed in the study is described in the following section.

3.7.4.2.1 Two sample *t*-test

A two-sample *t*-test, also known as an independent sample test, determines or evaluates whether a significant difference exists between the mean values of a two-parent population (group) within a normal distribution (Peat & Barton, 2005:68). This test was used to assess whether the mean number of antihypertensive drugs prescribed is significantly different between males and females. According to Hartley (2013:33), the formula for calculating a *t*-value, when variances are equal is:

$$t = \frac{(x_1 - x_2)}{\sqrt{\left(\frac{Sp_2}{n_1} + \frac{Sp_2}{n_2}\right)}}$$

Where:

x = the mean.

Sp_2 = is the pooled variance.

n = the sample size of each group.

3.7.4.2.2 Chi-square test

A chi-square test makes use of categorical variables, therefore, determines whether the frequency of a condition is statistically different between two or more groups, knowing that the outcome and the exposure are independent (Peat & Barton, 2005:206). The chi-square test therefore assesses

whether an observed proportion agrees with expectations or if there is an association between two variables (Chernick & Friis, 2003:232). For this study, the chi-square test was used to determine the frequency of antihypertensive drugs prescribed according to age group or stratified by gender in this study. The Pearson chi-square value is calculated as follows:

$$Chi - square\ value = \left(\frac{(Observed\ frequency - Expected\ frequency)}{Expected\ frequency}\right)^2$$

Where:

Observed frequency = the observed data value

Expected frequency = the expected data value

The sample size may influence the *p*-value, and the larger the chi-square the more significant the *p*-value (Peat & Barton, 2005:210).

3.7.4.3 Analysis of effect size

Effect size is defined as "*the magnitude of the difference between groups*" (Sullivan & Feinn, 2012:279). In this study, Cohen's *d*-value and Cramér's *V* were used to indicate the effect size of statistically significant results, measured as a two-sided *p*-value of 0.05.

3.7.4.3.1 Cohen's *d*-value

Cohen's *d*-value is the effect size used to help in reporting a two sample *t*-test, analysis or variance; it describes the magnitude of the difference between mean values of two or more study groups relative to the size of their standard deviations (Peat & Barton, 2005:53). For instance, in this study Cohen's *d*-value was used to determine whether there is a significant difference in age between the male and female. A *d*-value of 0.2 indicates a small effect, 0.5 a medium effect and 0.8 a large effect (Peat & Barton, 2005:54). Cohen's *d*-value is obtained by the difference in mean values divided by the calculated standard deviations (SD) (Peat & Barton, 2005:53):

$$Cohen's\ d = \frac{(\bar{x}_1 - \bar{x}_2)}{SD}$$

Where:

$\bar{x}_1$= mean of first observation

$\bar{x}_2$= mean of second observation

SD = pool standard deviation

3.7.4.3.2 Cramer's *V*

Cramér's *V* is the effect size used to report a chi-square test; it measures the strength of association between two categorical (nominal) variables that include more than two levels (McHugh, 2013:148). A *V*-value of 0.1 indicates a smaller effect, 0.3 a medium effect and 0.5 a larger effect. (Rutten, 2013:41):

$$V = \sqrt{\frac{X^2}{n\,(k-1)}}$$

Where:

X^2 = the chi square formula (equation 3.6).

n = the total number of cases.

k = smallest number of categories of the two variables, that is the smallest number of the total number of rows or columns in the contingency table.

3.8 Chapter summary

This study described the research methodology, including data collection process, study population, variables used, data analysis and statistical analysis. The results and discussion pertaining to this study will be described in Chapter 4.

CHAPTER 4 RESULTS AND DISCUSSION

4.1 Introduction

The results of the empirical investigation are reported and discussed in this chapter. The specific objectives of the empirical investigation were addressed in paragraph 1.3.2 of this dissertation. The objectives were attained in different sections of this chapter, as depicted in Table 4-1.

Table 4-1: Empirical investigation: results presentation and outlay

Objectives	Cross-reference
To analyse the prescribing patterns of antihypertensive drugs stratified according to age, gender and prescribing health professional, pharmacological class, defined daily dose and generic indicators using prescriptions in a private pharmacy situated in Libreville, Gabon.	Paragraph 4.2-4-5; Tables 4-2 - 4-10
To determine the cost of all antihypertensive drugs prescribed from the CNAMGS prescriptions, using prescriptions in a private pharmacy situated in Libreville, Gabon.	Paragraph 4.6 – 4.6.8 Tables 4-11- 4-20
To determine potential cost savings through generic substitution for antihypertensive drugs using prescriptions in a private pharmacy situated in Libreville, Gabon	Paragraph 4.7 Tables 4-21

The following notes and definitions pertain to the data analysis and/or reporting of results in this chapter:

- Costs are given in XAF (Central African Franc). It is the currency used in six independent states in Central Africa, namely Cameroon, Central African Republic, Chad, Republic of the Congo, Equatorial Guinea and Gabon (one XAF was equal to R0.0223 for the period 1 June 2013 to 31 May 2014) (OANDA Corporation, 2017).

- The values of the data used were rounded to two decimals and may, therefore, not always add up to 100%.

- The term ‘Brand name drug’ according to the United States Food and Drug Administration (FDA, 2017), is a “*drug marketed under the proprietary, trademarked-protected name*”.

- A “generic drug” is a pharmaceutical drug that is equivalent to a brand-name product in dosage, strength, route of administration, quality, performance and intended use (FDA, 2017). A generic medicine works in the same way and provides the same clinical benefit as its brand-name version. The term may also refer to any drug marketed under its chemical name without advertising (CDER, 2017) or to the chemical makeup of a drug

rather than the brand name under which the drug is sold (CDER, 2017).

- "Plain formulations" are defined by WHO Collaborating Centre for Drug Statistics Methodology (2016) as "*preparations containing one active component (including stereo-isomeric mixtures)"*. Fixed-dose combinations (FDCs) are defined as the combination of several active agents in single pharmaceutical formulation (WHO, 2005:2017).

- Two-drug combination therapy in this study indicates the combination of two plain formulations, while fixed-dose combination therapy indicates two or more active substances in a single pharmaceutical formulation. The three-drug combination therapy indicates the concurrent prescribing of three plain formulations, whereas fixed-dose combination of three active substances implies three active substances in single formulation. Combination therapy in this study indicates the combination of two or more single pharmaceutical formulations.

4.2 General overview of the study population

Overall, 28 289 patients with national health insurance (NHI) visited the study setting during the study period. Of these, 1 586 (5.61%) claimed for antihypertensives at least once during the study period, thus forming the study population. Table 4-2 portrays the basic demographic characteristics of the study population.

Table 4-2: Demographic profile of the study population

Variables	Frequency n (%)
Study population, n (%)*	1 586 (5.6)
Average age, mean ± SD (95% CI)	56.53 ± 14.77 (55.80, 57.26)
Females, n (%) †	1 097 (69.2)
Age groups, n (%) ‡ < 30 years	44 (4.0)
30-44 years	205 (18.7)
45-65 years	522 (47.6)
> 65 years	326 (29.7)
Males, n (%) †	489 (30.8)
Age groups, n (%) ‡ < 30 years	7 (1.4)
30-44 years	93 (19.0)
45-65 years	267 (54.6)
> 65 years	122 (24.9)

Variables	Frequency n (%)
* Percentage calculated using the total number of patients with national health insurance (NHI) (N = 28 289) who visited the study setting during the study period, as denominator. † Percentage calculated using the total number of patients in the study population (N = 1 586), as denominator. ‡ Percentage calculated using the total number of patients within the gender groups (female, N = 1 097, and male, N = 489), as denominators.	

Table 4-2 shows that the majority of patients in the study population (69.2%) were female. The association between female gender and the treatment of hypertension was statistically significant and practically visible ($p < 0.0001$, Cramér's $V = 0.4$). Overall, significantly more patients (~50%) were between the ages of 45-65 years ($p < 0.001$, Cramér's $V = 0.4$). A total of 22% of patients were below the age of 44 years, with the elderly population (>65 years) representing 28% of patients (Table 4-2). The mean age of the study population was 56.53 ± 14.77 (95% CI, 55.81 - 57.26) years. There was no significant difference in the mean age between males (56.23 ± 13.34 years) (95% CI, 55.04 - 57.41) and females (56.67 ± 15.38 years) (95% CI, 55.76 - 57.58) ($p = 0.560$; Cohen's $d = 0.03$).

Age represents a non-modifiable risk factor of developing hypertension; by age 50 years and older the risk of having elevated blood pressure doubles among individuals (Pinto, 2007:111). Increasing age has also been proven to be a risk factor in developing other cardiovascular diseases such heart failure, stroke, ischemic heart diseases and chronic kidney diseases (Drozdz & Kawecka-Jaszez, 2013:1507; Ogah *et al*., 2012:335), therefore, by age 40 years and older, lifestyle modifications, such as adopting good diet habits, promoting alcohol and smoking cessation through education may increase awareness and prevent hypertension. An earlier survey conducted in Ntoum, northeast Gabon, showed that one in six people over the age of 40 years suffer from high blood pressure, making hypertension a major public health issue (Ngoungou *et al.,* 2012:77). In support of the literature, the present study showed that the majority of patients in the study population were between the ages of 55.80 and 57.26 years; however, results showed that younger adults had hypertension. According to Van de Vijver *et al*. (2013:17-18), the prevalence of hypertension among young adults has increased over the past decades, particularly in young adults' age 18 years and above.

Akinlua *et al.* (2015:9) furthermore demonstrated that higher prevalence of increased blood pressure was reported in urban areas compared with rural areas in Nigeria. Libreville, as the capital of Gabon, is one of the largest cities regarded as an urban area, where most health personnel are found (Saleh *et al.,* 2012:94). Urban lifestyle may have a huge impact in the development of high blood pressure in young adults (Sarki *et al.*, 2015:1); due to factors such as nutritional transition with high salt intake, snacking and consummation of fat in processed food, stress, metabolic patterns such as diabetes, hormonal regulation and obesity (Reddy *et al.*,

2015:33). The prevalence of hypertension among young adults in India, for instance, has shown that there was a correlation between obesity and the increase of blood pressure (Reddy *et al.,* 2015:37). Sliwa *et al.* (2014:518) also reported that obesity was a common risk factor that contributes to development of hypertension and cardiovascular diseases, particularly in young women residing in urban areas in South Africa. The prevalence of obesity among young adults (~18 years) in Gabon was 29.9% in 2014 (Global Health Observatory, 2017). A pilot study conducted by Slawaya *et al*. (2015:2) on hyperglycaemia, hypertension and obesity in Libreville, found the prevalence of overweight and obesity to be 29.1% and 24.8%, respectively. In Gabon, obesity appears to be three times as common in adult women (20%) than in men (7.7%) (Oxford Business group, 2013:178; WHO, 2014b). The prevalence of obesity has increased through the past 20 years and in countries such as Gabon (14.9% (95% CI, 13.9 -15.8), Cameroon, Comoros and Zimbabwe have the higher prevalence (>20%) of obesity among women in the sub-Saharan region (Neupane *et al*., 2016:4).

Although there were significantly more females in the study population than males, there was no practical significant association between gender and age group of patients in the study population overall ($p = 0.004$, Cramér's $V = 0.1$). Sliwa *et al.* (2014:520) emphasised that due to the epidemiological transition occurring with geographic and socioeconomic factors across African countries, high blood pressure has become more prevalent in African women. Within gender group analysis of patients per age group in the present study (among young adults below the age of 30 years), there were more women than men in the study population (4.0% *vs* 1.4%, respectively), whereas at age 30-44 years, the rate was similar (18.7% *vs* 19.0%, respectively) (Table 4-2). Among older adults 45-65 years, there were more men than women (54.6% *vs* 47.6%, respectively). Meanwhile among the elderly >65 years, there were more women than men in the study population (29.7% *vs* 24.9%).

There is no doubt that age is a significant risk factor in developing CVD (Pinto, 2007:111). Hypertension in young women may attribute to the presence of risk factors such as obesity, dietary habits, exposure to stress and pregnancy (Jääskeläinen *et al*., 2014:2-4; Johnson & Tough, 2012:86). Blood pressure normally increases as people get older (>50 years), but men compared with women have higher systolic blood pressure in early adulthood, whereas women tend to develop blood pressure in the fifth or sixth decade of their life (Pemu & Ofili, 2008:406) (refer to paragraph 2.6.4). According to Sandberg and Ji (2012:12), high levels of follicle-stimulating hormone (FSH) in women during menopause is associated to an increase in blood pressure, as fertility declines due to a decrease in the production of ovarian follicles. In addition, Yang and Reckelhoff (2011:133) state that young women presenting with early menopause due to ovarian dysfunction have an increased risk of developing cardiovascular diseases. Therefore, oestrogen provides a cardio-protective effect by reducing oxidative stress and increasing protein

S-nitrosylation (Yang & Reckelhoff, 2012:133). Compared to the present study, this may explain why, in the age group of 45-65 with hypertension, there were more men than women (54.6% vs 47.6% in women); as premenopausal women have a lower risk of developing high blood pressure.

4.3 Prescriptions for antihypertensive drugs

Table 4-3 shows the distribution of prescriptions claimed with the period of study.

Table 4-3: General analysis of prescriptions within the period of study

Variables	Frequency (n),%
Number of CNAMGS prescriptions claimed**	49 334 (24.6)
Prescriptions claimed with antihypertensive drugs from CNAMGS**	2504 (1.2)
Prescriptions claimed on other mutual and private medical aids **	9 107 (4.5)
Other prescriptions claimed **	139 347 (69.4)
Total	**200 292 (100)**
**Percentage was obtained using the total amount of prescriptions within the period of study period (N = 200 292 prescriptions)	

According to the distribution of prescriptions within the study period, CNAMGS prescriptions represented 24.6% of the total number of prescriptions claimed in the specific pharmacy (study setting) during the study period, compared to prescriptions claimed from other mutual and private medical aid schemes (4.5%), and other cash prescriptions (69.6%) (Table 4-3). Claims for CNAMGS prescriptions containing at least one antihypertensive accounted for 1.2% (n = 2 504) of all prescriptions (Table 4-4).

Table 4-4 indicates the number of prescriptions claimed during the study period stratified by gender, age group and prescriber speciality. Overall, 51 838 prescriptions were claimed during the study period at the study site. Of these, 2 504 (4.8%) prescriptions contained antihypertensive drugs.

In agreement to the higher number of women in the study population (Table 4-2), significantly more prescriptions were claimed for female patients (70.2%) ($p < 0.0001$; Cramér's $V = 0.4$) (Table 4-4). The number of prescriptions within each age group was significantly different ($p < 0.0001$; Cramér's $V = 0.4$), with more prescriptions (80%) claimed within the age group 45 years and above.

Furthermore, an analysis by prescriber's speciality (Table 4-4) showed that significantly more

prescriptions were prescribed by general practitioners (n = 1 108, 44.2%) and specialists (n = 1 049, 41.9%) ($p < 0.0001$, Cramér's $V = 0.4$).

Table 4-4: Number of prescriptions claimed, stratified by gender, age group and prescriber speciality

Variable	Frequency n (%)	*p*-value	Effect size*
Total number of CNAMGS prescriptions claimed during the study period	51 838		
Total number of prescriptions containing antihypertensives†	2 504 (4.8)		
Gender, n (%)‡ Female Male	 1 759 (70.2) 745 (29.8)	 <0.001	 0.4
Age groups (years), n (%)‡ <30 30-44 years 45-65 years > 65 years	 75 (3.0) 427 (17.1) 1 287 (51.4) 715 (28.6)	 <0.001	 0.4
Prescriber's specialty, n (%)§ Specialist Intern General practitioners Nurse	 1 049 (41.9) 176 (7.0) 1 108 (44.2) 170 (6.8)	 <0.001	 0.4

* Effect size computed using Cramér's *V*.
†Percentage calculated using the total number of prescriptions claimed during the study period at the study site as denominator.
‡Percentage calculated using the total number of antihypertensive prescriptions claimed during the study period at the study site as denominator.
§ Because of missing values, the percentage is calculated using the total number of antihypertensive prescriptions claimed per prescriber's specialty group (N = 2 504) as denominator.

Table 4-5 portrays the number of prescriptions claimed per patient in the study population during the study period, stratified by gender. The majority of patients in the study population (n = 1 093, 68.9%) claimed only one prescription during the study period.

Table 4-5: Total number of prescriptions claimed per patient, stratified by gender

Number of prescriptions per patient	Female n (%)*	Male n (%)*
1	746 (67.4)	347 (72.4)
2	217 (19.6)	82 (17.1)
3	68 (6.1)	22 (4.6)
4	28 (2.5)	14 (2.9)
5	18 (1.6)	6 (1.3)
6	16 (1.4)	0 (0.0)
7	12 (1.1)	5 (1.0)

Number of prescriptions per patient	Female n (%)*	Male n (%)*
8	2 (0.2)	3 (0.6)
Average number of prescriptions, mean ± SD (95% CI)	1.61 ± 1.18 (95 % CI, 1.68 – 1.54)	1.51 ± 1.12 (95% CI, 1.61 – 1.51)
*Percentage calculated using the total number of females (N = 1 107) and males (N = 479) in the study population, as denominator.		

The CNAMGS allows three months' supply for chronic disease medication. In this study, antihypertensive drugs were mostly prescribed for 30 days (79.5%), 2 months (12.7%) or even three months (8.3%).

In developing countries such as Gabon, access to the healthcare system is limited compared to developed countries (Jarari *et al.,* 2016:3). Access to healthcare services is much better in urban areas (Libreville for instance), as compared to rural areas; medical structures are more developed and better equipped than primary healthcare structures, where drugs and basic equipment are old and limited (Bourgarel *et al.,* 2010:7). More than 60% of Gabonese Government's health resources are allocated in the main cities and their surroundings (Bourgarel *et al*., 2010:7). For instance, in 2010, the urban areas in Gabon had 58% pharmacists working for the government versus 42% in rural areas, and 75% medical doctors in urban areas versus 25% in rural areas (Bourgarel *et al.,* 2010:9). Patients usually seek medical attention from their primary care providers, particularly non-specialist physicians (Bello *et al.,* 2016:6), even for chronic conditions such as hypertension. The limited access to healthcare system, longer waiting time to see a cardiologist, shortage of specialists or the cost of a consultation or clinic fees, for instance, may influence hypertension treatment, control and medication compliance (Iwelunmor *et al.,* 2015:12), explaining why the majority of patients had only one prescription during the period of study. According to Pemu and Ofili (2008:406), women are more likely to be aware of their hypertension and to look for medical advice than men are. In contrast, Table 4-4 further show that there was no significant difference between males (1.51 ± 1.12, 95% CI, 1.61 – 1.51) and females (1.61 ± 1.18, 95 % CI, 1.68 – 1.54) regarding the mean number of prescriptions per patient (p = 0.100; Cohen's d = 0.1).

A total of 3 360 antihypertensive drugs were claimed during the study period. Table 4-6 shows the total number of antihypertensive drugs (plain and fixed-dose combinations) prescribed during the study period, stratified by pharmacological class.

Table 4-6: Total number of antihypertensive drug prescribed according to pharmacological drug class

Drug	Brand name	Generic indicator	Number of prescriptions, n (%)*
Plain antihypertensives			
Angiotensin converting enzyme inhibitors			**288 (8.6)**
Enalapril	Renitec®	O	2 (0.1)
Perindopril	Coversyl®	O	133 (4.0)
Ramipril	Triatec®	O	47 (1.4)
Captopril	Lopril®	O	40 (1.2)
	Captopril EG	G	66 (1.9)
Angiotensin receptor blockers			**99 (3.0)**
Candesartan	Atacand®	O	46 (1.4)
Valsartan	Tareg®	O	53 (1.6)
Beta-blockers			**224 (6.7)**
Acebutolol	Sectral®	O	1 (0.03)
Atenolol	Tenormine®	O	63 (1.9)
Carvedilol	Kredex®	O	12 (0.4)
Labetalol	Trandate®	O	1 (0.03)
Propranolol	Avlocardyl®	O	9 (0.3)
Bisoprolol	Cardensiel®	O	9 (0.3)
	Detensiel®	O	129 (3.8)
Calcium channel blockers			**744 (22.2)**
Diltiazem	Mono-tildiem®	O	5 (0.2)
Lercanidipine	Zanidip®	O	31 (0.9)
Nicardipine	Loxen®	O	305 (9.1)
Nifedipine	Adalat®	O	18 (0.5)
Verapamil	Isoptine®	O	1 (0.03)
Amlodipine	Amlor®	O	235 (7.0)
	Amcard®	O	1 (0.03)
	Asomex®	O	1 (0.03)
	Amaday®	G	125 (3.7)
	Amlibon®	G	2 (0.06)
	Amlo denk	G	3 (0.09)
	Lopine®	G	17 (0.5)
Centrally acting agents			**135 (4.0)**
Alpha-methyldopa	Aldomet®	O	135 (4.0)
Thiazide diuretics			**518 (15.4)**
Furosemide	Lasilix®	O	220 (6.6)
HCTZ	Esidrex®	O	19 (0.6)
Indapamide	Fludex®	O	279 (8.3)
Potassium-sparing agents			**66 (2.0)**
Spironolactone	Aldactone®	O	66 (2.0)
Fixed dose combinations (FDCs)			**1 286**
Angiotensin converting enzyme inhibitors / calcium channel blockers			**288 (8.6)**
Perindopril / amlodipine	Coveram®	O	289 (8.6)
Angiotensin converting enzyme inhibitors / diuretics			**683 (20.3)**
Perindopril / indapamide	Bipreterax®	O	426 (12.7)
	Preterax®	O	79 (2.4)
Captopril/HCTZ	Ecazide®	O	2 (0.1)
	Denk®	G	15 (0.4)
Quinapril / HCTZ	Acuilix®	O	13 (0.4)
Ramipril / HCTZ	Tritazide®	O	148 (4.4)
Angiotensin receptor blockers / diuretics			**115 (3.4)**
Candesartan / HCTZ	Hytacand®	O	55 (1.6)
Irbesartan / HCTZ	Co-Approvel®	O	1 (0.03)

Drug	Brand name	Generic indicator	Number of prescriptions, n (%)*
Losartan / HCTZ	Hyzaar®	O	7 (0.2)
Valsartan / HCTZ	Co-Tareg®	O	52 (1.5)
Beta-blockers / calcium channel blockers			**43 (1.3)**
Atenolol / nifedipine	Tenordate®	O	43 (1.3)
Beta-blockers / diuretics			**69 (2.5)**
Atenolol / nifedipine	Tenordate®	O	43 (1.3)
Beta-blockers / diuretics			**69 (2.5)**
Atenolol / chlorthalidone	Tenoretic®	O	40 (1.2)
	Blokium Diu®	O	18 (0.5)
Bisoprolol / chlorthalidone	Lodoz®	O	11 (0.3)
Calcium channel blockers / angiotensin receptor blockers			**34 (0.1)**
Amlodipine / valsartan	Exforge®	O	34 (0.1)
Calcium channel blockers / angiotensin receptor blocker / diuretics			**12 (0.4)**
Amlodipine / valsartan/HCTZ	Exforge® HCT	O	12 (0.4)
Potassium-sparing agents / diuretics			**41 (1.2)**
Amiloride / HCTZ	Moduretic®	O	5 (0.2)
Spironolactone / HCTZ	Aldactazine®	O	36 (1.1)

HCTZ: Hydrochlorothiazide; Generic status: O: Original; G: generic equivalent
*Percentage calculated using the total number of drugs prescribed (N = 3 360) within the period of study as a denominator.

The general prescribing patterns based on generic indicator, treatment regimens, pharmacological drug class, active ingredient and Anatomical Therapeutic Chemical (ATC)-classification system are described in subsequent paragraphs.

4.3.1 Prescribing based on active ingredients, ATC-classification and pharmacological drug class

A total of 18 from 39 active ingredients prescribed were within the DU90% segment, in which fixed-dose combination perindopril/indapamide was the most prescribed (n = 505, 15.0%), followed by the plain formulation of amlodipine (n = 384, 11.4%) and nicardipine (n = 308, 9.2%) (Table 4-6). Perindopril as plain formulation was the tenth most prescribed drug (n = 133, 4.0%). A study performed by Tomas *et al.* (2016:535) found angiotensin converting enzyme inhibitors to be vastly used compared to other antihypertensive drugs in the city of Novi Sad (Serbia); this might be due to prescriber's preference according to patient's characteristics.

Drugs not included in the DU90%, included acebutolol (n =1, 0.03%) and labetalol (n = 1, 0.03%), verapamil (n = 1, 0.03%) and irbesartan and hydrochlorothiazide fixed-dose combination (n = 1, 0.03%).

Drugs prescribed within the ATC-code include C09 (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin converting enzyme inhibitors in combination with diuretics, angiotensin receptor blockers or calcium channel blockers), C08 (calcium channel

blockers), C07 (beta-blockers alone or in combination with diuretics), C03 (diuretics, alone or in combination with diuretics).

The majority of antihypertensive drugs prescribed were calcium channel blockers (C08) (n = 744, 22.2%), followed by diuretics (C03) (n = 518, 15.4%), potassium sparing agents (n = 66, 2.0%), angiotensin converting enzyme inhibitors (C09) (n = 288, 8.6%), beta-blockers (C07) (n = 224, 6.7%), central acting agents (C02) (n = 135, 4.0%), and angiotensin receptor blockers (C09) (n = 99, 3.0%) (Table 4-6).

The calcium channel blockers, amlodipine and nicardipine were the most prescribed plain formulations. This finding is in line with literature, showing that calcium channel blockers are the preferred drugs for reducing blood pressure in those of African descent, geriatric patients and patients presenting a history of stroke, peripheral artery disease and left ventricular hypertrophy (Sica, 2006:56; Tocci *et al*., 2014:2). The findings of the present study are also in accordance with other studies where calcium channel blockers were used as first-line agents; for instance in India (Rachana *et al*., 2014:20), Nigeria (Nwaka *et al*., 2015:544), South Africa (Mpe, 2007:35), and in the USA (Bucci *et al*., 2008:629). According to Jarari *et al*. (2016:5), studies show that calcium channel blockers, mainly amlodipine, were frequently used on geriatric hypertension patients. Datta (2017:36) confirmed in his study that a calcium channel blocker such as amlodipine is the drug of choice in monotherapy compared with other plain drugs. In the present study, the population was mostly from African descent with an average age of 56.53 ± 14.77 (95% CI, 55.80 - 57.26 years old), therefore, the use of calcium channel blockers may be justified.

The use of calcium channel blockers as plain formulation was followed by thiazide diuretics (n = 518, 15.4%). This included active ingredients such as indapamide (n = 279, 8.3%), hydrochlorothiazide (n = 19, 0.6%) and the sulphonamide loop diuretic, furosemide (n = 220, 6.6%) (Table 4.6). In this study, thiazide diuretics were mostly used, either as a plain formulation or in a combination for the treatment of hypertension (Table 4-6). Okonta *et al*. (2013:14), in Nigeria, where the rate of diuretics prescribed was 16.7% and was the third most frequently prescribed drug after angiotensin converting enzyme inhibitors and calcium channel blockers, showed similar results. Thiazide diuretics are considered the most popular drugs for the management of high blood pressure and compared to other antihypertensive drugs, they are also largely considered by the JNC-7 as first-line agents for essential hypertension (Jennings & Cook, 2003:8) and in combination with other antihypertensive drugs to enhance blood pressure reduction.

The use of alpha-methyldopa was also frequent as plain formulation (n = 135, 4.0%). Alpha-methyldopa is the drug of choice in pregnancy (Michel & Hoffman, 2009:773), and along with hydralazine, alpha-methyldopa is recommended by the WHO (2015:28) in pregnancy-induced

high blood pressure. The possible reasons for the use of alpha-methyldopa may be attributable to more patients within the age groups >30 and 30-44 being female, which is generally the childbearing age (refer to Table 4-2).

Fixed dose combination therapy included mainly diuretics, hydrochlorothiazide in particular (Table 4-6), in combination with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers and potassium sparing agents (Table 4-6). The most prescribed fixed-dose combination consisted of angiotensin converting enzyme inhibitors and a diuretic (n = 683, 20.3%), of which perindopril and indapamide represented 73.9% (n = 505) and ramipril in combination with hydrochlorothiazide at 21.7% (n = 148). Perindopril and amlodipine combination (angiotensin converting enzyme inhibitors and calcium channel blocker) was the second most prevalent prescribed fixed-dose combinations at 42.3% (n = 289). The prescribing of fixed-dose combination therapy in this study is in line with other studies conducted previously in Nigeria, for instance, by Nwaka *et al*. (2015:545) and in India by Jarari *et al*. (2016:5).

The eighth report of Joint National Committee (JNC-8) on the Detection, Evaluation, Prevention and Treatment of Hypertension (James *et al*., 2015:512) recommends starting with single drug therapy for mild to moderate hypertension, such as thiazides, calcium channel blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers. According to Barry (2014:5), ramipril is the drug of choice in the treatment of hypertension among angiotensin converting enzyme inhibitors. If the target blood pressure cannot be reached using these agents, another drug should be added along with lifestyle changes until normal blood pressure values are obtained (James *et al*., 2014:516). The 2015-WHO/Essential medicine list (WHO, 2015:28) recommends amlodipine, bisoprolol or other beta-blockers (atenolol, carvedilol and propranolol), and enalapril and hydrochlorothiazide as first-line agents for the management of hypertension.

The choice of antihypertensive agent utilised, depends on the indication thereof (Figure 2-1) (WHO, 2003). The 2003 WHO/International Society of Hypertension, the European Society of Hypertension and the Joint National Committee (JNC-7) guidelines (Lemogoum *et al*., 2003:1994) recommend low thiazide diuretics such as hydrochlorothiazide to be used to initiate treatment in the absence of compelling indications. If blood pressure is not controlled, the dose of the same drug should be increased or a small dose of second drug from a different class should be added (Lemogoum *et al*., 2003:1996).

Angiotensin receptor blockers reduce blood pressure by blocking angiotensin II receptors; therefore, they have a similar effect to the angiotensin converting enzyme inhibitors. Angiotensin receptor blockers have proven their efficacy in reduction of mortality, myocardial infarction, stroke and other cardiovascular events (Hermanowski *et al.*, 2013:80). They should be used when the angiotensin converting enzyme inhibitors has failed to reach the target blood pressure in some

patients. Furthermore, reimbursement should be limited to patients who cannot tolerate angiotensin converting enzyme inhibitors (Hedberg & Jacob, 2008:11). The JNC-8 guidelines recommend angiotensin receptor blockers along with thiazide-diuretics, calcium channel blockers or angiotensin converting enzyme inhibitors for the non-black population, including those with diabetes (Bell *et al*., 2015:4) as first-line therapy. In black population, evidence has shown that there is a small reduction in blood pressure when angiotensin converting enzyme inhibitors or angiotensin receptor blockers are taken alone (Bell *et al*., 2015:4). In addition, according to Khan and Beavers (2005:1106), beta-blockers also appear to be less effective in people from African descent when used as monotherapy. It is therefore recommended that loop diuretics along with calcium channel blockers be used to initiate hypertension treatment, particularly in black populations (Khan & Beevers, 2005:1106).

4.3.1.1 Patterns of antihypertensive drug classes prescribed on the basis of gender and age

Table 4-7 portrays the overall prescribing of antihypertensive drug classes based on gender and age. The number of drug classes prescribed was significantly different between women and men (p = 0.001, Cohen's d = 0.8), this can be explained by the higher number of women in the study population (Table 4-2).

More fixed-dose combination drugs were prescribed for women compared to men (i.e. 41.0% *vs*. 87.1%). Compared to women, men in the study population received more diuretics (19.8% *vs*. 16.3%), angiotensin converting enzyme inhibitors (9.6% vs. 8.1%) and beta-blockers (7.6% *vs*. 6.3%). The least prescribed drug class for men was central acting agents (i.e. alpha-methyldopa), with 1.8%, compared to women, with 5.0%. This may be due to alpha-methyldopa being recommended as the antihypertensive drug of choice in pregnancy on the essential list of medicine by the WHO (2017:35) and because of its proven use in pregnancy (Townsend *et al*., 2016:92). Calcium channel blockers were the second most prescribed drugs in women (n = 567, 24.3%); angiotensin receptor blockers were equally prescribed in both gender groups at 2.9% and 3.0% for females and males, respectively, whereas diuretics were the most prescribed in males.

Based on Table 4-7, centrally acting agents (alpha-methyldopa) were mainly prescribed for the age group 30-44 years old (48.1%) compared to other group ages at 16.3% for <30 age group, 17.8% for 45-65 age group and 17.8% for >65 age group. Age group 45-65 years had the most antihypertensive drug classes prescribed with fixed-dose combination as the most prescribed group (n = 725, 56.2%), followed by calcium channel blockers (n = 343, 46.1%) and diuretics (n = 225, 38.5%).

Table 4-7: Antihypertensive drug classes prescribed according to age and gender

Variables	Age group in years				Gender		*P* value
Drugs	**<30 n, (%) ****	**30-40 n, (%) ****	**45-65 n, (%) ****	**>65 n, (%) ****	**Males, n, (%)***	**Females , n, (%)***	
ACE inhibitors	2 (0.7)	58 (20.1)	130 (45.1)	98 (34.0)	99 (9.6)	189 (8.1)	0.01
Angiotensin receptor blockers	-	9 (0.1)	53 (53.5)	37 (37.4)	31 (3.0)	68 (2.9)	
Beta-blockers	8 (3.6)	33 (14.7)	132 (58.9)	51 (22.8)	78 (7.6)	146 (6.3)	**Effect size**
Central acting agents	22 (16.3)	65 (48.1)	24 (17.8)	24 (17.8)	18 (1.8)	117 (5.0)	0.8
Diuretics	14 (2.4)	89 (10.2)	256 (43.8)	225 (38.5)	203 (19.8)	381 (16.3)	
Calcium channel blockers	32 (4.3)	129 (17.3)	343 (46.1)	238 (32.0)	117 (17.2)	567 (24.3)	
Fixed-dose combination	10 (0.8)	187 (14.5)	725 (14.5)	366 (28.5)	422 (41.0)	864 (87.1)	
Total, n	**88**	**570**	**1 663**	**1 039**	**1 028**	**2 332**	

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BB: beta-blocker, CCB: Calcium channel blockers; CAA: Central acting agents; FDC: fixed-dose combinations
*Percentages obtained using the total number of drug classes prescribed as a denominator for males (N= 1 028) and for females (N= 2 332); **Percentages obtained using the total number of each drug class as a denominators (ACEI, n = 288), (ARBs, n = 99), (BB, n = 224), (CAA, n = 135), (Diuretics, n = 584), (CCBs, n = 744), (FDCs, n = 1 286)

4.3.2 Prescribing based on treatment regimens

Table 4-8 shows the various treatment regimen combinations used for the treatment of high blood pressure in this study.

Table 4-8: Treatment regimens used for prescribing of antihypertensive drugs

Drug regimens	Number of patients, n (%*)
Four drug combination therapy	**12 (0.7)**
ACE Inhibitors + diuretic + CAA + CCB	2 (0.1)
ACE Inhibitors + ACE Inhibitors + diuretic + CCB	2 (0.1)
ACE Inhibitors + BB + CCB + Diuretic	1 (0.06)
ACE Inhibitors/CCB + ARB + BB + diuretic	1 (0.06)
ARB + CCB + diuretic + potassium sparing	2 (0.1)
ARB + CAA + CCB + diuretic	3 (0.2)
ARB/diuretic + BB + CAA + CCB	1 (0.06)
Three drug combination therapy	**85 (5.3)**
ACE Inhibitors + potassium sparing + diuretic	21 (1.3)
ACE I + BB + diuretic	4 (0.3)

Drug regimens	Number of patients, n (%*)
ACE Inhibitors +BB + CCB	1 (0.06)
ACE Inhibitors + BB/diuretic +diuretic	1 (0.06)
ACE Inhibitors + CCB +diuretic	7 (0.4)
ACE Inhibitors + CAA + diuretic	1 (0.06)
ACE Inhibitors + CAA + CCB	1 (0.06)
ACE Inhibitors/CCB + CAA + diuretic	2 (0.1)
ACE Inhibitors/CCB + BB + diuretic	2 (0.1)
ACE Inhibitors + CCB + CAA	2 (0.1)
ACE Inhibitors/diuretic + BB/CCB + diuretic	1 (0.06)
ACE Inhibitors/diuretic + CAA + CCB	2 (0.1)
ACE Inhibitors/diuretic + CCB + BB	8 (0.5)
ACE Inhibitors/diuretic + ARB/diuretic + BB	1 (0.06)
ACE Inhibitors/diuretic + potassium sparing + diuretic	1 (0.06)
ARB + CCB + diuretic	3 (0.2)
ARB + CAA + CCB	1 (0.06)
ARB/diuretic + CCB + BB	2 (0.1)
ARB/diuretic + CCB + diuretic	3 (0.2)
ARB/diuretic + CAA + CCB	4 (0.3)
ARB + diuretic + BB	4 (0.3)
BB + potassium sparing + diuretic	1 (0.06)
BB + CCB + CAA	1 (0.06)
BB/diuretic + CCB + diuretic	1 (0.06)
BB + CCB + diuretic	6 (0.4)
CCB + potassium sparing + diuretic	3 (0.2)
CCB/ARB + CCB + Diuretic	1 (0.06)
Two drug combination therapy	**380 (24.0)**
ACE Inhibitors + diuretic	24 (1.5)
ACE Inhibitors + CCB	26 (1.6)
ACE Inhibitors + BB/CCB	2 (0.1)
ACE Inhibitors + ACE Inhibitors	1 (0.06)
ACE Inhibitors + BB	21 (1.3)
ACE Inhibitors + potassium sparing/diuretic	5 (0.3)
ACE Inhibitors +ACEI/CCB	1 (0.06)
ACE Inhibitors/CCB + diuretic	36 (2.3)
ACE Inhibitors/CCB + BB	4 (0.3)
ACE Inhibitors/CCB + potassium spring/diuretic	2 (0.1)
ACE Inhibitors/CCB + CAA	1 (0.06)
ACE Inhibitors/CCB + ACEI/diuretic	2 (0.1)
ACE Inhibitors/CCB + BB/diuretic	3 (0.2)
ACE Inhibitors/CCB + CCB	1 (0.06)
ACE Inhibitors/diuretic + CCB	98 (6.2)
ACE Inhibitors/diuretic +BB	13 (0.8)
ACE Inhibitors/diuretic + BB/diuretic	2 (0.1)
ACE Inhibitors/diuretic + BB/CCB	8 (0.5)
ACE Inhibitors/diuretic + diuretic	5 (0.3)
ACE Inhibitors/diuretic + CAA	2 (0.1)

Drug regimens	Number of patients, n (%*)
ACE Inhibitors/diuretic + ACE Inhibitors/diuretic	1 (0.06)
ARB + diuretic	4 (0.3)
ARB + CCB	10 (0.6)
ARB + BB	4 (0.3)
ARB + BB/CCB	1 (0.06)
ARB/diuretic + BB/CCB	2 (0.1)
ARB/diuretic + CCB	12 (0.8)
ARB/diuretic + BB	1 (0.06)
CCB + BB	17 (1.1)
CCB + BB/diuretic	1 (0.06)
BB + diuretic	4 (0.3)
BB/CCB + diuretic	5 (0.3)
BB + potassium sparing/diuretic	2 (0.1)
CAA + CCB	9 (0.6)
CAA + BB	1 (0.06)
CAA + diuretic	2 (0.1)
CCB + BB/diuretic	2 (0.1)
CCB + CCB	4 (0.3)
CCB + diuretic	41 (2.6)
Single drug therapy	**1 110 (70.0%)**
ACE Inhibitors	72 (4.5)
ACE Inhibitors/CCB	118 (7.4)
ACE Inhibitors/diuretic	315 (19.9)
ARB	21 (1.3)
ARB/diuretic	45 (2.8)
BB	41 (2.6)
BB/CCB	10 (0.6)
BB/diuretic	28 (1.8)
CAA	52 (3.3)
CCBs	234 (14.8)
CCB/ARB	14 (0.9)
CCB/ARB/diuretic	6 (0.4)
diuretics	144 (9.1)
Potassium sparing agents	10 (0.6)

ACE Inhibitors: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blocker; BB: beta-blocker, CAA: central acting agents, CCB: Calcium channel blocker; HCTZ: hydrochlorothiazide*Percentage was obtain using the total number of patients (N=1 586) as a denominator

Based on Table 4-8, single drug treatment (i.e. an antihypertensive treatment regimen consisting of either a singular plain formulation or a fixed-dose combination) was most commonly prescribed (70.0%). Furthermore, Table 4-8 shows that in the present study, 11 (0.7%) patients received four-drug combinations, 85 (5.3%) received three-drug combinations and 380 (24.0%) patients received two-drug combinations.

A total of 776, (48.9%) patients received fixed-dose combinations in their prescriptions. Multiple drug regimens (30%) were observed as multiple drug combination therapies. In his study, Rathnakar *et al*. (2011:2) also observed polypharmacy in drug prescriptions, in which fixed-dose combination represented 63.8% of the total prescriptions. The use of more than one antihypertensive drug can be explained by the presence of other conditions such as diabetes. Most of the drugs used in this study act on the renin angiotensin system (C09).

Among patients on a single drug therapy, most claimed for the fixed-dose combination of angiotensin converting enzyme inhibitors and diuretics (n = 315, 19.9%), followed by the plain formulation calcium channel blockers (n = 234, 14.8%).

Patients receiving the two-drug combination therapy, mostly claimed for fixed-dose combination formulations of angiotensin converting enzyme inhibitors plus diuretics and calcium channel blockers (n = 98, 6.2%). Among three-drug combination regimens, it was the combination of an angiotensin converting enzyme inhibitor with a potassium sparing agent and a diuretic that was mostly claimed (n = 21, 1.3%), whereas in the four-drug combination therapy there was a combination of drugs such as angiotensin receptor blockers along with diuretics, calcium channel blockers and centrally acting agent (n = 3, 0.2%). These findings were similar to that of Romday *et al*. (2016:5129) conducted in India, and Joel *et al. (*2014:1097) in South India. Wan *et al*. (2013:6) suggested that when a blood pressure target cannot be reached with two drug combinations, triple drug combination could be used. Based on the 2013 ESH/ESC guidelines, there is an advantage of initiating treatment with combination therapy (Mancia *et al*., 2013b:2189). Particularly in patients who cannot reach their target blood pressure value (Mancia *et al*., 2013b:2189). Moreover, with fixed-dose combination therapy there is a greater probability of achieving that value and improving adherence (Mancia *et al*., 2013b:2189). Overall, based on the findings of the present study, it appears that the CNAMGS prescriptions claimed during the study period, complied with the hypertension guidelines from the 2003 WHO/International Society of Hypertension; the European Society of Hypertension and the Joint National Committee (JNC-7) guidelines (Lemogoum *et al.*, 2003:1994).

4.4 Prescribing patterns of antihypertensive drugs based on defined daily doses (DDD)

Antihypertensive drugs utilisation was analysed in this study using the Anatomical Therapeutic Chemical (ATC) classification and defined daily doses (DDD) of the WHO Collaborating Center for Drug Statistics Methodology for plain products (Table 4-9) (WHO, 2016) and fixed-dose combinations (Table 4-10). The DDD/1000 inhabitants/day was calculated to determine the rate of antihypertensive drugs utilised within the study period (1 June 2013 - 31 May 2014) for a total population of 28 289 patients covered by CNAMGS, visiting the pharmacy during this period (refer to paragraph 3.5). These tables are discussed in paragraphs 4.4.1-4.4.2.2.

Table 4-9: Antihypertensive drug utilisation using the defined daily dose for plain products

Drug/ Drug class	ATC-classification	Quantity dispensed (gram)	WHO DDDs (gram)	DDDs	DDD/1000 inhabitants/ day
Angiotensin converting enzyme inhibitors	**CO9A**			**14 250**	**1.38**
Enalapril	CO9AA02	2.4	0.01	240.0	0.02
Captopril	CO9AA01	120.75	0.05	2 415.0	0.24
Perindopril	CO9AA04	34.2	0.004	8 550.0	0.86
Ramipril	CO9AA05	7.61	0.003	3 045.0	0.30
Angiotensin receptor inhibitors	**CO9C**			**5 540**	**0.54**
Candesartan	CO9CA06	20.64	0.008	2 580.0	0.25
Valsartan	CO9CA03	236.80	0.08	2 960.0	0.29
Beta-blockers	**CO7A**			**8 072.8**	**0.79**
Acebutolol	CO7AB04	6	0.4	15.0	0.003
Atenolol	CO7AB03	217.5	0.075	2 900.0	0.29
Bisoprolol	CO7AB07	47.89	0.01	4 788.8	0.47
Carvedilol	CO7AG01	5.78	0.038	154.0	0.01
Labetalol	CO7AG02	6	0.6	10.0	0.001
Propranolol	CO7AA05	32.8	0.16	205.0	0.02
Calcium channel blockers	**CO8**			**39 097.1**	**3.80**
Amlodipine	CO8CA01	135.93	0.005	27 186.0	2.64
Diltiazem	CO8DB01	10.4	0.24	43.3	0.004
Lercanidipine	CO8CA13	10.5	0.01	1 050.0	0.10
Nicardipine	CO8CA04	941.2	0.09	10 457.8	1.01
Nifedipine	CO8CA05	9.9	0.03	330.0	0.04
Verapamil	CO8DA01	7.2	0.24	30	0.003
Central acting agents	**CO2A**			**2 040**	**0.20**
Methyldopa	CO2AB01	2 040	1	2 040	0.20
Diuretics and potassium-sparing agents	**CO3**			**17 203.5**	**1.54**
Furosemide	CO3CA01	359.5	0.04	8 987.5	0.86
Hydrochlorothiazide	CO3AA03	22.5	0.05	450.0	0.04
Indapamide	CO3BA11	16.56	0.003	6 624.0	0.64
Spironolactone	CO3DA01	85.65	0.075	1 142.0	0.11
Total				**86 203.4**	**8.35**

ATC: Anatomic Therapeutic Classification; DDD: defined daily dose assigned by WHO (WHO, 2017)

DDD/1000 inhabitants/day: calculated using as the number of people visiting the pharmacy at the time of study (N = 28 289) (inhabitants) over 365 days times 1000 (refer to paragraph 3.7.1.3).

4.4.1 Total number of defined daily doses

Plain formulation antihypertensive drugs were prescribed at a total of 86 203.4 DDDs during the study period (Table 4-9). Among the antihypertensive drugs, calcium channel blockers were mostly used at 39 097.1 DDDs, followed by diuretics and potassium sparing agents at 17 203.5 DDD, and angiotensin converting enzyme inhibitors at 14 250 DDDs. Angiotensin receptor blockers and centrally acting alpha-methyldopa represented 5 540 DDDs and 2 040 DDDs, respectively. The fixed-dose combinations were prescribed at a total of 50 586 DDDs. Fixed-dose combinations of angiotensin converting enzyme inhibitors and diuretics were largely prescribed at 28 124 DDDs, followed by the combination of angiotensin converting enzyme inhibitors and calcium channel blockers at 10 740 DDDs.

4.4.2 Number of DDDs/1000 inhabitants/day

The total consumption of plain antihypertensive drugs in this study was 8.35 DDDs/1000 inhabitants/day (Table 4-9) and 4.90 DDDs/1000 inhabitants/day for fixed-dose combinations (Table 4-10).

4.4.2.1 The DDDs/1000 inhabitants/year for plain products

Calcium channel blockers were the most prescribed drugs to patients at 3.80 DDDs/1000 inhabitants/day, followed by thiazide diuretics and potassium sparing agents at 1.54 DDDs/1000 inhabitants/day, angiotensin converting enzyme inhibitors at 1.38 DDDs/1000 inhabitants/day and beta-blockers at 0.79 DDDs/1000 inhabitants/day. Angiotensin receptor blockers had a prescribing rate at 0.54 DDDs/1000 inhabitants/day, while central acting drugs had the lowest drugs prescribing rate at 0.20 DDDs/1000 inhabitants/day.

Among the calcium channel blockers, amlodipine was the most prescribed drug at 2.64 DDDs/1000 inhabitants/day, followed by nicardipine at 1.01 DDDs/1000 inhabitants/day. Perindopril was largely prescribed at 0.83 DDDs/1000 inhabitants/day; followed by ramipril at 0.30 DDDs/1000 inhabitants/day; whereas there was a low utilisation of enalapril at 0.02 DDDs/1000 inhabitants per day. Furosemide and indapamide, both diuretics, had a prescribing rate of 0.85 and 0.64 DDDs/1000 inhabitants/day, respectively; whereas hydrochlorothiazide was the least prescribed at 0.04 DDDs/1000 inhabitants/day compared to other diuretics dispensed in this study. Amongst the beta-blockers, bisoprolol was the most prescribed at 0.47 DDDs/1000 inhabitants/day followed by atenolol at 0.29 DDDs/1000 inhabitants/day. Atenolol and bisoprolol seem to be favoured over propranolol, labetalol, carvedilol and acebutolol in this study.

Based on the DDDs/1000 inhabitants/day, amlodipine was the drug most commonly prescribed in the study (Table 4-9). Amlodipine, including nicardipine, lercanidipine and nifedipine, are

dihydropyridine derivatives and selective calcium channel blockers with mainly vascular effects. Del Pozo *et al.* (2004:242), in their study regarding the use of antihypertensive drugs in Spain, found that amlodipine was one of the most commonly used drugs in 2001 (13.3 DDDs/1000 inhabitants/day). In Serbia, patterns of prescription analysis found amlodipine the most commonly prescribed antihypertensive drug between year 2011 and 2012 (≥18% of total consumption); followed by nifedipine and diltiazem (Tomas *et al.*, 2016:533-534). Similar observations were made in studies conducted by Joel *et al.* (2014:1094), and by Nachiya *et al.* (2015:391) in tertiary care hospitals, reporting the consumption rate of amlodipine at 33 DDDs/100 bed-days and 32.55 DDDs/100 bed-days, respectively. Statistics from Malaysia (Ahmad *et al*., 2007:42) also showed amlodipine to be the most used calcium channel blocker in 2007 (8.93 DDDs/1000 inhabitants/day).

4.4.2.2 The DDDs/1000 inhabitants/day for fixed-dose combinations

Table 4-10 depicts the prescribing of fixed-dose antihypertensives, based on the number of DDDs/1000 inhabitants/day.

Table 4-10: Antihypertensive drugs utilisation using defined daily dose for fixed-dose combination therapy

Drug/Drug class	ATC code	Unit Dose	DDDs	DDDs/1000 inhabitants/day
ACE Inhibitors / calcium channel blockers	**CO9B**		**10 740**	**1.04**
Perindopril / amlodipine	CO9BB04	1	10 740	1.04
ACE Inhibitors / diuretics	**CO9BA**		**28 124**	**2.72**
Perindopril / indapamide	CO9A04	1	19 620	1.90
Quinapril / HCTZ	CO9BA06	1	644	0.06
Captopril / HCTZ	CO9BA01	1	2 260	0.22
Ramipril / HCTZ	CO9BA05	1	5 600	0.54
Calcium channel blockers / angiotensin receptor blockers	**CO9D**			**0.10**
Amlodipine/valsartan	CO9DB01	1	1 008	0.10
Calcium channel blockers / angiotensin receptor blockers / diuretics	**CO9DX**			**0.40**
Amlodipine / valsartan / HCTZ	CO9DX01	1	448	0.04
Beta-blockers / diuretics			**830**	**0.26**
Atenolol / chlorthalidone	CO7BB03	1	200	0.20
Bisoprolol / HCTZ	CO7BB07	1	630	0.06
Beta-blockers / calcium channel blockers	CO7FB		**1 710**	**0.17**

Drug/Drug class	ATC code	Unit Dose	DDDs	DDDs/1000 inhabitants/day
Atenolol / nifedipine	CO7FB03	1	1 710	0.17
K-sparing / thiazide diuretic	**CO3E**		**1 578**	**0.25**
Spironolactone / altizide Amiloride / HCTZ	CO3EA04 CO3EA01	1 1	1 428 150	0.14 0.01
Angiotensin receptor blockers / diuretics	**CO9DA**		**4 348**	**0.42**
Valsartan / HCTZ Candesartan / HCTZ Irbesartan / HCTZ Losartan / HCTZ	CO9DA03 CO9DA06 CO9DA04 CO9DA01	1 1 1 1	1 754 2 340 30 224	0.17 0.23 0.003 0.02
Total			**50 586**	**4.90**

HCTZ: Hydrochlorothiazide; K-sparing: Potassium sparing agent
ATC-code : Anatomic Therapeutic Classification code. DDD/1000 inhabitants/day: calculated using the number of people visiting the pharmacy at the time of study population (N = 28 289) (inhabitants) over 365 days, multiplied by 1000

In the present study, FDCs for 18 brand names, reimbursed by CNAMGS, were prescribed at 50 586 DDDs (Table 4-10). Fixed-dose combinations of angiotensin converting enzyme inhibitors and diuretics had the largest DDD 28 124, followed by the combination of angiotensin converting enzyme inhibitors and calcium channel blockers at 10 740 DDDs. Other combinations used in this study, included fixed-dose combinations of angiotensin receptor blockers and diuretics (4 348 DDDs). Furthermore, beta-blockers and diuretics (830 DDDs), two diuretics (1 578 DDDs), beta-blockers and calcium channel blockers (1 710 DDDs), calcium channel blockers and angiotensin receptor blockers (1 008 DDDs) and finally fixed-dose combination of calcium channel blockers, angiotensin receptor blockers and diuretics (448 DDDs).

The combination of angiotensin converting enzyme inhibitors and diuretics at 2.72 DDDs/1000 inhabitants per day, followed by angiotensin converting enzyme inhibitors and calcium channel blockers at 1.04 DDDs/1000 inhabitants per day were the most prescribed medicines in this study. In angiotensin converting enzyme inhibitors/diuretics group, the fixed combination perindopril and indapamide were the most prescribed at 1.90 DDDs/1000 inhabitants per day, followed by ramipril and hydrochlorothiazide combination at 0.54 DDDs/1000 inhabitants per year. Results for a study done by Mitkova *et al.* (2016:11) showed that the combination of angiotensin converting enzyme inhibitors and diuretics were most preferred, whilst the use of perindopril/indapamide had increased from 0.73 to 6.95 DDDs/1000 inhabitants/day within their study, due to decreased reference price and the use of generic equivalents.

Fixed-dose combinations of angiotensin receptor blockers with diuretics (mostly candesartan and

hydrochlorothiazide, or valsartan and hydrochlorothiazide) were prescribed at 0.42 DDDs/1000 inhabitants/day. Fixed-dose combinations of beta-blockers and diuretics (bisoprolol and hydrochlorothiazide or atenolol and chlorthalidone) were prescribed at 0.26 DDDs/1000 inhabitants/day, that of calcium channel blockers and angiotensin receptor blockers were prescribed at 0.10 DDDs/1000 inhabitants/day. The least prescribed fixed-dose combinations were amiloride and hydrochlorothiazide at 0.01 DDDs/1000 inhabitants/day, a potassium sparing agent combined with thiazide diuretic and the fixed-dose combination of beta-blockers with calcium channel blockers (0.17 DDDs/1000 inhabitants/day). Fixed-dose combinations in this study were mostly the combination of two drugs; except for the combination of amlodipine, valsartan and hydrochlorothiazide at 0.04 DDDs/1000 inhabitants per day. In the present study, fixed-dose combinations of angiotensin converting enzyme inhibitors and diuretics were largely prescribed at 6.05 DDDs/1000 inhabitants/day, followed by angiotensin converting enzyme inhibitors and calcium channel blockers (3.48 DDDs/1000 inhabitants/day).

4.5 Prescribing based on generic indicators

Based on Table 4-6, original drugs were largely used in this study (n = 3 132, 93.2%) compared to generic equivalents (n = 228, 6.8%). The only generic equivalent prescribed as plain formulations were captopril (n = 66, 2.0%) and amlodipine (n = 147, 4.4%); and as FDCs, captopril/hydrochlorothiazide (n = 15, 0.5%). The ten most prescribed brand names (Table 4-6) were Bipreterax® (n = 426), Loxen® (n = 305), Coveram® (n = 289), Fludex® (n = 279), Amlor (n = 235), Lasilix® (n = 220), Tritazide® (n = 148), Aldomet® (n = 135) and Coversyl® (n = 133). Among these top ten trade names, only amlodipine (Amlor®) and captopril/hydrochlorothiazide (Tritazide®) had generic equivalents. Alpha-methyldopa was prescribed as a generic equivalent only.

With the exception of Austria, generic substitution is widely endorsed in other countries, e.g. Denmark, Canada, France, Germany, Ireland, Poland, the UK, and USA, while it is even mandatory in others (for example, Belgium, Finland, Greece, the Netherlands, Portugal, Spain, Italy, Sweden and South Africa) (Anis, 2000:524; Deroukakis, 2007:63; Panteli *et al.,* 2016:67; Law, 2013:18; Posner & Griffin, 2011:731; Vivian, 2008:31). A number of countries also incentivise generic substitution, e.g. France, where generic substitution is incentivised through the pay-for-performance remuneration scheme for doctors and through higher profit margins or add-on payments for pharmacists (Panteli *et al.,* 2016:67). In Gabon, the NHI list of reimbursed medicine only have 25% of generic equivalents (Musango & Inoua, 2010:36; WHO, 2016:9), which may be the reason for less frequent prescribing of generic equivalents in this study. Furthermore, medical practitioners tend to prescribe innovator drugs to patients, even when generic drugs are available (Cooper-DeHoff & Elliot, 2013:345); because of the misconception that innovator drugs may be clinically better than generic drugs (Kesselheim *et al*., 2008:2515).

Patients, if asked to choose between generic equivalents and innovators, may prioritise the use of innovators. In USA for instance, requiring patients' consents prior to generic substitution led to 25% reduction of generic substitution (Shrank *et al.,* 2010:1387).

4.6 General cost analysis of antihypertensive drugs reimbursed by CNAMGS

Table 4.11 shows the overall cost of all antihypertensive drugs reimbursed by CNAMGS within the period of study. Costs are indicated in Central African Franc (XAF). One XAF was equal to R0.0223 for the period 1 June 2013 to 31 May 2014 (OANDA Corporation, 2017).

Table 4-11: General cost analysis of antihypertensive drugs reimbursed by CNAMGS

Aspect	Cost of antihypertensive drugs in Central African CFA Francs (XAF)
Total expenditure on antihypertensive drugs, N	46 570 511
Mean cost per prescription, mean ± SD (95% CI)	18 598 ± 13 836 (95%CI, 18 056 - 19 140)
Mean cost per drug, mean ± SD	10 853 ± 6 336 (95% CI, 10 639 - 11 068)
Total cost reimbursed by CNAMGS, n (%)*	27 217 870 (58.4)
Mean cost per prescription reimbursed by CNAMGS, mean ± SD (95% CI)	10 870 ± 7 617 (95% CI, 10 571 - 11 168)
Total cost paid by patients	19 352 641 (41.6)
Mean cost per prescription paid by patients, mean ± SD (95% CI)	7 729 ± 6 801 (95% CI, 7 461 - 7 995)
Total cost for generic equivalents, n (%)*	2 117 003 (4.6)
Total cost for originals, n (%)*	44 435 508 (95.4)
* Percentage calculated using the total cost of antihypertensive drugs (N = 46 570 511) as a denominator	

For 2 504 prescriptions (refer to paragraph 4.3), the total cost of antihypertensive drugs overall, within the period of study, amounted to 46 570 511 XAF, of which CNAMGS reimbursed 58.4% (n = 27 217 870 XAF) (Table 4-11). The remaining cost of 19 352 641 XAF or 41.6% were patients' co-payments.

The mean cost of a prescription during the study period amounted to 18 598 ± 13 836 XAF (95% CI, 18 056 - 19 140 XAF), whereas the mean cost per drug was 10 853 ± 6 336 XAF (95% CI, 10 639 - 11 068 XAF). According to Osibogun and Okwor (2014:161), in Nigeria people would spend a tenth or more of their incomes on healthcare expenses. In this study, the mean cost per prescription of antihypertensive drugs paid by patient was 7 729 ± 6 801 XAF (95% CI, 7 461 - 7 955 XAF), this represents ~ 5% of the legal monthly minimum wage of 150 000 XAF in Gabon (African Development Bank Group, 2011:17).

The majority of drugs prescribed were originals, at a total cost of 44 435 508 XAF, or 95.4% of the total cost, whilst the cost of generic equivalents accounted for 4.6% of the total cost (n = 2 117 003 XAF). Solanski *et al.* (2013:65) found similar trends in a study performed in India, where the share cost of antihypertensive drugs was higher (56.58%) due to more innovator drugs prescribed as compared to generic equivalents. Rachana *et al*. (2014:21) also observed this in their study, where patients and prescribers preferred more expensive brand name drugs.

The cost of antihypertensive drugs over the study period accounted for 1.7% (N= 46 570 511) of the total revenue of the study setting during the study period. On average, an antihypertensive drug costs CNAMGS 10 870 ± 7 617 (95% CI, 10 571 - 11 168) and expensive antihypertensive drugs were reimbursed at a rate of 50%.

Table 4-12 indicates the total cost of each antihypertensive drug class prescribed as plain products and fixed-dose combinations in total, as well as the percentage reimbursed by CNAMGS. The cost of fixed-dose combination drugs represented 22 220 050 XAF (47.7% of the total cost of antihypertensives prescribed during the study period); of which 55% was reimbursed by CNAMGS. The total cost of plain formulations added up to 24 350 461 XAF, or 52.3% of the total cost of antihypertensives prescribed during the study period. About 61% of this cost was reimbursed by CNAMGS.

Table 4-12: Total cost per class of antihypertensive drugs

Drug class	Total cost in XAF, n (%)*	CNAMGS reimbursement cost in XAF n (%)**
ACE-inhibitors	4 173 483 (8.9)	2 317 17 (53.5)
Angiotensin receptor blockers	2 641 765 (5.7)	1 320 883 (50.0)
Beta-blockers	1 518 190 (3.3)	1 230 373 (81.0)
Central acting agents	644 370 (1.4)	515 496 (80.0)
Diuretics	3 574 318 (7.7)	2 749 320 (76.9)
Calcium channel blockers	11 798 335 (25.3)	6 700 523.5 (56.8)
Fixed dose combinations	22 220 050 (47.7)	12 221 027 (55.0)

ACE = Angiotensin converting enzyme
*Percentage calculated using the total cost of antihypertensive drugs with N = 46 570 511 XAF as denominator
** Percentage calculated using the total cost of each class of antihypertensive drug as denominator

4.6.1 General cost analysis of angiotensin converting enzyme inhibitors (plain formulations)

The total cost of plain angiotensin converting enzyme inhibitors amounted to 4 173 483 XAF (9.0%

of the total cost of antihypertensive drugs); of which 55.3% was reimbursed by CNAMGS (refer to Table 4-12).

Table 4-13 shows the total cost of plain angiotensin converting enzyme inhibitors according to active substance and strength. Active substances within the class of angiotensin converting enzyme inhibitors prescribed during the study period included captopril, enalapril, perindopril and ramipril.

Table 4-13: Cost of angiotensin converting enzyme inhibitors within the study period according to active substance and strength

Active substance and strength (mg)	Cost (XAF), mean ± SD (95% CI)	Total cost (XAF), n (%)	Cost reimbursed (XAF), n (%)	Cost/DDD
Captopril 25 mg**	3 054 ± 9.1 (3 041 - 3 057)	192 400 (4.6)	153 920 (6.6)	419.4
Captopril 50 mg**	5 084 ± 4 (5 084 - 5 086)	213 548 (5.5)	170 838 (7.4)	
Captopril 25 mg	6 927 ± 6.7 (6 923 - 6 930)	96 975 (2.3)	77 580 (3.3)	
Captopril 50 mg	12 409 ± 216 (12 327 - 12 492)	509 885 (12.2)	254 943 (11.0)	
Perindopril 10 mg	17 294 ± 30.2 (12 298 - 12 302)	1 089 605 (26.1)	544 803 (23.5)	269.8
Perindopril 5 mg	11 917 ± 109 (11 893 - 11 941)	1 215 890 (29.1)	608 645 (26.3)	
Enalapril 20 mg	11 740 ± 0	46 960 (1.1)	23 460 (1.0)	195.6
Ramipril 1.25 mg	8 340 ± 0	41 700 (1.0)	20 850 (0.9)	260.5
Ramipril 2.5 mg	10 125 ± 12.3 (10 133 - 10 146)	192 630 (4.6)	170 838 (7.4)	
Ramipril 5 mg	14 607 ± 23.6 (14 597 - 14 616)	540 555 (12.9)	270 280 (11.7)	
Ramipril 10 mg	11 092 ± 24.7 (16 445 - 16 890)	33 335 (0.8)	16 668 (0.7)	
Total	**16 668 ± 4 945 (11 518 - 11 667)**	**4 173 483 (8.9)**	**2 317 117 (53.5)**	**302.9**

** Generic equivalent
Cost/DDD: obtained by dividing the total cost of each drug over the defined daily dose of each drug obtained within the period of study (as defined in Table 4.9)

The mean cost of angiotensin converting enzyme-inhibitors overall was 16 668 ± 4 945 XAF (95% CI, 11 518 - 11 667 XAF). The mean cost of ramipril in this study ranged from 8 340 ± 0 XAF for the 1.25 mg formulation to 11 092 ± 24.7 XAF (95%CI, 16 445 - 16 890 XAF) for 10 mg. The cost/DDD for ramipril, however, amounted to 260.5, which was marginally lower than that of perindopril (269.8) and captopril (419.4). Perindopril 10 mg was the most expensive angiotensin converting enzyme inhibitor at a mean cost of 17 295 ± 30.2 XAF (95% CI, 12 298 - 12 302 XAF).

The highest cost/DDD ratio among angiotensin converting enzyme-inhibitors (419.4) was reported for captopril, compared to enalapril, with the lowest cost/DDD of 195.6 overall. Captopril was the only drug prescribed as generic equivalent, at a total cost of 192 400 XAF (4.6% of the total cost of ACE-inhibitors) for 25 mg formulations and 213 548 XAF (5.5% of the total cost of angiotensin converting enzyme inhibitors) for 50 mg formulations, respectively. The original captopril 25 mg and 50 mg appeared to be more expensive than the generic equivalents at 6 927 ± 6.7 XAF (95%CI, 6 923 – 6 930 XAF) and 12 409 ± 216 XAF (95%CI, 12 327 – 12 492 XAF) respectively. Moreover, mean generic equivalent cost was 3 054 ± 9.1 XAF (95% CI, 3 041 - 3 057 XAF) for captopril 25 mg formulation and 5 084 ± 4 XAF (95% CI, 5 084 – 5 086 XAF) for captopril 50 mg formulation.

4.6.2 General cost analysis of angiotensin receptor blockers (plain formulations)

The total cost of plain angiotensin receptor blockers amounted to 2 641 765 XAF (5.7% of the total cost); of which 50% (1 320 883 XAF) was reimbursed by CNAMGS (Table 4-12). Table 4-14 indicates the overall cost of angiotensin receptor blockers claimed during the study period. Active substances within the class of angiotensin receptor blockers include candesartan and valsartan.

Table 4-14: General cost analysis of angiotensin receptor blockers

Active substance and strength (mg)	Cost (XAF) Mean ± SD (95% CI)	Total cost (XAF), n (%)	Cost reimbursed (XAF), n (%)	Cost/DDD*
Candesartan 4 mg*	14 370 ± 10 (14 361 - 14 380)	100 595 (4.1)	50 298 (4.1)	443.9
Candesartan 8 mg*	19 034 ± 5 (19 031 - 19 306)	456 820 (18.7)	228 410 (18.7)	
Candesartan 16 mg*	20 232 ± 154 (20 163 - 20 300)	587 950 (24.1)	293 975 (24.1)	
Valsartan 80 mg*	20 155 ± 0	483 720 (19.8)	241 860 (19.8)	505.4
Valsartan 160 mg*	25 290 ± 312 (25 174 - 25 406)	809 280 (33)	404 640 (33)	
Total	**21 127 ± 3 124 (21 503 - 20 750)**	**2 438 365 (5.2)**	**1 320 883 (50)**	**476.8**

*Drugs included by, and reimbursed by CNAMGS at 50% include Atacand® 4 mg, Atacand® 8 mg, Atacand® 16 mg, Tareg 80® mg, and Tareg 160® mg
Cost/DDD: obtained by calculating the total cost of each drug prescribed dividing by the defined daily dose (as defined in Table 4.9) of each drug.

The most expensive angiotensin receptor blocker in the study was valsartan 160 mg at a mean cost of 25 290 ± 312 XAF (95% CI, 25 174 - 25 406 XAF). The total cost/DDD of valsartan was 505.4 (Table 4-14).

Due to the high cost of angiotensin receptor blockers, some states in the United States recommended the use of angiotensin converting enzyme inhibitors before initiating treatment with angiotensin receptor blockers. This policy reduced angiotensin receptor blocker prescribing by 1.6% (Wettermark *et al*., 2009:227). The Swedish Pharmaceutical Benefit Board (Hedberg & Jacob, 2008:16) estimated that angiotensin receptor blockers are too expensive, compared to other well-documented and less expensive drugs. However, angiotensin receptor blockers present better tolerability and compliance than angiotensin converting enzyme inhibitors (Neutel, 2012:213) and less adverse effects than angiotensin converting enzyme inhibitors, better control of hypertension and protective end organ damage (Asmar, 2005:318). According to Ravera *et al.* (2006:46), the use of angiotensin receptor blockers in their study, proved to be life and cost saving, compared with traditional antihypertensive drugs, particularly for patients with type 2 diabetes mellitus, nephropathy and hypertension, leading to an annual cost saving of 150 million euro (0.2% decrease in the overall national health expenditure in Italy). In their study, irbesartan, for instance, generated a cost saving of 13 550 Euro, compared to other drugs such as amlodipine (Ravera *et al.,* 2006:46).

4.6.3 General cost analysis of central acting drugs (plain formulations)

The overall cost of alpha-methyldopa in this study amounted to 644 370 XAF, representing 1.4% of the total cost of antihypertensives claimed during the study period (Table 4-12). CNAMGS reimbursed 80% of this cost. The mean cost of alpha-methyldopa was 3 975 XAF for 500 mg and 3 220 XAF ± 14 XAF (95% CI, 3 217 - 3 225) for 250 mg formulations (Table 4-15). The cost/DDD of alpha-methyldopa in this study was 315.9.

Table 4-15: General cost analysis of central acting drugs

Active substance and strength (mg)*	**Cost (XAF), Mean ± SD (95% CI)**	**Total Cost (XAF), n (%)**	**Cost reimbursed (XAF), n (%)**	**Cost/DDD***
Alpha-methyldopa 250 mg	3 221 ± 14 (3 217 - 3 225)	270 720 (42.0)	216 576 (42.0)	315.8
Alpha-methyldopa 500 mg	3 975 ± 0	373 650 58.0	298 920 (58.0)	
Total	**3 634 ± 377 (3 570 - 3 699)**	**644 370 1.4**	**515 496 (80)**	

*Central acting drugs reimbursed by CNAMGS at 80% included: Aldomet® 250 mg, Aldomet ®500 mg
Cost/DDD: calculated using the total cost of each drug divided by the defined daily dose (DDD) (as calculated in Table 4-9)

4.6.4 General cost analysis of diuretics (plain formulations)

The total cost of plain diuretics (n = 3 574 318 XAF) amounted to 7.7% of the total cost of antihypertensives prescribed during the study period, of which 80% was reimbursed by CNAMGS (Table 4-12). Table 4-16 depicts the cost of plain diuretics prescribed within the study period.

The least expensive diuretic was hydrochlorothiazide at a mean cost of 820 ± 9 XAF (95% CI, 815 – 824) (cost/DDD = 54.7), whereas the most expensive diuretics were furosemide 500 mg (mean cost 28 650 ± 0 XAF) and spironolactone 75 mg at a mean cost of 11 307 ± 63 XAF (95% CI, 11 304 - 11 310) (cost/DDD = 358.6). According to Twagirumukiza *et al.* (2010:358), hydrochlorothiazide is affordable in the majority of sub-Saharan African countries compared to drugs such as captopril (2.6 times less expensive) and amlodipine (13.2 times less expensive). Similar results were found in the present study, with the cost of hydrochlorothiazide being 3.7 times less expensive than the captopril 25 mg generic equivalent and 8.3 times less expensive than amlodipine 5 mg generic equivalent. Based on these comparisons, diuretics, in the present study, are the least expensive compared to other classes.

Table 4-16: General cost analysis of diuretics

Active substances and strength (mg)	Cost (XAF) Mean ± SD (95% CI)	Total cost (XAF), n (%)	Cost reimbursed (XAF), n (%)	Cost/DDD*
Furosemide 20 mg (oral)	1 552 ± 159 (1 520 - 1 586)	240 340 (7.0)	192 272 (7.0)	95.9
Furosemide 20 mg (inj.)	952 ± 125 (893 - 1 010)	96 590 (2.8)	77 272 (2.8)	
Furosemide 40 mg (oral)	2 388 ± 8 (92 386 - 2 389)	382 095 (11.1)	305 676 (11.1)	
Furosemide 500 mg (oral)	28 650 ± 0	143 250 (4.2)	114 600 (4.2)	
Hydrochlorothiazide 25 mg	820 ± 9 (815- 824)	24 630 (0.7)	19 704 (0.7)	54.7
Indapamide 1.5 mg	5 768 ± 12 (5 766 - 5 769)	2 140 195 (62.3)	1 712 156 (62.3)	323.1
Spironolactone 25 mg	5 055 ± 0	5 055 (0.1)	4 044 (0.1)	358.7
Spironolactone 50 mg	4 689 ± 744 (4 468 - 4 910)	133 135 (3.9)	106 508 (3.9)	
Spironolactone 75 mg	11 307 ± 6.3 (11 304 - 11 310)	271 360 (7.9)	217 088 (7.9)	
Total	**4 382 ± 2 892 (4 147- 4 617)**	**3 574 318 (7.4)**	**2 749 320 (80)**	**199.8**

Inj = injection
cost/DDD: calculated using the total cost of each drug divided by the defined daily dose (DDD) in Table 4.9

4.6.5 General cost analysis of beta-blockers (plain formulations)

Beta-blockers accounted for a total cost of 1 518 190 XAF (3.3% of the total antihypertensive drugs), of which 81% were reimbursed by CNAMGS (Table 2-12). Table 4-17 portrays the general cost analysis of beta-blockers, and the amounts reimbursed by CNAMGS.

Table 4-17: General cost analysis of beta-blockers

Active substance and strength (mg)	Cost (XAF), mean ± SD (95% CI)	Total cost (XAF), n (%)	Cost reimbursed (XAF), n (%)	Cost/DDD
Propranolol 160 mg	6 425 ± 0	6 425 (0.4)	5 140 (0.4)	226.0
Propranolol 40 mg	2 565 ± 0	35 910 (2.6)	28 728 (2.3)	
Bisoprolol 1.25 mg	6 950 ± 0	20 850 (1.3)	16 680 (1.3)	
Bisoprolol 2.5 mg	5 530 ± 0	16 590 (1.1)	13 272 (1.1)	168.5
Bisoprolol 5 mg	4 950 ± 0	19 825 (1.3)	15 860 (1.3)	
Bisoprolol 10 mg	4 774 ± 5 (4 773 - 4 774)	749 495 (48.4)	599 596 (48.7)	
Carvedilol 6.25 mg	6 990 ± 0	90 870 (5.9)	72 696 (5.7)	849.5
Carvedilol 25 mg	6 990 ± 0	39 950 (2.6)	31 960 (2.6)	
Atenolol 50 mg	3 560 ± 10 (7 492 - 7 499)	138 720 (8.9)	110 976 (9.0)	184.9
Atenolol 100 mg	7 500 ± 7 (3 554 - 3 560)	397 365 (25.7)	317 892 (25.8)	
Labetalol 200 mg	14 585 ± 0	14 585 (0.9)	7292.5 (0.6)	1 458.5
Acebutolol 200 mg	12 850 ± 0	12 850 (0.8)	10 280 (0.8)	856.7
Total	**5 273 ± 1 465 (5 079 - 5 466)**	**1 518 190 (3.3)**	**1 230 373 (79.5%)**	**191.7**
Cost/DDD was obtained using the total cost of each beta-blocker prescribed divided by the total DDD (Table 4.9) of each drug				

Six types of beta-blockers were prescribed, including propranolol (40 mg and 160 mg), bisoprolol (1.25 mg, 5.5 mg, 5 mg and 10 mg), carvedilol (6.25 mg and 25 mg), atenolol (50 mg and 100 mg), labetalol (200 mg) and acebutolol (200 mg) (Table 4-17). Labetalol 200 mg (total cost of 14 585 XAF), acebutolol (total cost of 12 850 XAF) and carvedilol were the most expensive beta-blockers in this study, at cost/DDDs of 1 485.5, 856.7 and 849.5, respectively.

Propranolol 40 mg was the least expensive beta-blocker, accounting for a total cost of 2 565 XAF. Bisoprolol 10 mg was the most frequently prescribed drug among beta-blockers, at a total cost of 749 495 XAF (mean cost 4 774 ± 5 XAF, 95% CI, 4 774 - 4 775). Bisoprolol had the lowest cost/DDD (168.5), followed by atenolol (cost/DDD = 184.9) and propranolol (cost/DDD= 225.0).

4.6.6 General cost analysis of calcium channel blockers (plain formulations)

Calcium channel blockers amounted to a total cost of 11 798 335 XAF (25.3% of the all antihypertensive drugs prescribed), of which CNAMGS reimbursed 56.8% (Table 4-12). Amlodipine was the only calcium channel blocker for which generic equivalents were prescribed.

Table 4-18 depicts the cost of each calcium channel blocker prescribed within the period of study. In this study, different names of amlodipine were prescribed and only four were generic equivalents. The amlodipine 10 mg innovators had a mean cost of 13 749 ± 141 XAF (95% CI, 13 728 – 13 771 XAF); this was relatively more expensive than the generic equivalent amlodipine 10 mg, with a mean cost of 8 418 ± 1 543 XAF (95% CI, 8 070 – 8 766 XAF). Similar trends were observed in amlodipine 5 mg, where the innovators' mean cost of 12 259 ± 497 XAF (95% CI, 12 137 – 12 381) was ~2 times more expensive than that of the generic equivalent.

The mean cost of diltiazem was 13 470 ± 0 XAF for 200 mg and 13 570 ± 0 XAF for 300 mg; this is relatively higher and was as expensive as amlodipine and nicardipine, and there were no generic equivalents prescribed.

Nicardipine was the second most prescribed calcium channel blocker after amlodipine, with a total cost of 5 194 395 XAF (accounting for 44.0% of the cost of CCBs). Nicardipine was dispensed as either injections (10 mg) or tablets (20 mg and 50 mg). There was no generic for nicardipine. Nicardipine 50 mg has a mean cost of 14 492 ± 15 XAF (95% CI, 14 490 - 14 494).

Nifedipine (10 mg, 20 mg and 30 mg) has demonstrated its efficacy and safety in controlling hypertension in pregnancy and after pregnancy (Hall, 2014:71), and its mean cost varied between 3 525 ± 0 XAF and 8 090 XAF in this study. Nifedipine appears to be the less expensive among calcium channel blockers prescribed

Lercanidipine (10 mg and 20 mg) has a mean cost of 11 195 ± 0 XAF and 12 060 ± 0 XAF. Due to the high cost of lercanidipine, The Swedish Pharmaceutical Benefit Plan (Hedberg & Jacob, 2008:94) suggested the use of other less expensive and effective calcium channel blocker drugs such as felodipine.

The overall cost per DDD for calcium channel blockers was 301.8. Among these calcium channel blockers, the largest cost/DDD was reported for diltiazem (1 564.7), followed by nicardipine (cost/DDD = 496.7), nifedipine (cost/DDD = 344.2) and lercanidipine (cost/DDD = 343.4). Verapamil, the least prescribed CCB in this study, had the lowest cost/DDD of 207.8, followed by amlodipine, the most prescribed drug with a cost/DDD of 222.8.

Access to less costly quality drugs remains a huge problem in sub-Saharan African countries

(Auta *et al.,* 2013:53), particularly in Gabon. Although CCBs have proven their efficacy in treating hypertension in those of African descent, their cost may affect compliance. Adigun *et al.* (2003:282) found similar trends in Nigeria, where some patients could hardly afford newer and more expensive drugs such as calcium channel blockers. The relatively high cost of calcium channel blockers among antihypertensive drugs prescribed during the period of study, could be explained by the fact that innovator drugs were mostly prescribed, along with expensive generic equivalents.

Table 4-18: General cost analysis of calcium channel blockers

Active substance and strength (mg)	Cost (XAF), mean ± SD (95% CI)	Cost (XAF), n (%)	Cost reimbursed (XAF), n (%)	Cost /DDD
Amlodipine 5 mg	12 259 ± 497 (12 137 – 12 381)	1 174 260 (10.0)	587 130 (8.8)	222.8
Amlodipine 5 mg**	6 647 ± 439 (6 540 - 6 753)	662 660 (5.6)	530 128 (7.9)	
Amlodipine 10 mg	13 749 ± 141 (13 728 – 13 771)	3 273 035 (27.7)	1 636 517.5 (24.4)	
Amlodipine 10 mg**	8 418 ± 1 543 (8 070 - 8 766)	945 795 (8.0)	736 045.5 (11.0)	
Diltiazem 200 mg	13 470 ± 0	13 470 (0.1)	6 735 (0.1)	1 564.7
Diltiazem 300 mg	13 570 ± 0	54 280 (0.5)	27 140 (0.4)	
Nifedipine 10 mg	3 525 ± 0	14 100 (0.1)	11 280 (0.2)	344.2
Nifedipine 20 mg	7 030 ± 0	91 390 (0.8)	73 112 (1.1)	
Nifedipine 30 mg	8 090 ± 0	8 090 (0.07)	6 472 (0.09)	
Nicardipine 10 mg IV	8 185 ± 20 (8 180 – 8 190)	654 840 (5.6)	523 872 (7.8)	496.7
Nicardipine 20 mg	4 640 ± 0	32 480 (0.3)	25 984 (0.4)	
Nicardipine 50 mg	14 492 ± 15 (14 490 – 14 494)	4 507 075 (38.2)	2 253 537.5 (33.6)	
Lercanidipine 10 mg	11 185 ± 0	324 365 (2.7)	259 492 (3.9)	343.4
Lercanidipine 20 mg	12 060 ± 0	36 180 (0.3)	18 090 (0.3)	
Verapamil 240 mg	6 235 ± 0	6 235 (0.05)	4 988 (0.07)	207.8
Total	**11 836 ± 3 054 (11 316 – 12 055)**	**11 798 335**	**6 700 523.5**	**301.8**

Percentage calculated using the total cost of calcium channel blockers as a denominator (N= 11 798 335 for total cost and N = 6 700 523.5 for cost reimbursed). Cost/DDD calculated using the total cost divided by the defined daily dose of each CCB drugs calculated in Table 4-9; ** generic equivalent

4.6.7 General cost analysis of fixed-dose combination antihypertensives

The overall cost of fixed-dose combinations prescribed for the treatment of hypertension in the study period is portrayed in Table 4-12. Fixed-dose combination drugs had the highest cost compared with other classes of antihypertensive drugs at 22 220 050 XAF (47.7% of the total cost), of which 55% was reimbursed by CNAMGS.

Table 4-19 depict the general cost analysis of individual fixed-dose combination antihypertensive drugs.

Table 4-19: General cost analysis of fixed-dose combination antihypertensive drugs

Active substance combination and strengths (mg)	Cost (XAF), mean ± SD (95% CI)	Total cost (XAF), n (%)	Cost reimbursed (XAF), n (%)	Cost/DDD
Quinapril/hydrochlorothiazide 20/12.5 mg	7 150 ± 0	164 450 (0.7)	131 560 (1.0)	255.3
Spironolactone/altizide 15/25 mg	3 975 ± 0	202 725 (0.9)	162 180 (1.3)	478.8
Perindopril/indapamide 10/2.5 mg	18 186 ± 7 (18 185 - 18 188)	3 091 440 (13.9)	1 545 720 (12.6)	
Perindopril/indapamide 5/1.25 mg	13 109 ± 12 (13 107- 13 110)	4 981 060 (22.4)	2 490 530 (20.3)	
Perindopril/indapamide 2.5/0.625 mg	10 752 ± 14 (10 749 - 10 755)	1 118 500 (5.0)	894 800 (7.3)	
Perindopril/amlodipine 10/10 mg	18 446 ± 84 (18 431 - 18 461)	2 844 380 (12.8)	1 422 190 (11.7)	504.6
Perindopril/amlodipine 5/10 mg	12 918 ± 745 (12 710 - 13 126)	897 160 (4.0)	448 580 (3.7)	
Perindopril/amlodipine 5/5 mg	12 743 ± 1 430 (12 473 - 13 013)	1 677 940 (7.6)	838 970 (6.9)	
Amlodipine/valsartan 5/160 mg	21 470 ± 0	150 290 (0.7)	75 145 (0.6)	766.2
Amlodipine/valsartan 10/160 mg	21 452 ± 6 (21 450 - 21 455)	622 050 (2.8)	311 025 (2.5)	
Amlodipine/valsartan/ hydrochlorothiazide 5/160/25 mg	21 470 ± 0	21 470 (0.1)	10 735 (0.09)	766.8
Amlodipine/valsartan/ hydrochlorothiazide 10/160/25 mg	21 470 ± 0	322 050 (1.4)	161 025 (1.3)	
Amiloride/hydrochlorothiazide 5/50 mg	5 790 ± 0	8 950 (0.1)	23 160 (0.1)	193.0
Atenolol/chlorthalidone 50/12.5 mg	3 720 ± 0	48 360 (0.2)	38 688 (0.3)	1 709.2
Atenolol/chlorthalidone 20/12.5 mg	5 060 ± 3 (5 059 - 5 061)	293 480 (1.3)	234 784 (1.9)	
Valsartan/hydrochlorothiazide 160/12.5 mg	25 390 ± 0	101 560 (0.5)	50 780 (0.4)	876.5
Valsartan/hydrochlorothiazide 80/12.5 mg	20 325 ± 0	182 925 (0.8)	91 462.5 (0.7)	
Valsartan/hydrochlorothiazide 160/25 mg	25 410 ± 0	1 245 090 (5.6)	622 545 (5.0)	
Candesartan/hydrochlorothiazide 8/12.5 mg	20 155 ± 0	302 325 (1.4)	151 162.5 (1.2)	699.9

Active substance combination and strengths (mg)	Cost (XAF), mean ± SD (95% CI)	Total cost (XAF), n (%)	Cost reimbursed (XAF), n (%)	Cost/DDD
Candesartan/hydrochlorothiazide 16/12.5 mg	21 044 ± 903 (20 769 - 21 319)	1 335 420 (6.0)	667 710 (5.5)	
Nifedipine/atenolol 20/50 mg	12 459 ± 14 (12 454 - 12 464)	710 200 (3.2)	355 100 (2.9)	415.3
Bisoprolol/hydrochlorothiazide 2.5/6.25 mg	9 290 ± 0	65 030 (0.3)	52 024 (0.4)	309.3
Bisoprolol/hydrochlorothiazide 5/6.25 mg	9 270 ± 0	111 240 (0.5)	88 992 (0.7)	
Bisoprolol/hydrochlorothiazide 10/6.25 mg	9 290 ± 0	18 580 (0.08)	14 864 (0.1)	
Ramipril/hydrochlorothiazide 5/12.5 mg	4 896 ± 540 (4 643 – 5 149)	129 035 (0.6)	103 228 (0.8)	253.0
Ramipril/hydrochlorothiazide 5/25 mg	7 188 ± 8 (7 186 - 7 190)	934 700 (4.2)	747 760 (6.1)	
Ramipril/hydrochlorothiazide 10/12.5 mg	7 765 ± 0	62 120 (0.3)	49 696 (0.4)	
Ramipril/hydrochlorothiazide 10/25 mg	8 329 ± 15 (8 322 - 8 335)	291 360 (1.3)	233 088 (1.9)	
Captopril hydrochlorothiazide**	4 664 ± 4 (4 662 - 4 666)	103 260 (0.5)	82 608 (0.7)	53.9
Captopril/hydrochlorothiazide mg	9 330 ± 0	18 660 (0.08)	14 928 (0.1)	
Losartan/hydrochlorothiazide 50/12.5 mg	15 970 ± 0	127 760 (0.6)	102 208 (0.8)	570.3
Irbesartan/hydrochlorothiazide mg	17 160 ± 0	17 160 (0.08)	8 580 (0.07)	572.0
Total	**13 583 ± 5 265 (13 294 - 13 873)**	**22 220 050**	**12 221 027**	**439.3**

** Generic, Cost/DDD was calculated using the total cost of each drug divided by the defined daily dose (Table 4-10) of these drugs; percentages were obtained using the total cost (N= 22 220 050 for the overall cost and N = 12 221 027 for the total cost reimbursed) of fixed-dose combinations.

The combination of perindopril and indapamide (angiotensin converting enzyme inhibitors and diuretics) had a total cost of 3 091 400 XAF for doses of 10 /2.5 mg, 4 981 060 XAF for doses of 5/1.25 mg and 1 118 500 XAF for doses of 2.5/0.625 mg (Table 4-19). The overall cost of perindopril and indapamide amounted to 9 191 000 XAF (41.4% of the total cost of fixed-dose combinations). The mean costs of these three drugs were 18 186 ± 7 XAF (95% CI, 18 185 - 18 188), 13 109 ± 12 XAF (95% CI, 13 107 - 13 110) and 10 755 ± 14 XAF (95% CI, 10 755 - 10 769), respectively.

The least costly combination of angiotensin converting enzyme inhibitors with diuretics, was the generic equivalent captopril and hydrochlorothiazide at a mean cost of 4 664 ± 4 XAF (95% CI, 4 662 - 4 666), in comparison to the innovator captopril and hydrochlorothiazide (mean cost 9 330 ± 0 XAF). Angiotensin converting enzyme inhibitors combined with diuretics also include ramipril and hydrochlorothiazide, and quinapril and hydrochlorothiazide. Ramipril and hydrochlorothiazide combination (5/12.5 mg) had a mean cost of 4 896 ± 540 XAF (95% CI, 4 648

– 5 149), whereas the 5/25 mg formulation had a mean cost of 7 188 ± 8 XAF (95% CI, 7 186 - 7 190). The 10/12.5 mg formulation had a mean cost of 7 765 ± 0 XAF, and 10/25 mg had a mean cost of 8 329 ± 15 XAF (95% CI, 8 335 - 8 332). Quinapril and HCTZ (20/12.5 mg) combination cost on 7 150 ± 0 XAF on average.

The fixed-dose combination of valsartan and hydrochlorothiazide (160/25 mg) (angiotensin receptor blockers and diuretic) was the most expensive fixed-dose combination claimed during the study period (mean cost 25 410 ± 0 XAF). This is followed by the combination of valsartan plus amlodipine and hydrochlorothiazide (angiotensin receptor blockers plus calcium channel blockers and diuretic) at a mean cost of 21 470 ± 0 XAF. Three drug fixed-dose combination therapy is recommended for patients whose blood pressure cannot be controlled with two drug fixed-dose combination therapy (Mishchenko *et al*., 2014:67). Furthermore, Mishchenko *et al*. (2014:73) demonstrated, in a pharmacoeconomic analysis, that the triple fixed-dose combination of valsartan and amlodipine plus hydrochlorothiazide provides greater clinical efficacy (70.8% patients achieved the target blood pressure) compared to other dual fixed-dose combinations.

The most expensive fixed-dose combination with diuretics were that of angiotensin receptor blockers and diuretics, at a cost >20 000 XAF, except for irbesartan and hydrochlorothiazide combination at a mean cost of 17 160 ± 0 XAF, and losartan and hydrochlorothiazide at a mean cost of 15 970 ± 0 XAF. Although the combination of angiotensin receptor blockers and diuretics are mainly used (Tomas *et al*., 2016: 535), factors such as cost may limit their use in a developing country such as Gabon. Using different drugs for hypertension, such as thiazide diuretics, tend to have an additive effect (Mpe, 2007:37). The fixed-dose combination of perindopril and amlodipine (angiotensin converting enzyme inhibitor and calcium channel blocker), was prescribed at a mean cost varying from 12 743 ± 1 430 XAF (95% CI, 12 473 - 13 013) to 18 466 ± 84 XAF (95% CI, 18 431 - 18 461) depending on the strength of the drug.

Potassium channel blockers combined with thiazide diuretics, had the lower cost than other fixed-dose combinations prescribed in this study. Mean cost of spironolactone combined with altizide was 3 975 ± 0 XAF, and amiloride with hydrochlorothiazide was 5 790 ± 0 XAF. The combination of atenolol and chlorthalidone had a mean cost of 5 060 ± 3 (95% CI, 5 059 - 5 061) and 3 720 ± 0 XAF, whereas the mean cost of bisoprolol and hydrochlorothiazide fixed-dose combinations were between 9 270 ± 0 XAF and 9 290 ± 0 XAF. The combination of nifedipine and atenolol (beta-blocker/ calcium channel blocker) had a mean cost of 12 459 ± 14 XAF (95% CI, 12 454 - 12 464).

The combination of atenolol and chlorthalidone (50/12.5 mg) had the highest cost/DDD (1 709.2) compared to other fixed-dose combinations prescribed and the drugs with lower cost/DDD among these fixed-dose combinations was the captopril and hydrochlorothiazide combination (53.9). The

FDC of perindopril/indapamide had a cost/DDD of 478.8.

4.6.8 Comparison of the cost prescribing ratios of plain antihypertensive drugs and fixed-dose combinations

Table 4-20 portrays the cost per DDD of each class of antihypertensive drugs prescribed. Fixed-dose combinations accounted for 47.7% of the total drugs cost — the largest cost share (Table 4-20), whereas the angiotensin receptor blockers were the least prescribed drugs but had a cost prevalence of 5.7%. Diuretics were the second largest group of drugs prescribed, whereas plain formulation 17.4% was only responsible for 7.4% of the total cost (Table 4-20).

Table 4-20: Summary of cost per DDD per antihypertensive drug class

Drug Classes	Cost in XAF(%)	DDDs	Cost/DDD
Angiotensin converting enzyme inhibitors	4 315 763 (9.3)	14 250.0	302.9
Angiotensin receptor blockers	2 641 765 (5.7)	5 540.0	476.9
Beta-blockers	1 547 435 (3.3)	8 072.8	191.7
Central acting agent	644 370 (1.4)	2 040	315.9
Diuretics	3 436 650 (7.4)	17 203.5	199.8
Calcium channel blockers	11 798 255 (25.3)	39 097.1	301.8
Fixed dose combinations	22 220 050 (47.7)	50 586	439.3

It is clear that in this study (Table 4-20), hypertension medication was relatively expensive; results have raised concern regarding the frequent use of some antihypertensive drugs, particularly angiotensin receptor blockers, fixed-dose combinations and angiotensin converting enzyme inhibitors. The cost/DDD of angiotensin receptor blockers was higher compared to other classes of antihypertensive drugs at 476.9, followed by fixed-dose combinations (cost/DDD = 439.3), then central acting agents (cost/DDD = 315.9), angiotensin converting enzyme inhibitors (cost/DDD of 302.9) and calcium channel blockers (cost/DDD = 301.8). The cost/DDD of diuretics and beta-blockers were relatively lower (199.8 and 191.7, respectively) than the other classes of antihypertensive drugs used in this study. Concerning these findings, angiotensin receptor blockers appear to be the most expensive drug class.

Fixed-dose combination, compared with a free combination of single drugs, is associated with lower healthcare cost (Bramlage & Hasford, 2009:11). Diuretics with a DDD of 17 203.5, represented only 7.4% of the total drug cost, higher than angiotensin receptor blockers (5.7%), and central acting drugs (1.4%), therefore, diuretics appeared to have a better overall cost prescribing ratio compared to other antihypertensive drug classes.

Calcium channel blockers were largely prescribed (22.2%, n = 744) (Table 4-6); the cost/DDD was 301.8, thus marginally less expensive than angiotensin converting enzyme inhibitors at a cost/DDD of 302.9. Altagracia-Martinez *et al.* (2006:22) reported in their study that calcium channel blockers and angiotensin converting enzyme inhibitors had the biggest share value of the total cardiovascular market in Mexico. Bramlage and Hasford (2009:7) stated that in a study performed by Degli-Esposti in 2004, patients on diuretics had the lowest average cost and that the highest drug cost was reported for patients using angiotensin receptor blockers and calcium channel blockers.

4.7 Potential cost savings through a 100 % generic substitution

According to Ekwunife and Ubaka (2010:027), the WHO/ISH recommends the use of generic equivalents and least expensive drugs to minimise the cost. The majority of drugs prescribed at the time of this study were innovators; generic equivalents were only available for drugs such as captopril (Table 4-13), amlodipine (Table 4-18), furosemide injections (Table 4-16) and the fixed-dose combination of captopril/HCTZ (Table 4-19). Table 4-21 portrays the mean cost difference of generic equivalents reimbursed by CNAMGS and their original formulations along with the potential cost saving that could have been generated, if these original formulations were substituted by their generic equivalent.

Table 4-21: Mean cost difference between original and generic equivalents and potential cost savings based on a 100% substitution

Drugs	Generic equivalent cost, mean ± SD (95% CI) (XAF) (a)	Original Drug cost, mean ± SD (95% CI) (XAF) (b)	Cost difference, (XAF) (%)*(c)	Potential cost saving (XAF) (%)** (d)
Angiotensin converting enzyme inhibitors				
Captopril 25 mg	3 054 ± 9.1 (3 041 - 3 057)	6 927 ± 6.7 (6 923 - 6 930)	3 873 (55.9)	43 367 (0.2)
Captopril 50 mg	5 084 ± 4(5 084 – 5 086)	12 409 ± 216 (12 327 -12 492)	7 325 (59.0)	150 416 (0.7)
Calcium channel blockers				
Amlodipine 5 mg	6 647 ± 439 (6 040 - 6 753)	12 259 ± 497 (12 137 – 12 381)	5 612 (45.8)	268 906 (1.2)
Amlodipine 10 mg	8 418 ± 1 543 (8 070 - 8 766)	13 749 ± 141 (13 728 - 13 771)	5 331 (38.8)	634 969 (2.3)
Thiazide diuretics				
Furosemide 20 mg injection	215 ± 0	952 ± 125 (813 - 1 010)	737 (77.4)	59 809 (0.2)
Fixed dose combination				

Drugs	Generic equivalent cost, mean ± SD (95% CI) (XAF) (a)	Original Drug cost, mean ± SD (95% CI) (XAF) (b)	Cost difference, (XAF) (%)*(c)	Potential cost saving (XAF) (%)** (d)
Captopril HCTZ 50/25 mg	4 664 ± 4 (4 662 - 4 666)	9 330 ± 0	4 666 (50.0)	7 464 (0.03)

*The cost difference was determined by subtracting the mean cost of generic equivalents (a) from the mean cost of original brand name products (b). The percentage was obtained using the mean cost of original brand name products in the table as a denominator (c=(a-b)/b)

**Potential cost savings (d) were calculated using the product of the cost of original brand drugs reimbursed (refer to Tables 4-13, 4-16, 4-18, 4-19) and the percentage difference in mean costs between original brand and generic equivalents (c). The percentage potential cost saving was obtained by using the total cost reimbursed by CNAMGS for all antihypertensive drugs prescribed during the study period (N= 22 217 870 XAF) as a denominator

Dunne *et al.* (2013:13) stated that increasing the use of generic equivalents, was associated with cost savings; and that the use of generics had saved the US economy $931 billion between 2001 and 2010. From Tables 4-6 and 4-21, it can be deducted that only a few generic equivalent antihypertensives were available on the market at the time of the study.

Substitution for all claims for captopril 25 mg and captopril 50 mg with generic equivalents could potentially have saved 43 367 XAF (0.2% of the total cost reimbursed of antihypertensive drugs prescribed) and 150 416 XAF (0.7% of the total cost), respectively. The launch of generic equivalents of angiotensin converting enzyme inhibitors in the UK, for example, led to a 28.3% decrease in the cost of angiotensin converting enzyme inhibitors (Baker *et al.,* 2015:11). If captopril was prescribed as a generic equivalent only, a cost of 193 783 XAF (0.9%) would have been saved by CNAMGS. The difference in mean cost between amlodipine generic equivalents and its original brand name accounted for 5 612 XAF and 5 331 XAF, for amlodipine 5 mg and 10 mg, respectively.

Substitution of amlodipine 10 mg by generic equivalents would have led to a potential saving of 634 969 XAF (2.3% of the total cost), whereas substitution of amlodipine 5 mg could potentially save 268 906 XAF (1.2% of the total cost). Huge saving could have been obtained if amlodipine generic equivalents were used. The only diuretic in this study with generic equivalents available was the furosemide 20 mg injection, and if a generic equivalent was used it could have saved 0.2% of the total cost (n=59 809 XAF).

Substitution of all claims for originator drugs (plain formulations and fixed-dose combination), where generic equivalents were available, would have led to a potential cost saving of 2 246 594 XAF (4.8% of the total cost of all antihypertensives claimed during the study period), or 1 313 009 XAF would have been saved from CNAMGS.

The prescribing of generic equivalents has allowed some governments to continue to provide

quality and equitable healthcare without an increase in either taxes or health insurance premiums (Godman *et al.,* 2012:26). According to Posner and Griffin (2011:731), generic substitution was implemented in USA, Sweden and Finland by reimbursement authorities, healthcare services or insurance-based claims; as a result, in Sweden and Finland, it generated 5% saving of the national drugs expenditure. In Canada, generic equivalents represented the majority of all prescriptions because the use of generic equivalents is encouraged by provincial drug plans and some private drug plans (Law, 2013:18). South Africa implemented mandatory generic substitution in May 2003. The Act No. 90 of 1997, therefore, compels pharmacists to dispense generic equivalents, unless the drug is indicated 'non-substitutable' by the prescriber (Deroukakis, 2007:63).

Generic substitution is one of the several methods used to cut down drug expenditure (Bello, 2012:009). In the case of hypertension, cost of medications may be a barrier to drug compliance, therefore, practitioners and pharmacists should adopt procedures that increase generic equivalent use; In Nigeria, for instance, the high rate of generics used, improved adherence by 67.7% in the treatment of hypertension (Bello, 2012:015). Many US policy-makers and payers support substitution laws and tiered formularies to improve the use of generics and cost saving (Sarpatwari *et al*., 2015:2).

4.8 Chapter summary

In this chapter, an empirical investigation of antihypertensive drugs reimbursed by CNAMGS has been discussed; from this analysis the prevalence of antihypertensive drugs used among the insured could be analysed along with the cost of antihypertensive drugs, as well as the prescribing patterns among health professionals. The following chapter contains the conclusions and recommendations derived from the study.

CHAPTER 5 CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction

This dissertation consisted of five chapters. Chapter 1 contained an overview, problem statements and ethical considerations pertaining to the study. Chapter 2 addressed a literature review on CNAMGS, drug selection programs in other countries, prevention and treatment of hypertension. Chapter 3 is a description of the methodology followed during the empirical investigation. Chapter 4 contained the results of the empirical investigation. This final chapter will entail the conclusions along with the recommendations derived from the study, and detail the strengths and limitations of the study.

5.2 Conclusions derived from the literature review

The specific objectives of the literature review were to: (i) review the background and history of the CNAMGS; (ii) to compare drug selection criteria of the CNAMGS to that of other Social Health Insurance plans in other international countries; and (iii) to conceptualise the classification, use and management of hypertension. The conclusions derived from this investigation are summarised in following paragraphs.

5.2.1 Review of the background and history of the CNAMGS

In order to determine the prescribing patterns and the cost of antihypertensive drugs reimbursed by CNAMGS in this study, it was important to have some knowledge on the background and history of CNAMGS. The background and history of the CNAMGS was discussed in section 2.2 and 2.3 (Chapter 2 of this study).

Gabon aims to enhance the quality of healthcare through universal health coverage for all citizens; consequently, the Gabonese government in 2007, by order (0022 / PR / 2007 of 21 August 2007), implemented a fund called Caisse d'Assurance de Maladie ET de Guarantee Sociale (CNAMGS). This fund is compulsory for all the citizens living in Gabon and one of the main goals of the fund was to overcome socio-economic and health inequalities among the population.

The fund is an autonomous organisation under the Ministry of Health and Public Hygiene, Gabon. Funds to run the structure are collected on taxation-based financing by the population working in the private and public sector, the government enterprises and private enterprises. There are three funds, namely the GEF fund (for Gabonese with monthly incomes lower that 80 000 XAF), the public fund for those working in the public sector and the private fund for the private sector employees. Package offers by the scheme, include external care (mainly consultations to the doctors, nurses and dentist), laboratory tests (blood test, x-rays), ambulatory and emergency

care, hospitalisations and transfer of the patients abroad for conditions that cannot be handled in the country. To date, only 32.5% of pharmacies in Gabon are accredited to work with the fund. Drug procurement has become an issue for pharmacists, particularly for chronic medications. Some community pharmacies are faced with delayed payments, leading to drug shortages and financial problems. For the sustainability of the fund and the community pharmacy, pharmacists should be involved in decision-making, particularly drug selection for the formularies.

5.2.2 Drug selection criteria of the CNAMGS compared to that of other Social Health Insurance plans in other international countries

Establishing a drug reimbursement formulary is an important process in the healthcare system and medical aid providers. Drug selection processes in other international countries were discussed in section 2.4 to 2.5.6 of Chapter 2. It was concluded that drug or therapeutic committees are the most appropriate bodies to develop drug policies; these committees should be composed of representatives from Ministry of Health, medical and paramedical practitioners, hospital and districts pharmacists, hospital directors, pharmacologists and other specialists (Holloway & Green, 2003:7). Countries such as France, Canada, USA, Ghana or South Africa, established their drug formularies based on WHO guidelines and essential medicine list.

In France, once the drug has received a market authorisation, a committee of experts evaluate the drug based on two criteria. The first one would be the effect of the drug on the disease, the second one the improvement of the medical benefit (Nguyen *et al.,* 2005). In Canada, once the department in charge of drug policy has approved the safety, the efficacy and the quality of drug, the drug is reviewed by a committee of experts based on criteria such as the therapeutic advantages and disadvantages, cost effectiveness, safety, efficacy and quality-adjusted life years (Paris & Docteur, 2007:22). Others countries such the U.S., in addition to the safety and quality, would evaluate the net cost and effectiveness of the drug, and would assess clinical information such as therapeutic class, published information, pharmacoeconomic studies, drug utilisation review, the U.S. pharmacopeia and meta-analysis (Medpac, 2004). Drug selection in South Africa is done based on criteria that complies with National Drug Policy, such as health needs, effectiveness, safety, risk/benefit ratio and the pharmacological active ingredients (Department of Health, 2015). In Ghana, once a drug has a market approval from the Ghana Food and Drug Board, the drug evaluation focuses on treatment indicated for a priority health condition. Therefore, the National essential drug list is used as a support to establish their drug reimbursement list (MOHDNP, 2010). Drug selection in these countries is a process done through the recommendations or approval of expert committees and by obtaining market approval (France and Ghana). The committees are mostly composed of physicians, pharmacists, pharmacologists, nurses, medical practitioners and other health professionals (refer to section 2.5-2.5.6, Chapter 2). In Gabon, CNAMGS has a list of reimbursed medicine that is revised every two years. The list

has become an important tool for health professionals and the CNAMGS.

5.2.3 Conceptualisation of the classification, the use, and management of hypertension

The study aimed to analyse the antihypertensive drugs reimbursed by CNAMGS. Therefore, section 2.6 to 2.6.5.2.8 of Chapter 2 mainly focused on hypertension classification and treatment. Hypertension as described by Weber *et al.* (2014) is a persistently raised blood pressure to the blood vessel and is defined as blood pressure exceeding 140/90 mmHg. The Joint National Committee (JNC-7) and the ESC/ESH guidelines classified hypertension into several categories, namely optimal, normal, high normal, grade 1, 2, 3 and isolated systolic blood pressure (Whitworth, 2003:1985). Hypertension affects many people. In Sub-Saharan Africa, 10 to 20 million of 650 million people have hypertension and by year 2025, the number of people with high blood pressure will be 150 million (Guwatudde *et al.,* 2015:2, Van Vijver *et al.*, 2013:2). Factors such as age, smoking, alcohol intake, bad diet habits, obesity and lack of physical activity are the main precursors of developing hypertension and other cardiovascular diseases (Camici *et al*., 2009:134, Cappuccio & Campbell, 2016:300, Pinto, 2007:111, WHO, 2010:17). Furthermore, social determinants such as urbanisation, globalisation, geolocality, poor education or low income, genetics and pregnancy can have adverse effects on blood pressure (Khatib & El-Guindy, 2005:40-41, WHO, 2013:18). From the literature review, the main goal of treating hypertension is to keep blood pressure levels below 140/90 mmHg.

There is currently a non-pharmacological and a pharmacological approach to manage elevated blood pressure. The non-pharmacological approach consists of lifestyle modifications, involving weight reduction, using dietary approaches to reduce hypertension, salt intake reduction, cigarette smoking cessation, moderate alcohol consumption and increasing physical activity (Seedat *et al.*, 2014:290). If the target blood pressure is not obtained within 3 to 6 months after correction of lifestyle modification, drug treatment should be initiated (Seedat *et al*., 2014:289).

The antihypertension drug group includes diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, central acting agents, calcium channel blockers, beta-blockers and alpha-blockers, and combination therapy (Khatib & EL-Guindy, 2005:55). Diuretics and calcium channel blockers are the first-line agents when treating hypertension in people older than 55 years and in people of African descent (Catena *et al.*, 2012:67). Loop diuretics are the preferred drugs for individuals with renal diseases, heart failure and pulmonary oedema (Nguyen *et al.,* 2010:49). Thiazide diuretics are first-line drugs for patients with hypertension, nephrolithiasis, isolated systolic blood pressure and congestive heart failure (Catena *et al.*, 2012:67). Angiotensin converting enzyme inhibitors are drugs of choice for individuals with diabetes associated with proteinuria, post myocardial infarction, congestive heart failure and left ventricular hypertrophy (Hanif *et al.*, 2010:13-14). Angiotensin receptor blockers are usually well tolerated compared to

angiotensin converting enzyme inhibitors and are less likely to cause cough (Barreras & Gurk-Turner, 2003:124). Furthermore, calcium channel blockers are recommended in the treatment of essential elevated blood pressure and hypertension associated with others conditions such as diabetes (Sica, 2006:53-54; Nguyen *et al*., 2010:53). Beta-blockers have lower efficacy in patients from African descent and those of advanced age (Weber *et al.,* 2014:12).

Combination therapy is effective in reaching desired blood pressure, improving compliance and is potentially cost saving (Mitkova *et al*., 2016:2, Schellack & Malan, 2014:208). A combination of angiotensin converting enzyme inhibitors or angiotensin receptor blockers and diuretics works better for people with hypertension and other conditions such as diabetes, particularly in those of African descent (Reboldi *et al.*, 2009:413-414, Shultz, 2009:28). A central acting agent such as alpha-methyldopa is mainly used for hypertension-related pregnancy (Michel & Hoffman, 2009:773). Labetalol can decrease blood pressure in pregnancy without compromising utero placental blood flow, birth weight or causing neonatal hypoglycaemia (Ghanem & Movahed, 2008:42). Despite potential differences in antihypertensive effects, drug therapy selection should be based on compelling indications with what is recommended for the hypertensive population in general (refer to section 2.7, Chapter 2).

5.3 Conclusions derived from the empirical investigation

The specific objectives of the empirical investigation phase of the study were to:

(i) Analyse the prescribing patterns of antihypertensive drugs stratified according to age, gender and the prescribing health professional using prescriptions in a private pharmacy situated in Libreville, Gabon.

(ii) To determine the cost of all antihypertensive drugs prescribed from the CNAMGS prescriptions in a private pharmacy situated in Libreville, Gabon; and

(iii) To determine potential cost savings through generic substitution for antihypertensive drugs using prescriptions in a private pharmacy situated in Libreville, Gabon.

The conclusions derived from the findings of this investigation are highlighted in subsequent paragraphs.

5.3.1 Prescribing patterns of antihypertensive drugs stratified according to age, gender and the prescribing health professional using prescriptions in a private pharmacy situated in Libreville, Gabon

The empirical investigation of this study was elaborated in Chapter 4. The prescribing patterns of antihypertensive drugs stratified according to age, gender and the prescribing health professional were discussed in section 4.1 to 4.5, Chapter 4. Results showed that of the 28 289 patients on CNAMGS that visited the pharmacy at the time of the study, only 1 586 (5.6%) claimed for

antihypertensive drugs. Most patients were within the mean age of 55.80 to 57.26 years old. There were more females (69.2%) than men (30.8%), but there was no significant association between gender and age groups.

Over 2 504 prescriptions (1.2% of the total prescription received at the time of the study) for antihypertensive drugs were claimed; most of them were prescribed by general practitioners (44.2%) and specialists (41.9%). The fixed-dose combination of perindopril/indapamide were the most prescribed active ingredients (ATC/code C09). As plain formulation, calcium channel blockers were the most prescribed class of antihypertensive drugs (22.2%), particularly amlodipine. Similar results were observed in India (Rachana *et al*., 2014:20), Nigeria (Nwaka *et al*., 2015:544), South Africa (Mpe, 2007:35), and in the USA (Bucci *et al*., 2008:629). According to the literature (refer to section 2.6.5.2.4), calcium channel blockers are the preferred drugs for reducing blood pressure in those of African descent, geriatric patients and patients presenting a history of stroke, peripheral artery disease and left ventricular hypertrophy (Sica, 2006:56; Tocci *et al*., 2014:2). Most of the fixed-dose combination contains hydrochlorothiazide as a diuretic. Alpha-methyldopa was mainly prescribed within the age group ≥ 30 years old (16.3%) and between 30-44 years old (48.1%) (Table 4-7). Based on the findings of the present study, the CNAMGS prescriptions claimed during the study period, complied with the hypertension guidelines from the 2003 WHO/International Society of Hypertension, the European Society of Hypertension and the Joint National Committee.

Multiple antihypertensive drugs used in combination therapy was observed in this study. Based on the total number of DDDs, plain formulation drugs were the most prescribed at 86 203.4 DDDs for a total of 8.04 DDD/1000 inhabitants/day; whereas fixed-dose combination had a total DDD of 50 586 for 4.90 DDD/1000 inhabitants/day. Only 6.8% of generic equivalents (amlodipine, captopril and combination of captopril with hydrochlorothiazide) were prescribed as compared to original drugs (93.2%).

5.3.2 Cost of all antihypertensive drugs prescribed from the CNAMGS prescriptions in a private pharmacy situated in Libreville, Gabon

Cost analysis of all antihypertensive drugs prescribed from the CNAMGS prescription was discussed in section 4.6 to 4.6.8 of Chapter 4. The total cost for antihypertensive drugs prescribed accounted for 46 570 511 XAF, in which generics represented only 4.6% of the total expenditure. A total of 27 217 870 XAF (58.4% of the total cost) was reimbursed by CNAMGS and the mean cost of a prescription reimbursed by CNAMGS was 10 870 ± 7 617 XAF (95% CI, 10 571 - 11 168 XAF). Prescriptions for generic equivalents accounted for only 4.6% of the total cost (n = 2 117 003 XAF). Fixed-dose combination therapy has the highest cost share (47.7%), followed by calcium channel blockers (25.3%) and angiotensin converting enzyme inhibitors

(8.9%).

Diuretics, compared to other drug classes in this study were the least expensive, particularly for thiazide diuretics or thiazide-type diuretics such as furosemide. It can thus be concluded that diuretics were the most economical drugs (cost/DDD = 199.8). Angiotensin receptor blockers were the most expensive drugs at a mean cost of 21 127 ± 3 124 XAF (95% CI, 21 503 - 20 750 XAF) and a cost/DDD of 476.9. Fixed-dose combinations at a cost/DDD of 439.3 followed the angiotensin receptor blockers.

5.3.3 Potential cost savings through generic substitution for antihypertensive drugs using prescriptions in a private pharmacy situated in Libreville, Gabon

The World Health Organization and the International Society of Hypertension recommends the use of generic equivalents and least expensive drugs to minimise the cost (Ekwunife & Ubaka, 2010:27). Section 4.7 of Chapter 4 entails the potential cost saving by CNAMGS if only generic equivalents of antihypertensive drugs were prescribed. Therefore, if original drugs were substituted by their generic equivalent it would have generated a potential cost saving of 4.8% of the total cost of all antihypertensives claimed during the period of study. Consequently 1 313 009 XAF would have been saved by CNAMGS. The relatively high cost of calcium channel blockers among antihypertensive drugs prescribed during the period of study, could be explained by the fact that innovator drugs were mostly prescribed, along with expensive generic equivalents.

It can be concluded that drugs procurement remains a challenge in Gabon. Therefore, because of the high cost of drugs, the use of generic equivalent drugs should be made a priority for the CNAMGS. Generic substitution of amlodipine and captopril could generate huge potential cost savings if only generics are prescribed.

5.4 Study strengths and limitations

Prescriptions from CNAMGS are made of three identical sheets called a “volet” (i.e. sheet); one is sent to CNAMGS for reimbursement, the second one goes to the patient as a receipt and the third is for the pharmacy. Data on these sheets allowed performing a quantitative cross-sectional study. All information needed regarding the drugs prescribed and dispensed was accessible. These CNAMGS prescriptions helped to gather information regarding the age and gender of the patient, the prescriber, the quantity and the cost of the drug prescribed. Many African countries are moving towards universal coverage, moreover, with drug expenditure, particularly for chronic diseases. Therefore, it is important to elaborate on tools such as drug utilisation review or cost analysis.

Limitations encountered within the study included that all data used were obtained from CNAMGS

prescriptions received at that pharmacy alone at the time of the study; therefore, the exact history of the patient's blood pressure reading was not monitored. The findings of the study can also only be generalised to the specific setting and study population.

5.5 Recommendations

Hypertension as a chronic disease will always be part of the CNAMGS plan, due to high prevalence of hypertension and the need of medications for prolonged periods. However, antihypertensive drugs are relatively expensive. Based on the present study, the following recommendations are made for future research:

- A database should be developed and used in pharmacies or other health entities working with the CNAMGS. Developing a database will provide the CNAMGS with the ability to integrate economic and clinical data; therefore, there will be more control over drug utilisation, prescribing patterns and patient records as well as prescribers.

- The CNAMGS should use the Gabon national essential drug list in terms of formulary decision-making, thereby it will allow establishing a list that is cost-effective and appropriate, as well as affordable for the population and the CNAMGS itself in the long term. One of the effective measures of containing the cost of chronic medication is drug utilisation reviews and the use of formularies by medical aid schemes. The extent and impact of generic and therapeutic substitution should also be included in future drug utilisation review studies.

- Drug selection for formularies should be done based on criteria such as drug utilisation review findings, pharmacoeconomic evaluations, pharmacological data (efficacy and safety), the benefit/risk ratio, adverse effects of the drug, pharmacokinetics, cost effectiveness, cost advantage of the drugs and budget impact analysis (the total cost of the drug to the healthcare budget).

- Continuing the educating of prescribers and elaborating treatment guidelines may improve the rationale use of drugs, such as fixed-dose combination and multi-drug combination therapy. In order to limit the prescribing of antihypertensive drugs that are too expensive, CNAMGS should encourage the use of essential medicines, generic substitution and the use of first-line pharmacological treatments.

- Generic substitution of amlodipine, captopril and furosemide will generate large savings on the cost of antihypertensive drugs for CNAMGS in Gabon. Angiotensin receptor blockers are life- and cost-saving, particularly for patients with diabetes mellitus, and have less adverse effects compared to angiotensin converting enzyme receptor blockers. Substitution of original angiotensin receptor blockers with their generic equivalents will reduce the antihypertensive

drug expenditure. Drugs such as nicardipine, diltiazem and most of the fixed-dose combinations used are expensive; CNAMGS should integrate generic equivalents of these drugs in the list of reimbursed medicines. The entity should further implement regulation or legislation that ensures the quality of generic equivalent drugs.

- The CNAMGS, as recommended by WHO, should work with entities that regulate medicines and pharmaceutical products, the members of the Pharmacy Board in Gabon, hospital pharmacists, medical practitioners, nurses and pharmacologists, to establish their drug formulary. More policies should be implemented, particularly for the drug selection process. CNAMGS should take lessons learned by other countries that have a National Health Insurance.

- Public and professionals should work together to enhance the rational drug use. Patients need to be educated on the appropriate use of dispensed antihypertensive drugs. Training of health professionals, including prescribers, pharmacists and other allied medical professions on antihypertensive drugs could enhance better prescribing and then facilitate rational use.

- Drug utilisation reviews and pharmacoeconomic evaluations should be used by CNAMGS to identify the prescribing patterns and cost of antihypertensive drugs. The drug utilisation review will help to identify specific drug use problems; for instance, if drugs are overused or under-utilized, also the prescribing trends among health professionals. More studies need to be done on cost-effectiveness of antihypertensive drugs, so that drugs can be compared between the different active ingredients. CNAMGS will be able to record the actual cost of the disease and generate potential savings if more agents that are effective are used for the treatment of particular disease.

5.6 Chapter summary

The final chapter entailed a summary on the findings of this study, along with strengths, limitations and recommendations for future research. Hereby, the objectives of the study have been met.

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ANNEXURE A: PERMISSION TO USE THE PRESCRIPTION CLAIMS DATA

[redacted]

To whom it may concern

I , **Docteur Y-TOU Maganga**, owner and manager of The [redacted] of Libreville (Gabon) acknowledges that **Lisbeth Mboguilomouo Akebayeri** is an employee of the pharmacy and has been granted with permission to conduct a research study.

The undersigned is conducted a research study entitled **"Usage patterns and cost analysis of antihypertensive drugs reimbursed by the National Health Insurance (CNAMGS) in Gabon**, in partial fulfillment of requirements of **Master** in Pharmacy Practice.

The study was found to be of benefit for the pharmacy and the National Health Insurance

I can guarantee that the research is conducted in an ethical manner. This study is carried out rigorously and resources are managed with respect and integrity, the names of the patients present on prescriptions are removed along with the names of the prescribers and their addresses; copies of prescriptions will be made and information regarding the research will be recorded on excel sheet after work in a private office, only the researcher is allow to record the data.

After a prescription is claimed, the prescription remains the property of the pharmacy and the records are kept in the pharmacy for ten years. The researcher as an employee of the pharmacy has access to information required in the study on a daily basis as part of normal responsibilities as a pharmacist.

Anonymity is assured by not capturing the patients' name or address or CNAMGS membership number.

The data collection tool does not provide for the personal information of the patient (i.e. no patient name, address, and or CNAMGS membership number and the name of the prescriber will be collected). Only the researcher will be collecting the data.

All the necessary information will be provided to conduct the study and if you have any enquiries please do not hesitate to contact us

[redacted]

Libreville

ANNEXURE B: ETHICS APPROVAL CERTIFICATE

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT

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Institutional Research Ethics Regulatory Committee
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Email Ethics@nwu.ac.za

ETHICS APPROVAL CERTIFICATE OF PROJECT

Based on approval by **Health Research Ethics Committee (HREC)**, the North-West University Institutional Research Ethics Regulatory Committee (NWU-IRERC) hereby approves your project as indicated below. This implies that the NWU-IRERC 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: Usage patterns and cost analysis of antihypertensive drugs reimbursed by the national health insurance (CNAMGS) in Gabon.

Project Leader: Dr JR Burger
Student: ML Akebayeri

Ethics number: N W U - 0 0 2 0 0 - 1 5 - A 1
(Institution | Project Number | Year | Status)
Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

Approval date: 2016-02-08 Expiry date: 2016-11-30 Risk Minimal

Special conditions of the approval (if any):

- Translation of the informed consent document to the languages applicable to the study participants should be submitted to the HREC (if applicable).
- Any research at governmental or private institutions, permission must still be obtained from relevant authorities and provided to the HREC. Ethics approval is required BEFORE approval can be obtained from these authorities.
- Any further information and any report templates is obtainable from Carolien van Zyl at Carolien.VanZyl@nwu.ac.za.

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 (principle investigator) must report in the prescribed format to the NWU-IRERC and HREC:*
  - *annually (or as otherwise requested) on the progress of the project, and upon completion of the project*
  - *without any delay in case of any adverse event (or any matter that interrupts sound ethical principles) during the course of the project.*
  - *Annually a number of projects may be randomly selected for an external audit.*
- *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 HREC and NWU-IRERC. Would there be deviated 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-IRERC and new approval received before or on the expiry date.*
- *In the interest of ethical responsibility the NWU-IRERC and HREC retains the right to:*
  - *request access to any information or data at any time during the course or after completion of the project;*
  - *to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process.*
  - *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-IRERC 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 IRERC 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 IRERC for any further enquiries or requests for assistance.

Yours sincerely

Prof LA Du Plessis

Digitally signed by Prof LA Du Plessis
DN: cn=Prof LA Du Plessis, o=North-West University, ou=Campus Rector, email=Linda.DuPlessis@nwu.ac.za, c=ZA
Date: 2016.02.11 09:56:34 +02'00'

Prof Linda du Plessis
Chair NWU Institutional Research Ethics Regulatory Committee (IRERC)

ANNEXURE C: DATA-COLLECTION TOOL

Observation number	Date	Patient number	Age	Gender	Drug(s) trade name	ATC-code	Active ingredient(s)	Strengths (mg)	Generic indicator(s)	Quantity	Dosing instructions	Total cost	Amount reimbursed by CNAMGS	Patient levy	Prescriber-speciality