

Characterization of severe and complicated hypertension in Mozambican adults



by

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Declaration of originality

I, Naisa Abdul Manafe, hereby declare that the work on which this dissertation is based on my original work (except where acknowledgements indicate otherwise and where indicated in the case of laboratory work done in collaboration with others).

It is being submitted for the degree of Master of Sciences of Medicine in the Faculty of Health Sciences, University of Cape Town, Western Cape, South Africa.

The work contained in this thesis has not been submitted for any degree or examination in this university, or any other university.

Signature

Signed

Date

14.08.2017.

Declaration of Ethical Clearance

I, Naisa Abdul Manafe, hereby certify that the study contained in this thesis has the approval of the Local, Institutional and National Ethical Committee for Health, Maputo, Mozambique. The ethics reference is 38/CNBS/16.

Signature **Signed** Date 11/08/2017

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List of abbreviations

ABPM	Ambulatory blood pressure monitoring
ACC	Associated clinical condition
ACE	Angiotensin converting enzyme inhibitors
AIDS	Acquired immune deficiency syndrome
AMI	Acute myocardial infarction
ALT	Alanine aminotransferase
ARA	Angiotensin ii receptor antagonists
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
BIA	Bio impedance analysis
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CI	Confidential interval
CKD	Chronic kidney disease
Cm	Centimetre
CNBS	Bioethics National Committee for Health-Mozambique
CRF	Case report form
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
DALYs	Disability-adjusted life years
DBP	Diastolic blood pressure
DI	Decilitre
DM	Diabetes mellitus
ECS	European Society of Cardiology
ECG	Electrocardiography
ECHO 2D	Echocardiography bidimensional

EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESD	End-systolic diameter
ESH	European Society of Hypertension
GGT	Gamma-glutamyl transferase
GFR	Glomerular filtration rate
FBS	Fasting blood sugar
HBA1C	Haemoglobin a _{1c}
HBP	High blood pressure
HCTZ	Hydrochlorothiazide
HDL	High-density protein cholesterol
HF	Heart failure
HGB	Haemoglobin
HGM	Mavalane General Hospital
HHF	Hypertensive Heart Failure
HIV	Human Immunodeficiency Virus
HTN	Hypertension
HR	Heart rate
INS	Instituto Nacional de Saúde/National Institute of Health
IU	International units
IUGR	Intrauterine growth restriction
IVSd	Interventricular septal thickness at end diastole
JNC7	Seventh Report of the Joint National Committee
JVP	Jugular venous pressure
KD	Kidney Disease
Kg	Kilogram
L	Liter
LA	Left atrial
LAE	Left atrial enlargement
LDL	Low-Density Lipoprotein Cholesterol
LV	Left ventricle

LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MFS	Midwall fractional shortening
Umol	Micromole
Mg	Milligram
MI	Millilitre
MISAU/MOH	Ministério da Saúde/Ministry of Health
MRI	Magnetic resonance imaging
NCD	Non-Communicable Disease
OD	Organ damage
OR	Odds ratio
PhD	Philosophiae Doctor
PR	Pulmonary rate
PWD	Posterior wall thickness at end diastole
RF	Risk factors
SBP	Systolic Blood Pressure
SD	Standard Deviation
SSA	Sub-Saharan Africa
STEPS	Stepwise Approach to Chronic Disease Risk Factor Surveillance
STROKE	Cerebrovascular Accident
TAPSE	Tricuspid annular plane systolic excursion
TB	Tuberculosis
TDF	Tenofovir
TG	Triglycerides
THESUS	Sub-Saharan Africa Survey of Heart Failure Study
TIA	Transient ischaemic attack
TOD	Target organ damage
UCT	University of Cape Town
WC	Waist circumference
WHO	World Health Organization

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Dedication

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Abstract

Background and aims: Hypertension poses a great challenge to public health and is a major reason for hospitalisation and death. In Mozambique, there are currently very low levels in the detection, treatment and the control of the condition. However, data on target-organ damage and associated clinical conditions is lacking. We therefore aimed at characterising the clinical profile of patients with severe hypertension, describing the pattern of target organ damage and determining the outcomes at 6-month follow-up.

Methods: We designed a prospective descriptive cohort study to assess adult patients with severe and complicated hypertension defined according to the Joint National Committee VII guidelines. The study was conducted from July 2015 to May 2017 at Mavalane General Hospital in Maputo-Mozambique. Patients were characterized through physical examination, laboratory profile, electrocardiography, and echocardiography, and followed for six months to assess occurrence of complications such as hypertensive heart failure, stroke, renal failure, hospital admission and death. Data were analysed using SPSS software version 20.0. The study was approved by the National Bioethics Committee for Health of Mozambique.

Results: We studied 116 subjects (111 [95.7%] black; women 81 [70%]). Women were slightly younger than men 57 vs 59 years respectively; 18 of 116 (15.5%) patients were younger than 44 years. The risk profile of the studied population included obesity (46; 42.5%); dyslipidaemia (59; 54.1%); diabetes (10; 8.6%) and smoking (8; 6.9%). The baseline mean values recorded for systolic and diastolic blood pressure were 192.3 ± 23.6 and 104.2 ± 15.2 , respectively. Most subjects (93; 80.2%) reported being on antihypertensive treatment at the entry, but only 37.4% had BP controlled at the end of follow-up. The most frequent target-organ damage were left atrial enlargement in 91 (88.3%) with atrial fibrillation in 9 (7.9%); left ventricular hypertrophy in 57 (50.4%); hypertensive retinopathy in 30 (26.3%) and renal damage in 29 (25.7%) subjects. Major events during 6-month follow-up were hospitalisations (12; 10.3%) and death (10; 8.6%). Renal damage (4.2%), stroke (3.4%) and heart failure (1.7%) were the most common complications occurring over the follow up period.

Conclusion: Severe and complicated hypertension affects young people with higher incidence of obesity, diabetes and smoking than that found in general population. High occurrence of target organ damage is found at baseline, particularly heart damage, renal lesion and stroke. On follow up, severe hypertension is associated with high number of hospitalisations and high case-fatality rate. Moreover, renal damage, stroke and

hypertensive heart disease were common complications on follow up. Further research is needed to understand the determinants of these poor outcomes.

Key words: Severe hypertension; target-organ damage; clinical outcomes.

CHAPTER 1: INTRODUCTION AND JUSTIFICATION

1.1. Introduction

1.1.1. Epidemiology of Hypertension

Hypertension or high blood pressure (HBP) is a public health problem, with high prevalence in the world (Lim *et al.*, 2012; NCD risk factor collaboration, 2017). It is the most frequent cause of Non-Communicable Diseases (NCDs) and the major risk factor for most common severe complications such as stroke, acute myocardial infarction and kidney disease (WHO 2009; He *et al.*, 1997; Whelton, 1994). The World Health Organization (WHO) estimated that approximately 25% of the world's adult population had hypertension in 2000 and is predicted to increase to 1.56 billion in 2025. In addition, it has been suggested that there is no difference in the overall prevalence of hypertension in men and women worldwide and that such prevalence consistently increases with age in all regions (WHO Report, 2002).

The importance of systemic hypertension as a major cause of common serious disease has been recognized in most Western countries for over 50 years (Harrington *et al.*, 1959). Before this, malignant hypertension was a frequent reason for hospital admission and a common cause of sudden death. Safe and effective anti-hypertensive drug treatments first emerged in the 1960s and were shown to dramatically improve the prognosis associated with malignant hypertension (Yu *et al.*, 1986). Thereafter, blood pressure reduction treatments were provisioned to a larger group of patients who had severe cardiovascular disease (CVD), such as cerebrovascular accident and coronary heart disease. This importantly contributed to a reduction in the stroke and coronary heart disease death rates experienced in most Western populations (Unal *et al.*, 2005). However, in contrast to higher-income countries, the burden of hypertension and hypertension-related diseases increased in lower-income countries. This has been majorly attributed to an increase in urbanization (Singh *et al.*, 2000).

HBP remains a public health problem, with high prevalence in the world and its incidence increases with age. About a third of adults (30-45% of the general population) have hypertension (Mancia *et al.*, 2013). This is usually asymptomatic, so its diagnosis and treatment are often overlooked. The shortage of health workers in endemic areas also limits the diagnosis and proper management of its complications (Kider *et al.*, 2011).

Factors that indicate a worse HBP prognosis are the black race, young age, being male, having severe hypertension, smoking, diabetes mellitus, dyslipidaemia, obesity, premature CVD history and evidence of target organ damage (Weber *et al.*, 2014).

Moreover, hypertension (HTN) is a well-known risk factor for heart attacks and strokes, and it is associated with left ventricular hypertrophy (LVH), proteinuria and kidney failure, retinopathy and vascular dementia, which fall under the concept "target organ damage" (TOD) (Nadar *et al.*, 2006).

National surveys to assess the prevalence of HTN were conducted in the United States, Canada and Europe (Germany, Finland, Sweden, England, Spain, Italy) in the 1990s (survey sizes ranged from 1800 – 23100). Different prevalence was found in these countries: Italy: 37.7%, Sweden: 38.4%, England: 41.7%, Spain: 46.8%, Finland: 48.7%, Germany: 55.3%, United States: 27.8% and Canada: 27.4%. The prevalence of HTN for the European region was in average 44.2%, while that for the whole of North America was 27%. In these surveys, age-specific HTN prevalence demonstrated a significant peak similarly to systolic blood pressure (SBP) for individual countries. A higher intercept and slope were observed in Europe, compared to Canada and the United States. For example, the prevalence was 14% in North American countries and 27% in Europe for the age group 35-44 years, and this increased to 53% and 78% in America and Europe respectively, among patients aged 65-74 years (Wolf-Maier *et al.*, 2003).

Hypertension is one of the main reasons of demand for primary health care in African countries. In Nigeria, with the current definition of high blood pressure, according to the Seventh Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) guidelines, 20 to 25% of adult Nigerians affirmed as being hypertensive (Ogah, 2006). A systematic review of 25 studies (each containing more than 400 subjects) from 10 sub-Saharan African countries (Nigeria, Tanzania, South Africa, Ghana, Sudan, Cameroun, Liberia, Eritrea, Senegal and Gambia) revealed a prevalence of HTN ranging from 13 – 48% and having a rural to the urban gradient (Addo *et al.*, 2007; Stewart *et al.*, 2011). In cross-sectional surveys of HTN in four rural and urban communities in Sub-Saharan Africa (SSA), the age-standardized prevalence of HTN was as follows: Rural Nigeria (19.3%), rural Kenya (21.4%), urban Tanzania (23.7%) and in urban Namibia (38.0%) (Hendriks *et al.*, 2012).

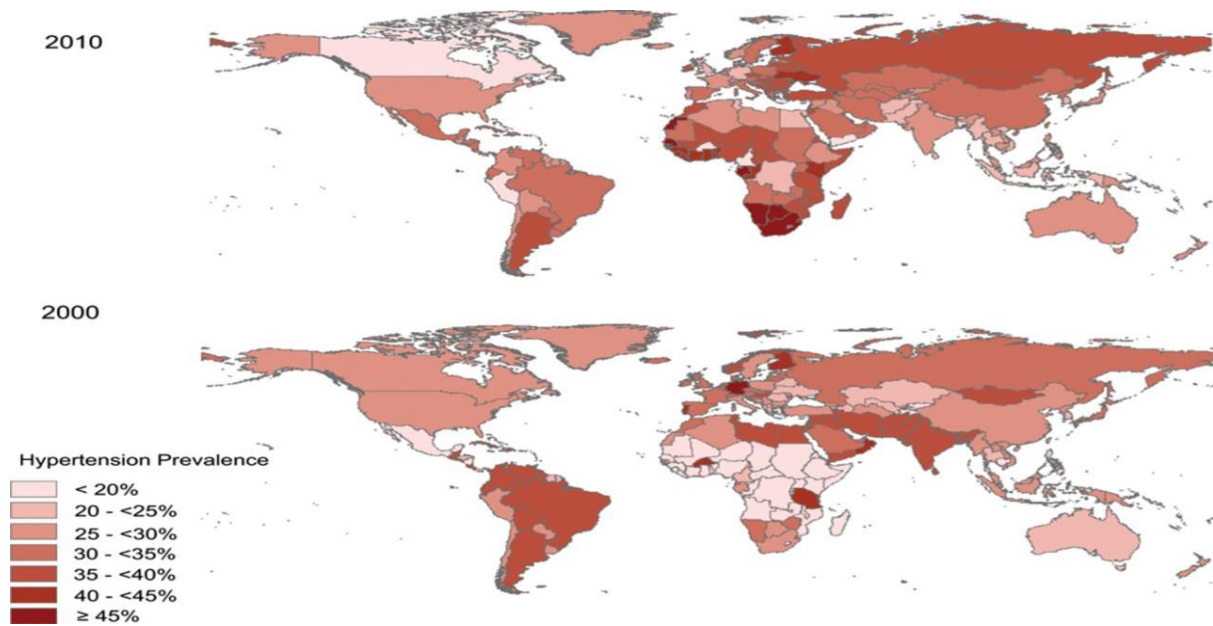


Figure 1: Map showing the change on hypertension prevalence in adults 20 years and older in 2000-2010 by country (Mills *et al.*, 2016).

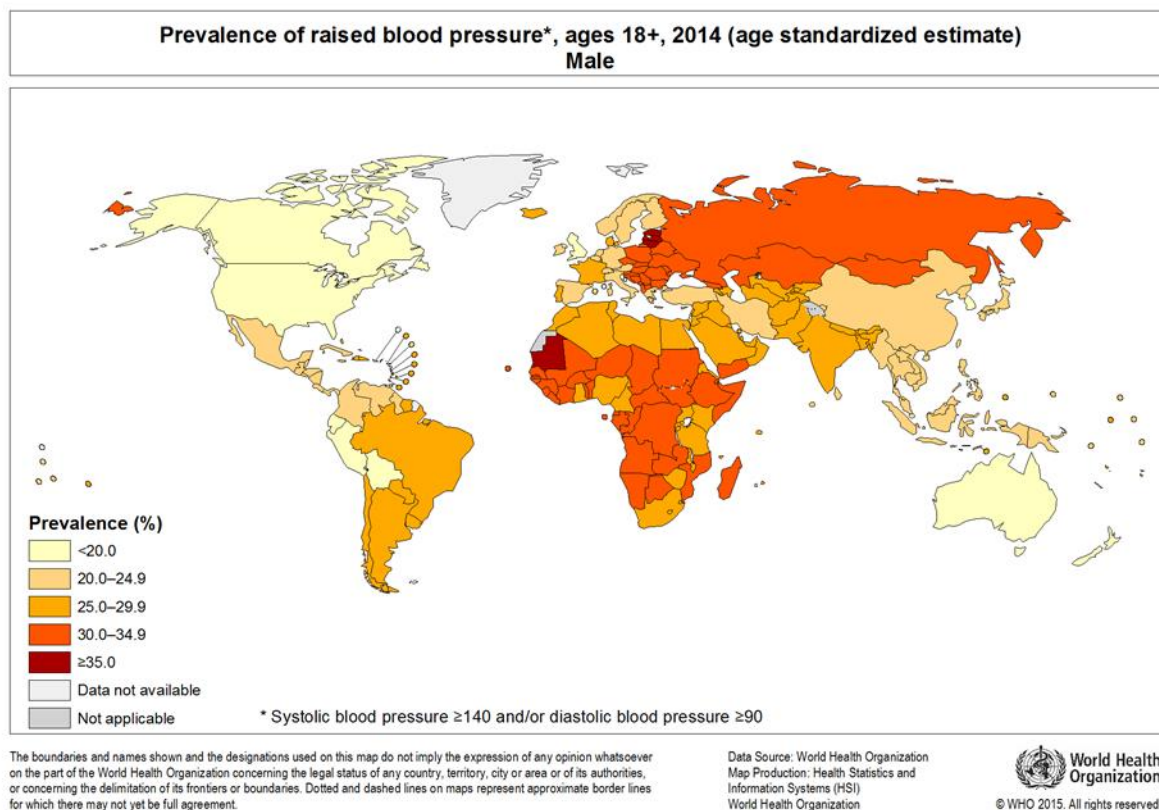


Figure 2: Map of the prevalence of raised blood pressure, aged 18+, 2014 (age standardised estimate) male (WHO NCD Report, 2015).

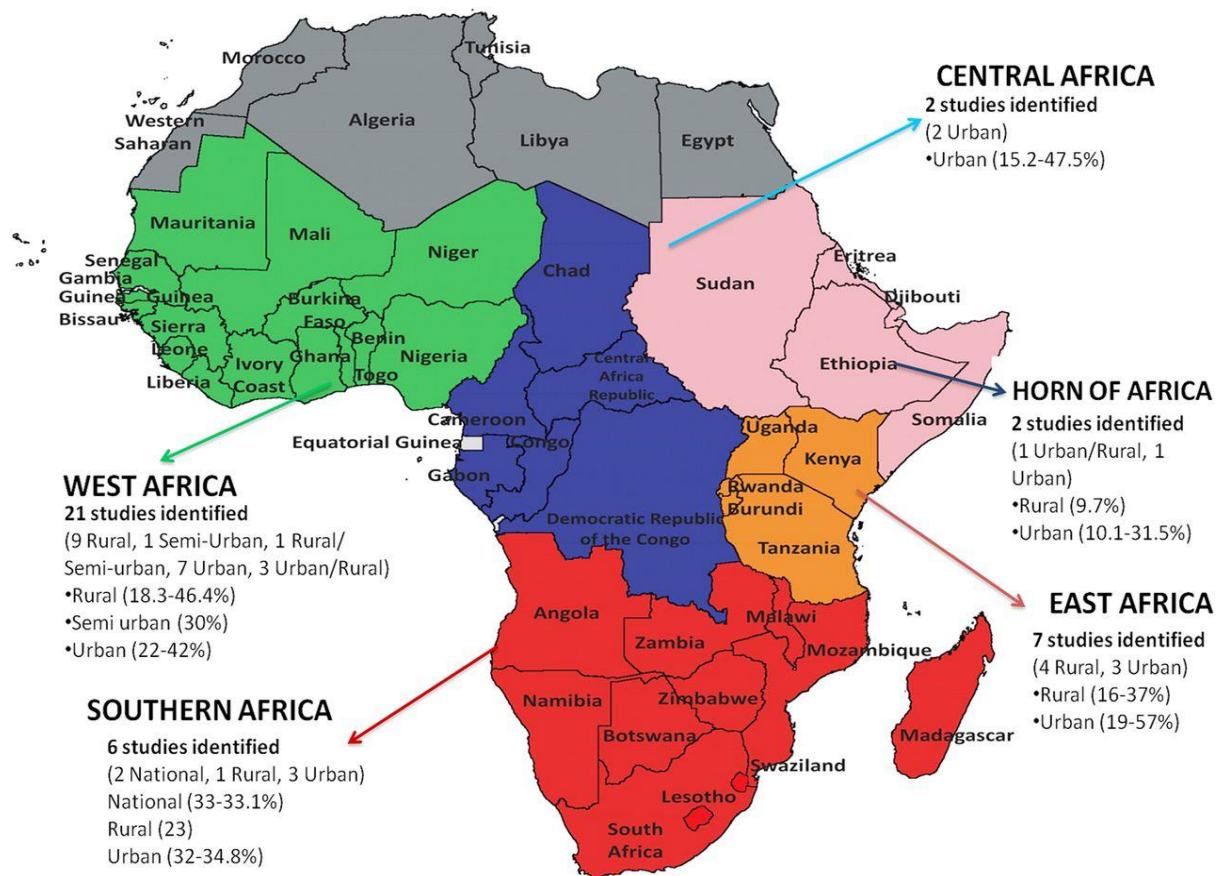


Figure 3: Map of Sub-Saharan Africa (SSA) showing the crude prevalence of hypertension in 38 recent studies in different parts of SSA, adapted by Map of the crude prevalence of HTN in 38 recent studies in different parts of Sub-Saharan Africa (Ogah and Rayner, 2013).

1.1.1.1. Hypertension in Mozambique

The first Stepwise Approach to Chronic Disease Risk Factor Surveillance (STEPS) following the WHO recommendations in Mozambique was conducted in 2005 aiming to determine the prevalence, awareness, treatment and control of HTN in urban and rural populations. The study included a representative sample population of 3,323 individuals aged between 25 and 64. The prevalence of HTN was 33.1% (women 31.2%, men 35.7%). Most participants (3/4) had at least 45 years of age and approximately 10% had more than 54 years of age. Of the individuals with HTN 14.8% (women 18.4%, men 10.6%) were aware of their disease; 51.6% (women 61.1%, men 33.3%) of those who had knowledge of their condition were under treatment, and only 29.9% (women 31.2%, men 28.7%) of those treated had a controlled blood pressure (BP). In women, HTN was more frequent in urban areas when compared

with rural areas (41% vs 26.8%, respectively). Diastolic blood pressure (DBP) was higher in the urban area in both sexes; there was no significant difference in SBP. Systolic BP and DBP increased with age in both sexes (Damasceno *et al.*, 2009).

Evidence of the high burden of complications related to the lack of control of HTN has been obtained from a study conducted in city of Maputo-Mozambique. This study showed a yearly incidence of stroke of 148.7 per 100,000 populations and 260.1 per 100,000 in the population with an age above 25 years (Damasceno *et al.*, 2010), considerably higher than 123.9 per 100,000 found in the UK (Wolfe *et al.*, 2000). HTN was the most important risk factor in these patients and determined high mortality rate (in-hospital mortality: 33.3%, 28 days of mortality: 49.6%), especially through haemorrhagic stroke associated with HTN.

1.1.2. Concepts on Hypertension

According to WHO, hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or use of anti-hypertensive drugs; the same classification is used in all age group subjects (WHO, 2009; JNC 6, 1997; Carretero *et al.*, 2000).

The cut-off mark for the definition of HTN has evolved over time. In 1980, HTN was defined when blood pressure was higher than systolic 160 mmHg and/or diastolic 95 mmHg. Currently, the definition most commonly used is that of the JNC7 which defines three levels of elevated blood pressure (Chobanian *et al.*, 2003; JNC7 Report, 2004). Stage 1 hypertension which is defined as SBP between 140-159 mmHg or DBP between 90-99 mmHg. Stage 2 HTN, on the other hand, refers to all levels of SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg. JNC7 also introduced the classification of blood pressure between 120 mmHg to 139 mmHg SBP or 80 to 89 mmHg DBP as pre-hypertension, based on the risk of progression and associated cardiovascular (CV) risk. Patients with blood pressure in the 130/80 to 139/89 mmHg range have been found to be at twice the risk of developing HTN, compared with those with lower values (Vasan *et al.*, 2000).

The risk of clinical events associated with HTN is determined by the level of BP and also by the presence of TOD. Equally important, is the presence of established cardiovascular disease (ischaemic heart disease or heart failure, stroke, peripheral vascular disease) or concomitant disease associated with high cardiovascular disease risk, e.g. diabetes or chronic kidney disease or the calculated cardiovascular risk (estimated from factors such as age, gender and smoking history).

1.1.2.1. Definitions and Classification

According to WHO the following definitions are used for HBP:

- **Mild hypertension (Grade 1)** is defined by values between 140-159 mm Hg SBP and 90-99 mm Hg DBP.
- **Moderate hypertension (Grade 2)** is defined by values between 160-179 mm Hg SBP and 100-109 mm Hg DBP.
- **Severe hypertension (Grade 3)** is defined as SBP values equal to or greater than 180 mm Hg and/or DBP equal to or higher than 110 mmHg; or SBP \geq 160 mmHg and DBP values \geq 100 mm Hg in the presence of 1 or 2 risk factors or target organ damage (Chobanian *et al.*, 2003; James *et al.*, 2014).
- **Complicated hypertension** is defined as values of blood pressure above 140 mm Hg SBP and 90 mm Hg DBP in the presence of injury or impairment in the function of a target organ such as the brain, arteries, heart, eyes and kidneys.
- **Resistant or refractory hypertension** is defined as blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose amounts. As defined, resistant hypertension includes patients whose blood pressure is controlled with use of more than 3 medications. That is, patients whose blood pressure is controlled but require 4 or more medications to do so should be considered resistant to treatment (Calhoun *et al.*, 2008). Multiple factors such as the lack of adherence to treatment recommendations, use of drugs in insufficient doses, drug interactions, the presence of sodium overload (high volume), associated clinical conditions, pseudo-hypertension or hypertension white coat must be considered when suspecting a resistance to treatment. Finally, possible causes of secondary hypertension should be disposed to consider the person have hypertension refractory to treatment.

Table 1: Definitions and classification of office blood pressure levels (Mancia *et al.*, 2013), European Society of Hypertension (ESH) and European Society of Cardiology Guidelines (ESC) for the management of arterial hypertension - The Task Force of the management of arterial hypertension of the European Society of Hypertension and of the European Society of Cardiology).

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Optimal	< 120	And	< 80
Normal	120 – 129	and/or	80 – 84
High Normal	130 – 139	and/or	85 – 89
Grade 1 hypertension	140 – 159	and/or	90 – 99
Grade 2 hypertension	160 – 179	and/or	100 – 109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	And	< 90

1.1.2.2. Etiology

Several factors contribute to the high prevalence of HTN including high salt and fat intake, poor nutrition (e.g. low consumption of fruits and vegetables), overweight and obesity, excessive consumption of alcohol, physical inactivity, ageing, genetic factors, psychological stress and socioeconomic determinants (WHO Report, 2014). Although the exact cause of HTN is unknown in the majority of cases, these risk factors are involved in its pathogenesis.

Modifiable risk factors for HTN include the following: obesity (defined as BMI ≥ 30 kg / m², or central or abdominal obesity in men: ≥ 102 cm, and women: ≥ 88 cm), sedentary habits, dietary habits (excessive consumption of salt), alcoholism, dyslipidaemia, and fasting plasma glucose or abnormal glucose tolerance test. On the other hand the non-modifiable risk factors include family history (early history of CVD, HTN, diabetes mellitus, obesity and dyslipidaemia in the family), age (men ≥ 55 years, women ≥ 65 years), sex (predominantly male), low birth weight, and black race (Mancia *et al.*, 2013; Weber *et al.*, 2014).

Several risk factors (RF) for HTN has been observed as more common in developing regions than in developed regions in the world (Ibrahim and Damasceno, 2012). The high prevalence of HTN is possibly caused by urbanization, ageing of population, changes in

dietary habits, and social stress (Ibrahim and Damasceno, 2012; Addo *et al.*, 2007; Agyemang *et al.*, 2005; Van der Sande, 2003; Mosley *et al.*, 1993). The risk factors (modifiable and non-modifiable RF) are described in the table below (Table 1.2).

Approximately 95% of the adult population with high blood pressure have primary HTN (commonly known as essential hypertension). It is thought that genetic and environmental factors are involved in the genesis of essential hypertension. Some genetically related factors include the inappropriately high activity of the renin-angiotensin-aldosterone system, the sympathetic nervous system and the susceptibility to the effects of dietary salt could play a role; and behavioural factors include sedentary lifestyle, inappropriate diet (high levels of salt and fat intake), and excessive consumption of alcohol also play a significant role. The smoking habit is a major risk factor for the complication of HTN, like ischaemic heart disease and stroke.

Furthermore, a frequent cause of HTN is the stiffening of the aorta with increasing age. This type of HTN is referred to as isolated or predominant systolic HTN and is marked by high SBP (often with normal DBP). It is mainly found in people with an advanced age (Weber *et al.*, 2014).

Table 2: High-Risk Features in HTN (Adapted from Kidder *et al.*, 2011, Chronic Care Integration for Endemic Non-Communicable Diseases).

High-risk feature	Points
Diagnosis of diabetes	2
Diagnosis of renal failure (creatinine \geq 100 μ mol/L)	2
Age \geq 65 years	1
BMI \geq 25 kg/m ²	1
Tobacco smoking	1
A total of 2 or more points is considered high risk and warrants more aggressive treatment.	

In a small number of HTN cases, about 3-5%, the aetiology of the rise in BP can be diagnosed and sometimes treated. This type of HTN can be suspected if HBP is very high and difficult to control, or has a sudden onset in a previously normotensive patient. The most common causes of secondary HTN are chronic kidney disease (CKD), renal artery stenosis, excessive aldosterone secretion, Cushing's syndrome, pheochromocytoma, thyroid disease and sleep apnoea. Intake of certain drugs, such as nonsteroidal anti-inflammatory, tricyclic

and other types of anti-depressants, previous high-dose oral contraceptives, anti-influenza or cold medications (e.g.: pseudoephedrine), migraine medications, cyclosporine and erythropoietin, can also cause HTN. Drugs like cocaine and herbal medicinal products can increase BP. Pregnancy HBP, aortic coarctation and aortic disease, renin-producing tumours, acromegaly, carcinoid syndrome and hyperparathyroidism are also causes of raised BP (Mancia *et al.*, 2013; Weber *et al.*, 2014).

1.1.2.3. Assessment of HBP and Stratification of total cardiovascular risk

Most patients with HTN have other RF for chronic diseases, including dyslipidaemia, hyperglycaemia or diabetes, a family history of premature cardiovascular events, obesity, smoking and alcohol habits (Weber *et al.*, 2014). Specific behaviours such as tobacco use, physical inactivity, poor diet and alcohol abuse, can lead to key metabolic changes, which are RF for increased blood pressure, overweight/obesity, hyperglycaemia and hyperlipidaemia (WHO, 2008). There is a close relationship between BP levels and the risk of cardiovascular events, cerebrovascular disease and renal disease. The chances of these events occurring is reduced with blood pressure levels below 115/75 mmHg. Above these values for each increase of 20 mmHg SBP or 10 mmHg DBP, the risk of cardiovascular events and stroke doubles (Chobanian *et al.*, 2003). Each 20 mmHg increase in SBP in the range of 115 – 185 mmHg doubles the risk of coronary heart disease and stroke mortality (Lewington *et al.*, 2002). HTN has also been found to be a causal factor in at least 70% of cerebrovascular accident mortality (Healey *et al.*, 2016), and persons with normal blood pressure have about half the lifetime stroke risk compared to those with HTN (Bronner *et al.*, 1995; Wolf *et al.*, 1991). Similarly, the incidence of the end-stage renal disease has been found to increase in parallel with systolic blood pressure. When normal systolic blood pressure of less than 120mmHg is compared with a systolic blood pressure of 140-159mmHg, the relative risk of end-stage renal disease is increased by three-fold and for systolic blood pressure of 160-179 mmHg, end-stage renal disease risk increases by six-fold (Klag *et al.*, 1996). Moreover, the association between HTN and cerebrovascular disease is double of that of cholesterol-CVD relationship (Lewington *et al.*, 2002; Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 1997). Finally, a relatively small decrease in systolic blood pressure (as low as 10 mmHg) has been shown to be associated with a 25% - 30% lower fatal stroke rate (Staessen *et al.*, 2001).

Based on the approximate relation concerning BP levels and the occurrence of CV events, stroke and renal disease, the total cardiovascular risk can be stratified taking all RF into account (Table 1.3).

Table 3: Stratification of total CV risk in categories of low, moderate, high and very high risk according to SBP and DBP and prevalence of RFs, asymptomatic OD, diabetes, CKD stage or symptomatic CVD (Mancia *et al.*, 2013).

Others risks factors, asymptomatic organ damage or disease	High Normal SBP 130 – 139 or DBP 85 – 89	Grade I HTN SBP 140 – 159 or DBP 90 – 99	Grade 2 HTN SBP 160 – 179 or DBP 100 – 109	Grade 3 SBP ≥ 180 or DBP ≥ 110
No other RF		Low risk	Moderate risk	High risk
1 – 2 RF	Low risk	Moderate risk	Moderate to High Risk	High risk
≥ 3 RF	Low to Moderate Risk	Moderate to High Risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to High Risk	High risk	High risk	Very High risk
Symptomatic CVD, CKD stage ≥ 4 or diabetes with OD/RFs	VeryHigh risk	Very High risk	Very High risk	Very High risk

BP= blood Pressure; CKD= chronic kidney disease; CVD= cardiovascular disease; diastolic blood pressure; HTN= hypertension; OD= organ damage; RF= risk factor; SBP= systolic blood pressure.

1.1.3. Clinical Evaluation

The evaluation of a patient with HTN at baseline should include the following: (1) HTN diagnosis should be confirmed, (2) secondary causes of HTN should be detected, and (3) the risk of cardiovascular disease, organ damage and concomitant clinical conditions should be assessed. This calls for BP measurement, personal medical history, family history, physical evaluation, laboratory investigations and further diagnostic exams (Mancia *et al.*, 2013; Weber M *et al.*, 2014; Chobanian *et al.*, 2003).

Most patients with HBP will be asymptomatic. The anamnesis should explore the previous diagnosis of HTN or antihypertensive treatment, occurrence of stroke, Coronary Artery Disease (CAD), Heart Failure (HF), kidney disease such as polycystic kidney and CKD, Diabetes Mellitus (DM), Sleep apnoea, HTN in pregnancy and postpartum and other risk factors such as family history of HTN, DM, dyslipidaemia, microalbuminuria, hyperuricemia, tobacco and drug history.

The white coat effect should be considered when first assessing the patient and if in doubt, assessment of BP outside the clinic or ambulatory blood pressure monitoring for 24hours (ABPM) must be considered. Factors that may affect BP include posture, breathing, emotion, exercise, alcohol, tobacco and other drugs, temperature, pain, meals, and bladder distension (Weber *et al.*, 2014; Mancia *et al.*, 2013; Chobanian *et al.*, 2003). Additionally, BP should be measured with appropriately size cuffs (eg: large cuffs for persons with large arms) to avoid over diagnosis (Campbell *et al.*, 2015).

High blood pressure/severe HTN without treatment can lead to stroke, hypertensive retinopathy, dementia, arteriosclerosis, HF, heart attack and kidney failure, conditions that are grouped under the term target organ damage (Nadar *et al.*, 2006). People with HTN do not often report or demonstrate any apparent symptoms until they develop TOD (WHO, 2013; WHO, 2007). Therefore, pro-active and cost-effective approaches must be put in place for early detection of HTN and TOD. It has been shown that targeted screening for assessment of total CV risk with BP measurement (and fast blood sugar testing) is more cost effective than screening the whole population for a single risk factor, and is more likely to identify individuals at high CV risk for lower cost (Lawson *et al.*, 2010; Baker *et al.*, 2013). To diagnose TOD and concomitant or associated clinical conditions (ACC), several diagnostic tests can be used namely funduscopy, electrocardiography, laboratory tests (blood sample and dipstick urine), home and 24-h ambulatory BP monitoring, echocardiography, exercise test, ultrasound of the carotid arteries, renal ultrasound and magnetic resonance imaging.

1.1.3.1. Funduscopy Examination

The funduscopy examination is part of a neurological examination that is indicated when suspected of hypertensive retinopathy in patients with severe or resistant hypertension. Funduscopy examination is important to detect haemorrhage, exudates and papilledema, which is associated with an elevated CV risk (Mancia *et al.*, 2013). Hypertensive retinopathy is classified into 4 grades successively minimal narrowing of the retinal arteries, sclerosis and tortuosity of the retinal arterioles (Table 1.4).

Table 4: Keith-Wagener-Barker (KWB) classification criteria of hypertensive retinopathy (Keith *et al.*, 1974).

GRADE	DESCRIPTION
GRADE 1	Slight narrowing, sclerosis and tortuosity of the retinal arterioles; Frequently is asymptomatic and associated with mild HTN
GRADE 2	Narrowing is more visible, focal constriction, sclerosis and arteriovenous nicking; elevated BP and more sustained; few, if any, symptoms referable to BP
GRADE 3	Retinopathy (cotton-wool) patches, arteriosclerosis, haemorrhages; elevated BP and more sustained; headaches, vertigo and nervousness; mild impairment of target organs function (e.g. brain, heart and kidneys)
GRADE 4	Neuroretinal oedema, including papilledema; Siegrist streaks, Elschnig spots; BP constantly high; headaches, asthenia, loss of weight, dyspnoea and visual disturbances; mild-severe impairment of cerebral, cardiac and renal function

Grade I: It is asymptomatic, non-malignant, mild HTN, and slight narrowing, focal constriction, sclerosis and arteriovenous nicking; BP is elevated and more sustained; **Grade II:** Little, or no symptoms related to BP and arteriovenous nipping and non-malignant retinopathy, arteriosclerosis, haemorrhages, hard exudation and cotton-wool spots; Elevated BP; **Grade III:** Cotton-wool patches, arteriosclerosis, haemorrhages; elevated BP; headaches, vertigo and nervousness; mild impairment of target organs function (e.g. brain, heart and kidneys); **Grade IV:** Mild and/or severe impairment of cerebral, cardiac and renal functions and malignant and neuroretinal oedema (papilledema, Siegrist streaks, Elschnig spots); BP persistently elevated; headaches, asthenia, loss of weight, dyspnoea and visual disturbances; This stage is malignant (Wong *et al.*, 2004; Walsh, 1982; Keith *et al.*, 1974).

1.1.3.2. Electrocardiography

A 12-lead electrocardiography (ECG) should be done routinely in all patients with hypertension (Chobanian *et al.*, 2003). The ECG helps in identifying ischemia conduction

abnormalities (former myocardial infarction), as well as left atrial dilatation and left ventricular hypertrophy (LVH), which are evidence of TOD and indicate the need of the adequate control of BP. There are several criteria used for the diagnosis of LVH, from the simplest to the most complex. ECG also assists in identifying ischemia conduction alterations, left atrial enlargement and cardiac arrhythmias such as atrial fibrillation (Mancia *et al.*, 2013; Kirchhof *et al.*, 2017), which are markers of heart damage.

In practice, the most used criteria for LVH are the Sokolow-Lyon index ($SV1 + RV5 > 3.5$ mV), the modified Sokolow-Lyon index (largest S-wave + largest R-wave > 3.5 mV), Romhilt-Estes and Cornell voltage QRS duration product ($> 244\text{mV}\cdot\text{ms}$) [Povoa *et al.*, 2008; Mancia *et al.*, 2013]. The following are used as electrocardiographic signs of LVH: Increased amplitude of the QRS complex; Increased Complex QRS duration in the left precordial leads (QRS $\geq 0:09$ sec); Electrical QRS axis deviation to the left $\geq -30^\circ$; Increased left atrial appendage (Morris signal); T wave flat, negative or biphasic in D1, V5; Delay in the onset of intrinsic deflection; S waves deep in the right precordial leads; Abnormality of ventricular repolarization pattern type strain; Bad prognosis: ST segment depression and negative T wave; QT interval shows greater dispersion as ventricular mass increases. The Sokolow-Lyon criteria, one of the oldest and still widely used criteria, consists on the addition of the S wave amplitude in lead V1 with the R-wave in lead V5 or V6 (always the larger of the two). If the sum is equal to or greater than 35mm, LVH is present (Mancia *et al.*, 2013; Kirchhof *et al.*, 2017).

1.1.3.3. Echocardiography

Echocardiography is more sensitive and sometimes more specific than electrocardiography in the identification of LVH and is useful in diagnosing CV and renal risk (Reichek *et al.*, 1981; Levy *et al.*, 1990; Tsioufis *et al.*, 2010; Mancia *et al.*, 2013). It may, therefore, help in the more precise stratification of the overall risk and in determining therapy (Cuspidi *et al.*, 2002).

Despite heart ultrasound being a tool with good sensitivity and specificity, high cost and low availability limit its use in large-scale in resource-constrained settings. However, in parts of the world such Mozambique, where there seems to be a high incidence of LV dysfunction related to uncontrolled severe HBP, it can be of great use. With the reduction in the cost of this technique and the availability of portable and battery powered devices, its use may increase in low-income settings. Focused or Abbreviated ultrasound collecting data on interventricular septal thickness at end diastole (IVSd), the posterior wall thickness at end diastole (PWD), end diastolic diameter and end systolic diameter, may be very important in

this context (Mancia *et al.*, 2013). Data on valve mobility, LV filling pattern (E and A waves) and the presence of arrhythmia may further help to manage the patients.

Cardiac ultrasound is also used for quantification of the ejection fraction (EF) in patients with suspected HF, although this test is not routinely in all hypertensive patients.

HTN is associated with abnormalities of LV relaxation and filling, currently defined as diastolic dysfunction. Moreover, HTN induced diastolic dysfunction is often linked with concentric geometry and can induce symptoms and/or signs of HF, even when EF is still normal (HF with preserved EF) [Hogg *et al.*, 2004; Mancia *et al.*, 2013].

1.1.3.4. 24-h ambulatory BP monitoring

When there is doubt regarding BP values in the clinic, home and 24-h ambulatory BP monitoring are recommended. These approaches allow us to obtain various measurements of BP throughout the day (during the daily routine activities and at night) in a non-hospital environment. In clinical practice, 24-h ambulatory BP monitoring measurements may be done at 15 minutes intervals during the day and every 30 minutes overnight/bed time (Mancia *et al.*, 2013).

ABPM is strongly related preclinical TOD than over the desk measurements. However, more research is required to evaluate the relationship of home BP with other indices of TOD (Bliziotis *et al.*, 2012). ABPM is therefore advisable under the following conditions: Suspected white coat hypertension; Suspected masked hypertension; Effect of identification white coat in hypertensive patients; Suspected irregular taking of antihypertensive; discard resistant hypertension (poor control of BP with antihypertensive); constant change BP during medical consultations; suspected postural hypotension, postprandial or drug induced; suspected pre-eclampsia in pregnancy and suspected nocturnal HTN (sleep apnoea and diabetes) [Mancia *et al.*, 2013].

1.1.3.5. Laboratory tests

Blood samples for assessment of HBP should preferably be taken with the patient fasting so that blood sugar level and more accurate lipid profiles can be obtained. Regarding electrolytes there is more attention on potassium and sodium; high levels of potassium can suggest renal disease, particularly if creatinine is elevated, and low values can suggest aldosterone excess. Increased serum creatinine and blood urea nitrogen (BUN) levels are generally indicative of renal damage; creatinine is also used in the formula for estimated glomerular filtration rate (eGFR). In the African setting, the formula designed for eGFR calculations should be used (National Kidney Foundation 2002).

The lipid profile is important in these patients since elevated low-density lipoprotein (LDL) cholesterol or low values of (HDL) high-density lipoprotein cholesterol are associated with increased cardiovascular risk (Mancia *et al.*, 2013; Weber *et al.*, 2014). Thus high LDL cholesterol should be treated with statins.

Liver function tests to have baseline values of Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) are indicated because certain BP remedies can affect liver function (; Mancia *et al.*, 2013; Weber *et al.*, 2014).

Fasting glucose concentration is also indicated because, if elevated could indicate impaired glucose tolerance, or, if high enough, could indicate DM (Chobanian *et al.*, 2003; Mancia *et al.*, 2013; Weber *et al.*, 2014).

A urine sample by dipstick urine is indicated especially when kidney disease is suspected. Albuminuria (30-300 mg/24h), proteinuria or albumin-creatinine ratio (30-300 mg/24h, 3.4 - 34 mg/mmol) are important signs of CKD (Levey *et al.*, 2005; National Kidney Foundation 2002).

In the African context with a high incidence of sickle cell anaemia associated with chronic kidney disease, haemoglobin/haematocrit can identify issues beyond HTN, which are important for management of HBP complications (Kider *et al.*, 2011).

1.1.3.6. Ultrasound of the carotid arteries

Ultrasound-Doppler of the carotid arteries should be required in the following circumstances as suspicion of arterial thrombosis, narrowing of the arteries research (stenosis), post stroke, post transient ischemic attack, other causes of blockage in the carotid arteries, investigation of an abnormal sound (blow) on the carotid arteries in the neck and risk stratification and atherosclerosis research (Mancia *et al.*, 2013).

1.1.3.7. Magnetic Resonance

The magnetic resonance (MRI) is indicated especially when suspected pheochromocytoma. It may also be useful in cases of suspicion of aortic coarctation, unspecific arteritis or HTN complications such as aneurysms. MRI should be considered to determine the size and mass of LV when echocardiography is technically not feasible and imaging of delayed enhancement would possibly imply therapeutic consequences (Codella *et al.*, 2012; Parsai *et al.*, 2012; Mancia *et al.*, 2013).

1.1.3.8. Renal ultrasound

Renal ultrasound is indicated especially when there is suspicion of renal artery stenosis and acute or chronic renal failure (Mancia *et al.*, 2013).

1.1.4. **Management of Hypertension**

The primary objective of treating HBP is the reduction of cardiovascular, renal, and ocular morbidity as well the mortality associated with these and other complications. For this, non-pharmacologic measures are used in isolation or associated with the use of antihypertensive drugs.

The target values for control of HBP are SBP below 140 and DBP below 90mmHg. Reductions below 130/80 mmHg are recommended for patients at high CV risk, especially with microalbuminuria, HF with renal impairment, those in secondary prevention of cerebrovascular disease and patients with type 2 DM (Ruilope *et al.*, 2008; Mancia *et al.*, 2013; Weber *et al.*, 2014).

1.1.4.1. Nonpharmacological treatment

Adopting a healthy lifestyle generally provides a significant drop in blood pressure, which may be enough to lower blood pressure to normal values. General measures to help reduce BP levels include salt restriction and its derivatives (broth, soy sauce), adequate consumption of vegetables and fruits and low-fat produce, moderate alcohol consumption, weight reduction, regular physical activity and to quit smoking. Lifestyle changes for up to 6-12 months can be attempted in the hopes that they may be sufficiently effective in discarding the use of anti-hypertensive drugs (Mancia *et al.*, 2013; Weber *et al.*, 2014; Chobanian *et al.*, 2003).

1.1.4.2. Pharmacological treatment

The primary objective of pharmacological treatment is to reduce BP levels and, through BP control, prevent fatal and non-fatal cardiovascular events. Appropriate combinations of antihypertensive medications should be used. The socio-economic condition of the patient (for example age, ethnicity/race and other conditions as diabetes and coronary disease and pregnancy in women) at the time of prescription medication should always be considered. Usually, a minimum period of 2 – 3 weeks is needed for dosage increase, replacing monotherapy or changing the drug association. Special consideration should be made in situations where there are concomitant risk factors; for instance, Angiotensin Converting

Enzyme inhibitors (ACE) must be used primarily in patients with DM (Weber *et al.*, 2014; Mancia *et al.*, 2013).

1.1.4.2.1. *Low dose diuretics*

Diuretics are the most studied drugs that have proven beneficial in reducing cardiovascular, cerebrovascular and renal events. They are low-cost drugs, have been used for a long time and are recommended as a first antihypertensive option for "monotherapy", especially for patients with HTN stage 1, who did not respond to non-drug measures. These agents increase the excretion of sodium by the kidneys and may also have some vasodilator properties. Their main side effects are metabolic namely hypokalemia, hyperglycaemia and hyperuricemia. Thiazides plus beta-blockers are an effective combination to reduce BP levels; however, both classes can increase blood sugar concentrations this combination should be used cautiously in patients at risk for developing DM (Weber *et al.*, 2014; Chobanian *et al.*, 2003).

The thiazides diuretics are favourable indicated in elderly patients, systolic HTN and post-stroke. Loop diuretics such as furosemide should be used in HTN associated with kidney disease and HF. The thiazide-like diuretics such as chlorthalidone and indapamide show to be more effective than thiazides (Mancia *et al.*, 2013; Chobanian *et al.*, 2003).

1.1.4.2.2. *Calcium channel blockers*

These agents decrease the BP levels through the blockage of the inward flow of calcium ions through the L channels of arterial smooth muscle cells. The main types of calcium channel blockers are: (1) dihydropyridines, such as amlodipine and nifedipine, which work by increasing the surface area of the arteries; and (2) non- dihydropyridines, such as diltiazem and verapamil, which dilate arteries somewhat less, but also lower the heart rate (HR) and contractility (Weber *et al.*, 2014).

The favourable indications for calcium channel blockers are elderly patients, angina pectoris and systolic HTN. Calcium channel blockers have potent effects of BP reduction, particularly when combined with ACE inhibitors or angiotensin receptor blockers. The effects of this class of anti-hypertensive drugs are similar in all racial and ethnic groups (Weber *et al.*, 2014). In some context, calcium channel blockers are considered the first-line treatment of HTN in black patients (instead of ARBs or ACEi).

The most common side effect of these agents is peripheral oedema, which increases with high doses (this can be attenuated by combining these agents with ACE inhibitors or

angiotensin receptor blockers). Nondihydropyridine calcium channel blockers are not recommended in patients with HF, but amlodipine appears to be safe when given to HF receiving ACE inhibitors for this condition (Weber *et al.*, 2014; El-Deeb *et al.*, 2015).

1.1.4.2.3. *Adrenergic antagonists*

The adrenergic antagonists can be beta-blockers or alpha-blockers.

Favourable indications for beta-blockers are previous infarction, angina pectoris, tachycardia, arrhythmias, diastolic dysfunction and after control of congestive HF in those with severe myocardial dysfunction. Propranolol is still used in patients with hemodynamic instability for its short duration of action, and because there is a low prevalence of peripheral arterial disease. The common side effects of this class of antihypertensive agents include reduction of the sexual function, hyperglycaemia, fatigue and reduction of the tolerance in the physical activity.

Alpha-blockers are less used but preferred in patients with benign prostate hyperplasia. They can also be used in treating resistant HTN when combined with diuretics, beta-blockers and ACE inhibitors (Weber *et al.*, 2014; Chobanian *et al.*, 2003).

1.1.4.2.4. *Angiotensin-converting enzyme inhibitors*

Angiotensin-converting enzyme (ACE) inhibitors agents decrease blood pressure through the blockage of the renin-angiotensin system, and they are well tolerated. The most widely used are captopril, enalapril, perindopril and lisinopril.

The favourable indications of ACE are HF, LV systolic dysfunction, post-myocardial infarction, diabetic and nondiabetic with chronic kidney disease, post-stroke, and proteinuria. The most frequent side effects are a cough (most common in women and in patients of African and Asian background) and angioedema (uncommon and severe complication). The side effects associated with ACE inhibitors are generally not dose-dependent, as they may happen at low doses or at high doses (Weber *et al.*, 2014; Chobanian *et al.*, 2003).

1.1.4.2.5. *Angiotensin II receptor antagonists*

Angiotensin II receptor antagonists (ARA), like angiotensin-converting enzyme inhibitors, antagonise the renin-angiotensin system (Weber *et al.*, 2014). Drugs in this class include Irbesartan, olmesartan, valsartan, losartan, candesartan and azilsartan medoxomil are available. The most commonly used in Mozambique are losartan, valsartan and irbesartan, sometimes in association with hydrochlorothiazide. They are chosen for treatment of HTN, especially when associated with conditions such as HF or kidney disease in people with

diabetes. On the other hand, angiotensin II receptor blockers compared to the ACE inhibitors are well tolerated and often do not cause a cough and rarely cause serious complications such as angioedema (Weber *et al.*, 2014; Mancina *et al.*, 2013; Chobanian *et al.*, 2003).

1.1.4.2.6. *Centrally Acting Agents*

The most commonly known are methyl dopa and clonidine, with methyl dopa being the most frequently used in our setting. The main effect of these agents is to reduce the sympathetic outflow from the central nervous system. They are effective in reduction of BP levels in patients with severe HTN and pregnancy. Their main side effects are drowsiness and dry mouth (Weber *et al.*, 2014; Chobanian *et al.*, 2003).

1.1.4.2.7. *Mineralocorticoid Receptor Antagonists*

The best known agent of this class is spironolactone, which has recently become part of standard treatment for HF. Eplerenone is a newer and well-tolerated agent. In resistant HTN, for patients not controlled on 3 agents, adding spironolactone will often be helpful. The symptomatic side effects are gynecomastia, sexual dysfunction and hyperkalaemia (Weber *et al.*, 2014; Chobanian *et al.*, 2003).

1.1.4.2.8. *Recommended Hypertensive Medication in Mozambique*

According to the National Strategic Plan for the Prevention and Control of NCDs at Ministry of Health (MOH), Mozambique is using four lines to HBP treatment (Damasceno, 2011).

First-line agents: The most commonly used in Mozambique is the thiazide diuretic as hydrochlorothiazide (HCTZ), associated with a potassium-sparing (amiloride) agent to prevent hypokalaemia. It is extraordinarily cheap, taken only once a day and incidence of hypokalaemia is reduced. However, in pregnancy, renal failure, or diabetes, a different medication should be used first.

Second-line agents: Of the drugs belonging to this group the most widely used in Mozambique are amlodipine and nifedipine, which have been demonstrated as having positive effects on CV and stroke outcomes in hypertension trials. Patients having moderate or severe HTN (stage 2 and 3) will likely need at least two drugs to achieve BP control. In such circumstances, at baseline, patients need to begin at the starting dose of both the first- and second-line agents.

Third-line agents: In many patients with stage 3 hypertension two drugs, even taken at high doses, may not be sufficient in controlling the BP levels. ACE inhibitors are the preferred third-line after the maximum dose of HCTZ and amlodipine have been reached. The most

widely used are enalapril and captopril. ACE inhibitors are contraindicated in pregnancy and renal failure (creatinine \geq 200 $\mu\text{mol/L}$).

Fourth-line agents: In some cases, patients may have high blood pressure that is resistant to antihypertension drugs. Four medications for BP control may be required. Of this group, the most commonly available in our setting are beta-blockers such as propranolol, atenolol, carvedilol, metoprolol and bisoprolol. Atenolol is the fourth-line antihypertensive recommended due to its availability and accessibility.

1.1.4.3. Special considerations

1.1.4.3.1. *HBP in Pregnancy*

Hypertensive disorders (preeclampsia, eclampsia gestational hypertension, and chronic hypertension with superimposed preeclampsia) are common complications of pregnancy, and it occurs in 6-8% of pregnancies and complicates about 5% to 10% of all pregnancies (Report of the National High Blood Pressure Education Program in Pregnancy, 2000). On the other hand, pregnancy may aggravate existing HTN before pregnancy (chronic HTN) and induce it in normotensive women (gestational HTN and preeclampsia).

HTN is the most common medical complication of pregnancy and a major cause of maternal mortality as well as perinatal morbidity and mortality worldwide (Berg *et al.*, 2010; Sliwa *et al.*, 2014). In Africa, hypertensive related conditions account for about 9% of overall maternal deaths (Khan *et al.*, 2006).

In pregnancy, the main objectives of antihypertensive treatment are to protect the mother from acute risks or irreversible damage during or immediately after pregnancy and to allow the delivery of a full-term healthy new-born. In a normal pregnancy, BP tends to fall. Blood pressure $>$ 140 mmHg systolic or $>$ 90 mmHg diastolic is considered elevated. Blood pressure $>$ 160 mmHg systolic or $>$ 100 mmHg diastolic is considered severely high (Martin *et al.*, 2005).

The management of HTN in pregnancy is complicated by the fact many common antihypertensive drugs cause birth defects. However, few clinical trials have investigated the treatment of HTN in pregnancy, and therefore there is significant disagreement on the subject. Considering the potential risks of antihypertensive therapy during pregnancy - drugs can reduce uteroplacental flow and compromise the fetus - treatment of diastolic blood pressure below 100 or 110 mmHg is usually avoided. When the diastolic blood pressure levels exceed 100 mmHg, treatment should be instituted to prevent maternal vascular injury. Medical therapy of severe HTN in pregnant women ($>$ 160 for SBP or $>$ 110 for DBP) is therefore highly recommended and beneficial (Abalos *et al.*, 2001). However, excessive

blood pressure reduction should be avoided, considering the risk of hypo perfusion of maternal and fetal compromise target organs by uteroplacental ischemia when 25% drop from the initial value is done.

To date, there is insufficient evidence to know what is the best drug therapy to use when starting treatment, how intense it should be and when it should be stopped. There is no scientific evidence that treatment with antihypertensive drugs in mild to moderate HTN ($\leq 160/110$ mmHg), improve perinatal outcome, e.g., decrease the incidence of complications, such as intrauterine growth restriction (IUGR), pre-eclampsia overlay, detachment premature placenta or perinatal mortality (Abalos *et al.*, 2001).

Recommended hypertensive agents include methyldopa, nifedipine, atenolol and hydralazine. Beta-blockers (propranolol) and thiazide diuretics have relative contraindications. ACE inhibitors and ARA are absolutely contraindicated due to undesirable side effects, both to the mother and the fetus (Mancia *et al.*, 2013).

1.1.4.3.2. *Management of Hypertension Emergency in Adults*

Critical increase in the blood pressure levels can result in TOD in a matter of hours. These hypertensive emergencies frequently happened when the BP is > 180 mmHg systolic or > 110 mmHg diastolic. Signs of a HTN emergency are: headaches and blurred vision caused by increased intracranial pressure, dyspnoea caused by an acute stiffening of heart and back-up of fluid into the lungs, and haematuria or flank pain caused by damage in the kidneys. Patients who present with these symptoms related to HTN and a BP level of $180/110$ mmHg or greater should be treated vigorously (nifedipine or captopril or hydralazine or furosemide) to lower their BP by approximately 25% in the first hour (Damasceno, 2011; Kider *et al.*, 2011).

1.2. **Justification**

HTN is one of the most frequent reasons of heart failure in the world, particularly in the African context, and most patients who develop HF have a background of HTN (Papademetriou, 2004; Dokainish *et al.*, 2016; Dokainish *et al.*, 2015). In the Global Burden of Disease 2010 Project (Murray *et al.*, 2012), hypertensive heart disease which comprises HTN, HTN with LVH and hypertensive heart failure (Ojji *et al.*, 2015) was one of the top causes of disability-adjusted life years (DALYs). In Africa, HTN is a major risk factor for CV events (Stewart *et al.*, 2008; Ojji *et al.*, 2009; Damasceno *et al.*, 2012; Ojji *et al.*, 2013) and a leading cause of cerebrovascular accident, chronic kidney disease and HF (Minino *et al.*,

2011). A registry of 1006 consecutive patients with acute HF, predominantly black patients from 9 African countries including Mozambique, revealed HBP as the most common cause of acute heart failure (453, 45.4%) [Damasceno *et al.*, 2012]. Several other studies corroborate these findings: HTN is a prominent cause of HF in Nigerians account for approximately 60% of the cases (Ojji *et al.*, 2009; Onwuchekwa *et al.*, 2009; Ojji *et al.*, 2013; Ojji Ojji *et al.*, 2015); in Cameroon, accounting for about 54% of all heart failure cases (Kinque *et al.*, 2005) and in South Africa it was responsible for 33% of HF in the Heart of Soweto study (Stewart *et al.*, 2008). In Abuja Heart Study (Ojji *et al.*, 2013), a cohort of 1,515 subjects attending a cardiac clinic in a tertiary set up, hypertensive heart failure (HHF) was the primary type of heart failure in 60% of the cases and accounted for 33% of the total cohort.

Early asymptomatic changes such as LVH, proteinuria and renal failure, heart attacks, stroke, retinopathy and vascular dementia occur (Nadar *et al.*, 2006), but due to its silent nature hypertension is frequently associated with sudden death. Recent studies on hypertensive TOD report that hypertensive heart disease, hypertensive nephropathy, hypertensive retinopathy, stroke, and ischaemic heart disease are frequent, even at the first contact in healthcare facilities in African settings (Peer *et al.*, 2008; Ekore *et al.*, 2009; Stewart *et al.*, 2009; Oladapo *et al.*, 2012). By the time of diagnosis, most patients would have developed TOD and ACC due to low levels of detection, adequate treatment, management and control. Moreover, in some SSA countries including Mozambique, HTN is the main reason for seeking health care services in the adult population (Ogah, 2006; Damasceno *et al.*, 2011).

The risk of developing TOD in some African populations is higher in patients with severe HTN; 3.61 (0.59-8.73) for those with recently diagnosed HTN compared to 4.76 (1.30-13.06) for those with BP equal or greater than 180/110 mmHg. (Oladapo *et al.*, 2012) In Nigeria TOD prevalence in hypertensives was twice as high as that found in non-hypertensive adults (32% and 15%, respectively), and severity of HTN was a strong determinant for target-organ damage [grade 1 odds ratio 2.66, 95% confidence interval (CI) 1.04-6.84; grade 2 OR 3.82, 95% CI 1.41-10.36] (Nelissen *et al.*, 2014). In the Sub-Saharan Africa Survey of Heart Failure Study (THESUS), 289 patients (30.6%) had glomerular filtration rate \leq 60ml/min (Damasceno *et al.*, 2012). Renal dysfunction during hospitalisation was detected in 53 (9.8%) of 543 patients with follow-up creatinine values. Renal dysfunction was also prevalent in young patients without acute non-ischemic HF in Africa, but severe renal dysfunction was less prevalent and was one of the different predictors compared to Western Cohorts (Sani *et al.*, 2014).

Finally, a study conducted in the capital city of Mozambique showed a yearly incidence of stroke of 148.7 per 100,000 populations and 260.1 per 100,000 in the population aged over

25 years (Damasceno *et al.*, 2010), much higher than 123.9 per 100,000 found in the United Kingdom (Wolfe *et al.*, 2000). HTN was the most important risk factor in these patients and determined high mortality rate (in-hospital mortality: 33.3%, 28 days of mortality: 49.6%), especially through haemorrhagic stroke associated with HTN (Damasceno *et al.*, 2010).

LVH, defined as left ventricular wall thickness and/or mass, is the best-studied marker of hypertensive heart disease (Mensah GA *et al.*, 1994). It is an independent CV risk factor, and as potent as systolic blood pressure or age in predicting a cerebrovascular accident, myocardial infarction, sudden death or HF (Kannel *et al.*, 2003).

Chronic systolic HTN demonstrates to be the main cause of left ventricular hypertrophy (Levy *et al.*, 1988; Rheeder *et al.*, 1999), which serves as an integrated surrogate for cumulated blood pressure load, and correlates well with mean 24-hour ambulatory blood pressure (Wendelin–Saarehovi *et al.*, 2002; Mancia *et al.*, 1997). Although healthy young blacks are known to have greater left ventricular wall thickness compared to white population (Aje *et al.*, 2009; Hinderliter *et al.*, 1992), hypertensive LVH is more prevalent in African-Americans (Post *et al.*, 2003, Houghton *et al.*, 1997; Chaturvedi *et al.*, 1994; Gott diener *et al.*, 1994; Gardin *et al.*, 1995; Koren *et al.*, 1993), highlighting the need for studies in the African population.

With the high prevalence of HTN at 33.1% and low rates of treatment and control (Damasceno *et al.*, 2009), Mozambique is expected to have a high occurrence of HHF. The mechanisms that determine HHF are still quite contested, but they would involve a stepwise progression from HTN to left ventricular hypertrophy, then to heart failure with preserved systolic function and eventually to ventricular dilatation and cardiac failure (Izzo and Grandman, 2004). The possible pathways include: (1) progression of HTN to concentric left ventricular hypertrophy, (2) progression of HTN directly to hypertensive heart with dilated left ventricle and reduced left ventricular systolic function with or without myocardial infarction, (3) progression of HTN through concentric hypertrophy to HF with or without transient myocardial infarction with reduced left ventricular systolic function, and (4) progression of HTN through concentric hypertrophy to HF with preserved ejection fraction (Drazner, 2005). In hypertensive subjects in SSA with a relatively low prevalence of coronary artery disease, the progression of HTN either directly to HF or through concentric left ventricular hypertrophy without transient myocardial infarction are favoured. Similarly, the mechanisms that lead to ventricular dilatation in patients with decompensating left ventricular hypertrophy are not completely comprehended (Slama *et al.*, 2003). It is implicated that in patients with systolic dysfunction, activation of the sympathetic nervous and renin-angiotensin-aldosterone systems causes, (1) vasoconstriction, (2) salt and water retention and (3) progressive ventricular dilatation and remodelling. All the above-mentioned processes constitute maladaptation events which create a vicious cycle that gradually aggravates cardiac

performance (Williams, 1999). As the cardiac function slowly declines, there is no additional increase in left ventricular mass due to apoptosis (Sun *et al.*, 2001).

In the myocardium, the modification of the gene expression pattern that accompanies the transition from left ventricular hypertrophy to heart failure includes a general decline in contractile proteins. Simultaneously, interstitial protein synthesis continues leading to myocardial stiffness, impaired diastolic relaxation and the reduction in the vigour of the physical activity tolerance (Rerkpattanapipat *et al.*, 2002). Ultimately, there is reduced myofibrillar activity, ventricular dilatation and heart failure (Weber *et al.*, 2001). In addition, concomitant large and small blood vessel changes intensify the progression from left ventricular hypertrophy to heart failure. The aorta gets hardened with impairment of ventricular vascular coupling and increased cardiac afterload (Chae *et al.*, 1999). Coronary flow reserve is also reduced by left ventricular hypertrophy and is eroded further by progressive ventricular dilatation (Cowie *et al.*, 2002). Follow up of patients with severe HTN, such as the one proposed in our study, may help understand the natural history of HHF.

Echocardiography, an important tool for evaluation of severe and complicated HTN, is currently done by specialists. It evaluates the geometric pattern of the LV, estimates cardiac output, systolic function, and coexistence of other cardiac diseases (such valvular or coronary). It is also helpful in quantifying the ejection fraction (EF) in patients when we suspect HF (Weber *et al.*, 2014), although this complementary exam is not routine in patients with hypertension. EF is a quantification of the heart's systolic function and is used to distinguish patients with HF with depressed or preserved EF). EF is commonly classified as normal ($\geq 55\%$), mildly reduced (40%-55%), and moderately to severely reduced ($< 40\%$). A moderately to severely reduced ejection fraction implies a patient has a cardiomyopathy. While echocardiography machines generate measurements of EF, qualitative visual assessment is also very consistent and may be through to non-cardiologists (Lebeau *et al.*, 2015). LVH regression with antihypertensive treatment, which also improves LV filling and performance, and consequently decreases morbidity and mortality from cardiac and cerebrovascular events, can also be assessed by ultrasound. The dissemination of ultrasound machines offers an opportunity for better management of patients with severe HBP and HHF at peripheral levels of the health system. Focused or abbreviated echocardiography performance by non-specialists has been introduced in some African countries as a way to improve access to better care for patients with HHF (Kider *et al.*, 2011; Lebeau *et al.*, 2015).

Mozambique has a high prevalence of HIV/AIDS 13.2% (IMASIDA Report, 2015) and thus concomitant HHF and HIV infection are not rare. Because HIV infection has also been associated with severe systolic dysfunction there is need to understand the role of this infectious agent in determining HHF. Two recent studies have observed at the impact of HIV

status on the prevalence of HTN in SSA at the community level. In 2003–2004, Barnighausen and his co-workers studied the effect of HIV on body mass and BP in a large general population in a rural area in South Africa before antiretroviral treatment (ART) became widely available (Geldsetzer *et al.*, 2016). After controlling for confounders such as age, gender, educational attainment, household wealth, marital status, and place of residence (urban vs. rural), HIV infection reduced SBP by 3.0 mm Hg ($p=0.005$). According to the authors, it was suggested that the possible reason for the results obtained may have been influenced by HIV-related hypoadrenalism and/or side effects of traditional medicines against HIV/AIDS. Malaza *et al.* (2012) published the results of a survey conducted in 2010 based on the WHO Stepwise approach in 14,198 adult participants living in rural areas in South Africa to determine factors associated with HTN and overweight/obesity, including HIV infection and ART status. They concluded that the prevalence of HTN differed between HIV positive and HIV negative individuals (19.5% vs 27.9%, $p=0.001$). HIV-uninfected women were significantly more likely to be hypertensive than HIV-infected women (31.4% vs 20.1%, $p=0.001$), while there was no association of HTN with HIV status among men ($p=0.099$). HIV-positive individuals on ART treatment had a reduced adjusted odds ratio (OR) of HTN (OR 0.60, 95% CI 0.49 to 0.75), compared to HIV-negative individuals, but the adjusted OR in HIV-positive individuals not on ART did not differ from HIV-negative individuals ($p=0.158$). With the advent of highly active ART, long-term survival of HIV-positive individuals is expected and this will be associated with cardiovascular and metabolic complications.

In summary, much of Africa has a limited capacity in the health care system to screen, diagnose, treat and control systematic HTN and their RF and complications (Campbell *et al.*, 2015). On the other hand, low literacy rates, poor access to healthcare services, inadequate dietary habits, scarcity of health insurance systems, poverty and high costs of antihypertensive treatment, all contribute to poor BP control (Ibrahim and Damasceno, 2012; Campbell *et al.*, 2015). This situation predisposes to TOD and serious cardiovascular events such as stroke and HF (Salako *et al.*, 2007; Campbell *et al.*, 2015).

Given the high incidence and prevalence of severe HTN in Mozambique and the lack of statistical data on its complications and clinical outcomes our study aims at characterising severe and complicated HTN assisted at a peripheral health facility with the use of biomarkers and abbreviated cardiac ultrasound, as well as follow-up these patients to assess outcomes in an environment with limited resources. The results of this study are expected to contribute to a better knowledge of the disease and allow the design of protocols for management of severe HTN and early detection of its complications at peripheral levels of the national health system.

CHAPTER 2: HYPOTHESES, AIMS AND OBJECTIVES

2.1. Hypotheses

Hypothesis 1: Patients with severe hypertension with at least two drugs have a unique clinical and biological profile, with high occurrence of TOD/ACC;

Hypothesis 2: Patients with severe and complicated hypertension can be characterized and managed by non-specialists, through the use of simplified diagnostic and management protocols including the use of biomarkers and abbreviated cardiac ultrasound.

2.2. Aims and Objectives

The general aim of the study is to characterise severe and complicated hypertension and determine the frequency of associated TOD and ACC in patients attending in a referral hospital in Maputo.

The specific objectives of the study were:

- a) To characterise the clinical profile of patients with severe HTN using biomarkers, fundoscopic and focused/abbreviated echocardiography;
- b) To determine the incidence of severe cardiovascular events (HHF, stroke), renal failure, hospitalisation and death on 6-month follow-up.

CHAPTER 3: METHODS

3.1. Methods

3.1.1. Study Area

The Mavalane General Hospital (HGM) is located in Maputo City and serves a population of 670,877 habitants, over an area of 168.4 km². This hospital has 260 beds and assists on average 700 patients daily in the outpatient clinic and emergency department. It is the referral hospital for 14 primary health centres and has several specialised services for Paediatrics, Internal Medicine, Psychiatry, Psychology, Cardiology, Gynaecology/Obstetrics, General Surgery, Dentistry, Ophthalmology and Anaesthesiology. (Relatório Anual do Hospital Geral de Mavalane, 2015). Support services include Laboratory of Clinical Analysis, Radiology, Blood Bank, Pharmacy, Emergency Service, Operating Blocks and Physiotherapy. The Cardiology Unit has only one cardiologist, four general practitioners and two trained nurses that have been trained for follow-up common conditions seen in our setting.

3.1.2. Study Population

Patients were referred from outpatient's clinic and wards of Internal Medicine, Surgery, Anaesthesiology, Gynaecology/Obstetrics, Ophthalmology, and emergency unit of HGM. We also received direct referrals from Mavalane Primary Health Care (physically attached to the Hospital) and.

Since there are no data on the percentage of patients with severe HTN in similar populations or the proportion of those who develop complications, the sample size was not calculated. We have decided to recruit at least 100 adult patients with a diagnosis of severe or complicated HTN during the 12 months.

3.1.3. Study Design

We designed a prospective descriptive cohort study, to assess patients with severe and complicated hypertension presenting to the Cardiology Department at Mavalane Hospital in Maputo. The study was conducted from July 2015 to May 2017.

a. Inclusion criteria:

- Adults \geq 18 years; and
- HTN grade 3 (BP \geq 180 / 110 mmHg or BP \geq 160 / 100 mmHg with presence of 1 or 2 RF) with or without antihypertensive drug or HTN (BP \geq 140 / 90 mmHg) with presence of target organ damage; and

- Residence in Maputo Province (within 100Km surrounding area); and
 - Availability for follow-up for a period of 6 months.
- b. **Exclusion criteria:** Presence of severe disease or psychiatric disorder not allowing the obtainment of informed consent.

3.1.4. Study Procedures

All participants provided a signed informed consent to participate in the study.

All participants had their blood collected to test for the following: fasting blood sugar (FBS), fasting lipid profile, electrolytes, urea, creatinine, aspartate aminotransferase, alanine aminotransferase and full blood count assessed. Blood chemical analysis was performed at the certified laboratory. They also had an abbreviated transthoracic echocardiography performed the same day that the samples were collected for routine analyses.

We scheduled 5 visits in a period of 6 months during which follow up was performed: Visit 1 – Baseline; Visit 2 - 1 week after V1; Visit 3 - 2 weeks after V2; Visit 4 - 4 weeks after V3; Visit 5 - 8 weeks after V4; and Visit 6 - 4 weeks after V5.

The candidate constituted a study team that consisted of:

- General Physician (candidate): Recruited and evaluated the participants in study (including verification of the informed consent), namely collected socio-demographic information, personal and family history; performed physical examination; requested laboratory tests and other complementary tests; prescribed therapy according to local protocols (Damasceno, 2011) and did the follow-up visits. Additionally, entered data and performed statistical analysis.
- Nurses: Hospital nurses invited the eligible participants to participate in the study, administered the informed consent, collected the vital signs and anthropometric data (BP, heart rate, height, weight, waist circumference and bio impedance analysis) and did the electrocardiogram in all patients.
- Laboratory Technician: collected blood samples, transferred them to the laboratory, and processed the samples and collected the results.
- Ophthalmologist: performed all funduscopic examinations.
- Cardiologist (supervisor AOM): assisted with clinical evaluation when needed; performed and interpreted abbreviated echocardiography.

- Data management was supported by members of the supervisor's team.

3.1.4.1. Description of Procedures

3.1.4.1.1. *Questionnaire*

A standard case report form (CRF) was used to collect baseline and follow up data from each participant. Due to the multiplicity of languages in Mozambique, the Portuguese questionnaire was not translated into any local languages; the majority of the participants were reasonably proficient in the Portuguese and, where there was a need for translation, both medical and para-medical staff (nurse) assisted the participant.

Detailed socio-demographic data was collected including date of birth, gender, race, occupation, school level and marital status. The structured questionnaire also included past personal medical history (previous diagnose of HTN, diabetes mellitus, cerebrovascular disease, HF and myocardial infarction), the pattern of physical activity, drinking (alcohol) and smoking habits (self-reported). Family history of HTN, DM, stroke and myocardial infarction was also requested. Use of anti-hypertensive medication or any other drugs (self-reported) were registered.

Regarding the level of education obtained, participants were classified as "Primary" when they had completed 7 years of education or less, "Secondary" when they had completed secondary school, meaning in total 12 years of education; and, finally, "Tertiary" when they had obtained a university or professional degree.

3.1.4.1.2. *Clinical Evaluation*

3.1.4.1.2.1. Anthropometric Measurements

Anthropometric measurements (weight, height and waist circumference) were performed using standardized methods. Height was measured to the nearest 0.1 cm using a portable Seca stadiometer. Weight was measured to the nearest 0.1 kg using a calibrated Seca weight scale.

Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared [weight (kg)/height (m²)]. BMI was categorized as per the World Health Organization guidelines (WHO, 1996), underweight (BMI < 18.5), normal (BMI ≥18.5 to ≤ 24.9), overweight (BMI ≥ 25.0 to ≤ 29.9) or obese (BMI ≥ 30.0). Waist circumference was

used as a measure of abdominal obesity; it was measured to the nearest 0.1 cm, using a constant tension tape, directly over the skin, at the level of the midpoint between the inferior margin of the last rib and the iliac crest in the midaxillary line in all patients. For analysis, the cut-offs used were waist-circumference ≥ 102 cm in men and ≥ 88 cm in women (WHO, 1997; WHO, 2008; WHO, 2011).

All measurements were performed with the participant dressed in light clothing and without shoes.

3.1.4.1.2.2. *Bio impedance analysis*

Bio impedance analysis (BIA), a non-invasive and low-cost technique commonly used to assess body composition, was done in all patients, except for those patients who are in the wheelchairs. BMI, body fat muscle, RM kcal and visceral fat were measured with the participants standing, wearing indoor clothes with no shoes.

3.1.4.1.2.3. *Conventional Blood Pressure Measurements*

Hypertension was defined according to the JNC VII guidelines (Chobanian *et al.*, 2003; JNC7 Report, 2004) and WHO-ISH, 1999. Blood pressure measurements were obtained by trained health workers (nurses and the candidate) according to International Society of Hypertension guidelines. (WHO-ISH, 1999; Chobanian *et al.*, 2003; American Society of Hypertension, 1992), A validated automatic sphygmomanometer was used (OMRON M2 Plus; OMRON Healthcare, Kyoto, Japan) and the appropriately sized cuff was chosen for each patient. SBP and DBP were measured in both arms with the patient in a sitting position. After 5 minutes rest, SBP and DBP were measured again in both arms. For analysis we took the mean of the 2 measurements from the right arm.

Mild HTN (grade 1) was defined by values between 140-159 mmHg SBP and 90-99 mmHg DBP; **Moderate HTN** (grade 2) was defined by values between 160-179 mmHg SBP and 100-109 mmHg DBP; and **Severe HTN** (grade 3) was defined as SBP values ≥ 180 mmHg and/or DBP ≥ 110 mmHg; or SBP ≥ 160 mmHg and SBP values ≥ 100 mmHg in the presence of 1 or 2 RF or TOD (Chobanian *et al.*, 2003) with or without antihypertensive treatment .

Complicated hypertension was defined by values above 140 mmHg for SBP and/or 90 mmHg for DBP, in the presence of impairment in the function of a target organ such as the brain, arteries, heart, eyes and kidneys. **Isolated systolic hypertension** was characterized

by SBP \geq 140 mmHg and DBP $<$ 90 mmHg (often with normal DBP). **Controlled BP** was defined as treated HTN with SBP $<$ 140 mmHg and DBP $<$ 90 mmHg in respondents using antihypertensive medication. The average on the follow-up visits was used as a criterion for the diagnosis of controlled HTN.

3.1.4.1.2.4. *Physical Examination*

On physical examination, the vital signs were assessed and evaluation of all palpable arterial pulses in the arms and limbs on both sides was made to discard aortic coarctation and Takayasu. Cardiovascular and abdominal examination included auscultation of precordial or chest murmurs (to discard aortic disease); systolic murmurs in carotid arteries (to discard atheroma plaques); search for 4th heart sound, arrhythmias, pulmonary rales, as well as murmurs on the abdomen to discard stenosis of the renal artery. Additionally, we searched signs of HF such as increased pressure/distended jugular veins (PJV), 3rd heart sound, congestive hepatomegaly and peripheral oedema.

Heart failure and HHF were diagnosed following the European Society of Cardiology guidelines (Swedberg *et al.*, 2005; Nieminen *et al.*, 2005). Stroke was defined as “a focal (or at times global) neurological impairment of sudden onset, lasting more than 24 hours (or leading to death), and of presumed vascular origin”, as per World Health Organization clinical definition (Hatano, 1976); it was identified through the history of a previous event (including transient ischaemic stroke) and a focused neurological examination looking for motor or sensorial defects.

An experienced ophthalmologist who was blinded to the blood pressure levels of the subjects carried out the funduscopic retinal examination. As this exam is not done routinely at this level of healthcare, we negotiated for a joint appointment with the ophthalmologist once a week. Even before the researchers have the result of the funduscopic (by the waiting time for the participant to take the exam and have its result), we would decide to start more intensive antihypertensive therapy to achieve BP control $<$ 140/90 mmHg. Hypertensive eye damage was diagnosed based on the Keith-Wagner-Barker criteria for hypertensive retinopathy, through which patients are divided into 4 grades (Keith *et al.*, 1974).

3.1.4.1.2.5. *Complementary Exams*

a) Blood Measurements

Venous blood samples were obtained via the ante-cubital vein for biochemical assessment, including the levels of fasting blood sugar, lipids (cholesterol and triglycerides), urea, creatinine, AST, ALT, uric acid, iron, gamma-glutamyl transferase (GGT), albumin and full

blood count. The samples were processed at the central certified laboratory of Mavalane Hospital using Pentra ABX 400/Beckman Coulter 640 and Sysmex KX-21N machines.

Hyperglycaemia was defined as fasting plasma glucose 5.6 – 6.9 mmol/L and **diabetes mellitus** (new-diagnosed) as fasting plasma glucose of 7.1mmol/L or above (Mancia *et al.*, 2013).

Hypercholesterolemia was defined as total cholesterol greater than 4.9mmol, **hypertriglyceridemia** as TG greater than 1.7 mmol/L (Mancia *et al.*, 2013), and **dyslipidaemia** was defined as total cholesterol ratio more than 5.2 mmol/L or recorded physician diagnosis or treatment with lipid-lowering drugs (Ojji *et al.*, 2013; Redon *et al.*, 2016).

Anaemia was defined as haemoglobin levels below 12gr/dl for non-pregnant women and 13gr/dl for men in 15 years of age and above. And, severe anaemia was defined as haemoglobin levels below 8 gr/dl in 15 years of age and above (WHO, 2011).

CKD was defined by a confirmed positive dipstick proteinuria or albuminuria (at least traces) and/or or eGFR < 90mL/min/1.73m². The Kidney Disease improving global Outcomes (K/DIGO) guidelines were used to stage participants for GFR categories and albuminuria categories of CKD (K/DIGO guidelines, 2013). The eGFR categories included: G1 (eGFR ≥ 90), G2 (eGFR 60-89), G3 (eGFR 30-59), G4 (eGFR 15-29), and G5 (eGFR < 15). The GFR (assessed by creatinine clearance) was calculated using the CKD-EPI Creatinine 2009 Equation (Schwartz *et al.*, 2009). Impaired eGFR was defined as an eGFR < 60mL/min/1.73m².

HIV tests were done using the *Determine* HIV test; if the result was positive an *Unigold* HIV test was used to confirm the results (as per standard at National Health Service). In HIV-positive participants, we assessed CD4 cells count using the FacsCalibur machine.

b) Urine test

A mid-stream clean-catch urine sample was collected from each patient in a sterile universal bottle for urine microscopy. The urine dipstick tests for albuminuria were done on the first urine sample and were processed in central laboratory of Mavalane Hospital or at our consultation when the laboratory could not perform it (as a point-of-care test using urine dipstick). The dipstick tests were done using the Urine Insta Test (urine reagent strips).

The albuminuria categories of CKD were as follows: P1 (negative), P2 (trace to 1+ [30 mg/dl]), and P3 (30-300 mg/dl) and P4 (> 300 mg/dl).

Albuminuria was defined as urine albumin excretion between greater than 15 mg/dl (P2) and 300 mg/dl (P4). Microalbuminuria was defined as urine albumin concentration of 30-300mg/dl in spot morning. Macroalbuminuria/proteinuria was defined as urine albumin

concentration greater than 300mg/dl in spot morning urine (Levey *et al.*, 2005; Nelissen *et al.*, 2014).

c) Electrocardiography

A 12-lead ECG was performed to all patients using the Schiller MAC 600 system. ECG-LVH by voltage was based on Sokolow-Lyon criteria, where the sum of $SV_2 + RV_6$ in males of ≥ 40 mm and females of ≥ 35 mm and $RI \geq 12$ mm (Sokolow *et al.*, 1949).

d) Transthoracic Echocardiography

Focused transthoracic echocardiography was performed by the supervisor (AOM), in the presence of the candidate. Subjects were examined using standard parasternal, short-axis and apical views using a commercially available Philips HD7 Diagnostic Ultrasound System (Figure 3.1). Under this focused protocol left atrial to initial aorta ratio and shortening fraction (MFS) were calculated, while left ventricular ejection fraction (LVEF) was visually assessed. The measurements were made according to the American Society of Echocardiography (Sahan *et al.*, 1978). Abnormal LV diastolic function (abnormal LV relaxation) was defined by the ratio A-wave/E-wave > 1 . Hypertensive cardiac damage was defined by fractional shortening below 25% and left atrial enlargement (LAE). The definition of atrial enlargement is done based on a left atrium bigger than the aorta diameter (Brown *et al.*, 1974). Aortic enlargement was defined as aortic root dimension above 40 cm (Brown *et al.*, 1974).



Figure 4: Ultrasound Machine used for the study.

3.1.5. Statistical Analysis

3.1.5.1. Data Analysis

Data were entered into an Excel database and analysed using SPSS software version 20.0 (SPSS Inc, Chicago, Illinois, USA). Descriptive analysis of the variables was performed to process the data as tables (cross-tabulations). Normal distributed continuous variables are represented as the means and standard deviation (SD), and non-Gaussian distributed variables as the median. Categorical variables were described using frequency tables (percentages). The independent Student's t -test was used for continuous variables and Chi-square tests were used to assess significance. Discrete variables were analysed via odds ratios with 95% confidence intervals. A (two-sided) P-value < 0.05 was considered statistically significant.

3.1.6. Implementation Issues

While the study started in July 2015 recruitment took place in two phases, due to an interruption from February 2016 to April 2016, related to funding limitations. Patients were recruited until November 2016 with the last follow-up completed in May 2017. Owing to the need to fulfil training courses and participation in scientific congresses the candidate had some support from colleagues from the National Health Institute to follow up the patients.

3.1.7. Ethical Issues

The study protocol was evaluated and approved by the National Mozambican Ethics Committee (approval reference number: 38/CNBS/16). Written informed consent was obtained from all of the participants, and it complies with the Helsinki Declaration.

CHAPTER 4: RESULTS

4.1. Results: Demographic and Clinical profile of subjects

4.1.1. Demographic data

4.1.1.1. *Socio-Demographic data of 116 subjects studied*

We have recruited 120 subjects with severe and/or complicated hypertension, of which four (3.3%) were excluded due to two were out of Maputo Province and two removed the informed consent for personal reasons. Thus only 116 subjects are included in the analysis. Most patients were black Africans (n=111 [95.7%]), and the study population contained more women (n=81 [70%]) than men. Women were slightly younger than men (mean 57 [SD 13] vs 59 [13] years); with 18 (15.5%) of 116 subjects younger than 44 years. Sixty-nine (59.5%) subjects were married, 31 (26.7%) were widows, 9 (7.8%) were single and only 4 (3.4%) were divorced/separated. Regarding the level of education, 20 (17.2%) did not have any formal education and only 4 subjects (3.4%) completed higher education. Fifty-four subjects (46.6%) did not have any occupation (jobless) and 21 (18.1%) were traders (Table 4.1).

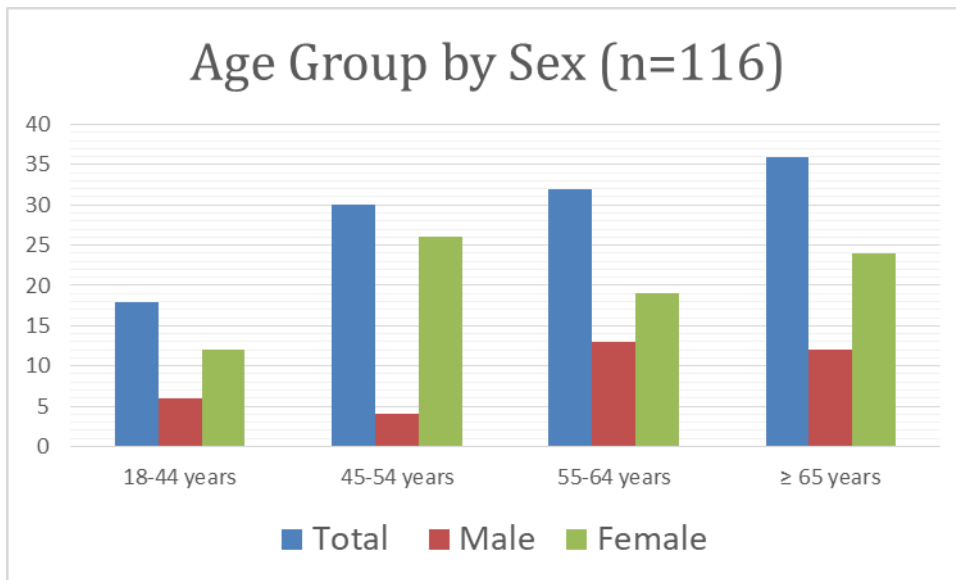


Figure 5: Distribution of sex by age group of 116 subjects enrolled in the study.

Variable	Total (n=116) (%)	Males (n=35) (%)	Females (n=81) (%)
Age			
Mean age. Years \pm SD	57.49 \pm 12.82	58.69 \pm 13.26	56.98 \pm 12.68
Median age. Years	58	61	57
18-44 years	18 (15.5)	6 (17.1)	12 (14)
45-54 years	30 (25.9)	4 (11.4)	26 (32.1)
55-64 years	32 (27.6)	13 (37.1)	19 (23.5)
\geq 65 years	36 (31.0)	12 (34.3)	24 (29.6)
Race			
Black	111 (95.7)	33 (94.3)	78 (96.3)
Asian	5 (4.3)	2 (5.7)	3 (3.7)
Level of education			
None	20 (17.2)	1 (2.9)	19 (23.5)
Primary	73 (62.9)	22 (62.9)	51 (63.0)
Secondary	19 (16.4)	9 (25.7)	10 (12.3)
Higher	4 (3.4)	3 (8.6)	1 (1.2)
Status Marital			
Single	9 (7.8)	3 (8.6)	6 (7.4)
Married	69 (59.5)	29 (82.9)	40 (49.4)
Divorced	7 (6.0)	1 (2.9)	6 (7.4)
Widower	31 (27.7)	2 (5.7)	29 (35.8)
Occupation			
Jobless	54 (46.6)	3 (8.6)	51 (63.0)
Traders	21 (18.1)	4 (11.4)	17 (21.0)
Housemaid	4 (3.4)	0 (0.0)	4 (4.9)
Guards	3 (2.6)	3 (8.6)	0 (0.0)
Teachers	2 (1.7)	2 (5.7)	0 (0.0)
Pensioners	7 (6.0)	7 (22.6)	0 (0.0)
Drivers	3 (2.6)	3 (8.6)	0 (0.0)
Others	21 (18.1)	12 (34.3)	9 (11.1)

Table 5: Socio-demographic data of 116 subjects enrolled in the study.

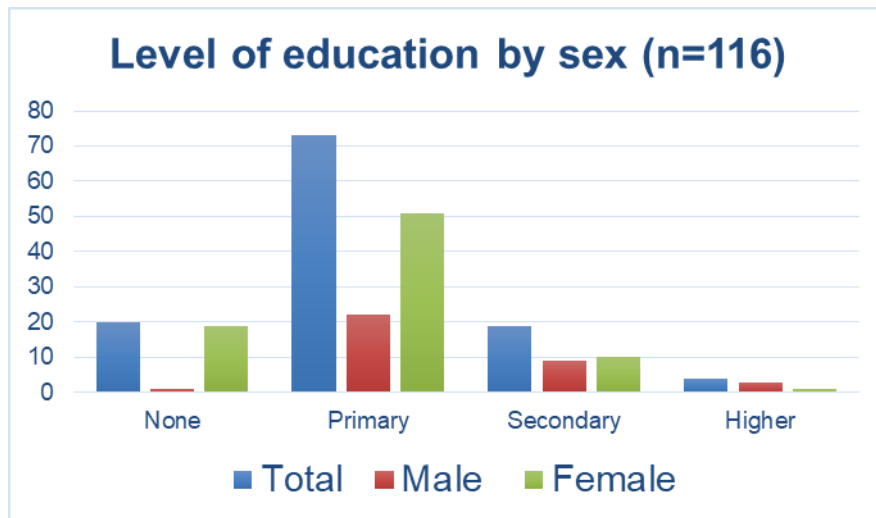


Figure 6: Level of education by sex of 116 subjects enrolled in the study.

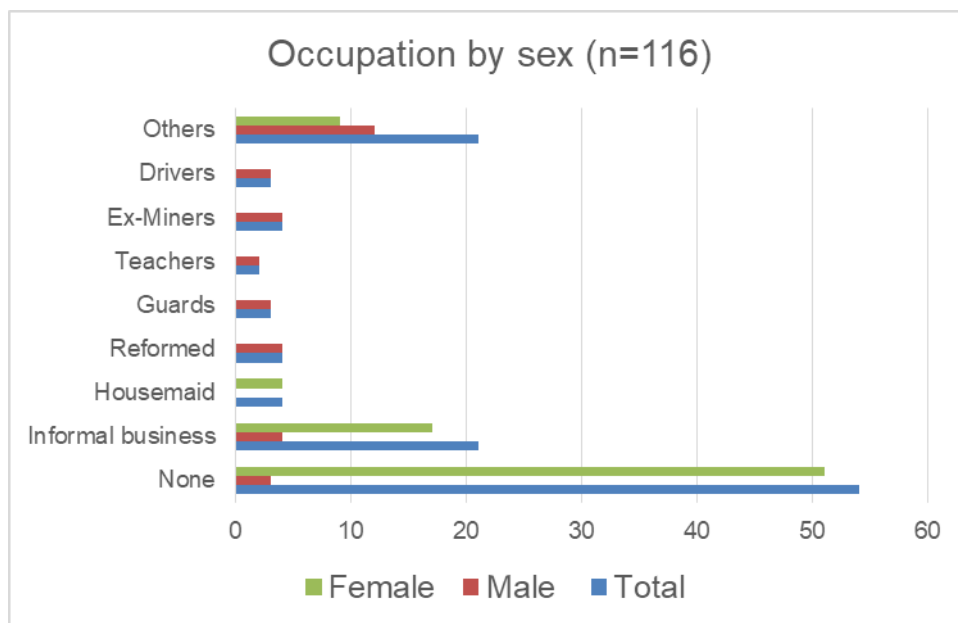


Figure 7: Occupation by sex of 116 subjects enrolled in the study.

4.1.2. Clinical and Laboratory characteristics of subjects

Self-reported established CVD and complications was 47.4% (55 of 116), where 23 (19.8%) subjects had a previous/present history of cerebrovascular disease (stroke) or transient ischaemic attacks and 22 (18.9%) had a previous/present history of heart failure.

4.1.2.1. Self-Reported Risk Factors

As shown in Table 4.2 the frequency of self-reported diabetes mellitus was 8.6% (11.1% in women and 2.9% in men). The frequency of smoking was 6.9% (all the cigarette smokers were men) and that of alcohol consumption was 47.4% (55 of 116). The history of alcohol consumption in men had a significantly higher difference ($p=0.001$) when compared with women. The physical activity below the recommended levels was reported by 109 subjects (93.9%). The family history of cardiovascular disease (HTN, stroke and/or myocardial infarction) was present in 58 (50.0%) subjects.

Variable	Total (n=116) (%)	Males (n=35) (%)	Females (n=81) (%)	p-value
Personal history of DM	10(8.6)	1(2.9)	9(11.1)	0.278
History of stroke or TIA	23(19.8)	10(28.6)	13(16.0)	0.121
History of HF	22(18.9)	6(17.1)	16(19.8)	0.742
History of smoking (current or former)	8(6.9)	4(11.4)	4(4.9)	0.450
History of Alcohol consumption	55(47.4)	25(71.4)	30(37.0)	0.001
History of physical inactivity	109(93.9)	33(94.3)	76(93.8)	0.924
Family history of CVD	58(50.0)	15(42.9)	43(53.1)	0.492

CVD Cardiovascular disease; DM Diabetes Mellitus; HF Heart Failure; TIA transient ischemic attack. Significant P values (< 0.05) in bold.

Table 6: Self-reported risk factors of 116 subjects enrolled in the study.

4.1.2.2. Risk Factors Assessment

The mean of BMI was 28.9 ± 5.9 kg/m²; Forty-eight (42.5%) subjects were obese (BMI ≥ 30 kg/m²). Mean of waist circumference was 97.1 ± 15.0 cm. Abdominal obesity was present in 13 out of 31 men (41.9%) and 59 out of 81 women (72.8%). The mean of body fat muscle was 37.9 ± 12.3 (27.8 ± 10.7 in men and 42.2 ± 10.3 in women) ($p < 0.001$). The mean of body visceral Fat was 10.6 ± 4.9 and men had a significantly higher difference (13.1 ± 6.2 in men vs 9.5 ± 3.8 in women) when compared to women ($p=0.003$).

Variable	Total Mean (±SD)	Males Mean (±SD)	Females Mean (±SD)	p-value
BMI. kg/m² ; N:113	28.9 (± 5.9)	28.3 (± 5.1)	29.1 (± 6.2)	0.479
BM 25-29.9 Kg/m²	(35) 31%	(13) 38.2%	(22) 27.8%	0.273
BMI ≥ 30kg/m²	(48) 42.5%	(12) 38.2%	(36) 45.6%	0.311
WC; N:115	97.1 (± 15.0)	99.3 (± 14.6)	96.2 (± 15.2)	0.507
WC	-	M: ≥102 cm 13/31 (41.9%)	W: ≥ 88 cm 59/81 (72.8%)	
Fat Muscle; N:110	37.9 (± 12.3)	27.8 (± 10.7)	42.2 (± 10.3)	<0.001
Visceral Fat; N:110	10.6 (± 4.9)	13.1 (± 6.2)	9.5 (± 3.8)	0.003
RM (kcal); N:110	1485.8 (± 222.6)	1652.7 (± 212.8)	1414.3 (± 186.5)	<0.001
Triglycerides (mg/dL) N: 110	1.51 (± 1.1)	1.4 (± 0.8)	1.6 (± 1.2)	0.507
TG > 1.7 mg/dL	(28) 25.5%	(7) 20.6%	(21) 27.6%	0.433
Total cholesterol (mmol/L) N:109	5.6 (± 1.5)	5.3 (± 1.2)	5.7 (± 1.6)	0.198
Cholesterol > 4.9 mmol/L	(69) 63.3%	(18) 54.5%	(51) 67.1%	0.211
Cholesterol > 5.2 mmol/L	(59) 54.1%	(15) 45.5%	(44) 57.9%	0.231
Mean FBS N:116	6.1 (± 2.1)	5.9 (± 1.7)	6.1 (± 2.3)	0.714
FBS ≥ 7.0mmol/l	(23) 19.8%	(7) 20.0%	(16) 19.8%	0.976
Serum uric acid (mg/dl); N:114	387 (± 120.8)	421 (± 97.8)	371 (± 127.2)	0.025

FBS Fasting blood sugar; TG Triglycerides; WC Waist circumference. Significant P values (< 0.05) in bold.

Table 7: Risk factors assessment of 116 subjects enrolled in the study.

Regarding biological markers mean total serum cholesterol was 5.6 ± 1.5, 69 of 109 (63.3%) subjects had hypercholesterolemia (cholesterol above 4.9mmol/L) and 54.1% had

dyslipidaemia (cholesterol above 5.2mmol/L). Mean of triglycerides blood level was 1.5 ± 1.1 mg/dL and 28 of 110 (25.5%) subjects had hypertriglyceridemia (TG above 1.7 mg/dL). Mean of fasting blood sugar 6.1 ± 2.1 mmol/L and 23 (19.8%) had diabetes (FBS above 7.0 mmol/L). The mean of serum uric acid was 387 ± 120.8 mg/dl (421 ± 97.8 in men and 371 ± 127.2 in women) ($p=0.025$).

4.1.2.3. Previous anti-hypertensive therapy

Table 4.4 shows that 93 subjects (80.2%) reported being on antihypertensive drugs for the three months preceding entry in the study. In the screening, none of those who reported being on antihypertensive therapy had their BP controlled to $< 140/90$ mmHg.

Variable	%
Detection of HTN	
Previously detected	(94) 81.0
Newly detected	(22) 19.0
Treatment of hypertension	
No treatment	(23) 19.8
Current treatment	(93) 80.2
Number of antihypertensive drugs	
1	(39) 33.6
2	(34) 29.6
3	(17) 14.7
4	(4) 3.4
≥ 4	(0); 0.0
Type of antihypertensive drug	
Diuretics	(91) 97.8
Calcium channel blockers	(40) 43.0
Angiotensin converting enzyme inhibitors	(34) 36.6
Angiotensin II antagonists	(0) 0.0
Beta-Blocking agents	(7) 7.5
Alpha-adrenergic antagonists	(1) 1.1
Centrally acting agents	(1) 1.1

Table 8: Frequency of detection and treatment (number and type) of 116 subjects enrolled in the study.

The antihypertensive drugs used (either alone or in combination) included thiazide diuretics in 97.8% (91 of 93), calcium channel blockers in 43.0% (40 of 93), 36.6% (34 of 93) ACE inhibitors, and 7.5% (7 of 93) Beta-Blockers agents.

We found 80.2% (93 of 116) subjects were receiving antihypertensive drugs, which 33.6% were receiving only one drug, 29.6% 2 drugs, 14.7% 3 drugs and only 3.4% were receiving 4 drugs. None of the subjects investigated had been receiving more than 4 drugs.

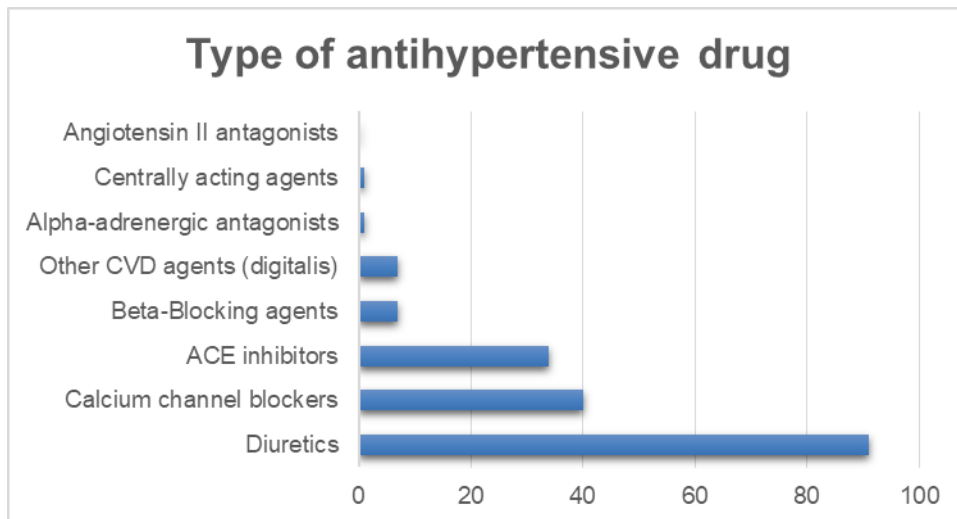


Figure 8: Type of antihypertensive drug of 116 subjects enrolled in the study.

4.1.2.4. Previous therapy for co-morbidities

Table 4.5 shows that 48.3% (56 of 116) of the study population were receiving others treatments. For example, 12.5% (7 of 56) subjects were receiving antidiabetics, 16.1% (9 of 56) antiplatelet (Aspirin), 37.5% (21 of 56) antiretroviral therapy, and 7.1% (4 of 56) were receiving anti-TB therapy (4DFC). And 7 (12.5%) subjects had been receiving digitalis (digoxin).

Variable	%
Subjects receiving other treatments	(56) 48.3
Antidiabetics	(7) 12.5
Digitals (Digoxin)	(7) 12.5
Antiplatelet (Aspirin %)	(9) 16.1
Anti-inflammatory	(3) 5.4
Nonsteroidal anti-inflammatory	(4) 7.1
Antidepressants	(1) 1.8
Antiretroviral therapy	(21) 37.5
Anti-TB therapy	(4) 7.1

Table 9: Previous therapy for co-morbidities of 116 subjects enrolled in the study.

4.1.2.5. Physical Examination

The mean values of SBP and DBP were 192.4 (SD \pm 23.6) and 104.2 (SD \pm 15.2) mmHg, respectively. SBP and DBP did not vary significantly according to the gender (Table 4.6).

Variable	Total (n=116) Mean (\pm SD)	Males (n=35) Mean (\pm SD)	Females (n=81) Mean (\pm SD)	p-value
Mean Heart rate (bpm)	79.6 (\pm 14.7)	77.4 (\pm 15.9)	80.5 (\pm 14.1)	0.294
HR \geq 100 bpm	(10) 8.6%	(2) 5.7%	(8) 9.9%	0.721
SBP (mmHg)	192.4 (\pm 23.6)	191 (\pm 22.3)	192.7 (\pm 24.3)	0.827
DBP (mmHg)	104.2 (\pm 15.2)	104.1 (\pm 16)	104.3 \pm 15.2	0.932
Cervical murmur	(47) 40.5%	(10) 28.6%	(37) 45.7%	0.085
JVP	(17) 14.7%	(4) 11.4%	(13) 16.0%	0.583
Congestion pulmonary	(8) 6.9%	(3) 8.6%	(5) 6.2%	0.696
Isolated ectopic beats	(41) 35.3%	(15) 42.9%	(26) 32.1%	0.266
3rd heart sound	(4) 3.4%	(0) 0.0%	(4) 4.9%	0.314
Mitral regurgitation	(29) 25.0%	(8) 22.9%	(21) 25.9%	0.726
Aortic regurgitation	(20) 17.2%	(6) 17.1%	(14) 17.3%	0.985
Hepatomegaly	(19) 16.4%	(6) 17.1%	(13) 16.0%	0.881
Oedema peripheral	(28) 24.1%	(12) 34.3%	(16) 18.8%	0.093

BMI Body mass index; DBP Diastolic blood pressure; HR Heart rate; JVP Jugular venous pressure; SBP Systolic blood pressure. BPM beats per minute. Significant P values (< 0.05) in bold.

Table 10: Physical examination of 116 subjects enrolled in the study.

Regarding clinical signs of HF at the time of recruitment, 10 (8.6%) subjects had a heart rate above 100 beats per minute (bpm), 17 subjects (14.7%) had high jugular venous pressure, 8 (6.9%) had congestion pulmonary, 19 (16.4%) had hepatomegaly and 28 (24.1%) had oedema peripheral. On cardiac auscultation, 4 (3.4%) had a third murmur and 41 (35.3%) had isolated ectopic beats. Cervical murmur was present in 47 (40.5%) subjects.

4.1.2.5.1. Severity of hypertension

Table 4.8 shows that 8 (6.9%) subjects were in HTN grade 1 (SBP 140-159 or DBP 90-99 mmHg with presence of OD), 29 (25%) were in HTN grade 2 (SBP 160-179 or DBP 100-109 mmHg) and 79 (68.1%) subjects were in HTN grade 3 (SBP \geq 180 or DBP \geq 110 mmHg). Isolated systolic hypertension (SBP \geq 140 and DBP < 90 mmHg) was present in 19 (16.3%).

Variable	Total (n=116) (%)	Males (n=35) (%)	Females (n=81) (%)	p-value
HBP grade 1	8 (6.9)	1 (2.9)	7 (8.6)	0.281
HBP grade 2	29 (25)	11 (31.4)	18 (22.2)	0.599
HBP grade 3	79 (68.1)	23 (65.7)	56 (69.1)	0.426
Isolated systolic HTN	19 (16.3)	2 (5.7)	17 (21.0)	0.055

DBP Diastolic blood pressure; SBP Systolic blood pressure. HTN Hypertension. Significant P values (< 0.05) in bold.

Table 11: Classification of severity HBP of 116 subjects enrolled in the study.

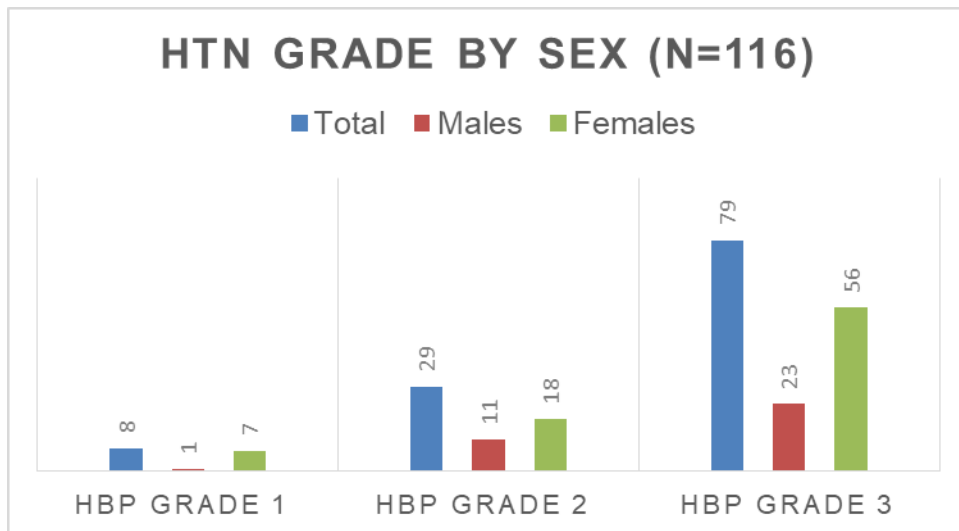


Figure 9: Classification of severity HTN by sex of 116 subjects enrolled in the study.

4.1.2.6. *Relevant Biological Profile*

Table 4.7 shows that mean of creatinine was 109.9 ± 81.7 $\mu\text{mol/L}$. The creatinine levels greater than 100 $\mu\text{mol/L}$ in men had statistically higher difference than women ($p < 0.001$). Mean of eGFR was 79.7 ± 33.8 . Using the K/DIGO classification, 36.2% had glomerular filtration rate of 90 ml/min or above and 27 of 116 (23.2%) had impaired GFR (eGFR below than 60 ml/min per 1.73 m^2).

Thirty-one (26.7%) of all subjects had anaemia (HGB < 12 mg/dl in women and HGB < 13 in men). The anaemia was significantly higher in women (37% vs 2.9%) than men ($p < 0.001$), and median of iron was 14.8 ± 8.1 $\mu\text{mol/L}$. Twenty-two subjects (19%) had HIV infection and median of CD4 was 620.8 ± 578.8 (median: 514) cells/mm^3 .

Variable	Total (%)	Males (%)	Females (%)	p-value
Creatinine umol/L (N:116)	109.9 ± 81.7	124.3 ± 69.7	103.6 ± 86.1	0.211
Creatinine ≥ 100 umol/L	44 (37.9)	23 (65.7)	21 (25.9)	<0.001
eGFR (ml/min per 1.73 m²)	79.7 ± 33.8	73.8 ± 24.4	82.3 ± 37.0	0.217
eGFR ≥ 90 ml/min per 1.73 m²	42 (36.2)	7 (20)	35 (43.2)	0.017
eGFR < 60 ml/min per 1.73 m²	27(23.2)	10 (28.6)	17(21.0)	0.375
GGT IU/L (N:105)	49.2 ± 45.1	56.5 ± 52.7	46.2 ± 41.7	0.276
HGB (gr/dl) N:116	12.9 ± 2.1	14.6 ± 1.7	12.3 ± 1.8	<0.001
Haematocrit (%); N:116	39.9 ± 6.1	44.5 ± 5.6	39.9 ± 5.2	<0.001
Anaemia (HGB< 12 gr/dl)	31 (26.7)	1 (2.9)	30 (37.0)	<0.001
Severe anaemia (HGB< 8)	1 (0.9)	0 (0.0)	1 (1.2)	
Iron (umol/L) N:102	14.8 ± 8.1	15.5 ± 9.4	14.5 ± 7.6	0.562
HIV positivity N:116	22 (19.0)	5 (14.3)	17 (21.0)	0.291
CD4 (cells/mm³) N: 20	620.8 ± 578.8	557 ± 325.8	642 ± 649	0.785

eGFR Estimated glomerular filtration rate; GGT Gamaglutamiltransferase; HGB Haemoglobin. Significant P values (< 0.05) in bold.

Table 12: Biological profile of 116 subjects enrolled in the study.

4.1.2.7. *Electrocardiography characteristics of 113 subjects*

Table 4.9 shows that 103 subjects (88.8%) were in sinus rhythm. The sinus rhythm was more frequent in women (p=0.0409) than men. The most common ECG abnormalities were left ventricular strain pattern found in 57 (50.4%) subjects. Nine (7.9%) subjects had atrial fibrillation and 5 (4.4%) had bundle branch block.

Variable	Total (n=113) (%)	Males (n=33) (%)	Females (n=80) (%)	p-value
12-lead ECG findings				
Sinus rhythm	103(88.8)	30(90.9)	73(91.2)	0.040
Atrial fibrillation	9(7.9)	3(9.1)	6(7.5)	0.119
LVH	57(50.4)	20(60.6)	37(46.3)	0.165
Bundle branch block	5(4.4)	2(6.1)	3(3.8)	0.628

LV Left ventricular; Significant P values (< 0.05) in bold.

Table 13: Electrocardiographic findings in 116 subjects enrolled in the study.

4.1.2.8. *Echocardiography characteristics of one-hundred and three subjects*

The mean of left ventricular ejection fraction was 70.4 ± 13.5 (Table 4.10) and the mean shortening fraction was 36.1 ± 10.3 ; Nineteen subjects (18.4%) had systolic dysfunction (MFS < 25%).

Variable	Total (n=103) (%)	Males (n=32) (%)	Females (n=71) (%)	p-value
Echocardiographic findings				
Mean LVEF	70.4 ± 13.5	67.6 ± 14.3	71.6 ± 13	0.168
MFS	36.1 ± 10.3	33.7 ± 10.2	37.2 ± 10.3	0.121
Systolic dysfunction	19(18.4)	9(28.1)	10(14.1)	0.083
LAE (LA/AO) >1	87(84.5)	26(81.3)	61(85.9)	0.545
Significant aortic enlargement	7(6.8)	5(15.6)	2(2.8)	0.029
Diastolic dysfunction	53(51.5)	19(59.4)	34(47.9)	0.064

AO aorta; LA Left atrial; LAE Left atrial enlargement; LVEF Left ventricular ejection fraction; MFS Midwall fractional shortening; Significant P values (< 0.05) in bold.

Table 14: Echocardiographic findings in 116 subjects enrolled in the study.

4.1.2.9. *Frequency of Target organ damage*

The most frequent TOD in this population were left atrial enlargement in 87 (84.5%) with atrial fibrillation in 9 (7.9%), left ventricular hypertrophy in 57 (50.4%), hypertensive retinopathy in 30 (26.3%) and renal damage in 29 (25.7%) subjects (Table 4.11).

Some form of albuminuria was found in 29 subjects (25.7%). Microalbuminuria was present in 17 (15.0%) subjects and 1.8% had macroalbuminuria/proteinuria.

Grade 1 hypertensive retinopathy was present in 0.9 % (1 of 114) of the study population, and the commonest retinopathy was grade 3 (13.2%) followed by grade 2 (12.3%). None of the subjects investigated had hypertensive retinopathy grade IV.

Target-organ damage	Number	Prevalence (%)
TOD		38.5
LVH	57/113	50.4
LAE	91/103	84.5
Atrial Fibrillation	9/113	8.0
Hypertensive Retinopathy	30/114	26.3
Grade 0	84/114	73.7
Grade 1	1/114	0.9
Grade 2	14/114	12.3
Grade 3	15/114	13.2
Grade 4	0	0.0
Albuminuria	29/113	25.7
Negative	84/113	74.3
Trace albuminuria (15-30 mg/dl)	10/113	8.8
Microalbuminuria (30-300 mg/dl)	17/113	15.0
Macroalbuminuria (> 300 mg/dl)	2/113	1.8
K/DIGO CKD stages		
Stage 1 GFR \geq 90	42	36.2
Stage 2 GFR 60-89	47	40.5
Stage 3 GFR 30-59	17	14.7
Stage 4 GFR 15-29	5	4.3
Stage 5 < 15	5	4.3

LVH = Left ventricular hypertrophy; LAE = Left atrial enlargement.

Table 15: Frequency of different forms of TOD in 116 subjects enrolled in the study.

4.1.2.10. Comparison of RF profile at the baseline and 6-months of follow-up

Table 4.12 shows that mean values of SBP and DBP on 6-month follow-up were 151 (SD \pm 26.63) and 82.88 (SD \pm 12.69) mmHg after they received (more) intensive antihypertensive treatment for six months.

Variable	At baseline (%)	After 6 months (%)
SBP Control	192.4 ± 23.6	151 ± 26.6
DBP Control	104.2 ± 15.2	82.9 ± 12.7
SBP < 140 mmHg	0 (0.0)	37 (37.4)
DBP < 90 mmHg	19 (16.4)	67 (67.7)
BMI ≥ 30kg/m²	48 (42.5)	35 (35.7)
eGFR < 60ml/min per 1,73 m²	27 (23.2)	15 (15.8)
Cholesterol > 4,9 mmol/L	69(63.3)	55 (57.6)
TG > 1,7 mg/dl	28 (25.5)	19 (20)
FBS ≥ 7.0	23 (19.8)	9 (9.5)

BMI Body mass index; DBP Diastolic blood pressure; eGFR Estimated glomerular filtration rate; FBS Fasting blood sugar; SBP Systolic blood pressure; TG Triglycerides. Significant P values (< 0.05) in bold.

Table 16: Comparison of BP controls and risk factors between baseline and follow-up of subjects enrolled in the study.

4.1.2.11. Frequency of new events during the six-month follow-up

Table 4.13 shows that 4 (3.4%) subjects had new events of stroke, 2 (1.7%) had a new event of heart failure and 4 (4.2%) had a new event of CKD over 6 months. Twelve (10.3%) subjects had a history of hospitalisations and 10 (8.6%) death.

Target-organ damage	Number of cases at baseline (%)	Number of new events over 6 months (%)
Stroke/TIA	23(19.8)	4 (3.4)
Heart Failure	22(18.9)	2 (1.7)
Renal Damage	27(23.2)	4 (4.2)
Hospitalisations	-	12 (10.3)
Deaths	-	10 (8.6)

GFR Glomerular filtration rate; TIA Transient ischaemic attack.

Table 17: Frequency of new events of TOD and clinical outcomes during the follow-up.

4.1.3. Summary of Results

The main findings in this study at first presentation were:

- ✓ 71% patients are less than 65 years old; 15.5% are less than 44 years; 68.1% presented in grade 3 HTN; 26.7% had anaemia and 19% were HIV positive;
- ✓ 80.1% had limited formal education (17.2% had never attended school and 62.9% had not completed the primary level); 64.7% had no fixed payday (46.6% unemployment and 18.1% informal traders);
- ✓ At baseline there was a high frequency of dyslipidaemia (54.1%), self-reported alcohol consumption (47.4%), obesity (42.5%), cervical murmur (40.5%), and type 2 diabetes (19.8%);
- ✓ 47.4% had already established cardiovascular complications at baseline, of which 50.4% had LVH, 18.4% systolic dysfunction, 7.9% atrial fibrillation;
- ✓ 23.2% had overt CKD (GFR below than 60 ml/min); 25.7% had albuminuria, 15% microalbuminuria and 2% had overt proteinuria;
- ✓ 26.3% had hypertensive retinopathy, the majority with grade 2 and 3 retinopathy
- ✓ 4 patients were lost to follow up; 3 patients travelled out of Maputo Province but were assessed by a phone call and are in good health.

Over 6-month follow-up: 3.4% patients had had a new stroke and 1.7% had a new event of congestive heart failure; 10.3% had hospitalisations and 8.6% died.

CHAPTER 5: DISCUSSION

5.1. Discussion

In this predominantly young population of African origin population, a high frequency of risk factors to CVD such as obesity, dyslipidaemia and diabetes was found. Importantly, there was a high frequency of established cardiovascular and other target-organ damage at baseline, and on six months follow-up there were high rates of hospitalizations and death.

This study confirms that in our country the majority of patients develop the disease at a young age. Almost three-quarters of all subjects (71%; 80 of 116) had less than 65 years of age, and 15.5% of them were younger than 44 years. Similar findings have been reported in other studies in SSA (Olack *et al.*, 2015; Nelissen *et al.*, 2014; Oladapo *et al.*, 2012; Addo *et al.*, 2009). It is of particular interest that in this population with severe HTN there was a high frequency of RF such as obesity, dyslipidaemia, diabetes, anaemia and HIV infection, which constitute an additional risk for developing early TOD, particularly cardiovascular complications (Nelissen *et al.*, 2014), and may explain the hospitalisations and death in this population (Redon *et al.*, 2016).

Almost two-thirds of the patients (64.7%) had no fixed payday (46.6% were unemployed and 18.1% traders), an expected finding in peri-urban settings of low-income countries such as Mozambique. Low and erratic family income may have determined the mode of presentation of these patients, which had advanced disease and several complications. In concordance with other countries in the SSA region, Mozambique has a low percentage of people with health insurance, related to the high rates of unemployment (Nulu S *et al.*, 2016; Nelissen *et al.*, 2014). Low insurance rates may have contributed to lower treatment coverage and BP control in this study population, as shown by other authors (Ibrahim and Damasceno, 2012; Hendriks *et al.*, 2012; Kayima *et al.*, 2013; Nulu S *et al.*, 2016). Other factors that may have contributed for presentation with severe disease are the high proportion of subjects living without a partner (single/separated and widows) and the high percentage of illiteracy (only 19.9% had the primary level completed). High adult illiteracy rates have been reported in developing countries (Nelissen *et al.*, 2014; Ibrahim and Damasceno, 2012; WHO, 2010). Although no questions regarding income were asked, illiteracy, loneliness and poverty are known determinants of uncontrolled BP, by leading to poor adherence to hypertensive treatment, stress and depression, especially in elderly subjects (Anand *et al.*, 2007; Ibrahim and Damasceno, 2012; Vaidya *et al.*, 2013; Maatouk *et al.*, 2016). This socio-demographic characteristic of this population influences understanding of the importance of adequate and

regular medication and needs to be taken in to account when designing health education strategies and policies.

Past history and Risk Factors

Our study corroborates the significant role of HTN in the causation of heart failure (Dokainish *et al.*, 2016; Dokainish *et al.*, 2015; Ojji *et al.*, 2013; Damasceno *et al.*, 2012; Sliwa *et al.*, 2008; Ayodele *et al.*, 2005; Papademetriou, 2004). We found a high prevalence of established cardiovascular complications (47.4%), namely previous history of stroke/TIA (19.8%) and of congestive HF (18.9%). In Mozambique, there is an extremely low level of awareness and HTN control (Damasceno *et al.*, 2009), and as a consequence, there is a high prevalence and incidence of stroke (Damasceno *et al.*, 2010).

The high prevalence of risk factors for NCDs found (high SBP, obesity, dyslipidaemia, type 2 diabetes, anaemia, smoking and alcohol habits) may justify the high prevalence of stroke and HF in this population (O'Donnell *et al.*, 2016; Padrão *et al.*, 2015; Damasceno *et al.*, 2012) and imposes a high economic burden of the health care system (Lemogoum D *et al.*, 2005). The frequency of overweight at 31% and that of obesity at 42.5% were higher than that obtained from the STEPS survey in Maputo-Mozambique, which found a prevalence of 39.3% for overweight and 21.6% for obesity in urban general populations (Gomes *et al.*, 2010) and lower than 59% of Hi-Hi study based on the community and urban population in Cape Town-South Africa (Peer N *et al.*, 2008). Gomes and co-workers found abdominal obesity in 22.6% of women and 4.5% of men in the urban area of Maputo City (Gomes *et al.*, 2011). Like the findings from previous studies (Sliwa *et al.*, 2008; Gomes *et al.*, 2011; Oladapo *et al.*, 2012; Olack *et al.*, 2015), we found a female predominance of obesity. This has become important in a culture where low weight is either associated with the stigma of malnutrition or HIV/AIDS, because it may render difficult to educate individuals about the dangers of excess weight (Pretorius *et al.*, 2011).

Self-reported type 2 diabetes (8.6%) and newly diagnosed type 2 diabetes mellitus 19% were both above the prevalence in those aged 25 to 64 years in Mozambique at 2.9% (Silva-Matos *et al.*, 2011) and the prevalence of diabetes in other regions of SSA (Manne-Goehler *et al.*, 2016) at 5% (range 2-14%). In Nigeria studies in hypertensive subjects in the community the prevalence of type 2 DM was 9.6% in 2012 and 6.9% in 2014 (Oladapo *et al.*, 2012; Nelissen *et al.*, 2014). In concordance with our finding, other study in Zambia reported high prevalence of type 2 DM of 42.5% in hypertensive subjects (Rasmussen JB *et al.*, 2016).

In contrast, with the low dyslipidaemia reported in several studies in SSA, including previous studies in Mozambique (Damasceno *et al.*, 2010; Nelissen *et al.*, 2014; Kaze *et al.*, 2016), we found that 54.1% of these high-risk subjects presented dyslipidaemia. The frequency of smoking in the studied population was 6.9%, similar to that reported in hypertensive subjects from Nigeria (Nelissen *et al.*, 2014), but in higher than that reported from Cameroon at 3.9% (Kaze *et al.*, 2016). Finally, the frequency of alcohol consumption was very high (47.4%) when compared to previous studies (Nelissen *et al.*, 2014; Olack *et al.*, 2015; Kaze *et al.*, 2016) and men contributed more than women.

Baseline Characterization

Mean SBP levels (192.4 ± 23.6 mmHg) and DBP (104.2 ± 15.2 mmHg) were higher than those obtained in similar studies in Nigeria and Cameroon (Oladapo *et al.*, 2012; Nelissen *et al.*, 2014; Kaze *et al.*, 2016; Boivin *et al.*, 2015). As expected 93 subjects had been receiving antihypertensive treatment; 97.8% were in treatment with thiazide diuretics associated with a potassium-sparing, followed by 43.0% with a calcium-channel blocker and 36.6% with ACE inhibitors; this latter drug is justified by the high prevalence of HF in our population. A comparable study found 91% (Peer N *et al.*, 2008) and 86.1% (Oladapo *et al.*, 2012) patients with treatment with thiazide diuretics, 10% (Peer N *et al.*, 2008) and 15.6% (Oladapo *et al.*, 2012) with calcium channel blocker and 46% (Peer N *et al.*, 2008) and 1.7% (Oladapo *et al.*, 2012) with ACE inhibitors. We also observed that 33.6% were receiving antihypertensive treatment with one drug, 29.6% with 2 drugs, 14.7% with 3 drugs and only 3.4% have been on treatment with 4 antihypertensive drugs.

Hypertension, HIV infection and anaemia constitute main drivers of cardiovascular risk in SSA region, including Mozambique (Damasceno *et al.*, 2012; Strijdom *et al.*, 2017; Dillon *et al.*, 2013; Chalmers *et al.*, 2012; Kider *et al.*, 2011; Triant *et al.*, 2007). At baseline, 26.7% (31 of 116 patients) presented anaemia – only one had severe anaemia (HGB <8 mg/dl). The mean haemoglobin concentration was lower in women compared to men (12.9 vs. 14.6 g/dl, $p < 0.0001$), is very common found in Mozambique where high rates of fertility, malnutrition and HIV infection are found (WHO, 2010; González *et al.*, 2017; Nhacolo *et al.*, 2006; Ogah *et al.*, 2015). Anaemia is mainly caused by iron deprivation in the diet in our context (Aguilar *et al.*, 2012), however in this study, women with anaemia presented serum iron slightly below the considered normal, but it was not statistically significant.

Mozambique suffers one of the SSA highest burdens of HIV and AIDS, and since 2004 started highly active antiretroviral therapy (Mozambique Ministry of Health, 2008). More recently, we adopted the “Prevent HIV, Test and Treat all” strategy, where all subjects tested positive for HIV should be initiated ARVs regardless of the CD4 value the according to WHO

guidelines (WHO, 2016). In this study, the frequency of HIV infection was 19% (22 of 116) slightly above the prevalence in general population, which was 13.2% in 2015 (IMASIDA Report, 2015). HIV infection can predispose to premature atherosclerosis through endothelial dysfunction, pro-inflammatory state and dyslipidaemia (Hsue *et al.*, 2005). In our study, almost all subjects (21 of 22 subjects) had been receiving ARV therapy. Long-term survival is expected to increase in these treated patients, who will, therefore, have a higher risk of cardiovascular and metabolic complications (Luchuo *et al.*, 2016). Additionally, infection with HIV has emerged as an important risk factor for stroke (Thakur *et al.*, 2016; Benjamin *et al.*, 2016; Walker *et al.*, 2013), though most stroke cases reported amongst HIV patients were ischemic stroke (Thakur *et al.*, 2016; Benjamin *et al.*, 2016; Heikinheimo *et al.*, 2012).

Nine subjects of our studied population have been receiving a low dose (100mg) of aspirin daily, but 23 of those had had previous stroke. Aspirin can reduce the risk of major cardiovascular events including stroke, particularly ischemic stroke (Thakur *et al.*, 2016; Benjamin *et al.*, 2016; Heikinheimo *et al.*, 2012), and is widely available and very inexpensive in our context. While there is substantial evidence showing that low dose aspirin is beneficial in the secondary prevention of stroke, its benefit is less certain for primary prevention (Bhatt *et al.*, 2010). In this studied population with uncontrolled BP aspirin may potentially increase the risk of having hemorrhagic stroke, a limiting factor to vulgarize the usage of low dose in our context (Luchuo *et al.*, 2016).

Target organ damage: We observed a high frequency of TOD of 38.5% in among adults with mostly severe HTN, corroborating reports from Nigeria and Ghana, which found 32% (Nelissen *et al.*, 2014), and 43.1% (Oladapo *et al.*, 2012) in Nigeria, and 48% in Ghana (Addo *et al.*, 2009). HTN severity is a strong determinant for TOD (Nelissen *et al.*, 2014) and is a public health problem in SSA, especially in African descent (Mensah *et al.*, 1994; Howard G *et al.*, 2013).

Hypertensive heart disease: Heart damage was the main driver of TOD, followed by hypertensive retinopathy and kidney damage. More than half (50.4%) of the subjects had LVH according to Sokolow-Lyon criteria, a percentage higher than that found in community-based studies in SSA, ranging from 15.9% to 33.3% (Addo *et al.*, 2009), (Oladapo *et al.*, 2012) (Nelissen *et al.*, 2014) and urban setting in South Africa at prevalence of 35% (Peer N *et al.*, 2008). Like Boivin and co-workers, we found that men developed more LVH than women (Boivin JM *et al.*, 2015). The high frequency of LVH found increases the risk of stroke or cerebrovascular disease, coronary heart disease, and HF and cardiac mortality (Catanzaro *et al.*, 2002; McCullough 2002; Cuspidi *et al.*, 2016). We recommend ECG to be used as a first-line marker for detection of subclinical cardiac damage in hypertensive

subjects in our setting, where 13 cardiologists exist for the whole population of around 27 million (Mocumbi, 2011), to reduce morbid cardiovascular events.

LAE has adverse prognostic implications in hypertension. The high occurrence of LAE and atrial fibrillation in our population is also important to mention. Longitudinal studies have identified left atrial size as an independent predictor of an incident of atrial fibrillation (Okin *et al.*, 2010), thrombo-embolic stroke (Nagarajaro *et al.*, 2008), congestive HF and cardiovascular death (Laukkanen *et al.*, 2005; Kim *et al.*, 2015). Additionally, cross-sectional analyses conducted in patients with non-valve atrial fibrillation concluded that the extent of LA dilatation is related to the severity of ischaemic stroke (Kim *et al.*, 2015).

The mean left ventricular ejection fraction in our population was 70.4 ± 13.5 . However, LV systolic dysfunction was observed in 18.4%. Similar studies in Nigeria (Salako *et al.*, 2007; Ojji *et al.*, 2009) and South Africa (Sliwa *et al.*, 2008) found lower values. Like Ojji and Ogah in Nigeria, we found the lower frequency of LV systolic dysfunction in women compared to men (Ogah *et al.*, 2015; Ojji *et al.*, 2009).

Echocardiography has become more available in Mozambique, but it is still restricted to a small number of referral centres of urban areas or to some tertiary centers in rural areas due to its costs and to the lack of expertise to perform the exams (Mocumbi, 2011; Mocumbi, 2012). However, in tertiary centers where the machines are available, they are used primarily for obstetric indications by a nurse trained to screen high-risk pregnancies. In our context with a shortage of cardiologists and other specialists (Mocumbi *et al.*, 2014; Mocumbi, 2011), we aim to decentralise the management of HBP and its complications to peripheral health facilities. We used abbreviated echocardiography to detect LAE and evaluate LV function in subjects with severe HTN. Our vision is that non-specialists medical and even non-medical staff (medical officers and nurses) could be trained to perform focused echocardiography to screen patients with severe HTN for cardiac damage, thus identifying those at high risk of poor outcomes.

Renal Damage: Several studies showed that the most common cause of end-stage renal failure in younger individuals in SSA was hypertension (Banaga AS *et al.*, 2015; Naicker S, 2010; Diouf B *et al.*, 2000). Albuminuria was present in 25.7% (29 of 113) of the subjects, using dipstick albuminuria method confirming the vulnerability of black patients to hypertensive kidney disease (Weber *et al.*, 2014) and risk of chronic renal failure. The frequency of microalbuminuria (15.0%) was higher than that reported in Nigeria (12.3%) (Oladapo *et al.*, 2012) and lower than values found in SSA regions – 26.9% in Zambia (Rasmussen JB *et al.*, 2016), 32.3% (Busari *et al.*, 2011) and 37% (Salako *et al.*, 2007) in Nigeria and 39.3% in Cameroon (Kaze *et al.*, 2016), and other studies done in North

America (21.6%) and Europe (16.8%) (Petrie *et al.*, 2016). The occurrence of macroalbuminuria (1.8%) was similar to that found in Nigeria (2.0%) (Salako *et al.*, 2007) and much higher values reported from Zambia Ghana and Nigeria, which were 8.9% (Rasmussen JB *et al.*, 2016), 13.4% (Addo *et al.*, 2009) and 15.2% (Oladapo *et al.*, 2012), respectively.

Importantly, the frequency of impaired eGRF was higher compared to some studies in SSA region (Sani *et al.*, 2014; Nelissen *et al.*, 2014; Addo *et al.*, 2009), as well as America and Europe (Petrie *et al.*, 2016) where 23.2% of the subjects had impaired eGRF. These results show a high burden of kidney disease and call for efforts on prevention through adequate control of HTN.

Hypertensive retinopathy: Thirty patients (26.3%) had hypertensive retinopathy, of which 25% had grades 2 and 3; no grade 4 disease was found. The frequency of grade 3 hypertensive retinopathy was higher than that found by Oladapo *et al.*, 2012; Addo *et al.*, 2009; Salako *et al.*, 2007 in similar populations. Despite, the frequency of hypertensive grade 3 being very high, it is in aligned with extremely low level of BP control in general population in Mozambique (Damasceno *et al.*, 2009). Additionally, there is a risk of blindness in these individuals which is often neglected in our setting.

This study highlights this simple, non-invasive, and accessible technique (funduscopy) as a tool to screen TOD in hypertensive patients in our context. We think that this tool can be used for risk-stratification at entry point of health unit (emergency and consultation), preferably done by general practitioners due to lack of specialists/ophthalmologists in our country.

Clinical outcomes: Only 37.4% subjects had BP controlled at the end of follow up, confirming the low HTN control rates found in community-based studies (Damasceno *et al.*, 2009; Ibrahim and Damasceno, 2012; Hendriks *et al.*, 2012; Kayima *et al.*, 2013). The results are only slightly better than those found in other studies: 35.6% (Oladapo *et al.*, 201), 27.3% (Nelissen *et al.*, 2014) and 15.2% (Addo *et al.*, 2009), and potentially explains the poor outcomes found on follow up. Over the 6-months follow up the occurrence of stroke, HF and impaired GFR was 3.4% (4 of 116), HF was 1.7% (2 of 116) and 4.2% (4 of 95), respectively. The high numbers of people with uncontrolled HTN, diabetes mellitus, obesity and dyslipidaemia, LVH and LAE may explain the high stroke incidence (Wolf, 1985; Mazza *et al.*, 2001; Nagarajaro *et al.*, 2008; O'Neal *et al.*, 2016) and its high in-hospital case fatality. A high incidence of stroke is known to occur in the Mozambican population (Damasceno *et al.*, 2010). Finally, high frequency of hospitalisations and deaths was found in our cohort in short-term follow-up, indicating the aggressive nature of HTN in our population.

5.2. Limitations

We used a non-representative sample and were forced to do parcelled recruitment due to lack funding. We, therefore, acknowledge that the results cannot be extrapolated to the general population. However, this study was realized in a first referral hospital and therefore is important in understanding the profile of patients needing care at peripheral levels of the health system.

We could not clearly define the type of stroke involved: ischemic, haemorrhagic or thrombo-embolic, because we could not perform CT (computed tomography) scans or MRI in all patients.

We did not perform NT-ProBNP and sST2 exams, because we did not have enough funds to conduct these cardiac biomarkers *ELISA* tests.

Finally, echocardiography, fundoscopic examination and urinalysis at 6 months would have been important to compare to baseline findings and precisely describe the outcomes, but this was not done due to reduced human resources and financial capacity.

Regarding clinical evaluation 24-h ambulatory BP monitoring was not performed. We recognize that it would have been important to precisely assess the rate of BP control. For subjects with evidence of proteinuria (2+ or 3+) on the urine dipstick, we did not obtain a spot urine protein-to-creatinine ratio (mg per mg) in 24 hours which would be a more appropriate measure of CKD. Though we found a high incidence of poor outcomes, during this exploratory study we were not able to correlate those with a risk factor and clinical features at baseline. Large numbers and further data analysis will be necessary to reach this objective.

The results we present on poor BP control do not allow us to draw any conclusion on adherence to anti-hypertensive treatment, an important factor that we did not explore. Further research needs to be done to understand why patients closely followed up had such low rates of control.

CHAPTER 6: CONCLUSIONS AND PERSPECTIVES

6.1. Conclusions and Perspectives

6.1.1. Conclusions

In this low-resourced urban setting of Africa severe and complicated HTN occurs in young people who present high-risk profile characterized by obesity, dyslipidaemia, diabetes and anaemia. Significant TOD is prevalent in the form of cardiac damage (including left ventricular dysfunction), kidney lesion (microalbuminuria and overt CKD), hypertensive retinopathy and stroke. Moreover, we found high case-fatality and hospitalisation rates on short follow-up, in accordance with low blood pressure control and high frequency of TOD.

Our results highlight the urgent need for prevention of hypertension and its complications. In our resource-constrained setting we propose the design of algorithms for diagnosis, management and follow up of hypertension using non-invasive tests, that can be done by non-specialists, namely ECG to detect LVH, atrial fibrillation, and ischaemic changes; urine dipstick to detect microalbuminuria; fundoscopic evaluation to discard hypertensive retinopathy; and, focused abbreviated echocardiographic evaluation to determine the presence of LAE and systolic dysfunction. This approach would not only stratify high-risk patients but also allow decentralization care to hypertensive subjects, allowing prevention of poor outcomes.

6.1.2. Perspectives

We aim to follow-up this research line to explore the usefulness of implementation of algorithms for risk stratification, diagnosis and management of hypertension and its complications. Such studies will include 24-h ambulatory BP monitoring, focused echocardiography performed by non-specialists and dissemination of the use of fundoscopy, as well as assess the efficacy and cost-effectiveness of TOD screening in Mozambique. Another important area of research will be the association between HIV infection and severe hypertension and its role as a risk factor for poor outcomes.

Evaluation of determinants for poor control and adherence to antihypertensive drugs must also be carried out, to understand how we can improve BP control rates. These should include psychosocial tests to discard cognitive changes in hypertensive patients. Implementation science should also be developed on tailored strategies for health education taking into account the socioeconomic and demographic profile of our patients.

RECOMMENDATIONS

Advocate for healthy public policy and a comprehensive national program for prevention and control of hypertension

a. Design algorithms for diagnosis, management and treatment of arterial hypertension and other NCD risk factors

Algorithms with simple information about diagnose, management and treatment can help the clinical staff to improve the health care provided to individuals with arterial hypertension and other NCD risk factors, mainly diabetes and dyslipidaemia. In this low-income setting, attempts should be improve early detection of hypertensive subjects; efforts may be directed particularly within the community, and managed appropriately before irreversible TOD and complications emerge. The National Program for the prevention and control of NCDs of MOH-Mozambique should take the lead in this process.

b. Screening and risk-stratification protocols to identify high-risk individuals

BP screening in asymptomatic individuals can assist in identifying high-risk individuals who would not otherwise seek treatment before developing other complications, but can also avoid overwhelming the fragile health infrastructure with individuals who have low levels of HBP that confer little risk of TOD. It identifies a spectrum of high- and low-risk individuals, which may be managed according to their risk. The National Program for the prevention and control of NCDs of MOH-Mozambique should promote the use of risk-stratification protocols available.

c. Clinical staff training for HTN management and TOD screening

Training of health professionals will play a role in assuring and proving a quality health care, treatment and follow-up. In our context, building capacity to address HTN and other risks factors for TOD, through decentralization of care to nurses and general physicians is very important. District-level nurses and generalist physician should be receive training in HBP diagnosis and management, as well as learn to identify and refer high-risk patients to higher levels of care. Integration of management of several RF in chronic disease consultations for HIV-positive subjects at health facilities would be a way of ensuring that most clinical staff are trained and, on the other hand, that all subjects seeking medical care are screened.

TOD screening for renal damage, cardiovascular complications and other associated conditions (diabetes, hypercholesterolemia and gout) must be available at the lower level of the health system. Pocket Guides should be available for health professionals.

d. Health education program in hospitals and communities

Health education for hypertensive subjects (or with other NDCs) and their families should be done together with campaigns for increasing public awareness, educate physicians, as well as policies for reducing salt intake and promoting healthy lifestyles. In Mozambique, the population presents a limited level of education; therefore, more health education programs with audio-visual instruments should be created, eg. Speeches about HTN and RF (prevention, screening and importance of regular and adequate treatment) and forms to prevent their complications in local language in radio stations and public television channels. Pamphlets and mobile text messages can also be used. Health education in schools may provide knowledge and skills early in life, and lead to the adoption of healthy lifestyles from young ages, including regular checking of BP, physical activity and healthy dietary habits for obesity prevention. Additionally, policies to limit marketing of alcohol should be created. Finally, to prevent and control hypertension in Mozambique multi-sectoral approaches are needed, involving health, education, agriculture, transport, finance among others sectors.

e. Access to medicines and regulations for the food industry

Availability of medicines to all in public hospital pharmacies is as important as the regular intake by individuals to prevent TOD. Mozambique's low socio-economic and formal employment levels determine weak purchasing power for medicines in private pharmacies. Universal health coverage principles determine that government has the responsibility to ensure that all citizens have continuous availability of low-cost generic medicines or free access to medicines for chronic conditions. Regulations for the food industry to the reduction of salt, sugar and fat, and increase the levels of fibre; and also potassium and calcium in foods should be created to prevent obesity and dyslipidaemia.

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APPENDICES

APPENDICE 1: Publications & Participation in Congresses (Posters & Oral Presentation)

July 2017: Denise Langa, **Naisa Manafe**, Beatriz Manuel, Igor Dobe, Norberto Lumbandali, Geoffrey Madeira, Samuel Sitefane, Maria Helena Anibal, Rosália Nhabete, Carlos Funzamo, Sérgio Chicumbe, Ana Olga Mocumbi. Doenças respiratórias crônicas no ambulatório do serviço de urgência dum hospital urbano, Moçambique. Poster presentation in 1º Congresso da Associação Respiratória de Língua Portuguesa.

April 2017: Ana Olga Mocumbi, Geoffrey Madeira, **Naisa Manafe** and Andrea Beaton. Rheumatic heart disease and endomyocardial fibrosis: Distinguishing the etiology of mitral regurgitation in low-resourced areas. SAHeart. Volume 12, Number 1; 2017; 14:36-41.

August 2016: Participation at “Stroke and Hypertension Congress”, Johannesburg, South Africa.

August 2016: Carlos Funzamo, **Naisa Manafe**, Denise Langa, Rosália Nhabete, Fulgência Simão, Carlos Macuácuá, Maria Helena Anibal, Ana Olga Mocumbi. High burden of Hypertension and Stroke on admissions for NCD targeted by the global strategy in an urban hospital in Maputo City, Mozambique. Poster oral presentation.

June 2016: Ana Mocumbi, Noorjehan Majid, **Naisa Manafe**, Aaron Carlin, Ines Zimba, Robert Scholley, Constance Benson. Anemia is a predictor of cardiac abnormalities and systolic function worsening in an African population with access to antiretroviral therapy. Poster presentation in World Congress of Cardiology & Cardiovascular Health, Mexico.

April 2016: Participation at “8th African Hypertension Teaching Seminar”, organized by The Africa Regional Advisor Group of the International Society of Hypertension, in collaboration with European Society of Hypertension (ESH), the Mozambican Heart Association (AMOCOR) and the International Forum for Hypertension Control and Prevention in Africa (IFHA), Maputo-Mozambique.

April 2016: Delfina Hlashwayo, Igor Dobe, Rosália Nhabete, Fulgência Simião, Teodósio Maculule, Cristolde Salomão, **Naisa Manafe**, Ana Olga Mocumbi. Feasibility of rapid cardiac markers and coagulation tests in HIV-positive patients in ambulatory consultation environment. Revista Moçambicana de Ciências de Saúde, Volume 3, Number 1, 2016.

September 2015: Participation at XV Health Journey of the National Public Health Institute, Maputo-Mozambique.

May 2015: **Manafe N**, Mocumbi AO. Non Communicable Disease: Research Priorities for Mozambique. Revista Moçambicana de Ciências de Saúde. Vol 2, Number 1, April 2015.

October 2014: Participation at “The 15th Annual SA Heart Congress”, in Durban, South Africa.

October 2014: **Manafe N**, Ngale A, Manuel B, Biquiza N, Bernardo E, Zimba I, Majid N, Mocumbi A.”Cardiovascular Disease in an African Population with High Adherence to Antiretroviral Therapy”, 15th Annual SA Heart Congress”, in Durban, South Africa. Poster Presentation

March 2014: Participation at Conference on “Physical Activity and Sport for Health and Development in Africa”, in Maputo.

December 2013: Participation at “The 17th International Conference on AIDS & STIs in Africa 2013” in Cape Town, South Africa.

September 2013: Participation at the Scientific Conferences of the Maputo Central Hospital, Maputo.

September 2012: **Manafe N**, Amad C, Djedje B, Massingue J, Hussein S, Bernardo E, Manuel B, Mocumbi A. “Profile of cardiovascular disease in outpatients assisted at a tertiary hospital”, XIV Mozambican National Public Health Institute Meeting, Maputo. Oral presentation.

APPENDICE 2: Training

June 2017: “Technical-Scientific Review of Protocols”, Hygiene and Tropical Medicine Tropical Institute, University of Lisbon and National Public Health Institute, Maputo-Mozambique.

November 2016: “Writing Scientific Articles”, Hygiene and Tropical Medicine Tropical Institute, University of Lisbon, *Mulheres STrop*, Mozambican Institute for Health Education and Research and University of Eduardo Mondlane, Maputo-Mozambique.

July 2016: “Train-the-Trainers” in Good Clinical Practice, University of Eduardo Mondlane, World Health Organization, For Research on diseases of poverty and Centro de Investigação da Manhiça, Maputo-Mozambique.

December 2015: “Writing Day”, National Public Health Institute, Maputo-Mozambique.

November 2015: “Fundamentals of Epidemiology Course”, University of Stellenbosch, Cape Town, South Africa.

May 2015: “Biostatistics Course”, KwaZulu- Natal Research Institute (K-RITH) for Tuberculosis and HIV, Durban, South Africa.

April 2015: “Non-Communicable disease Workshop: Epidemiology, diagnostic and treatment”, National Public Health Institute and SANOFI, Maputo-Mozambique.

December 2014: “Writing Scientific Articles”, National Public Health Institute, Maputo-Mozambique.

October 2014: “HeFSSA Cardiology Update for Non-Cardiologists”, at “The 15th Annual SA Heart Congress”, in Durban, South Africa.

October 2014: “References and literature review PubMed, Mendel and Zotero Workshop”, National Public Health Institute & World Health Organization, Beira-Mozambique.

APPENDICE 3: INFORMED CONSENT FORM



Caracterização da hipertensão arterial severa e suas complicações em pacientes atendidos no Hospital Geral de Mavalane

Declaração de Consentimento informado

1. Eu, _____ de _____ anos de idade, consinto em participar neste estudo que foi descrito no formulário de Informação do participante (em anexo).
2. Eu declaro que li o formulário do consentimento informado, que explica os objectivos e a natureza do estudo e possíveis riscos, e o formulário de informação do participante foi devidamente explicado para a minha satisfação.
3. Antes de assinar o formulário do consentimento, foi-me dada a oportunidade de fazer qualquer pergunta sobre aspectos relacionados com quaisquer possíveis danos que poderei vir a sofrer como o resultado da participação e recebi respostas satisfatórias.
4. Eu percebo que posso retirar-me deste estudo a qualquer momento sem que haja nenhum prejuízo.
5. Eu concordo que os dados desta pesquisa sejam publicados sem que minha identificação seja divulgada.
6. Eu percebo que caso tenha qualquer questão relacionada com minha participação nesta pesquisa, eu devo contactar a Investigadora Naisa Manafe pelo telefone +258 843482353, que estará sempre disponível a responder qualquer questão relacionada com esta pesquisa.
7. Eu declaro que recebi uma cópia do formulário do Consentimento Informado e do formulário de Informação.

Assinatura do Participante ou Impressão digital

Assinatura da Testemunha

Assinatura do investigador _____ Data ____/____/____

NIP _____

Hora: ____: ____

APPENDICE 4: APPROVAL LETTER FROM ETHICS COMMITTEE



REPÚBLICA DE MOÇAMBIQUE

MINISTÉRIO DA SAÚDE
COMITÉ NACIONAL DE BIOÉTICA PARA A SAÚDE
IRB00002657

Exma Senhora
Dr^a. Naisa Abdul Manafe
INS

Ref: 38/CNBS/16

Data 24 de Fevereiro de 2016

Assunto: Parecer do Comité Nacional de Bioética para saúde (CNBS) sobre o estudo: "*Frequência e caracterização da hipertensão arterial com lesão de órgão alvo em paciente atendidos num hospital de referencia da Cidade de Maputo versão 1.3*"

O Comité Nacional de Bioética para Saúde (CNBS) analisou as correcções efectuadas no protocolo intitulado: "*Frequência e caracterização da hipertensão arterial com lesão de órgão alvo em paciente atendidos num hospital de referencia da Cidade de Maputo versão 1.2*"

Registado no CNBS com o número 109/CNBS/2015, conforme os requisitos da Declaração de Helsínquia,

Não havendo nenhum inconveniente de ordem ética que impeça a realização do estudo, o CNBS dá a sua devida aprovação aos seguintes documentos:

- Protocolo de estudo versão 1.3
- Instrumento de recolha versão 1.3
- Consentimento Informado versão 1.3

Todavia, o CNBS informa que:

- 1- A presente aprovação não substitui a autorização administrativa.
- 2- Não houve declaração de conflitos de interesse por nenhum dos membros do CNBS.
- 3- A aprovação terá a validade de um ano, terminando esta a 24 de Fevereiro de 2017. Os investigadores deverão submeter o pedido de renovação da aprovação um mês antes de terminar o prazo.
- 4- Recomenda-se aos investigadores que mantenham o CNBS informado do decurso do estudo.
- 5- A lista actualizada dos membros do CNBS esta disponível na secretaria do Comité.

Com as nossas mais cordiais saudações.



Pr _____ evene

Cc/ Comité Institucional de Bioética par

ENDEREÇO:
MINISTÉRIO DA SAÚDE
C. POSTAL 264
Av. Eduardo Mondlane/Salvador Allende
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Signed