A RETROSPECTIVE REVIEW OF HYPERTENSION CONTROL AT HELEN JOSEPH HOSPITAL OVER A 3 MONTH PERIOD

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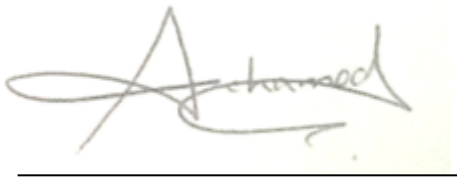
DECLARATION

I, Farzahna Mohamed, declare that this research report is my own unaided work. It is being submitted for the Degree of Master of Medicine in the Faculty of Sciences at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other University.



Farzahna Mohamed

Signed in Johannesburg on this, the 9th day of November 2016

I dedicate this work to my loving parents Yusuf and Rashida for having made numerous sacrifices so as to provide me an excellent education. Most of all, I would like to thank my loving husband, Ismail and my son, Muhammad Zaydan for always supporting me.

ABSTRACT

Background: The 66% global increase of people diagnosed with hypertension (HT) from 1980 to 2008 highlights the devastating economic and medical implications on the health sector. Appropriate treatment of HT is an important strategy to reduce global cardiovascular (CV) risk.

Objective: To determine the number of patients who achieved target blood pressure (BP) in accordance with the 2011 South African Hypertension Guidelines **(**SAHG). Secondary objectives were to assess compliance to the SAHG with regards to routine investigations carried out on patients and to compare differences between the controlled versus uncontrolled hypertensive groups with regards to demographics, body mass index (BMI), target organ damage (TOD), co-morbidities and therapy.

Methods: The study was a retrospective clinical audit involving medical records of 300 patients with primary hypertension, who had been on antihypertensive treatment for a minimum of one year attending the specialised Hypertension Clinic at Helen Joseph Hospital (HJH) between 1st January and 31s March 2012. A questionnaire was designed to assess all the parameters required to meet the objectives.

Results: The median age of the study population was 63 years, with a female predominance. This study showed that 49% of the study population achieved target BP. The prevalence of known diabetes, dyslipidaemia, TOD and chronic kidney disease (CKD) is 28%, 66%, 5%, and 11% respectively. The following variables were significantly higher in the uncontrolled BP group: age ≥ 65 years, hyperglycaemia, dyslipidaemia (specifically hypertriglyceridemia), obesity, elevated serum creatinine and proteinuria.

Conclusion: The study showed that the total number of patients achieving target BP, as recommended by the 2011 SAHG, at a specialised HT clinic is suboptimal. Compliance to guidelines regarding routine investigations was suboptimal. This can be attributed to both patient, physician and facility related factors.

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ABBREVIATIONS

AASK	The African American Study of Kidney Disease and Hypertension Trial
ABCD	The Appropriate Blood Pressure Control in Diabetes Trial
ACC	Associated Clinical Conditions
ACCOMPLISH	Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension Trial
ACCORD	The Action to Control Cardiovascular Risk in Diabetes Study
ACE-I	Angiotensin-Converting Enzyme Inhibitor
AIRE	The Acute Infarction Ramipril Efficacy Study
ALLHAT	The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints
APCSC	The Asia Pacific Cohort Study
ARB	Angiotensin Receptor Blocker
ARIC	Atherosclerotic Risk in Communities Study
ASPIRANT	The Addition of Spironolactone in Patients With Resistant Arterial Hypertension Trial
ATP III	Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)
BB	Beta Blocker
BENEDICT	The BErgamo NEphrologic DIabetes Complications Trial
BMI	Body Mass Index
BP	Blood Pressure

CAD	Coronary Artery Disease
CARE	Cholesterol and Recurrent Events Trial
CCB	Calcium Channel Blocker
CHARM	The Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
CVE	Cardiovascular Events
DALYs	Disability-Adjusted Life Years
DBP	Diastolic Blood Pressure
DECODA	Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Asia Study
DM	Diabetes Mellitus
DOA	Duration of Action
DOH	Department of Health
eGFR	Estimated Glomerular Filtration Rate
ECG	Electrocardiogram
ECHO	Echocardiography
ESCAPE	Effect of Strict Blood Pressure Control and ACE-Inhibition on Progression of Chronic Renal Failure in Paediatric Patients
ESH	European Society of Hypertension
ESRD	End Stage Renal Disease
FEVER	The Felodipine Event Reduction Study

GFR	Glomerular Filtration Rate
GTT	Glucose Tolerance Test
HbA1c	Haemoglobin A1c
HCTZ	Hydrochlorothiazide
HDL	High-Density Lipoprotein
HDS	The Hypertension in Diabetes Study
HF	Heart Failure
HJH	Helen Joseph Hospital
HOPE	The Heart Outcomes Prevention Evaluation Study
HOT	The Hypertension Optimal Treatment Study
HT	Hypertension
HYVET	The Hypertension in the Very Elderly Trial
IDF	International Diabetes Federation
IHD	Ischaemic Heart Disease
INSIGHT	Intervention as a Goal in Hypertension Treatment Study
ISH	Isolated Systolic Hypertension
ISHIB	International Society on Hypertension in Blacks
JNC	Joint National Committee
JNC 8	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LDL	Low-Density Lipoprotein
LIFE	The Losartan Intervention For Endpoint reduction in Hypertension Study
LVH	Left Ventricular Hypertrophy
mg	Milligram

mg/mmol	Milligram per Millimole
mm	Millimetre
mmol/L	Millimoles per litre
mmHg	Millimetre of Mercury
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction
MOSES	Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention
MRFIT	Multiple Risk Factor Intervention Trial
MS	Metabolic Syndrome
NHANES	The National Health and Nutrition Examination Survey
NHLS	National Health Laboratory Service
NICE	National Institute for Health and Clinical Excellence
OAC	The Obesity in Asia Collaboration
ONTARGET	The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
PAMELA	The Pressioni Arteriose Monitorate E Loro Associazioni study
P: Cr	Protein: Creatinine Ratio
PHC	Primary Health Care
PP	Pulse Pressure
PREVEND	The Prevention of Renal and Vascular End Stage Disease Study
PROCAM.	Prospective Cardiovascular Münster Heart Study
PRoFESS	The Prevention Regimen for Effectively Avoiding Second Strokes

PROGRESS	The Perindopril Protection Against Recurrent Stroke Study
PVD	Peripheral Vascular Disease
RALES	The Randomized Aldactone Evaluation Study
RAS	Renin-Angiotensin System
RCT	Randomised Controlled Trial
REACH	The Risk Evaluation and Communication Health and Utilisation Trial
REIN 2	Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease
SA	South Africa
SADHS	South African Demographic and Health Survey
SAHG	The South African Hypertension Guidelines
SAHS	The South African Hypertension Society
SARS	The South African Renal Society
SBP	Systolic Blood Pressure
SCORE	Systemic Coronary Risk Evaluation
SD	Standard Deviation
SEMDSA	Society for Endocrinology, Metabolism and Diabetes of South Africa
SOLVD	Studies of Left Ventricular Dysfunction
TC	Total Cholesterol
TG	Triglycerides
TIA	Transient Ischaemic Attack
TOD	Target Organ Damage
TRACE	The TRAndolapril Cardiac Evaluation study

TRANSCEND	Telmisartan Randomized Assessment Study in ACE-intolerant Subjects with Cardiovascular Disease
umol/L	Micromoles/Litre
UAE	Urinary Albumin Excretion
UKPDS	The United Kingdom Prospective Diabetes Study
Val-HeFT	Valsartan Heart Failure Trial
WC	Waist Circumference
WHO	The World Health Organisation
WHR	Waist-to-Hip Ratio

CHAPTER 1

1.1 INTRODUCTION

1.1.1 Background

According to the World Health Organisation (WHO), 40% of adults older than 25 years were diagnosed with HT in 2008. This reflected approximately a 66% global increase of people diagnosed with HT to one billion over 28 years from 1980. (World Health Organization, 2013). The number of adults with HT is predicted to increase to a total of 1.56 billion by 2025 (Kearney et al, 2005).

The 2011 SAHG define HT as a systolic blood pressure (SBP) measuring ≥ 140 or a diastolic blood pressure (DBP) of ≥ 90, measured on three separate occasions within a period of two months (Seedat & Rayner, 2011). HT is a significant risk factor in the development of all major cardiovascular diseases (CVD) including stroke, coronary artery disease (CAD), heart failure (HF), CKD and peripheral vascular disease (PVD).

HT affects both the developed and developing worlds although reported prevalence in low income countries (>40%) exceeds that of high income counties (>35%). The prevalence is highest in Africa (at 46%) and lowest in USA (at 35%) (World Health Organization, 2013).

According to the 1998 South African Demographic and Health Survey (SADHS), approximately one-fifth of the South African adult population were hypertensive at a BP cut-off point of 140/90 mmHg (Steyn et al, 1998). This implies that the rapidly increasing incidence of HT will have a devastating global impact on the health

sector; serious medical implications for individuals and high economic consequences on the state.

Together with risk factors such as obesity, dyslipidaemia (raised triglycerides or lowered high-density lipoprotein (HDL) cholesterol), diabetes mellitus (DM) and smoking, HT significantly contributes to the morbidity and mortality associated with CVD which is the leading cause of morbidity and mortality in Western countries. Hypertension-related cardiovascular events (CVE) affect about 37 million people per year worldwide (Van den Hoogen, 2000). CVD accounts for one third of the global mortality, with HT contributing approximately 50% of these (World Health Organization, 2013). The presence of high BP doubles the risk of ischaemic heart disease (IHD) and increases the incidence of stroke by four-fold (Van den Hoogen, 2000). HT was estimated to have caused 46 888 or 9% of all deaths in South Africa (SA) in the year 2000 and 390 860 or 2.4% of all disability-adjusted life years (DALYs) (Rayner, 2010). In SA, CVD is the leading cause of death among all population groups, except for Blacks, amongst whom it ranks third (Pestana et al, 1996). This infers that CVD, which is no longer a disease restricted to the developed world, has an enormous impact on the South African economy.

In SA, 25% of the country's health care budget is devoted to CVD (Leeder et al, 2004), with an estimated total cost of 4-5 billion rand in 1991 (Pestana et al, 1996). The social and economic impact of CVD therefore requires increasing emphasis on preventative strategies. Treatment of high BP signifies an important strategy to reduce global CV risk as hypertensive patients are at an increased risk of experiencing CVE. A reduction in SBP by 10 mmHg can decrease CV mortality by 20 to 40% and a decrease of DBP by 5-6 mmHg reduces the risk of stroke incidence by 35 to 40%; coronary heart disease (CHD) by 15 to 25%; and HF by 50%

(Mampuya, 2012; Chobanian et al, 2003). Additionally, a sustained reduction in SBP of 12 mm Hg over 10 years will prevent one death for every eleven patients treated (Chobanian et al, 2003). Despite all the evidence showing the benefits of achieving target BP, poor levels of control persist both internationally and locally.

A comparative United States National Health and Nutrition Examination Survey (NHANES) showed an improvement in BP control from 31% between 1999-2000 to approximately 51% between 2005-2008, (Ntusi, 2011; Brand et al, 2013). According to the 1998 SADHS, using a BP of ≤140/90 as target BP, only 10% of males and 18% of females achieved target BP (Steyn et al, 1998). More recent studies also show poor BP control. Rayner (2010), Brand et al (2013) and Steyn et al (1998) revealed that only 33% to 40% of hypertensive patients were achieving target BP, with control being worse amongst males. Failure to achieve target BP can be attributed to both patient and physician related factors. Identification of these factors is important when designing strategies to improve BP control.

A global strategy in the management of HT is the implementation of national guidelines. Since 1995, the South African Hypertension Society (SAHS) has published six guidelines to optimise patient care and target BP. The primary objective of these guidelines is to provide a cost effective and comprehensive approach in the national management of HT. The guidelines provide recommendations for measuring BP, risk stratification, routine investigations, and goals of therapy and principles of management. Despite efforts made by the SAHS to implement their use, control of HT remains elusive.

1.1.2 Justification for the study

The successful management of hypertension is dependent on patient and physician related factors. Although multiple patient related factors are associated with uncontrolled BP, the primary factor is lack of adherence to therapy. Any strategy implemented to improve outcomes should not ignore the role played by physicians in optimising patient care. Appropriate knowledge and practice of national guidelines by clinicians is also imperative in this regard.

An assessment of patient and physician related factors will provide greater insight into the reasons for poor BP control. This study focuses predominantly on physician related factors as stipulated by standardised national guidelines. These include compliance to the 2011 SAHG with regard to whether routine investigations are carried out and the frequency at which these are conducted. Thus, the literature review will focus on each component of these guidelines, including risk stratification; components of routine investigations; target BP and follow up. The intention is to provide an understanding of the importance of implementing the variables recommended by the SAHG. In addition, management will be assessed with special attention to the appropriateness of antihypertensive therapy. Patient related factors including the relationship of demographics and co-morbidities to BP control will be addressed. Assessment of strategies to improve lifestyle modification as well as adherence to therapy will not be assessed as this information cannot be extracted from patient records.

The Hypertension clinic at HJH is a specialised clinic structured in a manner that allows for routine investigations and protocols based on the SAHG. No study has been conducted at this clinic to determine if management plans are compliant to the guidelines or whether patients are achieving target BP. Local data regarding the

prevalence of achieving target BP was predominantly done at Primary Health Care (PHC) level and not at the tertiary level. Although local data shows poor BP control, there is minimal data showing the level of health care providers' compliance to the SAHG. The purpose of this study is to establish the degree of BP control in the population group serviced by health care providers at the Hypertension Clinic at HJH. It is envisaged that the results of the study, which will focus on the control of BP; level of compliance of health care providers to the SAHG; and appropriateness of anti-hypertensive therapy, will create a platform to implement strategies for improving care. These strategies can then be applied to public hospitals in the Johannesburg area as the study population is a good representation of patients attending these hospitals.

1.2 LITERATURE REVIEW

1.2.1 Definitions and classification of Hypertension

BP is one of the vital clinical signs that can be defined and determined physiologically by the following formula:

$$\mathbf{BP = cardiac\ output\ X\ peripheral\ vascular\ resistance}$$

Cardiac output is dependent on stroke volume and heart rate, where stroke volume represents the volume of blood pumped by the contracting ventricle with each heartbeat. HT can thus be considered to be an increase in either cardiac output and/or peripheral vascular resistance (Ker, 2006).

A BP of ≥ 140 SBP and/or 90mmHg DBP is now internationally recognised as HT (Seedat & Rayner, 2012). The cut-off value is based on evidence from randomised controlled trials (RCTs) whereby a treatment induced BP reduction is seen among patients with these BP values (Mancia et al, 2013). Based on the recommendations of the 2011 SAHG, the classification of BP is as follows:

Table 1 Classification of BP

Category	BP(mmHg)
Normal	SBP 120 – 129 or DBP 80 – 84
High normal	SBP 130 – 139 or DBP 85 – 89
Stage 1: mild HT	SBP 140-159 or DBP 90 – 99
Stage 2: moderate HT	SBP 160 – 179 or DBP 100 – 109
Stage 3: Severe HT	SBP > 180 or DBP > 110

Source: The South African Hypertension Guideline 2011 (Seedat & Rayner, 2012)

Whether systolic or diastolic, BP category is defined by its highest level (Mancia et al, 2013). This classification is used concurrently with other risk parameters to provide the degree of total CV risk as high normal BP is associated with an increased risk of CV disease. Longitudinal data obtained from the Framingham Heart Study indicates a two-fold increase in relative risk from CVD in individuals with a SBP 130-139mmHg or DBP 85-89mmHg as compared to SBP <120/80mmHg (Vasan et al, 2001). The advantage of implementing this classification is that it will allow for the early identification of patients in whom non-pharmacological intervention strategies will reduce BP and possibly delay, or prevent, progression to HT.

1.2.2 Resistant Hypertension

Resistant or refractory HT can be defined as a BP > 140/90mmHg despite a full dose regimen of 3 antihypertensive drugs, one of which is a diuretic (Seedat & Rayner, 2012). The diagnosis of refractory HT in patients with Isolated Systolic Hypertension (ISH) is made as described above but at a BP of >160/90 (Seedat & Rayner, 2012).

1.2.3 Isolated Systolic Hypertension

The most common form of HT is Isolated Systolic Hypertension (ISH) (Seedat & Rayner, 2012) which occurs predominantly in the elderly. While not clearly defined in the 2011 SAHG, recommendations developed by the 2013 European Society of Hypertension (ESH) and the 2014 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), define ISH as a BP ≥140/<90 mmHg and isolated diastolic hypertension as a blood pressure at <140/≥90 mmHg (Mancia et al, 2013; Domino & Kaplan, 2010; James et al, 2014). ISH is graded using the above classification but based only on SBP (Mancia et al, 2013). Data from NHANES III showed that 65% of uncontrolled hypertensive patients had ISH. 74% of these were older than 50 years (Franklin et al, 2001). ISH contributes to approximately two-thirds of hypertensive patients older than 60 years, increasing to almost 100% in those older than 75 years (Chobanian et al, 2003). Data from numerous studies including the Framingham Heart Study, NHANES III and a meta-analysis of 10 studies, have shown that SBP continues to increase from age 30 to 84 with a concurrent increase in DBP until age 60. After age 60, DBP decreases with an associated rise in pulse pressure (PP) (Franklin et al, 2001; Franklin et al, 1997) due to the stiffening of large arteries associated with an increase in age (Franklin et al, 1997). Significant patterns of BP changes occur with increasing age. In the age group below 50 years, DBP has a greater contribution towards CV risk compared to SBP. However, after the age of 60 years, SBP and PP are the major predictors of CAD. Data from the MRFIT study revealed that SBP was a stronger predictor of mortality related to CAD than DBP in all age groups (Franklin et al, 2001; Neaton & Wentworth, 1992). Clinical trials have demonstrated that control of ISH reduces total mortality, CV mortality, stroke, and HF events

(Chobanian et al, 2003). The increase in the prevalence of HT that occurs with age, which is also evident in the South African population, is not only secondary to the stiffening of large arteries but also associated with modifiable environmental risk factors such as obesity, reduced physical activity as well as excessive sodium and alcohol intake (Ker, 2006; Domino & Kaplan, 2010).

1.2.4 Hypertension in South Africa

The most reliable statistics regarding the prevalence of HT in South Africa are from the 1998 SADHS. The prevalence was approximately 50% higher in 1998 as compared to the 2003 survey. This discrepancy was considered secondary to the significantly lower DBP in all subjects and to observer error, as the field workers had incorrectly measured BP in 2003 (SADHS, 2003). Mean SBP was found to be higher in men than in women, whilst DBP showed no significant gender differences while the prevalence of HT in males and females was 23 and 25% respectively. The male and female breakdown prevalence rates on ethnic groups indicated Whites (38%; 29.1 %); Indian (29.9%; 22.1%); Coloured (25.9%; 29.5%); and African (20.2%; 23.5%). Urban Africans showed higher prevalence rates than rural-based ones. Thus, the highest prevalence among men was in Whites and among women was in Coloureds. Whilst the lowest prevalence among men was in the African group, in women it was lowest amongst Indians. In both sexes the prevalence increased with age, with the highest prevalence in the age group over 65 years (SADHS, 1998).

A South African study showed that HT is the most frequent of the CV risk factors but its prevalence, compared to other risk factors, is highest in the African group (Kearney et al, 2005). Although the 2003 results were found to be unreliable, the observer error was consistent across all participants and thus provided some useful information. One finding is the increasing prevalence of HT in Africans, especially in

the African urban women suggesting that the increasing urbanisation of Africans contributes to the higher prevalence of HT and CV risk factors (Department of Health, 2003). This is supported by Opie & Seedat (2005) who demonstrated that the rising prevalence of HT in black Africans in Sub Saharan Africa is attributed to urbanisation and also that urban societies have a higher risk of HT than rural ones. Thus, it would be of interest to assess if the rate of CV risk factors is higher in more urbanised individuals. Dennison et al (2007) conducted the HiHi study which compared BP control, CV risk and the presence of co-morbidities between the public and private sectors, in three townships near Cape Town. Although this was not a true representation of the rural African community, it is assumed that those that could afford private care are exposed to a greater number of modifiable risks. However, it was found that there wasn't an overall difference in CV risk, but a greater prevalence of obesity and DM among the subjects attending private care with a 20 and 11% difference in prevalence. The rising prevalence of HT in Africans is thought to be predominantly secondary to environmental influences, with not much evidence to support a genetic basis. In addition, complications associated with HT such as stroke, HF, hypertensive nephrosclerosis and malignant HT, with a lower rate of CHD, are becoming more common in black South Africans, compared to Whites and Asians (Seedat & Rayner, 2012; Kearney et al, 2005; Dennison, et al, 2007). These findings could be explained by their late presentation, poor follow up, lack of understanding of their disease and the high incidence of renal impairment (Opie & Seedat, 2005).

1.2.5 Aetiology

HT has two main types: primary and secondary with approximately 90-95% of adult hypertensive patients having primary HT and only 2-10% having secondary HT (Madhur & Maron, 2013; Carretero & Oparil, 2000).

Secondary HT may be endocrine, renal, vascular and drug induced in aetiology, but these will not be discussed as the study focussed on primary HT which is also known as essential or idiopathic HT. The pathogenesis is poorly understood and is multifactorial in aetiology, with both environmental and genetic factors as contributing causes. It is diagnosed in a patient with an elevated BP in whom secondary causes have been excluded.

Multiple twin studies have shown a genetic influence in the development of HT. A positive family history is common amongst hypertensive patients and is found to be twice as common in those with hypertensive parents (Kaplan et al, 2009). Majority of studies show the heritability of HT to range between 35 and 60%, with a predominance of polygenetic mutations (Mancia et al, 2013; Kupper et al, 2005; Luft, 2001; Ehret, 2010). Despite the identification of these genetic mutations, it has not yet been proven that genetic abnormalities contribute significantly to the development of HT in the general population as it has only a small effect on BP levels (Madhur & Maron, 2013; Chobanian et al, 2003; Jermendy et al, 2011). Numerous cardio-metabolic risk factors that are associated with essential HT have both genetic and environmental influences. Obesity was found to be highly heritable with between a 70 to 88% contribution, whilst dyslipidaemia and fasting glucose have a mixed influence with environmental factors contributing approximately 55 and 43% respectively (Jermendy et al, 2011). Thus, the identification of cardio-metabolic risk factors is central to any treatment strategy.

1.2.6 Guidelines

The objective of a national guideline is to provide standardised care to patients in both the public and private sector with a focus on providing evidence-based recommendations regarding diagnosis, risk stratification and management. In addition, the concept of risk stratification is intended to initiate pharmacological treatment on high risk patients, thus providing the low and moderate risk groups an opportunity to normalise BP by means of lifestyle modification. This is a strategy implemented to limit medical costs.

The first management guidelines for HT in SA were developed in 1992 at a Heart Foundation Hypertension Consensus Symposium. These were later endorsed by the Medical Research Council and the Hypertension Society of Southern Africa (Steyn et al, 2001). The SAHS issued the first guideline in 1995. This guideline defined HT as a BP ≥ 160/95mmHg. The SAHS soon thereafter revised the definition to the current figure of ≥140/90mmHg (Steyn et al, 2001). The SAHG has developed its risk stratification guideline from the ESH. The first combined guideline between the Department of Health (DOH) and the SAHS was published in 2006 and marked the beginning of a national standard of care in the management of HT (Atkinson & Veriava, 2006).

As the recommendations are evidence-based, they should be adhered to by physicians to facilitate an improvement in outcomes. Evidence from studies indicates that the rate of BP control had an inverse relationship with “therapeutic inertia” which is defined as the provider’s failure to increase therapy when the treatment goals are not met (Okonofua et al, 2006). This concept was confirmed in the Harris survey, whereby more than 30% of hypertensive patients reported that, despite failing to achieve a target BP of <140/90, their therapy was not altered by the clinician (Elliot,

2008). Therapeutic inertia was also demonstrated in the South African I-TARGET study which established that despite patients not achieving target BP, the physician failed to escalate therapy. Results revealed that 30.7% of hypertensive patients were on monotherapy, 42.8% on two drugs and only 26.5% were receiving more than two agents (Schoeman, 2009).

Common to every HT guideline is a risk stratification plan and the cornerstone of diagnosing and managing HT is to risk stratify the patient. Not only does a risk stratification guideline play a major role in the management of available resources in resource poor settings but is necessary to reduce CV risk.

1.2.7 Risk Stratification

In 1994, the ESH, recommended a total CV risk assessment to prevent CHD as pivotal in any hypertensive treatment strategy. The majority of patients with HT are co-morbid with other CV risk factors, which synergistically interact to increase morbidity.

Global risk equations such as the Framingham, Prospective Cardiovascular Munster and Systemic Coronary Risk Evaluation models, estimate CVD risk (Benner et al, 2008). The REACH trial was designed to assess whether a CHD risk stratification programme versus usual care altered the primary CV end point as measured by the Framingham 10 year CHD risk at 6 months. At the end of the six month study period, patients receiving the intervention, being risk assessed by the physician and communication with the patient regarding their disease, had an approximately 10% lower predicted ten year risk of CHD compared with patients given usual care only. The results, after six months, showed a mean predicted risk of 12.5% in the intervention group versus 13.7% in the group with usual care. In the intervention

group, 25% of patients achieved BP and low-density lipoprotein (LDL) cholesterol targets relative to only 14% of patients receiving usual care. Furthermore, 29.3% of patients in the intervention group quit smoking relative to only 21.4% of those in the control group (Benner et al, 2008). The MRFIT study showed that smokers with serum cholesterol and SBP levels in the highest quintiles had CHD death rates that were approximately 20 times greater than non-smoking men with SBP and cholesterol levels in the lowest quintile (Neaton & Wentworth, 1992). These studies demonstrate that a risk evaluation programme facilitates a significant reduction in cardiovascular risk.

Based on the 2011 SAHG, a general approach to CV risk assessment is based on three broad categories of patient related variables including the level of BP, presence of major risk factors, and the presence of TOD or Associated Clinical Conditions (ACC).

BP is one of the most important variables in risk assessment as it has an independent relationship with the risk of CV events (Chobanian et al, 2003). Data from 61 observational studies, collected on one million adults with no previous vascular disease, showed that the risk of mortality from a vascular event increases with a BP >115/75mmHg (Lewington et al, 2002). As mentioned previously, SBP is an important independent predictor of mortality and evidence shows that between the ages 40 and 69, for every increase in 20mmHg systolic and 10mmHg diastolic, mortality from IHD and stroke doubles (Neaton & Wentworth, 1992; Lewington et al, 2002). However, when predicting CV mortality, using the average of SBP and DBP is a better marker than either variable alone (Lewington et al, 2002). In addition to BP measurement, the assessment of major CV risk factors is vital as it exaggerates the risk of CV mortality.

Major risk factors for CVD include modifiable risk factors such as HT, DM, dyslipidaemia, obesity and smoking; and non-modifiable risk factors such as family history of CVD and age, with the upper limit being 55 years in males and 65 in females. The INTERHEART study identified 9 risk factors of CAD, which collectively accounted for 90% of myocardial infarction (MI) risk, of which all five modifiable risk factors above constituted 80% of this risk (Yusuf et al, 2004). CV risk is further increased with the presence of TOD. This needs to be actively investigated by the clinician as patients may be asymptomatic.

TOD and ACC further risk stratifies patients and thus guides the clinician in deciding when to initiate therapy. According to the 2011 SAHG, TOD and ACC are defined as follows:

Table 2: Definition of Target Organ Damage and Associated Clinical Conditions

TOD	ACC
LVH (Based on ECG)	CHD
Microalbuminuria Albumin : Creatinine ratio 3-30mg/mmol	HF
Elevated creatinine: 115-133umol/l (men) 107-124umol/l (women)	CKD Albuminuria > 30mg/mmol or Creatinine > 133umol/l (men) Creatinine > 124umol/l (women)
	Stroke or TIA
	Peripheral arterial disease
	Advanced retinopathy: Haemorrhages, or Exudates Pappiloedema

Source: The South African Hypertension Guideline 2011 (Seedat & Rayner, 2012)

Taking these three categories into account, the total CV risk is characterized as either low, moderate, high added risk or very high added risk. Majority of patients, approximately 60%, are at moderate risk of a CVE. The low risk and high risk groups

make up 25% and 30% respectively (Ker, 2006). The 2011 SAHG define these groups as follows:

Table 3: Definition of low risk and high risk for Cardiovascular Events

Low Risk	Stage 1 HT **OR** Normal/High normal BP + 1-2 major risk factors
Moderate Risk	Stage 2 HT **OR** Stage 1 HT + 1-2 major risk factors **OR** Normal BP + ≥ 3 major risk factors or TOD or DM or metabolic syndrome
High Risk	Stage 3 HT **OR** High normal BP/Stage 1 or 2 HT + ≥ 3 major risk factors TOD or DM or metabolic syndrome **OR** Normal BP with ACC
Very High Added Risk	Stage 3 HT + ≥ 1 major risk factor or TOD or DM or metabolic syndrome **OR** High normal BP/Any stage of HT + ACC

Source: The South African Hypertension Guideline 2011 (Seedat & Rayner, 2012)

The importance of risk stratification is to serve as a guideline for clinicians regarding when to start pharmacological therapy in addition to non-pharmacological interventions in the form of lifestyle modification.

The success of any risk stratification programme is dependent on the evaluation made by the clinician which begins with basic history-taking and physical examination, and extends to bed-side and laboratory investigations. Most routine investigations are performed annually unless the results are abnormal. The

frequency that the investigations should be carried out is discussed in chapter 3 under the methods section. The clinical relevance of each parameter investigated is discussed in greater detail under the respective headings below.

1.2.8 Metabolic Syndrome

The SAHG defines the metabolic syndrome (MS) using the International Diabetes Federation's (IDF) criteria which characterises MS by the presence of three of the following risk factors: HT, dyslipidaemia, raised fasting glucose, and central obesity. The metabolic syndrome has a rising prevalence worldwide, which can be largely attributed to increasing obesity and sedentary lifestyles (Alberti et al, 2009).

The IDF reports that 25% of the global adult population has MS while two South African studies report a prevalence rate of approximately 60% (Ntyintyane et al, 2005; Erasmus et al, 2012). In the THUSA study, the prevalence of MS in Black males and females was 12% and 28.4% respectively, with obesity reported as the major risk factor in the development of the MS (Van Rooyen et al, 2000).

The current SAHG classifies subjects with MS as moderate to high risk, which implies immediate therapy in these individuals. In addition, this group also has different target BP goals, as will be discussed under the subsection on target BP (Seedat & Rayner, 2012). However, some guidelines, including the JNC 7, still do not list MS as an independent risk factor. This is based on the premise that the presence of MS doesn't add further to the future predictive value of developing CVD, as compared to the individual risk components (Mancia et al, 2013; Volpe et al, 2012). The PAMELA study showed that HT, contributing 95.4%, was the most frequent component constituting the MS. This is followed by hypertriglyceridemia (77.1%), low plasma HDL (72.2%), central obesity (58.5%) and lastly impaired

fasting glucose (31.5%). However, after appropriate variable adjustments, it was concluded that the increased CV risk and all-cause mortality associated with MS are related only to BP and blood glucose (Mancia et al, 2007). Nevertheless, a definite association exists between the presence of MS and CVD.

Patients with MS have a two-fold increased risk of developing CVD and a five-fold increased risk of developing type 2 DM over five to ten years compared to those without the syndrome (Alberti et al, 2009). In addition there is an associated increase in risk for CHD and stroke (Volpe et al, 2012). Thus, MS usually precedes CVD and on this basis it highlights the importance of screening for the other associated CV risk factors before they develop.

Data from NHANES III shows an increasing prevalence of MS associated with an increase in BMI. The data showed the presence of the MS in 4.6%, 22.4% and 59.6% of normal weight, overweight and obese men, respectively, with similar results found in women (Park et al, 2003). This emphasizes the importance of diagnosing obesity in individuals, especially those with CV risk factors.

1.2.9 Obesity (Body Mass Index) Versus Abdominal waist circumference

The 2011 SAHG recommend that BMI be calculated at every visit. BMI is an index used to classify obesity as it has a linear relationship with body fat but a curvilinear relationship with percentage body fat (WHO, 2011). BMI is calculated by using the following formula:

$$\mathbf{BMI} = \mathbf{Weight} \div \mathbf{Height}^2$$

The 2011 SAHG classifies BMI into six categories, with each category having an associated risk.

Table 4: The six categories of Body Mass Index

	BMI	
Classification	**BMI (kg/m²)***	**Risk of chronic, non-communicable disease**
Under weight	< 18.5	Low
Normal weight	18.5-24.9	Average
Pre-obese (overweight)	25.0-29.9	Increased
Obese (class I)	30.0-34.9	Moderate
Obese (class II)	35.0-39.9	Severe
Obese (class III)	≥ 40.0	Very severe

Source: The South African Hypertension Guideline 2011 (Seedat & Rayner, 2012)

* Values are independent of age and sex

Although BMI is a convenient index used to diagnose obesity, there are additional measures of assessing abdominal obesity, including waist circumference (WC) and waist-to-hip ratio (WHR). According to the 2011 SAHG, WC or WHR should be measured at every visit. The SAHG and the IDF for sub Saharan Africa recommend a WC of less than 94cm in males and less than 80cm in females as ideal with an added substantial CV risk for values above this range. The WHO defines central obesity as a WHR higher than 0.90 for males and higher than 0.85 for females (WHO, 2011). However, ethnic differences are not taken into account as these values are based on studies carried out among the European population. The SADHS conducted in 2003, used cut-off values for WC in men and women of 102cm and 88cm respectively, and WHR greater than 1.0 in men and greater than 0.85 in females. These were values recommended by the IDF and ATP III for Europe, USA and Canada (Alberti et al, 2009).

The WHO has reported that in the last three decades, the prevalence of obesity has doubled. In 2008, 1.4 billion adults were overweight, of which 500 million were obese. Obesity was more prevalent in women, who represented approximately 60% of the total number of obese individuals (WHO, 2008). The SADHS conducted in

1998 and 2003 did not display much change in the prevalence of obesity. Data revealed a higher prevalence of obesity in females as compared to males with a prevalence rate of 27 and 9% respectively (DOH, 2003). Data from the SADHS 2003 showed two trends in relation to obesity. Firstly, the prevalence of obesity measured by both BMI and WC increases with age and is more prevalent in females older than 55 and men older than 65 years. Secondly, obesity is more common in individuals from urban areas, with no gender differentiation (DOH, 2003). Racial differences were noted in both sexes. The highest prevalence of obesity in men was seen in Whites with no change since 1998. The prevalence of overweight and obese females was greatest amongst Indian women followed by African urban women with rates of 59 and 56% respectively. When comparing data between the 1998 and 2003 obesity statistics, it is evident that the greatest increase in the prevalence of overweight individuals, regardless of sex, was among Indians. Indian men and women in the overweight category demonstrated an increase of 10 and 7% respectively. The greatest increase in obese females was also amongst Indians, but the greatest rise in males was amongst Coloureds (DOH, 2003). However, these ethnic variations in the prevalence of obesity differ when using WC and WHR as a measure of central obesity. These measures of central obesity are considered to be superior to BMI in predicting CVD risk based on the justification that increased visceral adipose tissue is associated with multiple metabolic abnormalities, including decreased glucose tolerance, reduced insulin sensitivity, and adverse lipid profiles, which are risk factors for type 2 DM and CVD (WHO, 2011; Huxley et al, 2009).

HT, type 2 DM and dyslipidaemia are among some of the major risk factors for developing CVD. Data from the SADHS, regarding BMI, showed the adjusted risk for HT was about twice higher in obese participants compared to those with normal

weight (Steyn et al, 2001). A small South African study conducted in Soweto, comparing the prevalence of HT, DM and dyslipidaemia, among 50 obese and 50 non obese women, showed an increased prevalence of all three risk factors in the obese group (Walker et al, 1990). Studies have shown conflicting results regarding the association between the three anthropometric measures of obesity which include BMI, WC and WHR. The Obesity in Asia Collaboration (OAC) and the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Asia Study (DECODA), showed no difference in the association of these three measures of obesity with HT and dyslipidaemia (Obesity in Asia Collaboration, 2008; The Decoda Study Group & Nyamdorj, 2008). These findings were replicated with regards to an association with DM, as evidenced by Vazquez et al (2007) and the DECODA study (Huxley et al, 2009). However, the association between diabetes and obesity display conflicting results as the OAC study revealed a strong association between measures of central obesity and diabetes as compared to BMI (Obesity in Asia Collaboration, 2008). Obesity is a major risk factor of CVD, but the relationship between the indices and CV risk is variable.

Numerous studies have shown an association between the risk of CVD and all three obesity indices including BMI, WC and WHR. The INTERHEART study revealed a positively linear relationship between these three indices and the risk of MI with as much as a 40% increased risk demonstrated. Furthermore, data showed that unlike BMI, WC and WHR are independent variables in predicting the risk of MI, with WHR being the strongest measure of risk (Yusuf et al, 2004). This independent relationship between the indices of central obesity and the risk of CVD was further demonstrated by De Koning et al (2007) and Lee et al (2008). The Asia Pacific Cohort Study (APCSC) provided an associated increase in risk between the same

three indices and CHD, with the strongest association demonstrated again in WHR. A WC above the recommended value is associated with a 46% incidence of MS within five years (Palaniappan et al, 2004). No association was proven between these anthropometric indices and stroke (APCSC, 2006). Central to all these studies is that the actual difference between the anthropometric measures was small and unlikely to be clinically meaningful, thus regardless of which anthropometric measure is used to define obesity; it is evident that both general and central obesity are major predictors of CV risk and mortality. Life expectancy is reduced by three and ten years in those with a BMI of 30-35kg/m^2 and 40-50kg/m^2 respectively (Huxley et al, 2009). This validates the reasoning for the different measures of obesity in forming an integral role as one of the routine investigations in any national HT guideline. In addition, it highlights the importance of weight reduction in reducing CV risk.

Not only does weight loss decrease CV risk, but it is also associated with an improvement in BP control. The Framingham Heart Study proved that a weight gain of 2,25kg is associated with a 20% increase in CV risk. In contrast, a weight loss of 2,25kg was associated with a decrease in CV risk of 40% in females and 48% in males (Chobanian et al, 2003; Wilson et al, 1999). These results were reproducible in the studies conducted by Neter et al (2003) and Murlow et al (1998), whereby data revealed that a weight loss of approximately 5kg or 4% to 8% of body weight is associated with a reduction in SBP and DBP of 3mmHg and 4mmHg respectively. A multidisciplinary approach should be adopted in any treatment strategy designed to achieve weight loss. These lifestyle modification strategies are essential in managing hypertensive patients, but will not be discussed as this study did not review these factors.

Obesity is frequently associated with dyslipidaemia. Results from NHANES II study showed that obesity was consistently associated with an elevated triglyceride and reduced HDL level. In addition, it is also associated with an elevated LDL, but this relationship is inconsistent. These findings are in keeping with a metabolically interrelated dyslipidaemia which is associated with insulin resistance (Howard et al, 2003). Thus, screening for dyslipidaemia is important in these high risk patients.

1.2.10 Dyslipidaemia

South African data regarding the prevalence of dyslipidaemia was collected using a random regional survey conducted in ten communities between 1982 and 1996, with the population sample of 25 to 64 years of age. Approximately 5.7 million people had hypercholesterolemia, which the study defined as a total cholesterol (TC) > 5mmol/l. The highest prevalence of hypercholesterolemia was amongst Whites and the lowest amongst Africans. Total prevalence amongst Whites, Coloureds, Indians and Africans was 97.9%, 90.4%, 89.9% and 44.7% respectively (Maritz, 1995). Other than lifestyle, familial hypercholesterolemia could be an explanation for the highest prevalence occurring amongst Whites. Steyn et al (1996) showed that familial hypercholesterolemia was more common in the Afrikaner population. All ethnic groups, except for Indians, showed a higher prevalence amongst females. Hypercholesterolemia increased with age, with the highest prevalence over 60 years. The trend was less marked in the African population. Indians showed a pattern of elevated triglycerides and decreased HDL. This lipid profile is associated with insulin resistance and implies a greater atherogenic CV risk. 25% of all Africans included in the study had an elevated TC, which correlates closely to the rate of HT in Africans (Maritz, 1995). Older African women had a higher rate of TC than older men. This was most likely attributed to increased obesity among African women. In the other

three groups, the rate in the elderly was similar in both sexes. Thus, it becomes extremely important that hypertensive patients are screened for dyslipidaemia.

The SAHG defines dyslipidaemia as the presence of the following:

$$\mathbf{TC} > \mathbf{5.1mmol/l\ or}$$

$$\mathbf{LDL} > \mathbf{3mmol/l\ or}$$

$$\mathbf{HDL} < \mathbf{1(men)and}\ < \mathbf{1.1mmol/l\ (women)}$$

HT and dyslipidaemia can coexist in an individual as part of the MS, or as independent risk factors of CVD. Epidemiologic studies show a very strong association between HT and dyslipidaemia, but evidence suggests that not only is dyslipidaemia a predictor of CVD, but may also predict incident hypertension. The Physicians Health Study analysed the lipid profile of 3110 normotensive men that were free of CV risk factors. After 14 years, results showed that 33% of the subjects developed HT. In addition, men in the highest quintile of TC, non- HDL, and TC:HDL ratio had an increased risk of developing HT of 23%, 39% and 54% respectively, as compared to participants in the lowest quintile. The study also emphasized the protective effect of HDL, whereby patients with HDL in the highest quintile had a 32% decreased risk of developing HT as compared to those in the lowest quintile (Halperin et al, 2006). These results show that dyslipidaemia, which is also one of the most important risk factors for CAD, is an important risk predictor as it may lead to HT. Thus, understanding the value of each variable in the lipogram is important when interpreting CV risk.

The MRFIT study was the largest cohort studying the relationship between serum cholesterol and mortality from CHD. The relationship was not a threshold one but continuously graded (Stamler et al, 1986). The Münster Heart Study (PROCAM), showed a significant association between elevated cholesterol levels and major CAD

events, with the LDL: HDL ratio being twice as high in men compared to women. Severe hypercholesterolemia of > 7.8mmol/l was found in 8% females and 5% males. There was a linear increase of triglycerides with age after which it plateaus from age 45 and 60 years in women and men respectively (Assmann, 1998).

Hypertriglyceridemia is not a criterion in the definition of dyslipidaemia. Previous studies failed to show hypertriglyceridemia as an independent risk factor for CVD, but recent ones have shown contrasting results of a positive relationship (Sarwar et al, 2007; Hulley et al, 1980). Despite the positive relationship with CV risk, the association is usually dependent on other risk factors, thus further studies are needed to assess an independent relationship. In addition, LDL is a pivotal and independent predictor of CAD. This was confirmed in the CARE trial, whereby the increase in CV risk with LDL was not linear while risk increased sharply at higher LDL values. It was further demonstrated that for every 0.6mmol/l increase in LDL, there was a 28% increase in the rate of non-fatal MI and mortality from a coronary event (Pfeffer et al, 1999). Elevated HDL levels confer a protective CV effect with a reduction in risk. Conversely, reduced HDL concentration is associated with an increased CV mortality and this is a relationship independent of other risk factors. Some studies have shown that HDL is most highly correlated with CV risk as compared to other lipid variables (Assmann et al, 1996; Wilson et al, 1980). The clustering of an elevated LDL and triglycerides with a reduced HDL constitutes a form of dyslipidaemia known as atherogenic dyslipidaemia (National Heart Lung and Blood Institute, 2002). This commonly occurs in obese and diabetic patients. Thus, screening for diabetes in these patients is important.

1.2.11 Diabetes Mellitus

Diabetes Mellitus (DM) is a metabolic disorder which, like HT is a rapidly growing epidemic. The IDF estimated that in 2011, 366 million people worldwide were living with DM. 80% of these were from low and middle-income countries. It is projected that in 2030, there will be a 70% increase in the global prevalence, bringing the total to 552 million people (SEMDSA, 2012). The 2003 SADHS reports a prevalence of 6.5% for young adults older than 15 years (DOH, 2007). It is one of the five criteria used in defining the MS with type 2 DM being the most common, contributing to over 90% of cases (SEMDSA, 2012).

The Hypertension in Diabetes Study (HDS) has shown that HT and DM commonly coexist with 39% of subjects with DM also having HT. The prevalence is higher in females than males. The hypertensive diabetic subjects had a higher prevalence of obesity and elevated fasting triglycerides than the normotensive subjects. However, the raised triglycerides may have been secondary to obesity. In addition, there was also a higher prevalence of CVE in the hypertensive patients, prior to the diagnosis of diabetes, as compared to the normotensive subjects with a rate of 4.8% and 2.5% respectively (Keil et al, 1993). This highlights two important associations found in hypertensive diabetic patients: the clustering of CV risk factors in this subgroup; and the possibility of a synergistic effect on the rate CVE, as each disease carries an independent CV risk. Studies in hypertensive subjects with co-morbid DM have shown an increase in risk of all CVD and cerebrovascular events (Kannel & McGee, 1979; Davis et al, 1999; Adler et al, 2000). Results following a 20 year observation of the Framingham cohort revealed a three-fold increase in CVD, with highest morbidity and mortality in diabetic women (Kannel & McGee, 1979). The UKPDS sub-study revealed that the incidence of CV complications in diabetic hypertensive patients

was significantly correlated with SBP (Adler et al, 2000). The sub-study also showed that every 10mmHg decrease of SBP in diabetic hypertensive patients was associated with a decline in CV risk and mortality of 12% and 15% respectively (Adler et al, 2000). The above data highlights the importance of targeted screening and treatment strategies in high risk patients.

This is evident in the SAHG, whereby an annual glucose, preferably fasting glucose, is recommended with the intent of further investigations if results are abnormal. The group of patients considered high risk is detailed above under the risk stratification subsection. In addition, according to the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines, risk free patients over the age of 45, should have random glucose measured every three years (SEMDSA, 2012). The benefits of achieving a recommended lower target BP in diabetic patients will be discussed in greater detail under the sub-section of target BP. The coexistence of the two diseases is particularly dangerous and should alert the clinician to actively search for asymptomatic subclinical organ damage.

The routine investigations used for the assessment of subclinical organ damage, involving the kidney and heart, include simple cost effective measures such as testing urine for microalbuminuria, serum creatinine and performing an electrocardiogram (ECG) for left ventricular hypertrophy (LVH). These investigations are recommended by the SAHG based on the premise of identifying asymptomatic organ damage. The presence of organ damage, as mentioned above, adds to the overall CV risk of the patient. Sehestedt et al (2010) and Volpe et al (2012) showed that subclinical organ damage is independent of the Systemic Coronary Risk Evaluation (SCORE) system as a predictor of CV death. SCORE is one of the most used risk stratification plans designed to assess ten year risk of CV death using five

parameters: age, gender, SBP, cholesterol, and smoking (Sehestedt et al, 2010). Primary prevention is initiated in those with a SCORE equal to or larger than 5%, thus subjects with a SCORE of less than 5% may be at risk of a CV event but remain unrecognised (Sehestedt et al, 2010). This is the reason why the SAHG, as per the ESH, recommend specific markers for the identification of TOD, which is used in risk stratification. Two of the four markers used in the study, both recommended by the SAHG, include urine albumin: creatinine ratio and an assessment of LVH.

1.2.12 Target Organ Damage

1.2.12.1 Microalbuminuria, proteinuria and CKD

CKD is becoming a global pandemic affecting approximately 500 million people with one in ten adults reported to have some form of kidney damage (Ritz & Bakris, 2009). Statistics regarding the prevalence of CKD in Africa are unreliable due to the absence of renal registries. A study on the prevalence of CKD in Sub Saharan Africa conducted by Naicker (2013) revealed that CKD predominantly affects young adults between 25 and 50 years and is primarily secondary to HT and glomerular diseases. In this study, HT contributed 45.6% of CKD cases in SA. HT is also responsible for 21% of patients with end stage renal disease (ESRD) on renal replacement therapy (Naicker, 2013). This is in contrast to the developing world where the age of presentation is predominantly middle age and secondary to DM and HT (Naicker, 2013). Secondly, HT was the leading cause of ESRD in blacks, representing 34.6% of cases while representing 20.9%, 13.8% and 4.3% in Coloureds, Indians and Whites respectively (Naicker, 2003).

Investigating for subclinical kidney damage in high risk patients has the benefit of earlier detection and prevention of CKD which can be easily detected using two simple tests which include a urine test for identifying proteinuria and a serum

creatinine done on blood for the estimation of glomerular filtration rate (GFR). The South African Renal Society (SARS) defines CKD as the presence of a GFR less than 60mL/min/1.73 m^2 or the presence of markers of kidney disease present for greater than three months. These markers include urine abnormalities such as proteinuria or haematuria; or abnormal renal imaging (South African Renal Society, 2014).

The SAHG recommend that an estimated glomerular filtration rate (eGFR) be calculated using the modified Modification of Diet in Renal Disease (MDRD) equation. This is also advocated by the SARS and the National Kidney Foundation (Eknoyan & Levin 2002; Moosa et al, 2004). Important factors to consider are that the MDRD equation has not yet been validated for children (<18 years), pregnancy, elderly (> 70 years) and subjects with normal kidney function (Moosa et al, 2004). In addition, Africans do not factor in the equation in SA. This is evidenced by an MDRD eGFR study on black South African CKD patients at Chris Hani Baragwanath Hospital in Soweto, Johannesburg, where a standardised creatinine assay was used and showed an overall eGFR median positive bias of 27% when applying the prescribed African-American ethnic factor of the MDRD equation. When the factor was not applied, the overall median positive bias decreased to 5%. For this reason, MDRD eGFR calculated by the National Health Laboratory Service (NHLS) laboratories uses the same MDRD formula for both black and white patients and thus the ethnicity factor is not used (Naicker, 2012).

Using the calculated GFR, the stage of CKD can be determined as follows:

Table 5: Chronic Kidney Disease stages calculated through Glomerular Filtration Rate

CKD Stage	GFR level (mL/min/1.73 m2)
Stage 1	≥ 90
Stage 2	60 – 89
Stage 3	30 – 59
Stage 4	15 – 29
Stage 5	< 15 or dialysis

Source: Eknoyan & Levin (2002).

NHANES III suggest that as many as 6.6 million people in the United States older than 60 years have a GFR less than 60 mL/min/1.73 (Manjunath et al, 2003). Age related decline in eGFR is evident from the third and fourth decade of life, with a progressive decline of approximately 1-2 ml/min/year. This related decrement in renal function is proportional to the level of BP, in particular SBP, whereby the rate of decline in eGFR decreases by 4-8ml/min/year if SBP remains uncontrolled (Chobanian et al, 2003). Manjunath et al (2003) showed that a decline in eGFR in the elderly (>65years) was an independent risk factor for CVD.

The INSIGHT study confirmed that renal function in hypertensive patients is an important predictor of CV risk. Findings from this study showed that elevated serum creatinine levels and low creatinine clearance (< 60ml/min) occurred in 15% and 9% of respective subjects with CV complications (Leeuw et al, 2004). These results were almost double those seen in patients with normal serum creatinine and high creatinine clearance. Most studies have shown that a reduced eGFR is an independent predictor of CVD in hypertensive and high risk patients (Ruilope et al, 2001; Viazzi et al, 2010; Sciarretta et al, 2010; Manjunath et al, 2003; Shulman et al, 1989). It was also shown that an eGFR of 30ml/min is associated with a 22% increase in CV risk, while normal renal function with an eGFR of 130ml/min is associated with only 15% (Sarnak et al, 2003). This risk was also shown by the ARIC study, where a 16% increase in CV risk was associated with an eGFR of less than

60ml/min (Manjunath et al, 2003). Not only is there an increase in CV risk with severe CKD, but evidence shows that this risk also exists with mild kidney dysfunction (Wison et al, 2003; Anderson et al, 2000; Reinecke et al, 2003). However, the MRFIT study failed to show an independent association between baseline creatinine and CV events. This was only demonstrated on six year follow up of these patients (Flack et al, 1993). Furthermore, the increasing urinary albumin excretion (UAE) confers an increase in CV mortality (Hillege et al, 2002). A meta-analysis conducted by the CKD Prognosis Consortium of more than 100 000 subjects, supported the above studies but in addition, also showed that eGFR and albuminuria were multiplicatively associated with risk of mortality without evidence of interaction (Matsushita et al, 2010).UAE has a diagnostic and prognostic value equivalent to reduced eGFR (Chobanian et al, 2003). Thus, proteinuria should be assessed in all hypertensives and high risk patients.

Since proteinuria in HT, DM and glomerular disease is primarily due to albumin excretion, it is important to measure UAE rather than protein as albuminuria is a more sensitive and specific marker than total protein for CKD secondary to the above diseases (Eknoyan & Levin, 2002). The earliest evidence of nephropathy is the presence of microalbuminuria. The 2011 SAHG defines microalbuminuria as a urine albumin: creatinine ratio 3-30mg/mmol and macroalbuminuria >30mg/mmol. Rayner & Becker (2006) study of hypertensive patients in private practice in South Africa showed that the prevalence of micro- and macroalbuminuria in non-diabetic hypertensives was 21.3% and 4.1%, respectively. The prevalence was higher in hypertensive diabetics with rates of micro- and macroalbuminuria of 32.3% and 10.4%, respectively. HT, DM and Asian ethnicity were independent predictors of microalbuminuria (Rayner & Becker, 2006). Racial differences in the prevalence of

CKD exist, with a higher incidence in black hypertensive patients. These differences can be attributed to genetic factors, particularly apolipoprotein L1 (APOL1) gene (Genovese et al, 2010). Microalbuminuria is a marker of early nephropathy in diabetics, and a marker of TOD in non-diabetic hypertensives (Rayner & Becker, 2006). Screening for microalbuminuria should be at the time of diagnosis in a type 2 diabetic and five years after diagnosis in a type 1 diabetic based on the different lag-time from onset of disease to time of diagnosis.

Numerous studies have shown that microalbuminuria confers an increased risk of CVE (Jensen et al, 2000; Wachtell et al, 2002; Gerstein et al, 2001; Bigazzi et al, 1998). The Prevention of Renal and Vascular End Stage Disease study (PREVEND) showed an independent association between microalbuminuria and CV morbidity, in which a two-fold increase in urine albumin excretion was associated with a 29% increased risk of CV mortality as compared to a 61% increased risk in the HOPE study (Gerstein et al, 2001; Hillege et al, 2002). This is contrary to the Framingham Heart Study, where an independent association between CV morbidity and microalbuminuria was not evident (Sarnak et al, 2003). The PREVEND study also showed that normal levels of albuminuria are associated with an increased risk for CV disease and thus may serve as an early marker for secondary prevention.

The LIFE sub-study showed an increased prevalence of micro- and macroalbuminuria in those hypertensive subjects with ECG features of LVH. This relationship was independent of age, level of BP, DM, serum creatinine or smoking thus confirming a direct correlation between cardiac damage and albuminuria (Wachtell et al, 2002). This highlights the importance of assessing for the presence of LVH in all hypertensive patients.

1.2.12.2 Left Ventricular Hypertrophy (LVH)

Rayner et al, in their study involving hypertensive patients in private practice in SA, found the prevalence of ECG determined LVH to be 18.9% (Rayner & Becker, 2006). Multiple regression analysis of data showed that LVH was strongly correlated with the severity of HT and Black ethnicity (Rayner & Becker, 2006).

There are many forms of LVH but the central component in all, is the presence of an increase in left ventricular mass (Chobanian et al 2003). In HT, there is a chronically increased workload on the heart secondary to an increase in afterload (Lorell & Carabello, 2000). The type of LVH that usually occurs in hypertension is concentric, characterised by circumferential and concentric hypertrophy of the myofibrils (Chobanian et al 2003). CVE and CV associated mortality is twice as likely to occur in subjects with LVH (Chobanian et al 2003). This highlights the importance of the need for a simple and cost effective measure in detecting LVH.

Although echocardiography (ECHO) has a higher sensitivity than the ECG in detecting LVH, the ECG has the advantage of being accessible, cost effective, and easy to operate. In addition, the ECG is highly specific in detecting LVH (Chobanian et al 2003; Pewsner et al, 2007). As a result, the 2011 SAHG recommends that a twelve lead resting ECG should be routinely done with the aim of assessing for LVH, and repeated annually if normal. There are numerous sets of criteria used to diagnose LVH via ECG, but the most commonly used criteria in clinical trials and recommended by ESH is the Sokolow-Lyon index and Cornell voltage criteria. The criteria are defined as follows:

Sokolow-Lyon Index:

$$\mathbf{S\ in\ V1} + \mathbf{R\ in\ V5\ or\ V6}\ (\mathbf{whichever\ is\ larger}) \geq \mathbf{35\ mm}\ (> \mathbf{3.5\ mV})$$
or
$$\mathbf{R\ in\ aVL}\ \geq \mathbf{11\ mm}\ (> \mathbf{1.1\ mV})$$

The Cornell product:

$$(\mathbf{S\ in\ V3}\ + \mathbf{R\ in\ avL}\ + \mathbf{6\ in\ females}) \times$$
$$\mathbf{QRS\ duration}\ > \mathbf{2440mm \times msec}$$

Studies have shown that the ECG findings of LVH are an independent risk predictor of CVE (Okin et al, 2004; Levy et al, 1994; Antikainen et al, 2003). The presence of LVH, irrespective of being diagnosed by ECG or ECHO, is associated with an increased risk of CV complications (Levy et al, 1994; Antikainen et al, 2003). Levy et al (1994) showed that the voltage abnormalities present on ECG are proportional to the level of CV risk, whereby subjects in the top quartile of voltage abnormalities had a three-fold CV risk as compared to those in the lower quartile (Levy et al, 1994; Schillaci et al, 2000). In addition, this study was one of the first to reveal that a decrease in voltage on ECG seen with the use of antihypertensive treatment is associated with a reduced CV risk and an improvement in prognosis (Levy et al, 1994). The HOPE and LIFE studies, together with other trials, further emphasized the findings that the reversal of LVH with antihypertensive therapy is independent of BP reduction (Okin et al, 2004; Mathew et al, 2001; Devereux et al, 2004; Verdecchia et al, 1998; Pierdomenico & Cuccurullo, 2010). For every reduction of 1SD (1050 mm x ms) reduction in Cornell product and 1SD (10.5 mm) in Sokolow-Lyon voltage, there is a 14% and 17% respective reduction in CV death, fatal or non-fatal stroke and MI (Volpe et al, 2012). Thus, it can be deduced that not only is LVH a major CV risk factor, but that treatment associated regression is an important target in the overall management of CV disease.

The primary determinants of LVH are age, elevated BP, obesity, stature and glucose intolerance (Kannel, 1991) The relationship between the severity of LVH and the degree of hypertension shows that an increase in BP is associated with an increase in ECG voltage criteria and that left ventricular mass has a positively linear correlation with CV risk in hypertensive patients (Levy et al, 1994; Schillaci et al, 2000).

1.2.13 Target BP

Target BP varies according to the patient's risk factor profile, TOD, or ACC. The target BP for all stages of HT is <140/90mmHg, and high risk patients with DM, renal disease and congestive heart failure need to achieve a lower target BP of <130/80mmHg within three months (Seedat & Rayner, 2012). The benefits of achieving target BP are evident in numerous studies, including the fact that the degree to which the BP is lowered correlates with a further decline in the rate of CVE. Despite implementing the appropriate drug therapy, optimisation of BP in the long term will require adequate patient education.

The HYVET and FEVER trials proved that treating BP is associated with a reduction in CVE by approximately 30% in both trials, the rate of stroke by 30% and 27% respectively and cardiovascular death by 23% and 33% respectively. The reduction in the rate of HF in the HYVET trial was double that in the FEVER trial with a rate of 64% and 30% respectively (Beckett et al, 2008; Liu et al, 2005). One of the factors that could be attributed to this discrepancy in results is the different antihypertensive regimen used in each trial. The FEVER trial provided further evidence to support the recommendations of target BP set by hypertension guidelines as the SBP in the treatment group was < 140mmHg. This was also evident in the HOT study, whereby patients were randomized to be treated in three groups to achieve a target diastolic

BP of <90, <85, or <80 mmHg. Although the actual mean diastolic BP in each of the three groups differed by 2 mmHg to the target BP, the difference in MI rate was significantly lower in the group with target DBP of <80mmHg. The most significant difference was amongst the diabetic patients, in whom the rate of major CVE was 24.4 per 1,000 patient-years in the group with the <90 mmHg target and 11.9 per 1,000 patient-years among those with a <80 mmHg target (Hansson et al, 1998). This provides evidence that aiming to achieve target BP has significant reductions in mortality and CVD endpoints.

Evidence for the recommendations of a target BP of less than 130/80mmHg in high risk patients is inconsistent. Numerous trials conducted on diabetic hypertensive patients have shown that a reduction in BP is associated with a decrease in microvascular and macrovascular complications as well as death from CVE (Hansson et al, 1998; Zhang et al, 2011; Zanchetti et al, 2009; HOPE Study investigators, 2000; Patel, 2007; UKPDS Study Group, 1998; Estacio et al, 2000). However, inconsistent results were demonstrated in the ABCD hypertensive study which showed a reduction in overall mortality in the intensively treated group (mean BP 132/78mmHg) versus the moderately treated group (mean BP 138/86mmHg). No difference was demonstrated in creatinine clearance and progression of diabetic nephropathy and retinopathy (Estacio et al, 2000). From all these trials, a target BP of DBP of < 80mmHg, mean 78mmHg and 82mmHg was only evident in the HOT, ABCD and UKPDS studies respectively (Hansson et al, 1998; The HOPE Study investigators, 2000; Estacio et al, 2000). None of these trials achieved a SBP of <130mmHg, except for the ABCD normotensive trial (Mancia et al, 2013; Zanchetti et al, 2009). Despite a reduction in progression of certain microvascular complications, including diabetic nephropathy and retinopathy, as well as the macrovascular

complication of stroke, there was no change in creatinine clearance which was the primary end point (Schrier et al, 2002). An important limitation of this trial is that the sample size was small. Although the evidence is inconsistent, achieving a target BP of <130/80 in diabetic patients is still recommended but it is important to recognise that more intensive therapy control to levels lower than the target set by guidelines does not significantly reduce the primary cardiovascular outcome or mortality. This was shown in the ACCORD study, whereby targeting a SBP of <120mmHg did not reduce the rate of CVE as compared to the group with a SBP <140mmHg (Cushman et al, 2010). These inconsistent results in the reduction of CV outcomes with lower target BP is further observed in data from the PROFESS and TRANSCEND studies. Data showed no reduction in primary outcome measures that included the rate of recurrent stroke and the other major CVE in high risk patients (Køber et al 1995; Yusuf et al, 2008).

The association between intensive BP control of less than 130/80mmHg and the development of ESRD has also proven to be inconsistent. The MDRD, AASK and REIN 2 trials were all conducted on non-diabetic proteinuric nephropathies to assess the benefit of intensive BP lowering with regards to progression of hypertensive nephrosclerosis to ESRD (Klahr et al, 1994; Wright et al, 2002; Ruggenenti et al, 2005). All three trials showed no difference in the rate of progression of CKD. However, long term follow up from the MDRD and AASK trials revealed that the benefit of intensive BP therapy was evident in patients with higher baseline proteinuria, measured by 24 hour urine protein: creatinine ratios (P: Cr) (Wright et al, 2002; Sarnak et al, 2005; Appel et al, 2010). In the AASK study, benefit was seen with P: Cr higher than 0.22mg/24hour, which is equivalent to 300mg of protein per day, as compared to higher levels of proteinuria in MDRD where the most benefit

was in patients with baseline proteinuria of 1-3 grams per day (Appel et al, 2010). These benefits were also seen in the ESCAPE trial conducted in children between 3 to 18 years with CKD. Therefore, associations in the adult population cannot be drawn from these results (Wuehl et al, 2009). However, the ESCAPE trial is one of the only studies whereby intensive BP lowering therapy was associated with a delay of progression to ESRD and it also presented a 35% risk reduction in losing 50% of kidney function. Despite guideline recommendations, trial evidence is limited (Wuehl et al, 2009).

Current guidelines do not recommend tight BP control of <130/80mmHg for non-diabetic hypertensive patients. The Cardio-Sis trial randomised patients into two groups of BP control, one with usual control of SBP <140mmHg and the other with tight control of SBP <130mmHg (Cardio-Sis Study Group, 2008). The primary end point was the rate of electrographic LVH, 2 years post randomisation. A post hoc analysis with 2 subgroups including the presence and absence of CVD revealed a significantly lower rate of LVH in the group with tight BP control in both subgroups. LVH rate was less common in the tight BP control group than in the usual control group in patients without established CVD (10.8% versus 15.2%) and with established CVD (14.1% versus 23.5%). This may mark the beginning of further research regarding the benefits of lower targets in low risk patients (Reboldi et al, 2014).

The evidence presented above highlights the importance of treating HT as it usually co-morbid with other chronic conditions. This necessitates a multi-disciplinary approach in its management. Lifestyle modification is the cornerstone of managing HT regardless of the stage of BP. In addition, patient education is important in risk

factor modification. These models of therapy are not discussed as this study is focussed on pharmacological therapy.

1.2.14 Pharmacological Therapy

The SAHG requires a risk assessment of patients before initiating drug therapy as high risk patients should be initiated immediately on antihypertensive therapy. Moderate and low risk patients should be given a trial of lifestyle modification for a maximum of 6-12 months respectively (Seedat & Rayner, 2012). However, the 1998 SADHS revealed that only 39% of men and 55% of women with moderate or severe HT were taking an appropriate antihypertensive regimen

Uncomplicated essential HT should be treated with one of three drugs from the first line class: diuretic, which includes a thiazide or thiazide like diuretic; an angiotensin-converting enzyme inhibitor (ACE-I) and calcium channel blocker (CCB). The ALLHAT is the only study designed to compare the efficacy of different classes of antihypertensive agents including an ACE-I, CCB and thiazide type diuretic. Results showed no significant difference in primary CHD outcomes or in all-cause mortality (Davis et al, 2002). Thus, all three drugs are first line recommendations. The guidelines recommend starting with combination therapy at the time of initiation, if BP ≥20/10mmHg above target or the presence of ISH, DM, CKD or overt CVD. Combination therapy has the benefit of a synergistic effect when used in the appropriate combinations, thus improving outcomes. This effect is seen with ACE-I/Angiotensin Receptor Blocker (ARB) with a CCB or diuretic. If patients on monotherapy fail to reach target BP, then a drug should be added from one of the three first line drugs (Seedat & Rayner, 2012). The SAHG-recommended combinations include diuretics with β-blockers, diuretics with long-acting CCBs, ACE-Is or ARBs, and β- and α-blockers.

1.2.14.1 Diuretic

The importance of a diuretic to any antihypertensive regimen is evident from the fact that it has remained the cornerstone of antihypertensive therapy since the first JNC report in 1977 and the first WHO report in 1978. It is still a drug of first line treatment as per the SAHG, as well as the first-choice drug by which to start treatment in both the JNC-8 and the WHO hypertension guidelines (Mancia et al, 2013). The ALLHAT study showed that a thiazide-type diuretic is superior to an ACE-I and CCB in lowering SBP, and preventing one or more major forms of CVD (Davis et al, 2002) and should be preferred for first-step antihypertensive therapy. The ACCOMPLISH trial was the only trial to show that a CCB was superior to a diuretic, but these results were not reproducible. As a result, most guidelines still recommend a thiazide type diuretic as the first choice drug (Jamerson et al, 2008).

The 1998 SADHS data revealed that, of all the anti-hypertensives used, 48.6% were a diuretic, either as monotherapy or in combination with other agents (Kearney et al, 2005). The diuretic of choice should be hydrochlorothiazide (HCTZ) at a dose of 12.5mg-25mg daily or indapamide (thiazide like diuretic) at a dose of 1.25mg-2.5mg daily. A loop diuretic is not recommended due to its short duration of action (DOA) and is thus only used in patients with CKD less than 45ml/min or HF (Seedat & Rayner, 2012). The 2011 NICE hypertension guidelines recommend using indapamide in preference to HCTZ (National Clinical Guideline Centre, 2008). However, there is insufficient data on the preferred choice of thiazide type diuretic that should be used. Krum et al (2003) compared HCTZ to indapamide, both on a background of an ACE-I, showing that the BP and metabolic profile were similar between the two groups. However, conclusions cannot be drawn from this study as it was a study of only 18 subjects over 8 weeks (Krum et al, 2003). The AISHA study

comparing these two drugs will provide insight into this issue when the results become available (Ciobanu et al, 2007). Clear guidelines to preferential antihypertensive drug use, with a diuretic being one of the two preferred drugs, exist in Blacks. This is discussed further in the subsection of ethnic differences in therapy.

Regarding the use of other diuretics, the SAHG recommends a loop diuretic in patients with CKD, with a GFR of less than 45ml/min. However, in the absence of CKD or HF, a loop diuretic should not be used due to its short DOA (Seedat & Rayner, 2012). Anti-aldosterone diuretics, such as spironolactone, are recommended as a fourth line drug used in resistant HT, and can also be used in HF with the benefits documented in the RALES trial. This study showed significant reduction in morbidity and mortality in the group randomized to receive aldactone. There was a 30% reduction in mortality, a 35% reduction in the frequency of hospital admissions secondary to HF and a significant improvement in symptoms in the treatment group (Pitt et al, 1999). There has been no RCT done to show a benefit in the use of aldactone in uncomplicated HT. An important contra-indication to the use of spironolactone is the presence of hyperkalaemia and renal failure (Seedat & Rayner, 2012).

1.2.14.2 Angiotensin-Converting Enzyme Inhibitor (ACE-I) /Angiotensin Receptor Blocker (ARB):

Although ESH states that ACE-I and ARB's are the most widely used antihypertensives, data from SADHS revealed otherwise. The 1998 SADHS data showed that 18.7% of the drugs had a renin-angiotensin system (RAS) blocking agent (Kearney et al, 2005). The major classes of drugs that block the RAS system include ACE-I and ARB's, with a 95% and 75% blockade respectively (Seedat & Rayner, 2012).

ACE-I and ARB's have been shown to be effective in reducing proteinuria; reducing the progression of microalbuminuria from normoalbuminuria; and improving outcomes in HF. Thus, it is recommended by the SAHG for use in patients with proteinuria, diabetic and non-diabetic nephropathy, HF and left ventricular dysfunction (Seedat & Rayner, 2012). The effect of ACE-I on proteinuria in diabetics will be discussed further in the subsection on therapy in diabetics.

The benefit of an ACE-I or ARB in HF is supported by the findings in numerous studies. The RALES, TRACE, SOLVD and AIRE studies all show a significant reduction in all-cause mortality, CV mortality and morbidity associated with HF (Pitt et al, 1999; The SOLVD Investigators, 1991; The AIRE Study Investigators, 1993; Køber et al, 1995). The CHARM and Val-HeFT studies provide evidence supporting the benefits of an ARB in reducing CV mortality in patients with HF (McMurray et al, 2003; Cohn & Tognoni, 2001). Conflicting results were shown in the PROFESS and TRANSCEND studies, whereby the ARB, telmisartan, showed no significant reduction in the incidence of HF and hospitalisation from HF respectively (Køber et al, 1995; Yusuf et al, 2008). The ONTARGET study revealed that the ARB, telmisartan, was equivocal to the ACE-I, Ramipril, with regards to mortality from CVE; incidence of MI or stroke; and hospitalisation from HF. In addition, the combination of these drugs is associated with an increase in adverse outcomes and thus offers no enhanced benefits as shown by the ONTARGET and ALTITUDE study (Yusuf et al, 2008; Parving et al, 2012).

There are conflicting results on the benefit of an ACE-I or ARB in reducing the incidence of stroke. The PROGRESS and MOSES study showed that an ACE-I in combination with indapamide and the use of an ARB as monotherapy, compared to a CCB in the respective studies, was associated with a reduction in the risk of stroke

and mortality from CV -and cerebrovascular events (Staessen, & Jiguang, 2001; Schrader et al, 2005). However, the ALLHAT study also shows a higher incidence of stroke with the use of an ACE-I as compared to thiazide diuretics. This was predominantly in Blacks (Davis et al, 2002). Two separate meta-analyses have been conducted: one compares an ACE-I to different antihypertensive regimens, and the second comparing the ACE-I only to a CCB. Both studies showed that ACE-Is and ARBs reduce the risk of stroke but that ACE-I's are inferior to other drug classes in this respect (Blood Pressure Lowering Treatment Trialists' Collaboration, 2003; Verdecchia et al, 2005).

1.2.14.3 Calcium Channel Blockers (CCB)

The last class of drugs that constitute first line therapy is the calcium antagonists. The 1998 SADHS revealed that 9.3% of the drugs were CCB's. The 2011 SAHG recommend the use of a CCB in ISH, the elderly, PVD, carotid atherosclerosis, angina pectoris and pregnancy, with nifedipine being the drug of choice in pregnancy. Nifedipine is considered a contra-indication in HF (Seedat & Rayner, 2012). There are conflicting results regarding the use of a CCB in the presentation of HF. The largest meta-analysis of 147 RCTs showed that when comparing a diuretic to placebo, there is a 19% reduction in the onset of HF. When comparing the same outcome using CCBs versus the other four drug classes (Diuretic, ACE-Is, ARBs and beta blockers), the CCB was found to be statistically significantly less effective (Law et al, 2009). Analysis of data shows that this effect could be attributed to the study design, whereby essential drugs needed for HF were withdrawn at the onset of the study.

1.2.15 Special circumstances in therapy:

1.2.15.1 Ethnic differences:

Ethnic differences in treatment are existent with special recommendations in the treatment of Blacks. The guidelines suggest that Black patients respond poorly to monotherapy consisting of an ACE-I or beta blocker (BB), but have a better response to these drugs when used in combination with a diuretic. However, the best, most consistent response is the use of a CCB in this group of patients (Seedat & Rayner, 2012). The current International Society on Hypertension in Blacks (ISHIB) consensus statement reviews multiple studies regarding the treatment of HT in Blacks. According to the ISHIB, there are minimal differences between thiazide-type diuretics and CCBs regarding both the lowering of BP and clinical outcomes, with the exception of HF as discussed previously (Flack et al, 2010). The ACCOMPLISH trial was the first study with a large sample population carried out amongst Blacks. This trial showed that combination therapy using an ACE-I/CCB had improved BP control and a 2.2% risk reduction in CVE as compared to an ACE-I/diuretic (Jamerson et al, 2008; Flack et al, 2010).

1.2.15.2 Diabetic and non-diabetic nephropathy

The SAHG recommend that the combination of a thiazide diuretic and BB be avoided in DM because of the diabetogenic effects of these drugs together (Wright Jr et al, 2002; Lorell & Carabello 2000; Pewsner et al, 2007). This is supported by findings in a report that reviewed the evidence of numerous well known clinical trials. Collectively, data showed that thiazide diuretics and BBs increase risk for new onset diabetes (Sowers & Bakris, 2000). Another study showed conflicting data with regards to the diabetogenic risk of thiazide diuretics. It was found that the risk of DM among subjects taking a thiazide diuretic was not greater than those taking no

medication. However, the metabolic risk associated with the use of a BB was reproduced, with data showing a 28% higher risk to developing DM. The possible explanation for the conflicting data on risk associated with a thiazide is that other studies failed to account for coexistent HT in the subjects, which in itself is a risk predictor of DM (Gress et al, 2000).

Guidelines thus recommend the use of an ACE-I or ARB in combination with a thiazide like diuretic or CCB. HT and DM are extremely important causes of CKD and ESRD as discussed earlier in the literature review. Thus, the prevention of ESRD requires appropriate treatment of these chronic diseases, with the primary goal of monitoring and reducing albuminuria. Reduction of proteinuria, which includes both microalbuminuria and overt proteinuria are the targets of therapy. The SAHG recommend the use of an ACE-I or ARB in all patients with microalbuminuria or advanced nephropathy. Studies have shown that ACE-Is and ARBs prevent the onset and reduce the progression of microalbuminuria in type 2 DM. Data supporting the reno-protective effects of an ACE-I include the BENEDICT A and B trials. The BENEDICT study compared the use of an ACE-I/CCB combination versus both of these drugs used individually. The outcome measure, being a delay in onset of microalbuminuria, was similar in the combined therapy and the ACE-I monotherapy groups. However, the BENEDICT B study assessed patients with baseline microalbuminuria and measured the rate of persistence macroalbuminuria. Results showed that combination ACE-I/CCB therapy did not improve outcome as compared to an ACE-I alone (Ruggenenti et al, 2004; Ruggenenti et al, 2011). The reno-protective effect of ACE-I monotherapy is emphasized in another study whereby a doubling in serum creatinine in the ACE-I group as compared to the placebo group was 12% and 21% respectively. This study showed a 50% decline in mortality with

the use of an ACE-I (Lewis et al, 1993). The use of an ACE-I/CCB combination is more effective than an ACE-I/diuretic in preventing a doubling of serum creatinine (Bakris et al, 2010). Numerous studies have shown reno-protective effect of ARBs (Parving et al, 2001; Lewis et al, 2001; Kunz et al, 2008; Haller et al, 2011). A meta-analysis of 49 RCTs showed that ACE-Is and ARBs reduced albuminuria to a similar degree, with the combination of both resulting in a more pronounced reduction (Kunz et al, 2008). However, as stated earlier, this treatment regimen is not advisable.

Once CKD stage 4 or 5 is detected, guidelines recommend a loop diuretic such as furosemide to be prescribed twice a day, whilst continuing with the ACE-I or ARB. Precautionary measures should be taken when using the ACE-I in these patients in order to avoid failure of diagnosing hyperkalaemia.

1.2.15.3 Resistant Hypertension

The cornerstone of management in resistant HT is finding the cause. The SAHG recommend lifestyle modification and adherence to therapy prior to the addition of a fourth line drug. These drugs include the following (SAHG, 2011: Seedat & Rayner, 2012):

- direct vasodilators: hydralazine and minoxidil
- centrally acting drugs: methyldopa and moxonidine
- α-blockers: doxazosin
- β-blockers: many cardio-selective agents are available
- aldosterone antagonist: spironolactone and eplerenone

Results from the 1998 SADHS showed that approximately 75% of all antihypertensive drugs prescribed were from the first line class, 24.4% were antiadrenergic agents of which methyldopa constituted 14.8%, reserpine 7.3% and peripherally acting agents 1.5% (Kearney et al, 2005). The ASPIRANT trial was

designed to assess the effect of the addition of spironolactone on patients with resistant HT. Results showed a significant decrease in all measurers used to assess SBP, but the reduction in DBP was found to be insignificant (Václavík et al, 2011).

1.2.16 Follow Up

The 2011 SAHG are developed from the ESH guidelines and do not provide detailed recommendations regarding follow up visits. According to guidelines, follow up BP visits should only be done at three and six months once target BP has been achieved (Seedat & Rayner, 2012). This is based on evidence provided by a RCT conducted in Canada, where it was shown that these follow up intervals were equivalent with regard to mean BP, patient satisfaction, and adherence to treatment (Birtwhistle et al, 2004).

Guidelines do not specify a rigid time frame with regard to subjects with elevated BP, but it is clear that the failure to achieve target BP should be followed up within three months depending on the severity (Seedat & Rayner, 2012; Mancia et al, 2013). Subjects with features suggestive of subclinical organ damage require more frequent follow up. A two to four weekly follow up is required after initiating new drug therapy (Mancia et al, 2013). Follow up of asymptomatic severe HT should be within two to four weeks. Hypertensive urgency and emergency requires urgent admission and gentle BP control (Seedat et al, 2012). The ESH further specifies that if target BP is not achieved, the physician should actively search for a cause and manage the patient appropriately depending on their findings (Mancia et al, 2013).

1.3 AIMS AND OBJECTIVES

1.3.1 Aims

The aim of this study was to determine if target blood pressure in the selected group of hypertensive patients was achieved and to determine the level of compliance of the healthcare staff to national hypertension guidelines with a view to improving long term management of hypertensive patients.

1.3.2 Study Objectives

This study had two objectives. The **primary objective** was to determine the number of patients in who target blood pressure was achieved in accordance with the 2011 SAHG. The **Secondary objectives** of the study were to:

a) Describe the study population;

b) Determine compliance to the SAHG with regards to routine investigations carried out on patients and follow up scheduled;

c) Compare the differences between the group of patients that achieve target BP and those that fail to achieve target BP, specifically within the following parameters:

    a. Demographics;

    b. BMI;

    c. Evidence of TOD including proteinuria, serum creatinine and GFR;

    d. Co-morbidities;

    e. Number of antihypertensive drugs and class of antihypertensive drugs;

d) Assess the appropriateness of antihypertensive therapy being prescribed by clinicians; and

e) Determine the presence of any co-existing diseases:

    a. Type 2 diabetes mellitus;

b. Dyslipidaemia;

c. Chronic kidney disease.

CHAPTER 2: METHODS AND MATERIALS

2.1. Study Design

The study was a retrospective observational transverse clinical audit which has descriptive and comparative elements.

2.2. Study Setting

The study was conducted at the specialised Hypertension Clinic in the state run Helen Joseph Hospital, previously known as J. G. Strydom before 1997. The hospital, located in Auckland Park, Johannesburg, was a level 3 academic hospital before it was re-categorised as a tertiary hospital in January 2013. It provides services to approximately 1 million patients who are of the middle and low income financial classes, the majority of whom cannot afford private healthcare. While it has 484 approved beds, in February 2014, 539 in-patient beds were in use, thus highlighting the over utilisation of available resources. The hypertension clinic, open every Friday, is managed by the department of medicine.

2.3. Study population

Based on the profile of patients who utilise this hospital, the study assumes that those attending the Hypertension Clinic do not have health insurance and are from a lower socio-economic status.

2.3.1. Inclusion Criteria

a) Patients attending the specialist Hypertension Clinic;
b) Essential / Primary Hypertension; and
c) Managed with antihypertensive treatment for a minimum of one year prior to data collection.

2.3.2. Exclusion Criteria

a) Secondary Hypertension; and

b) Less than one year of antihypertensive treatment.

2.4. Sampling Method

A convenience sampling method was used.

2.5. Sampling Size

The sample population of 300 patients was chosen based on the database at the Hypertension clinic over the three-month study period. An estimated 420 patients booked at the specialised clinic for the 3-month period of January to March 2012. Assuming a margin of sampling error of 5%, a confidence level of 95% and a response distribution of 50%, a sample size of 201 patients was calculated to be adequate for this audit. A sample size of 300 was selected with a resultant margin of error of 3.03%.

2.6. Sample Selection

Patients with essential hypertension, who have been on antihypertensive treatment for a minimum of one year attending the Hypertension Clinic at HJH between 1st January and 31s March 2012 were included in the study.

2.7. Testing procedures, Measurement tools and instruments

2.7.1 Testing procedures

a) After patients consulted the clinician, the files were returned to the clinic archive. Data was then extracted from patient records stored in the archive;

b) The following measures were taken to avoid repetitive selection of a file:

   a. After the record review and extraction of data, the files were marked;

   b. Each file had a hospital number with a corresponding study number.

c) Collection of data included using a data collection sheet designed to draw a comparison between patient investigations at the clinic as compared to South African National Hypertension Guidelines 2011, in addition to demographics, management and co-morbidities (see Appendix A).

d) BP control was assessed based on a single BP recording at the last patient visit, during the specified time frame of data collection, provided the patient was on antihypertensive therapy for more than a year.

2.7.2. Measurement tools: The Questionnaire (Appendix A)

a) The first part of the questionnaire gathered data relating to the demographics of the patient, including age, gender and race;

b) A single BP reading was documented to assess BP control;

c) The second section consisted of a table used to assess the compliance of the healthcare providers at the Hypertension Clinic to the national hypertension guidelines. The table was constructed based on the routine investigations recommended by the South African Hypertension Society as per the hypertension guidelines published in 2011. These routine investigations are listed in six categories as follows: (1) body weight, (2) abdominal obesity, (3) urine dipstick, (4) microalbuminuria, (5) blood tests as specified in the questionnaire and (6) a resting ECG. The questionnaire also includes the frequency of which each of these parameters were assessed at the clinic;

d) The third section was designed to collect data related to therapy which included the number and class of antihypertensive drugs that was prescribed by the clinician;

e) The final section provided information on related co-morbidities.

2.7.3. Measurement instrument

The questionnaire was designed based on the South African Hypertension guidelines 2011. In order to answer the objectives, the focus was predominantly on three aspects within the guidelines, as discussed below:

a) Goals of BP lowering treatment

1. Target BP varies depending on the patients' cardiovascular risk profile, TOD and ACC;
2. Target BP should be achieved within three-months of therapy;
3. In this study, patients were considered to have diabetes mellitus if the following criteria, based on the SEMDSA 2012 guidelines, were met:
    i. Previously diagnosed with DM;
    ii. Taking diabetic therapy in the form of oral hypoglycaemic medication or insulin;
    iii. HbA1c ≥6.5%;
    iv. Random plasma glucose of ≥ 11.1 mmol/L;
    v. Fasting plasma glucose of ≥ 7.0mmol/L was not used as this information could not be extracted from the file. Due to the retrospective nature of the study, it could not be ascertained if the documented glucose results were taken whilst the patient was fasting (Amod et al, 2012).

b) Renal disease was assessed based on 2 criteria:

1. Microalbuminuria with an albumin: creatinine ratio of 3-30mg/mmol defined as TOD or albuminuria >30mg/mmol defined as ACC;
2. Elevated serum creatinine varying depending on sex:
    i. Men: 115-133umol/L (TOD); >133umol/L (ACC);

ii. Women: 107-124umol/L (TOD); >124umol/L (ACC)

3. eGFR using the MDRD formula as described in detail in the literature review.

Table 6: Goals of BP-lowering treatment

Stage	BP level
All stages	<140/90
High risk patients Diabetes mellitus Renal disease** Congestive heart failure **Microalbuminuria and/or elevated creatinine	<130/80

Source: The South African Hypertension Guideline 2011 (Seedat & Rayner, 2012)

c) Recommended routine basic investigations:

- Recommended routine investigations with suggested frequencies were assessed based on the hypertension guidelines

Table 7: Recommended routine basic investigations

Investigation	Clinic frequency	Comments
Body weight/overweight		
Body weight	Every visit	
Height	First visit	
BMI	Every visit <25kg/m²	
Abdominal obesity		
Waist circumference OR	Every visit	Men <94cm and women<80cm
Waist to hip ratio		Waist to hip ratio has a better predictive value than BMI
Urine dipstick		
Protein	First visit	
Blood	Yearly if normal	Abnormal dipstick :
Sugar	Repeat at next visit if abnormal	Proteinuria ≥ 2+ Haematuria ≥ 1+
Microalbuminuria		
Diabetes mellitus and selected hypertensives	First visit then yearly	Performed on DM type 2 or 5 years after type 1 DM diagnosis

Blood tests		
Creatinine	Yearly if normal	Calculate eGFR using MDRD
Potassium	Yearly if normal	
Glucose (fasting preferred)	Yearly if normal	Consider GTT in patients with fasting glucose >6.1mmol/L
Random total cholesterol	Yearly if normal	Measure fasting lipogram if cholesterol >5.1mmol/L or in high risk groups
ECG(resting)	Yearly if normal	

Source: The South African Hypertension Guideline 2011 (Seedat & Rayner, 2012)

d) Recommended drug therapy

2.8. Data Analysis

a) Demographics: descriptive statistics was used in the form of parametric and non-parametric measures;

b) Comparison of BP between the controlled versus uncontrolled group: BP is a continuous variable and the unpaired t-test was used;

c) The Chi square test was used to test the relationship between two categorical variables. A Fischer's exact test was used when comparing nominal variables and a Pearson's correlation co-efficient was used to assess the correlation between variables.

2.9. Ethics

a) The protocol was submitted for ethics approval to the relevant governing committees: Postgraduate Committee of the University of the Witwatersrand and the Human Research Ethical Committee of the University of the Witwatersrand. The ethical clearance certificate is attached in Appendix B.

b) The consent forms from the necessary Heads of Departments and Chief Executive Officer are attached in the appendix (Appendix C, D & E).

CHAPTER 3: RESULTS

Data from 300 patients attending the Hypertension clinic at HJH were analysed.

3.1 Demographics

The demographic profile of the study population is highlighted below.

3.1.1 Age and Gender

Females comprised the majority of the study population and the highest prevalence of race in both sexes was African. The median age of the study group was 63 years, with a mean age of 63.19 years and a mode of 58 years of age. The standard deviation (SD) was ±12.026 years of age. The sample age ranged from 29 to 93 years. The median was used in analysing data due to its statistical robustness and its immunity to outlier influence. One subject was less than 30 years while 177 were older than 60 years.

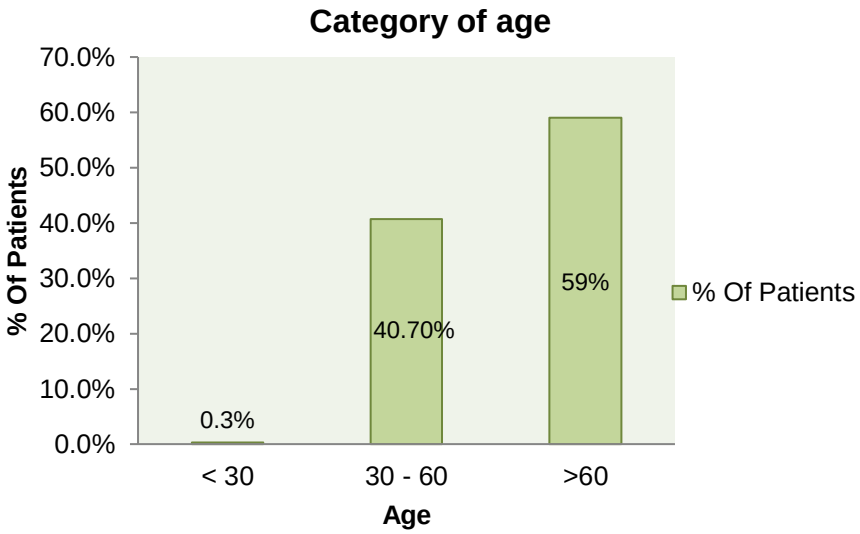

Figure 1: Category of age distribution in the total number of hypertensive patients

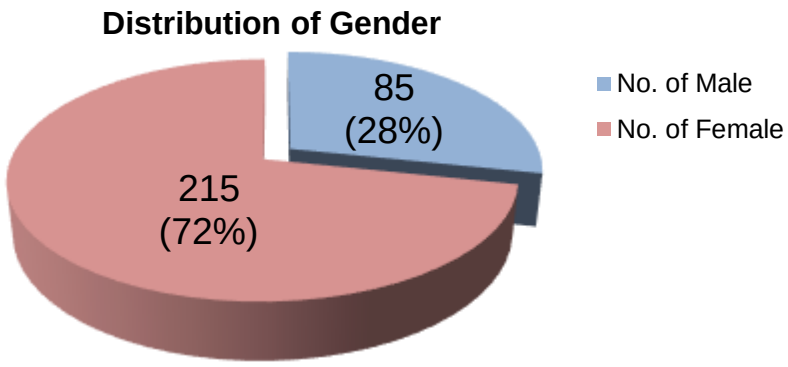

Figure 2: Distribution of gender in the total number of hypertensive patients

Table 8: Demographic data for the total sample population of hypertensive patients

Parameters	Results
Total no. of patients	200
Gender	
Males	85 (28%)
Females	215 (72%)
Age (years)	
Total Mean ± SD	63.19 ± 12.03
Median	63
Mode	58
Range	29-93
Male Mean ± SD	60.66 ± 12.67
Female Mean ± SD	64.19 ± 11.64

3.1.2 Race

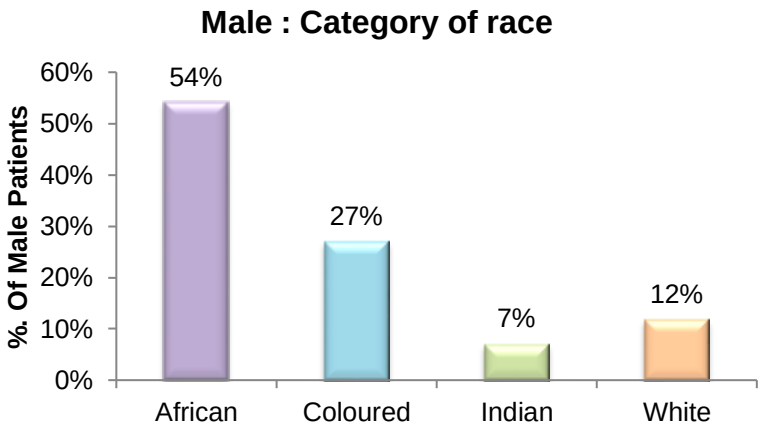

Figure 3: Category of race distribution in males

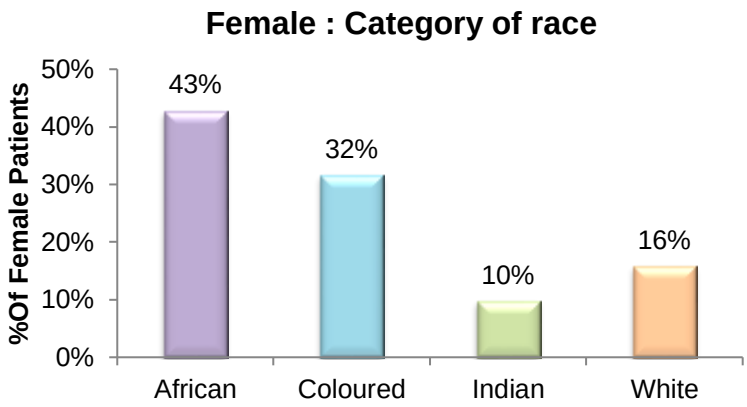

Figure 4: Category of race distribution in females

3.2 Co-morbidities and Major Risk factors

As discussed in the literature review, risk stratification is based on the level of BP and the number of major risk factors. Specified age categories, DM, dyslipidaemia and degree of obesity are some of the major risk factors that were analysed.

3.2.1 Age

The lower limit of age as a CV risk factor differs between women and men, with the age of 65 and 55 years as the threshold respectively.

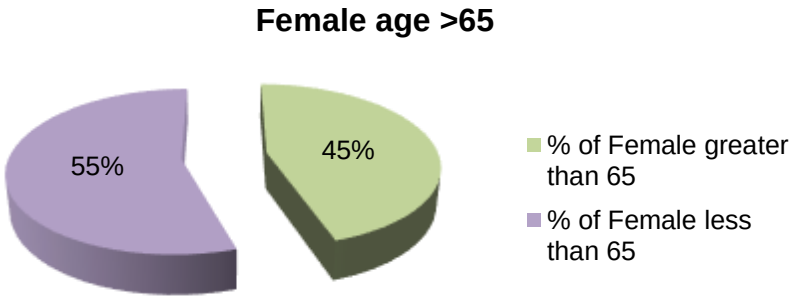

Figure 5: Distribution of total female hypertensive patients defined by CV risk

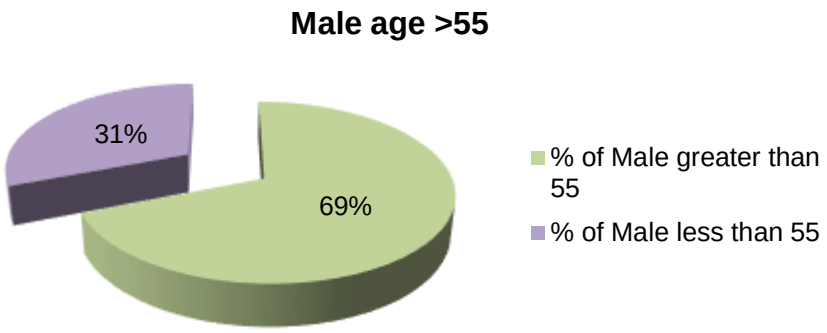

Figure 6: Distribution of total male hypertensive patients defined by CV risk

3.2.2 Diabetes Mellitus

Of the 300 patients, 28% (n=85) had co-morbid DM, 54% (n=161) were not diabetic and 18% (n=54) were unknown. The unknown patients had never had a random glucose or haemoglobin A1c (HbA1c) ever recorded in the patient records. Females comprised the majority of hypertensive patients with co-morbid DM, contributing to 74% (n=63) of the diabetic subgroup, whilst males contributed 26% (n=22). 71% (n=114) of the non-diabetic patients were female and 29% (n=47) were male. Females contributed 70% (n=38) of the unknown subgroup, whilst males constituted 30% (n=16).

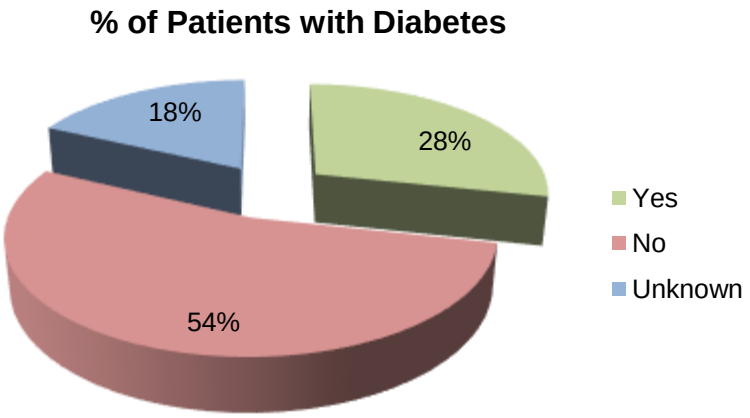

Figure 7: Distribution of total hypertensive patients with co-morbid diabetes mellitus

3.2.3 Dyslipidaemia

In the total sample population, 66% patients (n=198) were dyslipidaemic, with females contributing 74% (n=146) of this group and males comprising 26% (n=52). 30% (n= 89) did not have co-morbid dyslipidaemia, with females and males contributing 65% and 35% (n= 58; n=31) of this group respectively. There was no record of a lipogram in 4% (n= 13) of the study population.

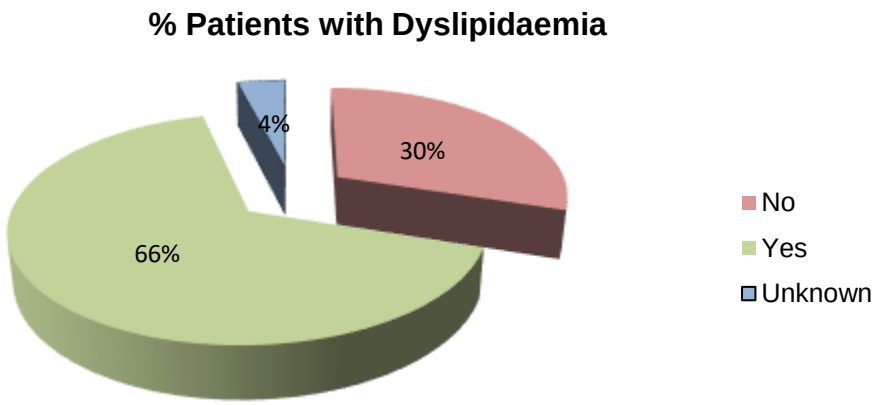

Figure 8: Distribution of total hypertensive patients with co-morbid dyslipidaemia

3.2.4 Body Mass Index (BMI)

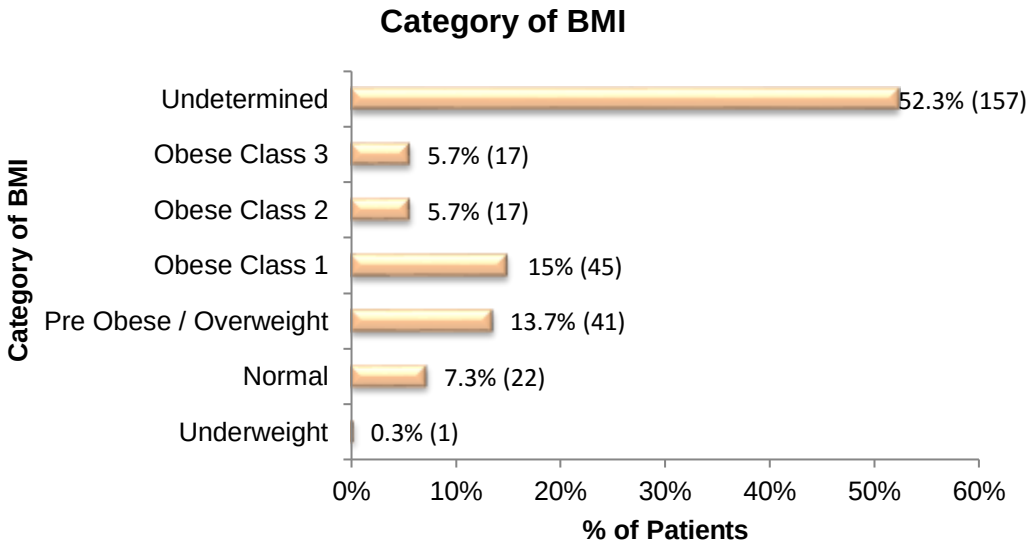

Figure 9: Distribution of BMI categories in the total hypertensive population

3.3 Blood Pressure and Hypertension

The mean systolic and diastolic blood pressure was 137.1 and 78.1mmHg respectively. The prevalence of HT among the various grades of HT as well as specific HT groups including ISH and resistant hypertension, are outlined below.

3.3.1 Mean Systolic and Diastolic Blood Pressure

Table 9: Systolic and Diastolic Blood Pressure with gender distribution

Parameter	BP
Mean BP	
Mean Systolic BP	137.1
Mean Diastolic BP	78.1
Male	
Mean Systolic BP	133.8
Mean Diastolic BP	80.6
Female	
Mean Systolic BP	138.3
Mean Diastolic BP	77.1

3.3.2 Grades of Hypertension

Normal BP was recorded in 40% (n=120) of the hypertensive patients, with females and males contributing 66% and 33% (n=80; n=40) of this category respectively. A total of 60% (n=180) of patients had a BP recording distributed between high normal to stage 3. The distribution of 135 female patients between the categories of high normal to stage 3 HT, in ascending order of severity of HT was 18% (n=39); 22% (n=48); 16% (n=34) and 7% (n=14) respectively. A total of 45 male patients had a BP recording that was categorised between high normal and stage 3 HT. The distribution was 18% (n=15); 25% (n=21), 6% (n=5) and 5% (n=4) in the respective order of increasing severity for the various grades of HT.

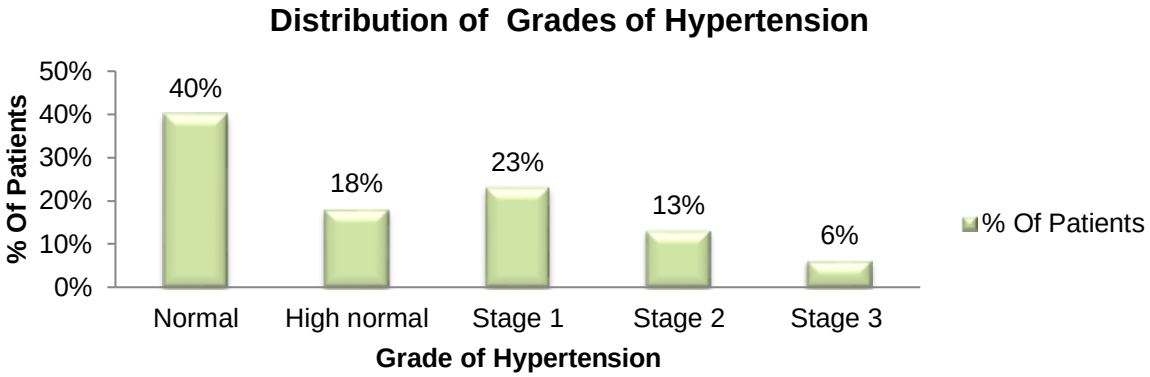

Figure 10: Distribution of the total sample population of hypertensive patients among the various grades of hypertension

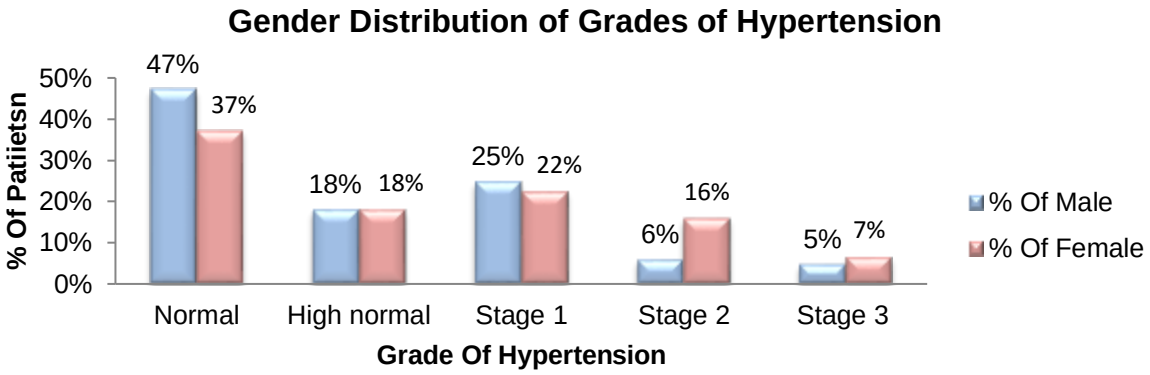

Figure 11: Gender distribution of the various grades of hypertension

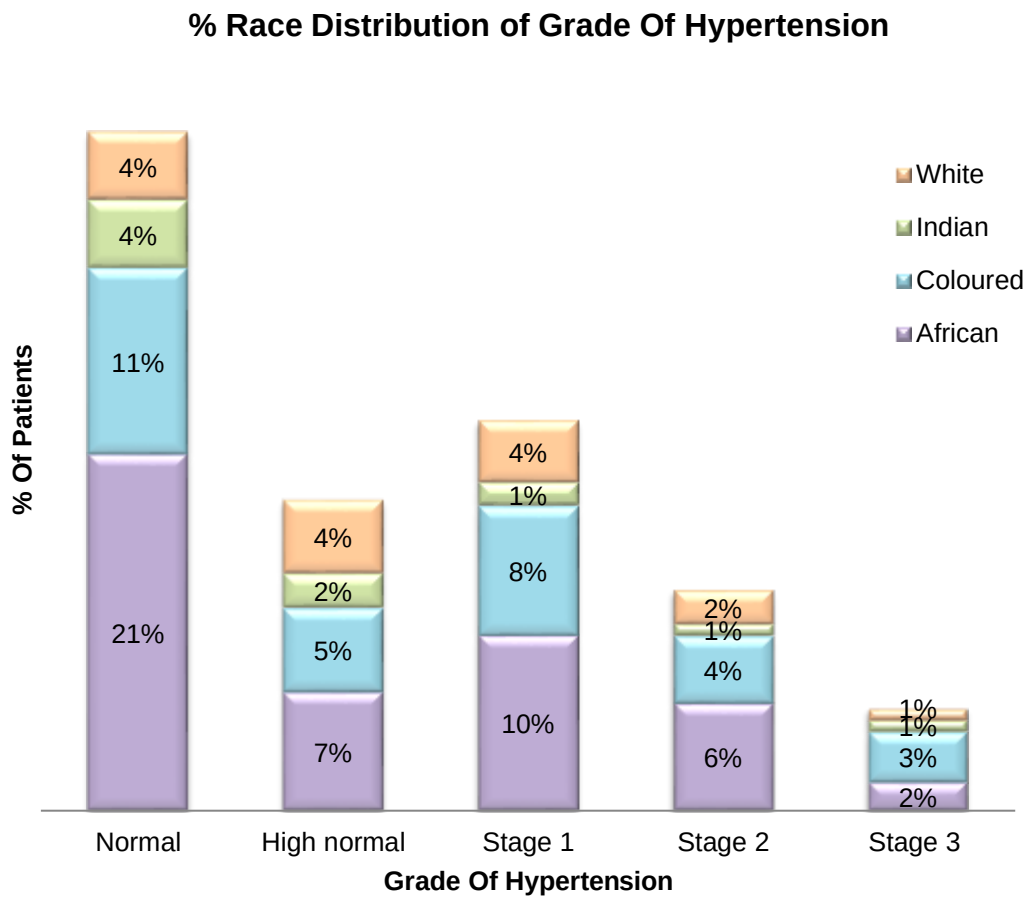

Figure 12: Race distribution of the various grades of hypertension

3.3.3 Isolated Systolic Hypertension (ISH)

A total of 21% (n=64) patients had ISH, with the major contribution of this total from age 60 to 74 years (n=37). A total of 84% (n=54) of patients with ISH were older than 60 years of age. There is a significant difference between categories of age >60 years and ≥30-≤60 ($p < 0.001$). There is insufficient data to compare the other category of less than 30.

DM was co-morbid with ISH in 31% (n=20) of these patients. Of these diabetic patients with ISH, 85% (n=17), were older than 60 years.

A chi-square test for the association between DM and ISH in the age group > 60 years was conducted. There was no statistically significant association found ($x^2(1)$ = 2.759, p= 0.252).

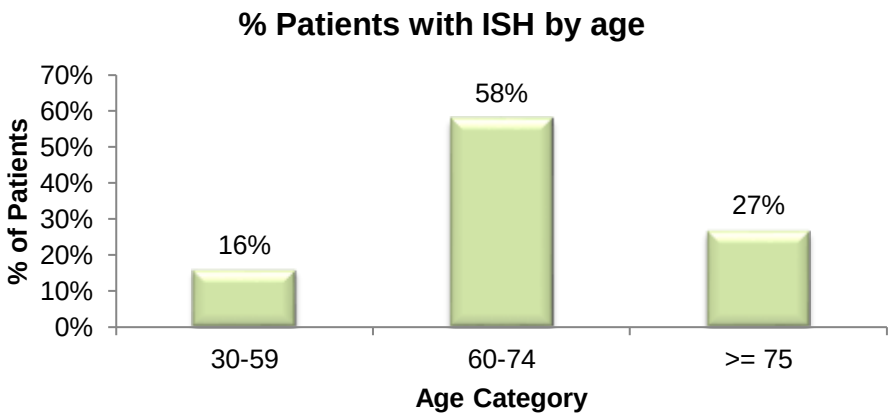

Figure 13: Distribution of ISH by age

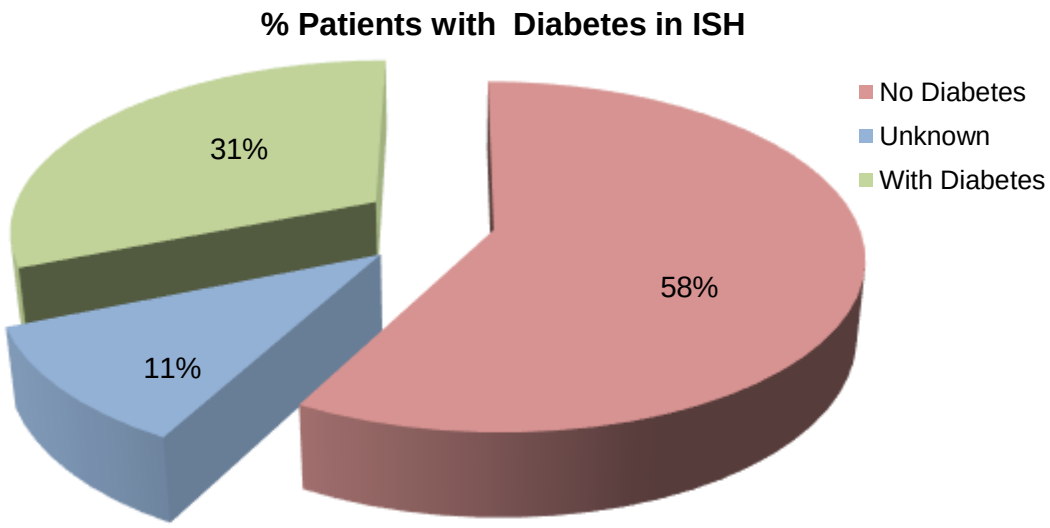

Figure 14: Distribution of Diabetes Mellitus in ISH

3.3.4 Resistant Hypertension

From the total sample population 21% (n=63) had resistant HT.

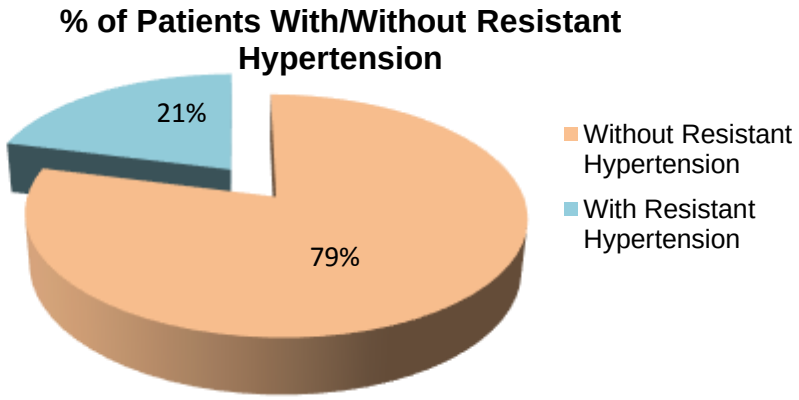

Figure 15: Distribution of Resistant Hypertension in the total sample population

3.3.5 Gender and Racial differences between Grades of Hypertension, ISH and Resistant Hypertension

Table 10: Gender and racial differences between grades of HT, ISH and Resistant Hypertension

Grade of HT	Total n=300	Female	Male	Race Total n=300	African	Indian	Coloured	White
High Normal	54	39	15	54	21	7	14	12
Normal	120	80	40	120	62	12	33	13
Stage 1	69	48	21	69	31	4	23	11
Stage 2	39	34	5	39	19	2	12	6
Stage 3	18	14	4	18	5	2	9	2
ISH	64	56	8	64	18	5	27	14
No ISH	236	159	77	236	120	22	64	30
Resistant HT	63	49	14	63	25	4	24	10
No Resistant HT	237	166	71	237	113	23	67	34

There were no significant differences for gender and race within the various categories of HT i.e. high normal, normal, stage 1, 2 and 3 (p=0.46 ; p=0.38) respectively.

With regards to gender and racial differences in resistant HT, there were no significant differences (p=0.23; p= 0.34) respectively.

A significantly higher prevalence of ISH was appreciated in females compared to males (p=0.001). Significant racial differences in ISH were notably higher in the African compared to the Coloured and White subgroups, (p=0.01; p=0.04) respectively.

3.4 Control of Blood Pressure

Target BP was achieved in 49% (n=148) of patients. A total of 52% (n=155) having SBP control and 72% (n=216) with DBP control.

3.4.1. Systolic and Diastolic blood pressure control

3.4.1.1 Total Controlled versus Uncontrolled

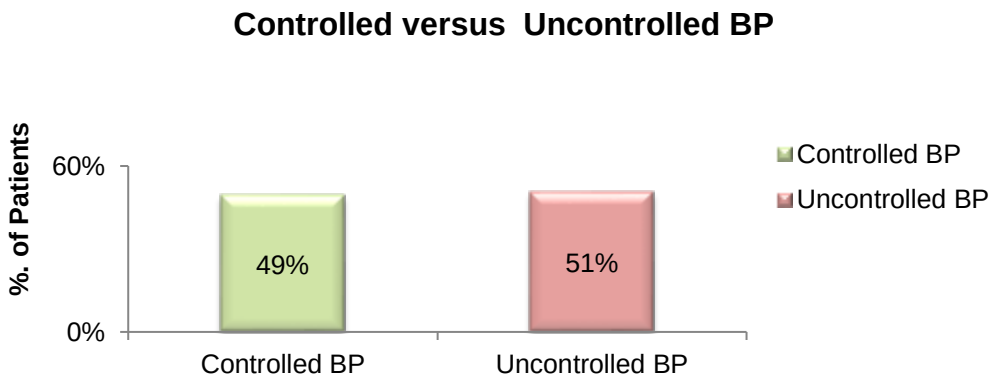

Figure 16: Distribution of control of BP in the total sample population

3.4.1.2 Systolic Controlled versus Uncontrolled

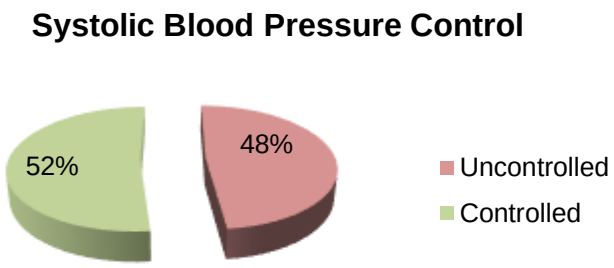

Figure 17: Distribution of systolic BP control in the total sample population

3.4.1.3 Diastolic Controlled versus Uncontrolled

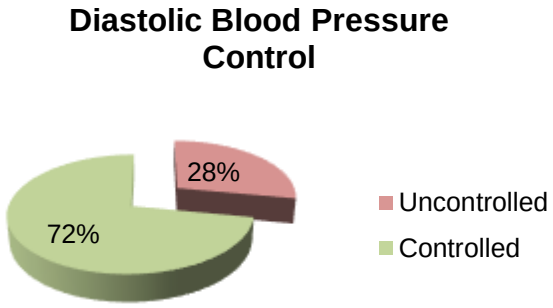

Figure 18: Distribution of Diastolic BP control in the total sample population

3.4.2 Control of Blood Pressure by demographic variables

Of the 148 controlled patients, females constituted 103 patients and the remaining 45 were male. Of the 152 uncontrolled patients, 112 were female and 40 were male. The distribution of uncontrolled versus controlled BP by race is shown in figure 20.

3.4.2.1 Age

Table 11: Mean and median age of total BP control

Mean Age of BP control	
Mean Age of controlled BP	61
Mean Age of uncontrolled BP	64

3.4.2.2 Gender

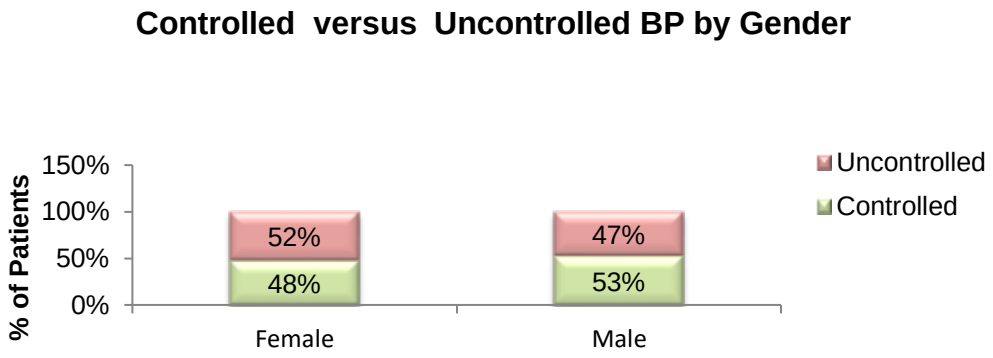

Figure 19: Distribution of control of BP by gender

Gender differences in BP control

Table 11: Gender differences in BP control

	Male	Female	Total	p-value
Controlled	45	103	148	0.45
Uncontrolled	40	112	152	0.26

Gender differences in Systolic and Diastolic BP control

Table 13: Gender differences in Systolic and Diastolic Mean BP control

	Male	Female	p-value
Mean SBP± SD	133.86 ± 22.59	138.36 ± 22.65	0.12
Mean DBP± SD	80.62 ± 14.61	77.14 ± 14.43	0.06

3.4.2.3 Differences in gender and age based on CV risk

There was no significant difference between the controlled and uncontrolled BP groups based on age > 55 years in males and age > 65 years in females (p= 0.52).

Table 14: Distribution of control of BP by gender and age based on CV risk

	Controlled	Uncontrolled
Male (>55 years)	31	31
Female (>65 years)	47	58

3.4.2.4. Race

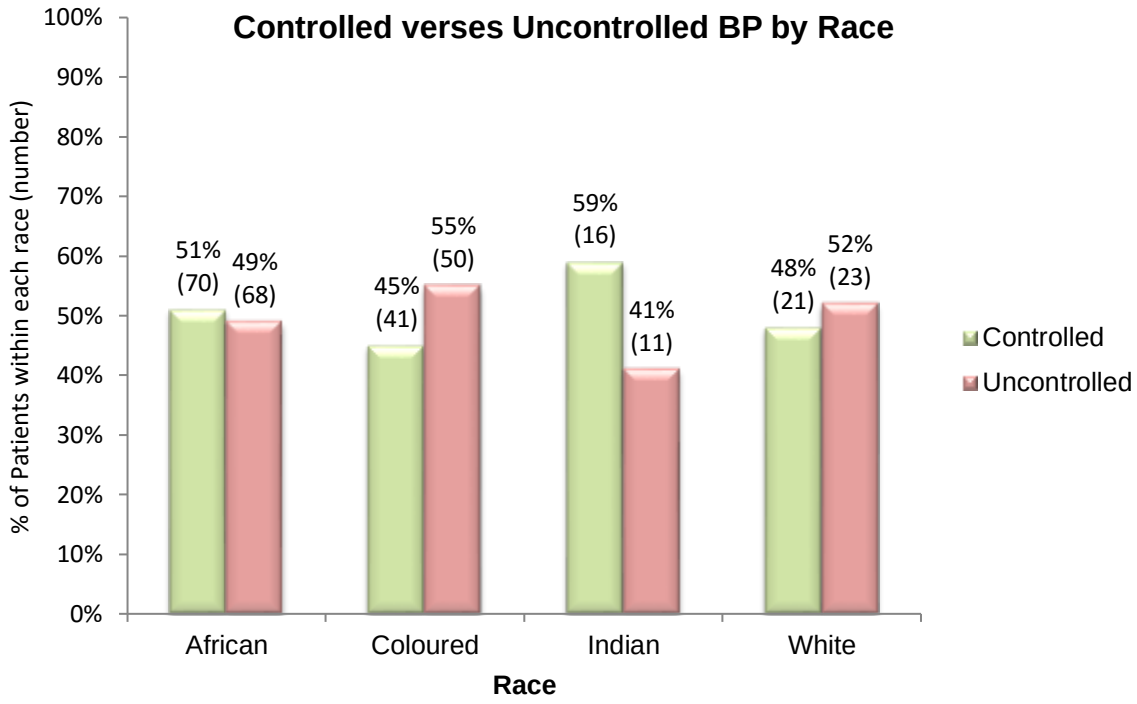

Figure 20: Distribution of control of BP by race

3.4.3 Control of Blood Pressure in patients with co-morbidities

3.4.3.1 Diabetes Mellitus

DM was co-morbid in 23% (n=34) and 33.6% (n=51) of the controlled and uncontrolled study groups, respectively. The distribution of DM in the controlled and

uncontrolled BP groups is shown in figure 21. The unknown group represented patients in whom the presence of DM was unknown. There was no significant difference in the prevalence of diabetes between the controlled and uncontrolled groups (p=0.11). Of the 34 controlled hypertensive diabetic patients, 23 were female and 11 were male. Of the 51 uncontrolled hypertensive diabetic patients, 40 were female and 11 were male. There was no significant difference in the total prevalence of diabetes in males and females (p=0.58).

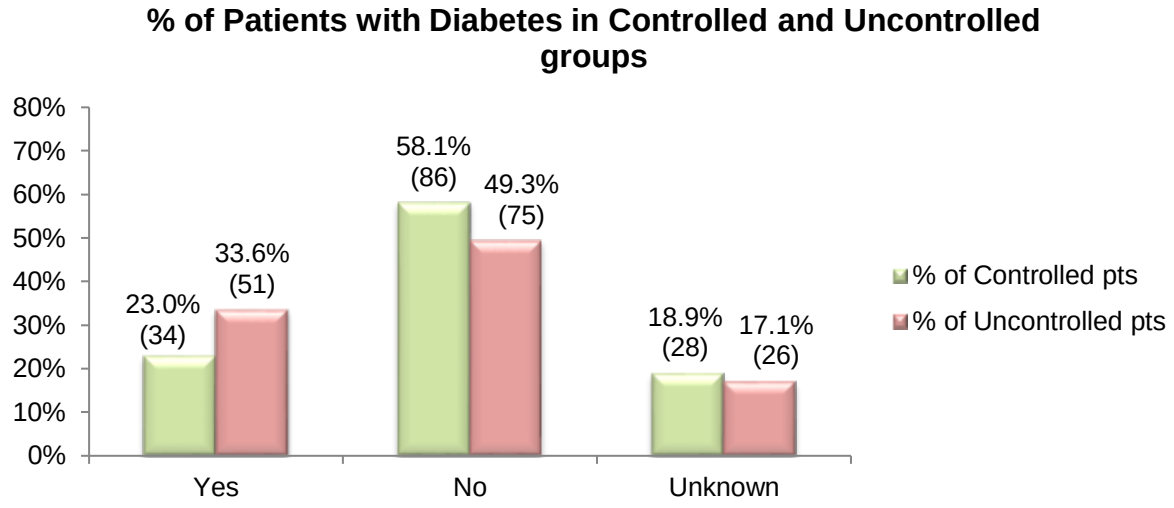

Figure 21: Distribution of control of BP with co-morbid Diabetes Mellitus

3.4.3.2. Dyslipidaemia

Dyslipidaemia was co-morbid in 60.8% (n=90) and 71.1% (n=108) of controlled and uncontrolled hypertensive patients respectively. The number of females and males in the controlled group that were dyslipidaemic were 63 and 27 respectively, compared to that in the uncontrolled group of 83 females and 25 males. The absence of dyslipidaemia in the controlled and uncontrolled hypertensive groups were 33.8% (n=50) and 25.7% (n=39) respectively. A total of 33 females and 17 males with controlled BP were not dyslipidaemic as compared to 25 females and 14 males with uncontrolled BP. The lipogram was not recorded in 5.5% and 3.3% of controlled and

uncontrolled hypertensive patients respectively. No significant difference was found in the prevalence of dyslipidaemia between males and females (p=0.59).

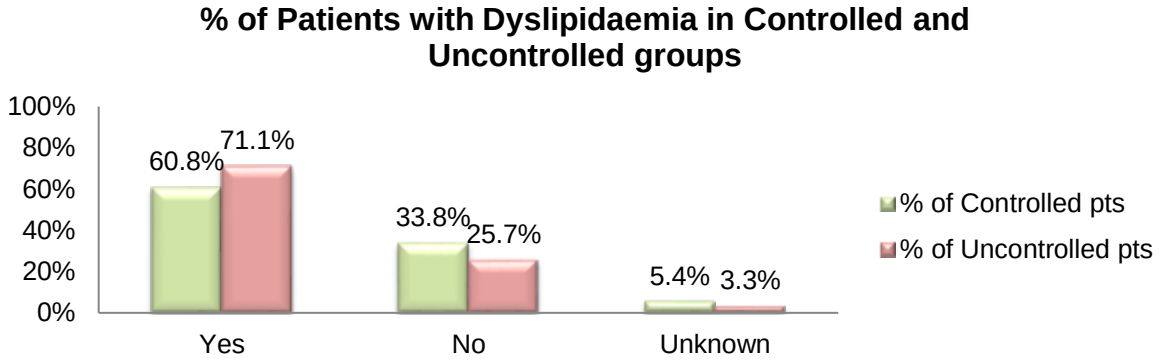

Figure 22: Distribution of control of BP with co-morbid dyslipidaemia

3.4.3.3 BMI categories

The categories of BMI were defined in the literature review. The BMI could not be determined in 52% (n=157) of the total study population. No significant difference was found in the prevalence of obesity between males and females (p= 0.41).

The distribution of patients BMI in the various categories is represented below.

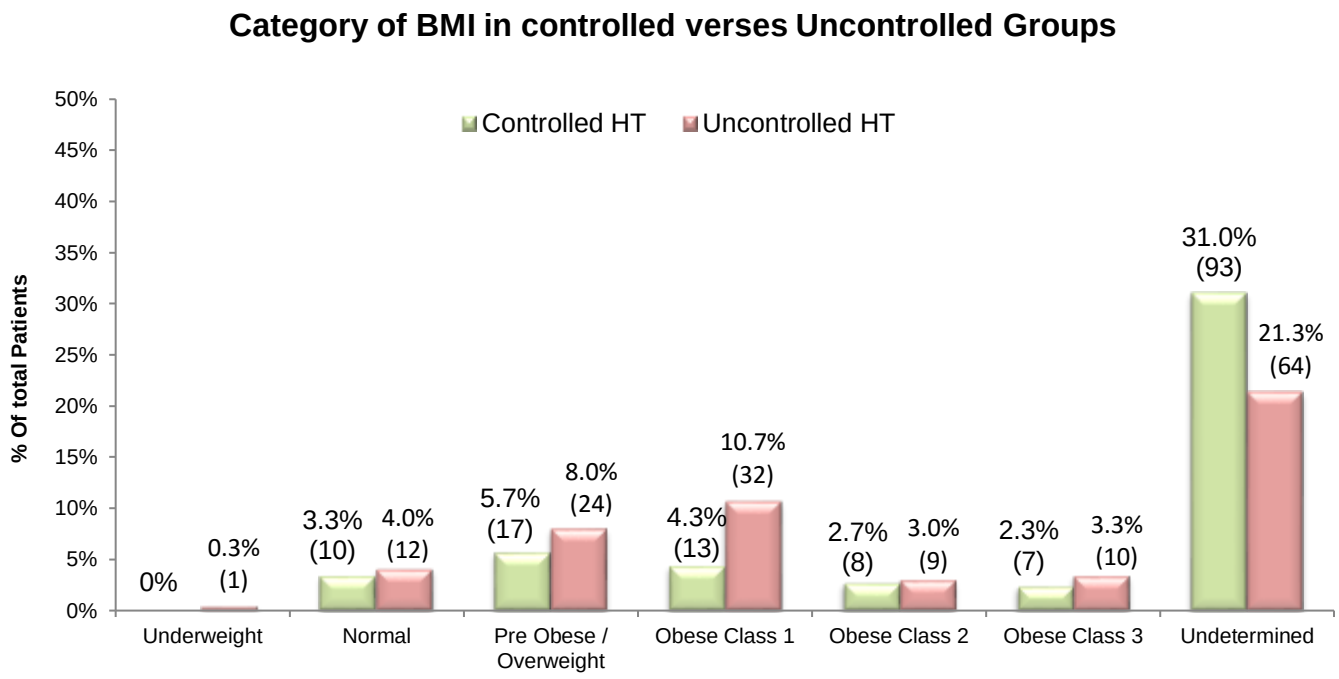

Figure 23: Category of BMI in controlled vs uncontrolled groups

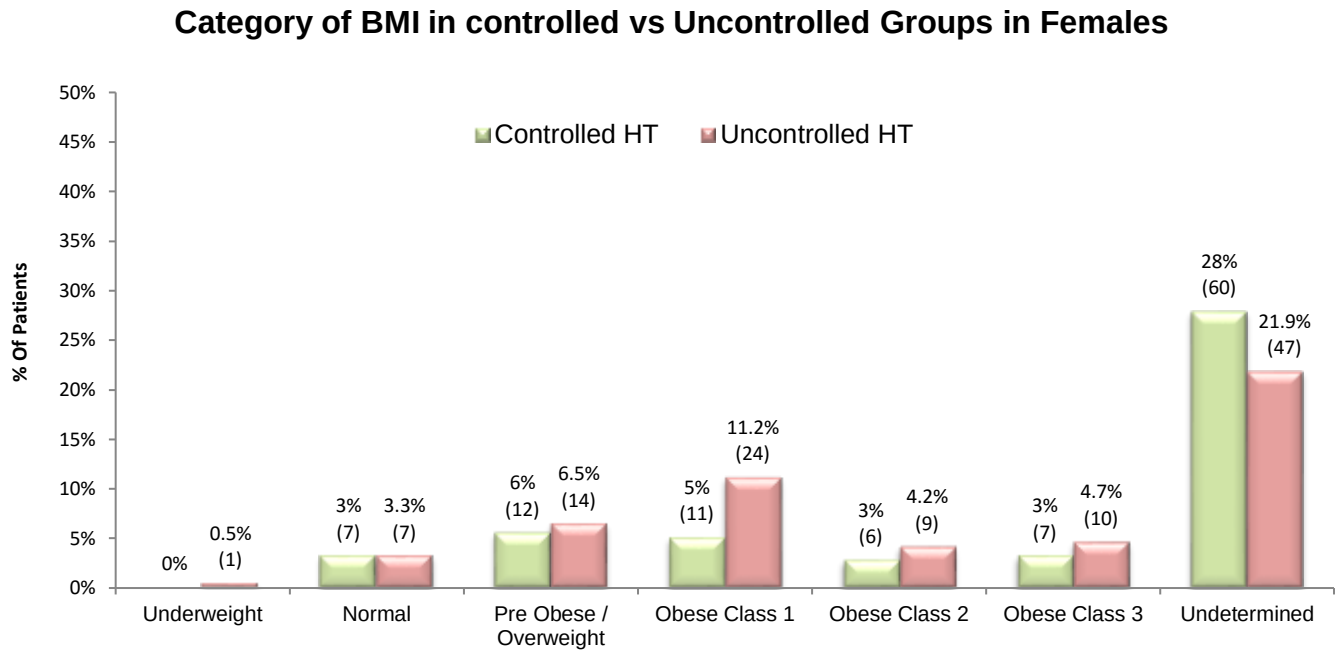

Figure 24: Category of BMI in controlled vs uncontrolled groups in females

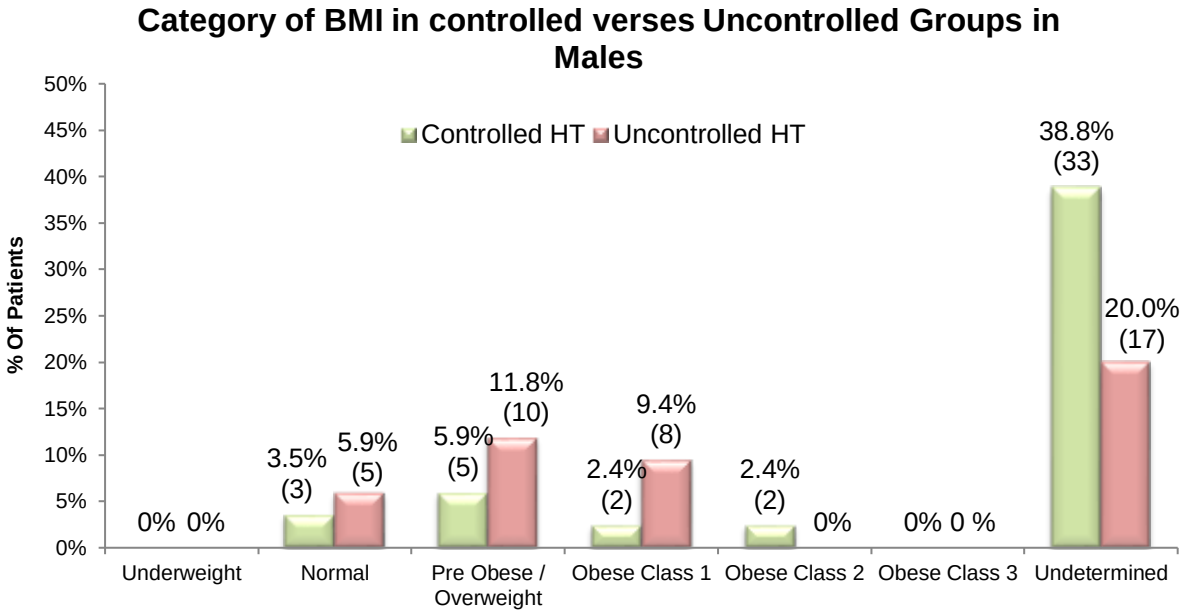

Figure 25: Category of BMI in controlled vs uncontrolled groups in males

3.4.3.4 Association between BMI and BP

Table 15: Association between BMI and BP for uncontrolled group (Pearson's correlation)

	BMI	BP
BMI	1	P= 0.02 R= 0.15

The above table indicates the association between BMI and BP for the uncontrolled group. There is very weak correlation between BMI and BP, (r= 0.15), which implies that there is no linear relationship between BMI and uncontrolled BP.

Table 16: Association between the various classes of obesity and BP control

	Class 1	Class 2	Class 3
Controlled	13	8	7
Uncontrolled	32	9	10

Overall p-value: there is a significant difference between the Controlled and Uncontrolled across the 3 classes, p= 0.01.

3.4.3.5 Association between Obesity, Diabetes and Uncontrolled BP

A Pearson Chi-square test of independence to assess the relationship between BMI Category (Obese classes 1-3) and DM in the group with uncontrolled BP showed that the relation between these variables was insignificant, ($x^2(1)$= 2.70, p= 0.84).

3.5 Target Organ Damage (TOD) and Chronic Kidney Disease (CKD)

3.5.1 Normal renal function, TOD and CKD

Creatinine is used as biomarker of TOD and the values used to classify TOD and CKD in males and females differ. These are discussed in the literature review. The creatinine of 6 patients was never recorded in the entirety of their hospital visits to the hypertension clinic. The creatinine results of the other 294 patients are not necessarily results obtained within the last year. In addition, abnormal urine dipstick results require further investigation.

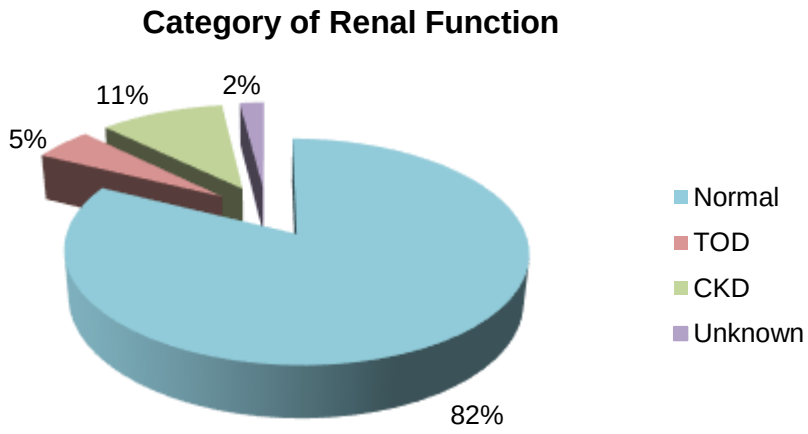

Figure 26: Category of renal function

3.5.2 Gender variation in creatinine

A total of 42% (n=128) of the sample population had normal creatinine levels. Within the controlled group of hypertensive patients, 86% had a normal creatinine. Of these patients, 92 females and 36 males had creatinine levels of < 107umol/l and <115umol/l respectively. There were 78% uncontrolled hypertensives with normal creatinine, of whom 96 were female and 23 were males. Creatinine of >124umol/l in females was present in 5 controlled and 11 uncontrolled hypertensive patients.

Whilst a creatinine of >133umol/l in males was present in 3 controlled and 13 uncontrolled hypertensive patients. An abnormal creatinine that did not meet criteria for CKD but rather TOD was found in 15 patients.

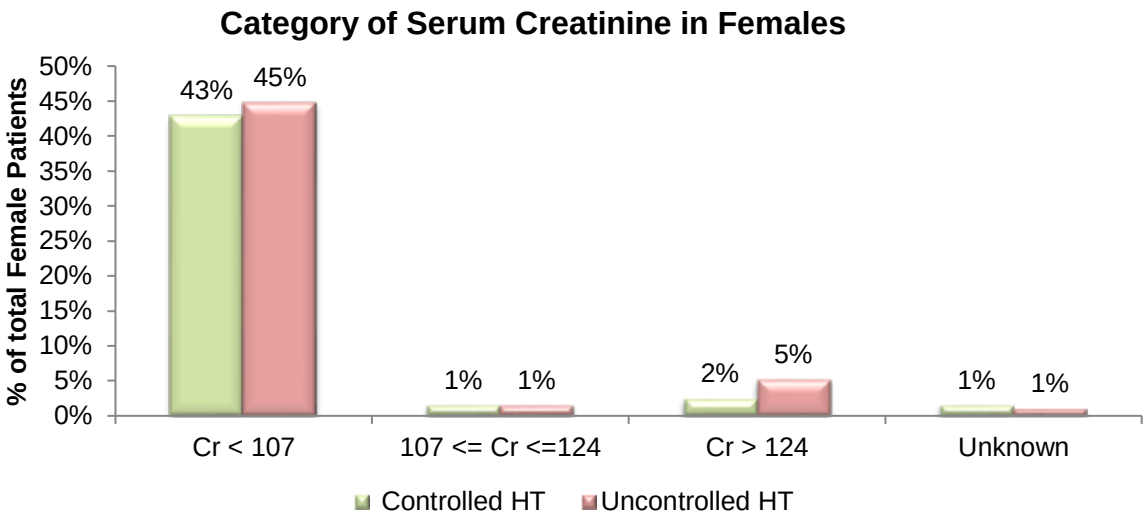

Figure 27: Category of Serum Creatinine in Females

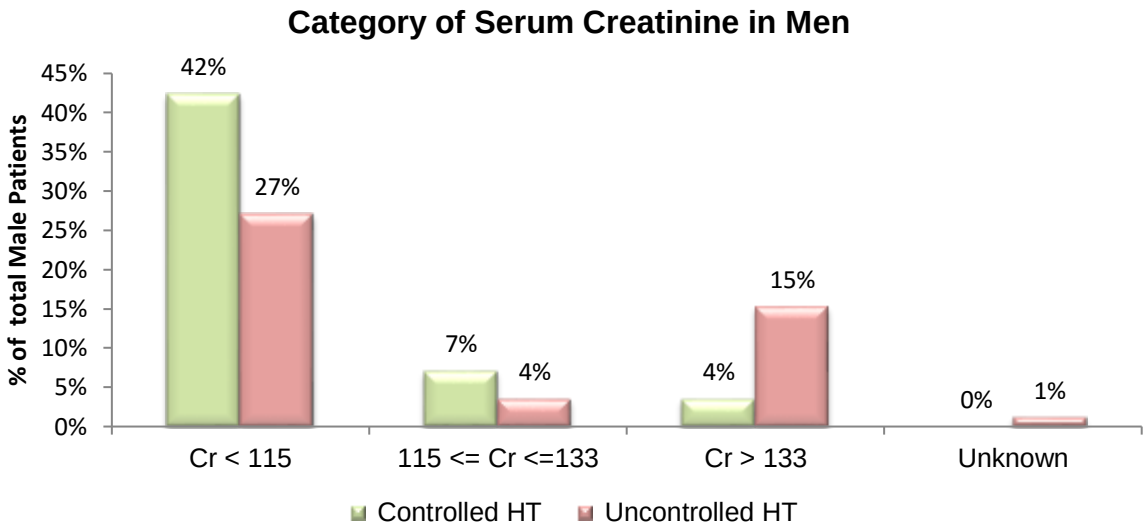

Figure 28: Category of Serum Creatinine in Men

3.5.3 eGFR in patients with abnormal creatinine

eGFR is inaccurate in patients with normal creatinine, thus eGFR was only analysed in those patients with abnormal creatinine. The in depth explanation for this is

highlighted within the literature review. Of the 47 patients with abnormal creatinine, 17 patients had controlled BP and 30 patients had uncontrolled BP. Of those with abnormal renal function, stage 3 CKD was present in 30% (n=14) and 43% (n=20) of controlled and uncontrolled patients respectively. Stage 4 CKD was present in 6% (n=3) and 13% (n=6) of controlled and uncontrolled hypertensives respectively. Stage 5 CKD was present in 8% (n=4) of uncontrolled hypertensives and was not present in any controlled subjects.

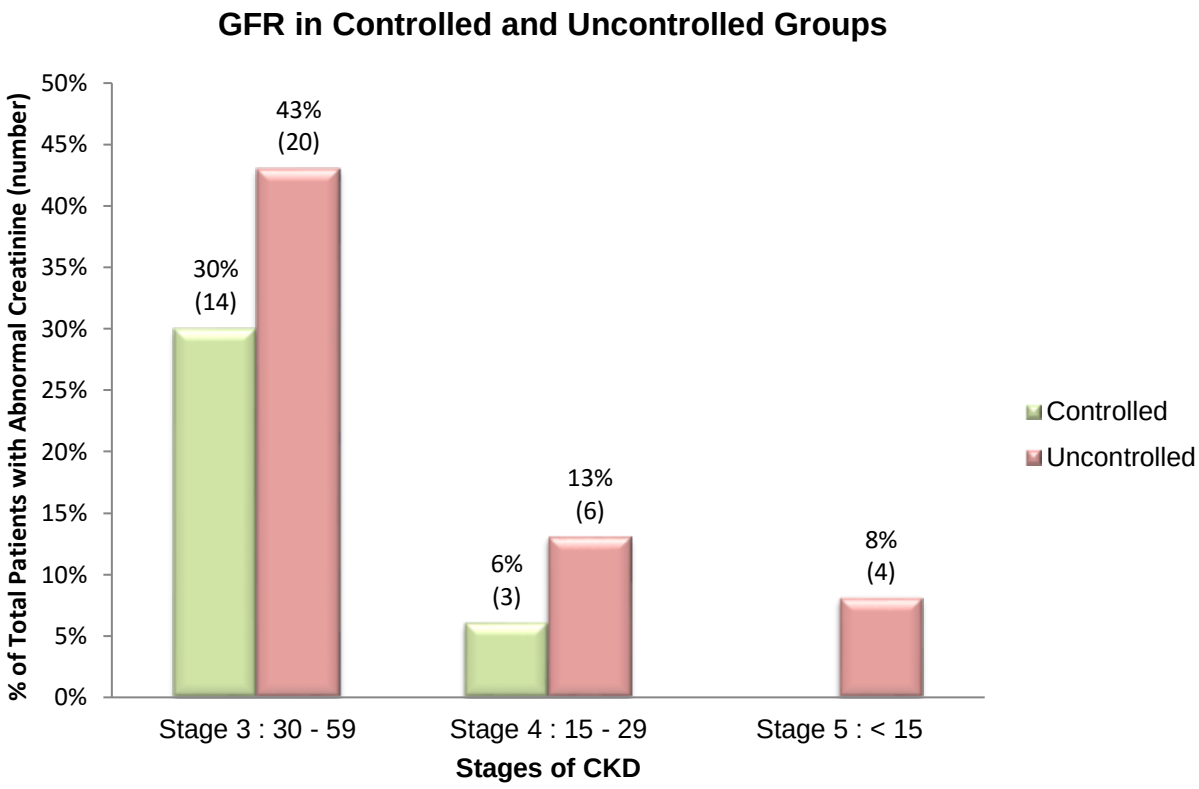

Figure 29: GFR in Controlled and Uncontrolled groups

3.5.4 Racial distribution of CKD

Table 17: Racial distribution of CKD

Race	Stage 3	Stage 4	Stage 5	Total
African	6	2	1	9
Indian	4	2	1	7
Coloured	17	3	1	21
White	7	2	1	10
Grand Total	34	9	4	47

The p-value for the differences in race is 0.93

3.5.5 Urine dipstick results

3.5.5.1 Abnormal urine dipstick

The 2011 SAHG consider the presence of ≥ 2+ proteinuria, or ≥ 1+ haematuria as an abnormal urine dipstick. Abnormal urine dipsticks were found in 10.4% (n=31), whilst 89.6% (n=266) were normal and 3 patients urinalysis was not performed.

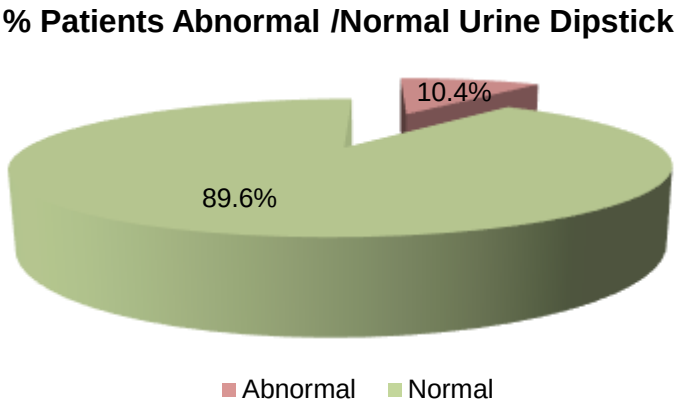

Figure 30: Percentage of abnormal/normal urine dipstick

3.5.5.2 Proteinuria

Proteinuria ≥ 2+ was found in 10 patients. Thus, from 300 subjects, 3% (n=9) were uncontrolled hypertensives and 0.3% (n=1) was controlled. Of these patients with ≥2

+ proteinuria, 4 were known diabetic patients, 2 were non-diabetic and the remaining 4 were unknown.

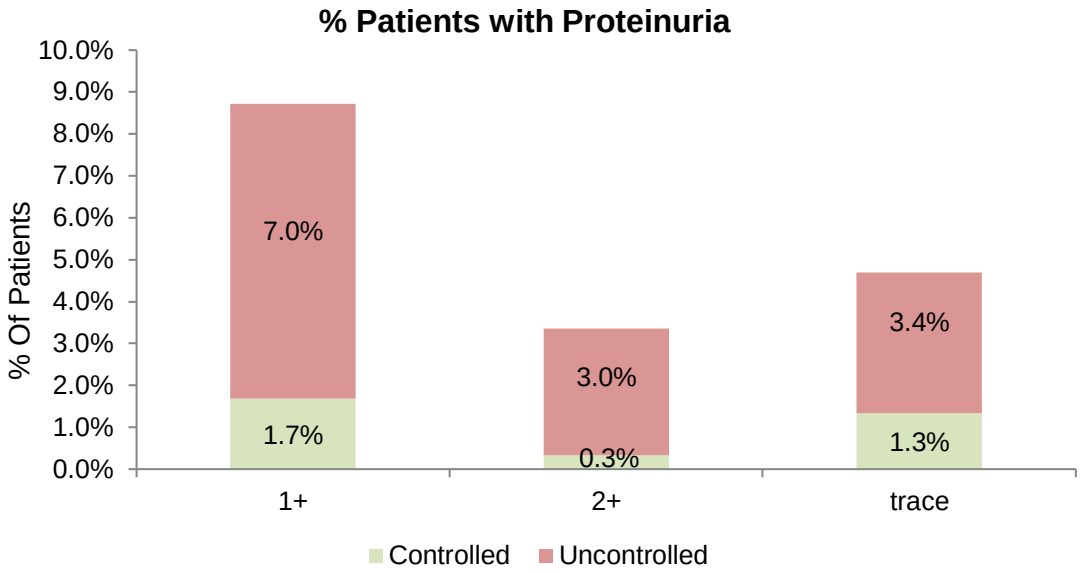

Figure 31: Percentage of patients with proteinuria

3.5.5.3 Haematuria

From the 300 sample population, 4 patients had ≥ 1+ haematuria.

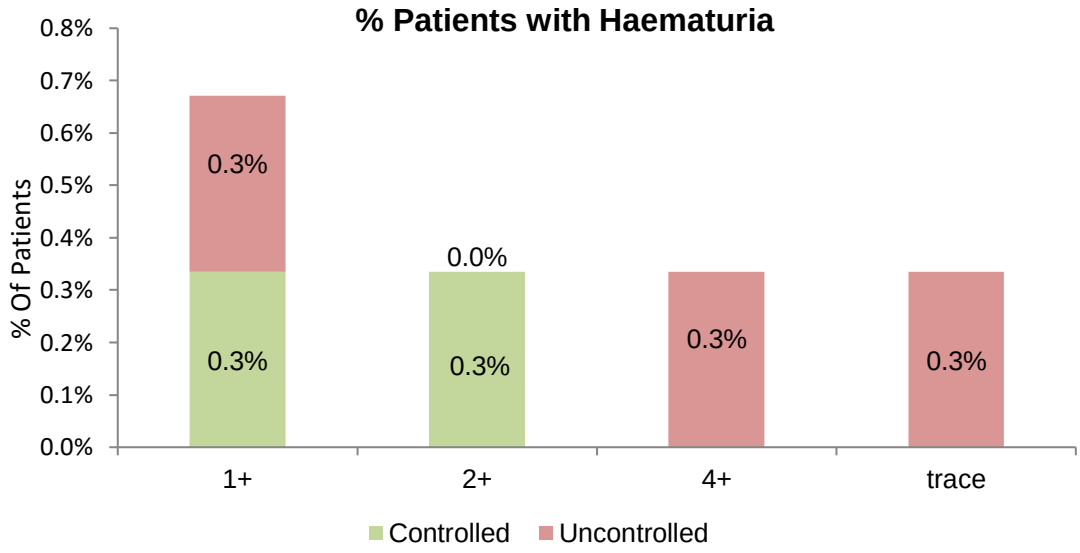

Figure 32: Percentage of patients with Haematuria

3.5.5.4 Glycosuria

A total of 18 patients had glycosuria. One of these patients was not diabetic and the remaining 17 were all known diabetic.

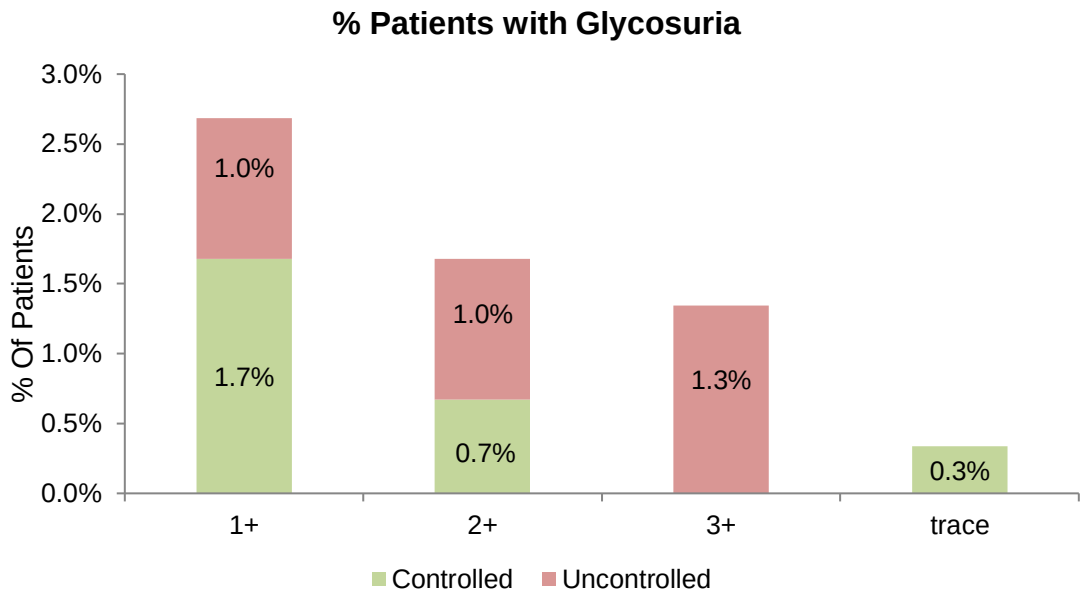

Figure 33: Percentage of patients with Glycosuria

3.6. Lipogram

A lipogram consists of 4 variables including Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL). The recommendations for the diagnosis of dyslipidaemia as well as the frequency of repeating the lipogram, as per SAHG 2011, are outlined in the literature review.

3.6.1 Total Cholesterol (TC)

According to the 2011 SAHG, target TC is <4.5mmol/l in high risk patients. A total of 49% (n=147) patients reached target TC as compared to 47% (n=141) that failed to achieve target TC. A TC was not documented in 4% (n=12) of patients.

Table 18: Total cholesterol level in mmol/l

Total cholesterol (mmol/l)	No. of Patients	% Of Patients	Mean Cholesterol (mmol/l)
≤ 4.5	147	49.0%	3.84
4.6 – 5.0	43	14.3%	4.8
5.1 – 6.0	69	23.0%	5.47
6.1 – 7.0	21	7.0%	6.51
≥ 7.1	8	2.7%	7.53
unknown	12	4.0%	-

3.6.2 Triglycerides

According to the 2011 SAHG, target TG in high risk patients is < 1.7mmol/l. A total of 65.3% (n=196) achieved target levels as compared to 29.3% (n=88) that failed to reach ideal levels. TG was not measured in 5.3% (n=16) patients

Table 19: Triglyceride level in mmol/l

Triglyceride (mmol/l)	No. of Patients	% Of Patients	Mean Triglyceride (mmol/l)
≤ 1.7	196	65.3%	1.17
1.8 - 2.5	60	20.0%	2.09
2.6 - 3.5	16	5.3%	2.99
3.6 - 4.5	9	3.0%	3.83
≥ 4.6	3	1.0%	7.56
Unknown	16	5.3%	-

3.6.3 High Density Lipoprotein (HDL) in females and males

The 2011 SAHG recommend a target HDL of > 1.2mmol/l in females and > 1mmol/l in males. A total of 41.4% (n=89) females achieved goal HDL as compared to 53% (n=114) who failed to reach target. In males, 56.5% (n=48) achieved ideal HDL levels as compared to 38.8% (n=33) who did not reach goal HDL.

Table 20: High Density Lipoprotein level in Females

HDL in Males (mmol/l)	No. of Patients	% Of Patients	Mean HDL (mmol/l)
≤ 1.0	33	38.8%	0.86
1.1 - 2.0	48	56.5%	1.36
2.1 - 3.0	0	0.0%	0
3.1 - 4.0	0	0.0%	0
≥ 4.1	0	0.0%	0
blank	4	4.7%	-

Table 2112: High Density Lipoprotein level in Males

HDL in Males (mmol/l)	No. of Patients	% Of Patients	Mean HDL (mmol/l)
≤ 1.0	33	38.8%	0.86
1.1 - 2.0	48	56.5%	1.36
2.1 - 3.0	0	0.0%	0
3.1 - 4.0	0	0.0%	0
≥ 4.1	0	0.0%	0
Unknown	4	4.7%	-

3.6.4 Low Density Lipoprotein (LDL)

The 2011 SAHG recommend a LDL goal of <2.5mmol/l. A total of 47.3% (n=142) achieved ideal LDL values, whilst 47% (n=141) did not reach target LDL.

Table 22: Low Density Lipoprotein level

LDL (mmol/l)	No. of Patients	% Of Patients	Mean LDL (mmol/l)
< 2.5	142	47.3%	1.94
2.6 - 3.5	92	30.7%	3.03
3.6 - 4.5	35	11.7%	3.98
≥ 4.6	14	4.7%	4.9
unknown	17	5.7%	0

3.6.5 Association between BMI and Triglycerides

The Pearson's correlation between BMI and TG in the controlled and uncontrolled BP group was weak and had no significant association (R value=0.072, p value= 0.140); (R value= 0.205, p value=0.341), respectively. While the association is not significant, there is a trend that suggests an increase in BMI is associated with an increase in TG. Of the 88 patients that had a TG > 1.7mmol/l, 28% (n=25) were obese, and 17% (n=15) were pre-obese/ overweight. BMI was unknown in 51% (n=45) of these patients and only 3 had a normal BMI.

3.7 Routine investigations and compliance to guidelines

The frequency of routine investigations carried out by the health care provider, as recommended by the SAHG 2011, was assessed.

3.7.1 Body weight, height, BMI and abdominal obesity

Measures of abdominal obesity including WC or WHR were not done in any of the patients reviewed in the study. Measures of BMI, including height and weight were thus assessed.

3.7.1.1 Weight and height

From the 300 patients, 51% (n=154) had no height measured during any of their hospital visits. Weight was not measured in 3% (n=10) of patients. 7 of these 10 patients were wheelchair bound and thus height was not measured. The reason for not measuring weight in the remaining 3 patients was not documented in the patient records.

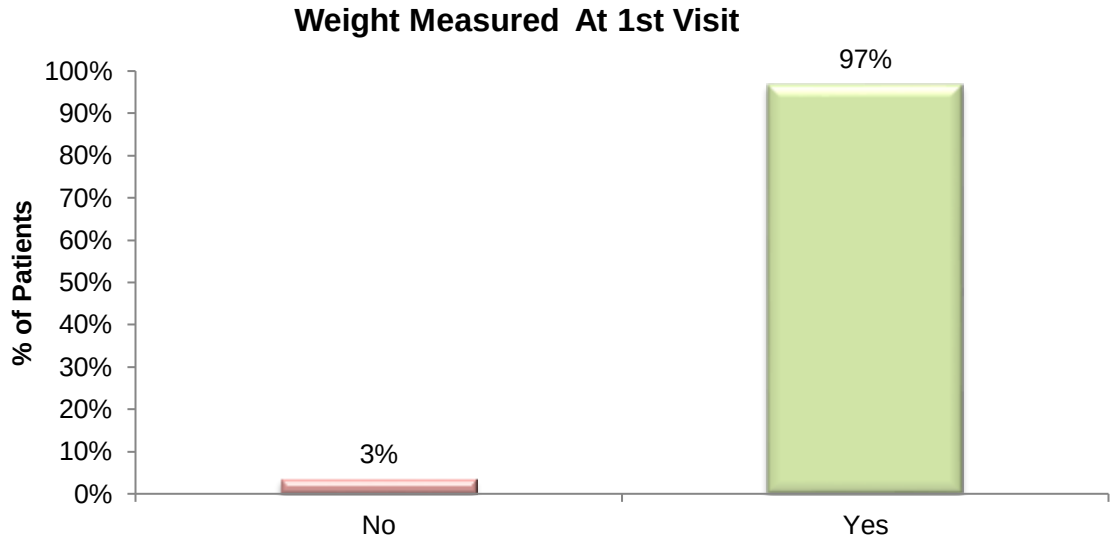

Figure 34: Weight measured at 1st visit

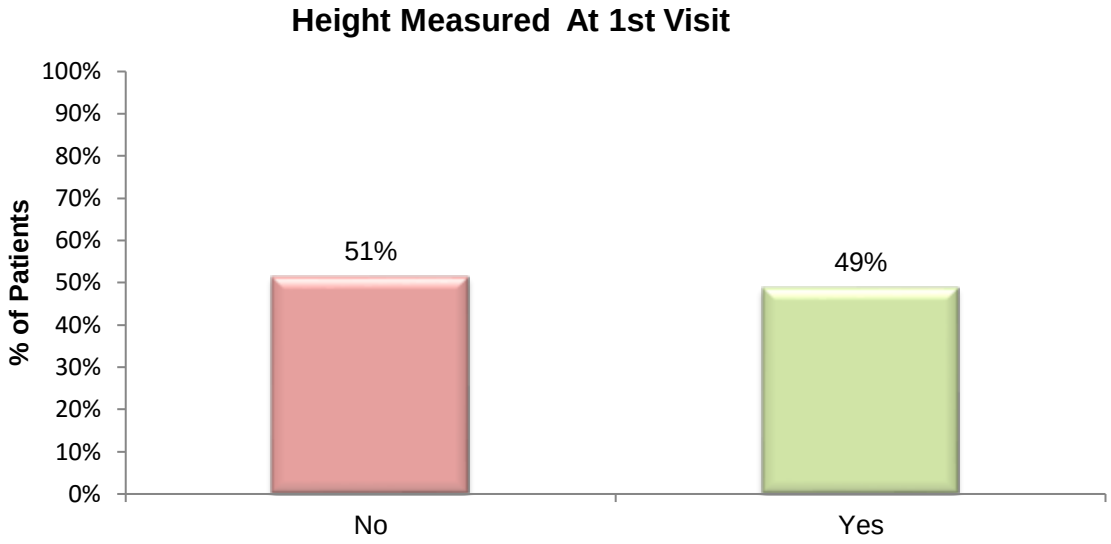

Figure 35: Height measured at 1st visit

3.7.1.2 BMI

BMI was calculated using the formula described in the literature review and methods section. The results depicted below are based on the number of patients in whom it was possible to calculate BMI, which was dependent on the availability of measures of height and weight.

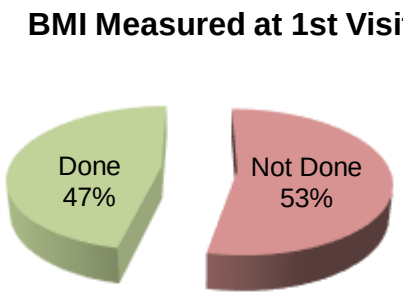

Figure 36: BMI measured at 1st visit

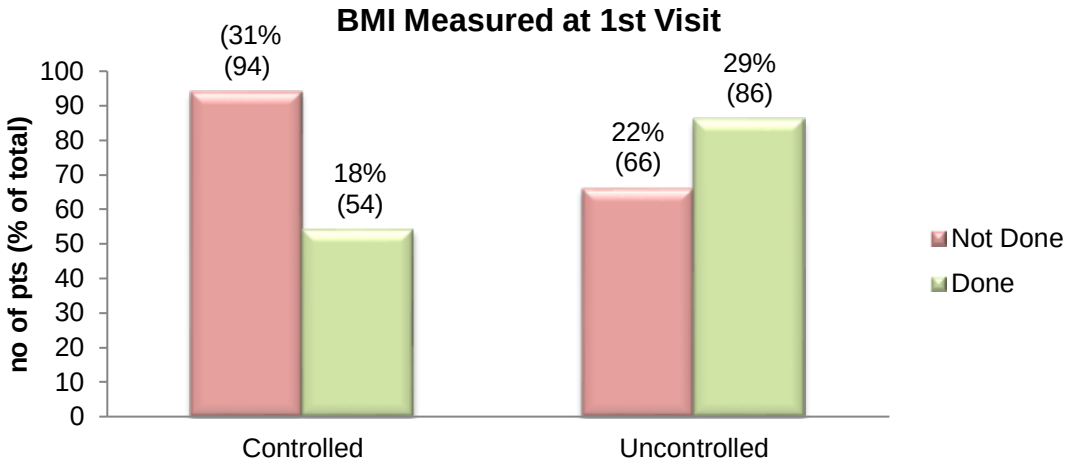

Figure 37: BMI measured at 1st visit (controlled and uncontrolled)

3.7.2 Urine dipstick

A urine dipstick was performed on 99% (n=297) of the patients. Of the 3 patients in whom urine dipstick analysis was done, 2 were wheelchair bound, with nappies.

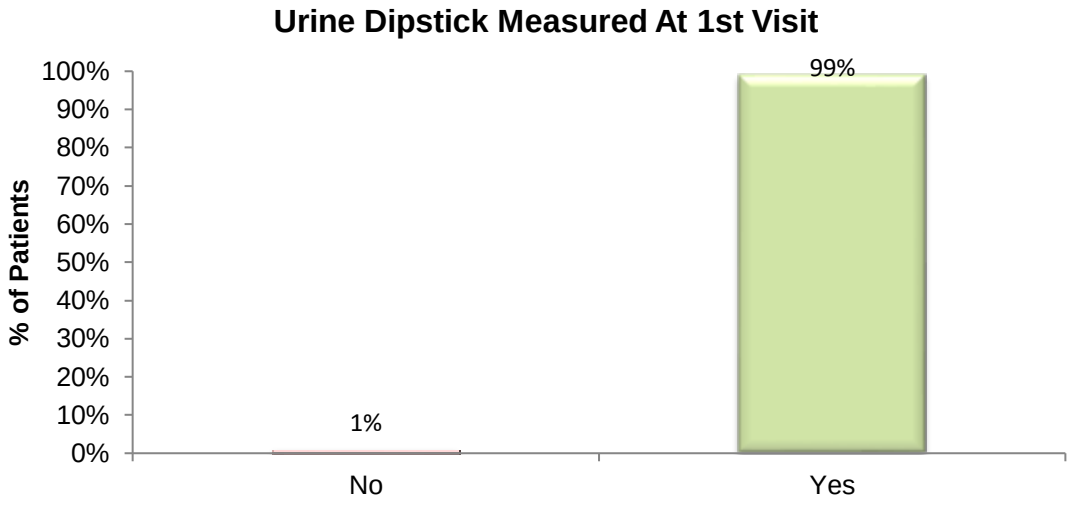

Figure 38: Urine dipstick measured at 1st visit

3.7.3 Microalbuminuria and Urine Protein: Creatinine ratio (P: Cr)

Microalbuminuria analysis was performed in a total of 7 patients. Although urine P:Cr is not recommended as a routine investigation, this investigation was requested

instead of microalbuminuria. Urine P: Cr was requested in 34% (n=101) of patients. Of the 10 hypertensive patients with a urine dipstick protein ≥ 2, only 4 were tested for P: Cr. A urine P: Cr was measured in 36 diabetic patients, of whom 36% (n=13) were controlled hypertensives and 64% (n=23) had uncontrolled BP.

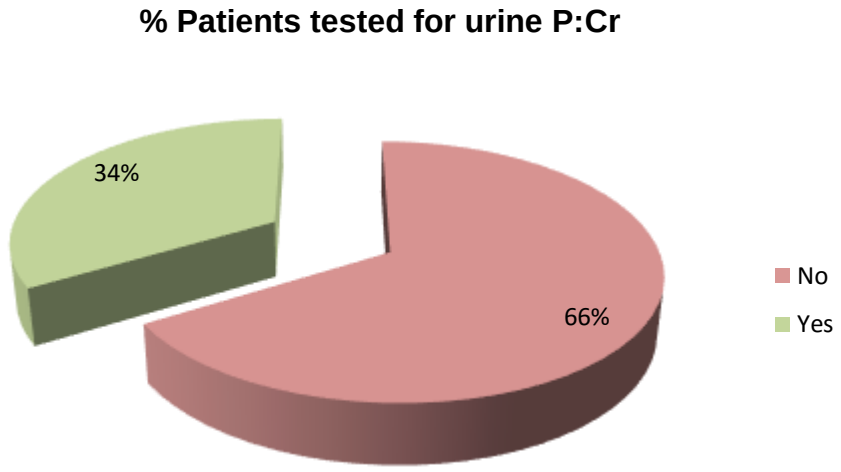

Figure 39: Percentage of hypertensive patients tested for urine P: Cr

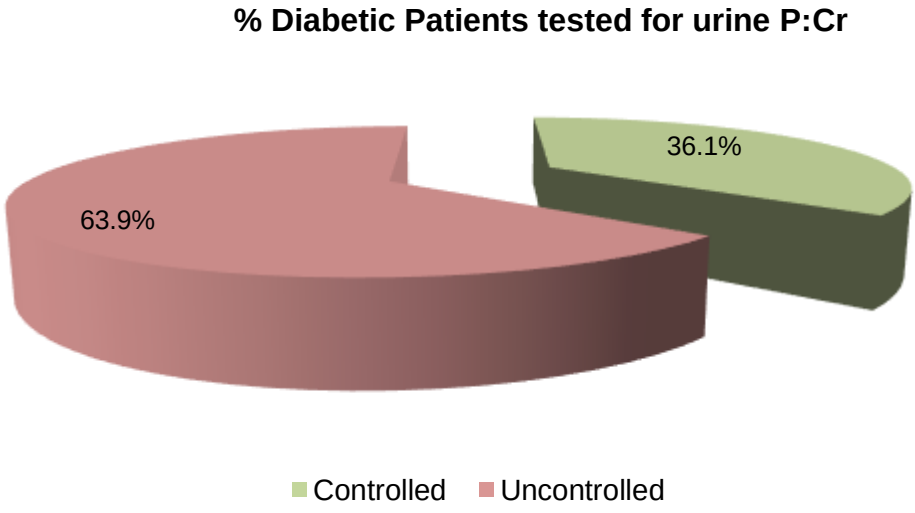

Figure 40: Percentage of Diabetic patients tested for urine P: Cr

3.7.4 Blood tests

3.7.4.1 Creatinine

Creatinine was measured at the first visit and annually in 54% (n=162) of patients and was not measured at the first visit or follow up visits in 46% (n=138) of subjects. Of the 138 patients in whom creatinine was not measured, 70 patients had uncontrolled BP and 68 had controlled BP.

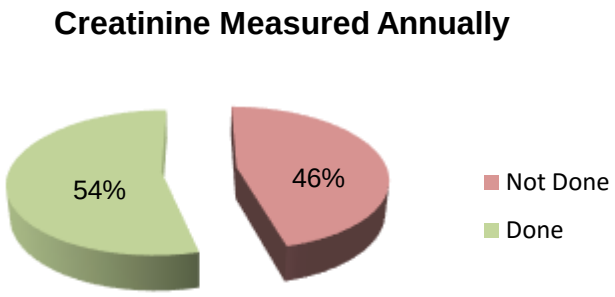

Figure 41: Creatinine measured annually

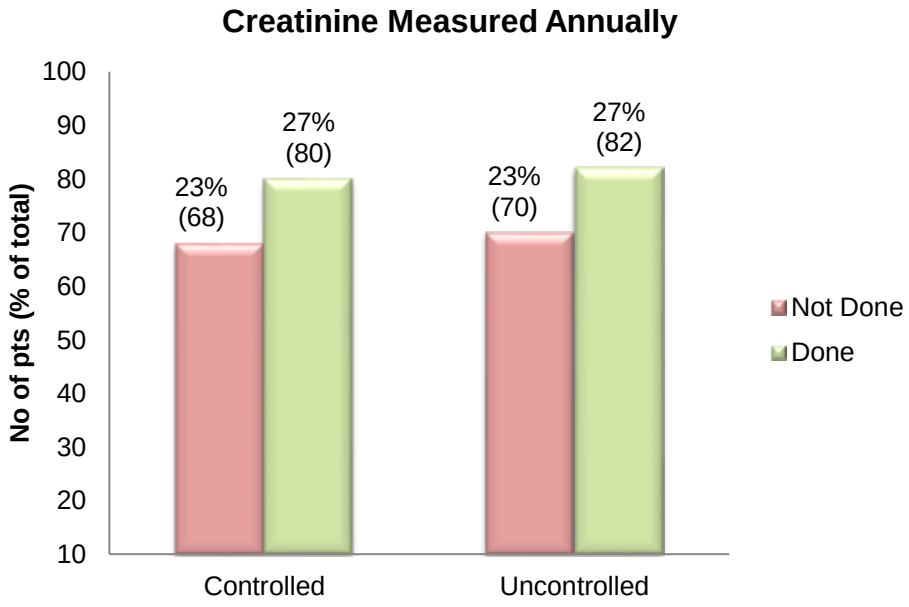

Figure 42: Creatinine measured annually (controlled and uncontrolled BP)

3.7.4.2 Potassium

Potassium is usually requested with creatinine as part of urea and electrolytes blood test. Thus, the number of patients in whom potassium was measured annually is similar to those that had creatinine measured, except for 2 patients that did not have potassium measured. Of the 140 patients that did not have a potassium measured annually, 69 patients had controlled hypertension and 71 had uncontrolled BP.

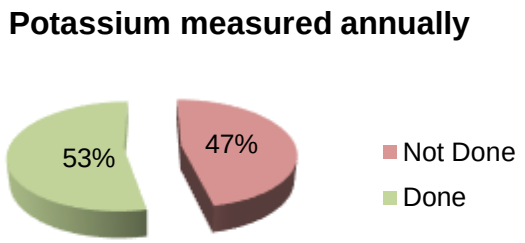

Figure 43: Potassium measured annually

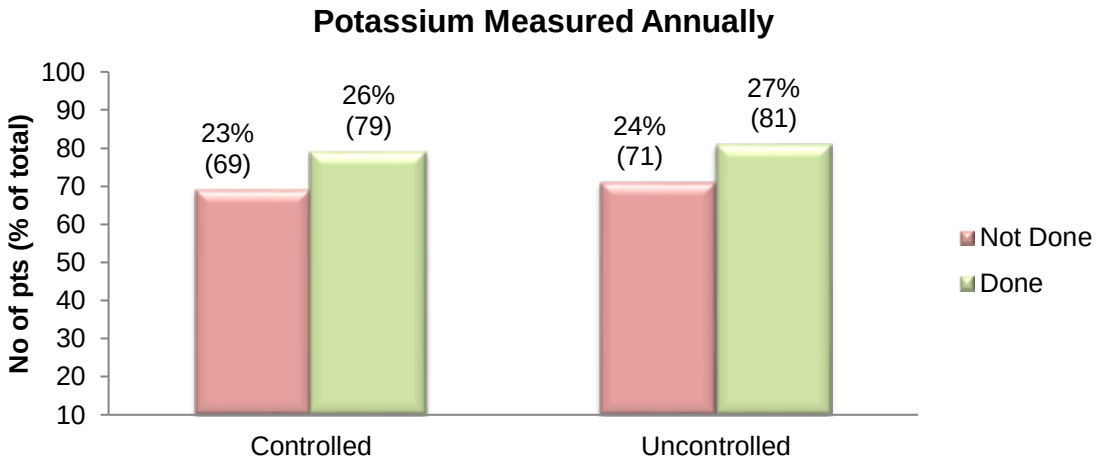

Figure 44: Potassium measured annually (controlled and uncontrolled BP)

3.7.4.3 Glucose

Glucose was not measured at any visit in 61% (n=182) of patients. Of the 182 patients, 84 had uncontrolled BP and 98 were controlled.

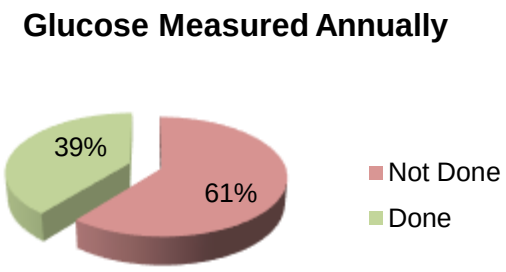

Figure 45: Glucose measured annually

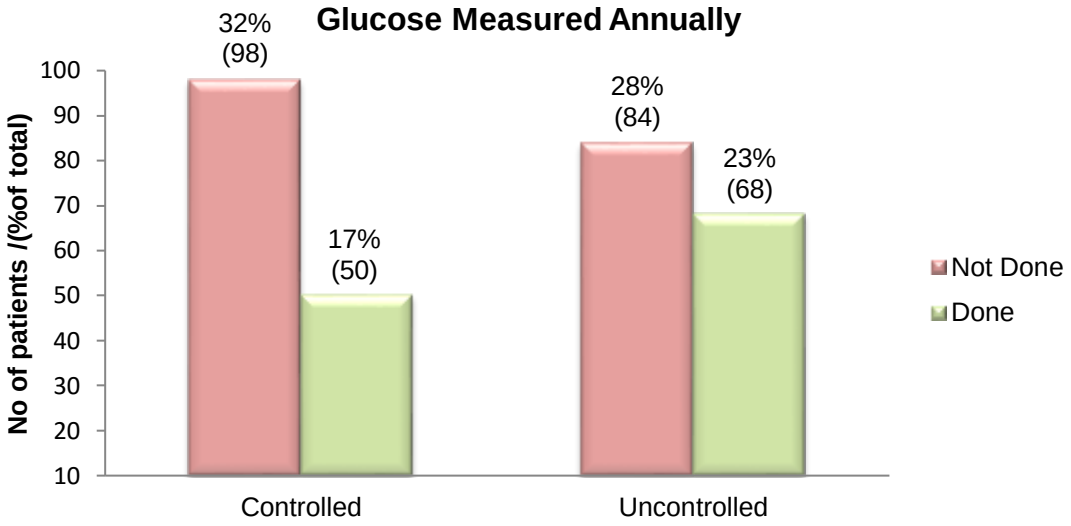

Figure 46: Glucose measured annually (controlled and uncontrolled BP)

3.7.4.4 Random Total Cholesterol (TC)

TC was not measured in 49% (n=146) of patients. Of these patients, 74 had uncontrolled hypertension and 72 had controlled BP. TC was measured annually in 51% (n=154) of patients, but this test was always requested as part of a full lipogram.

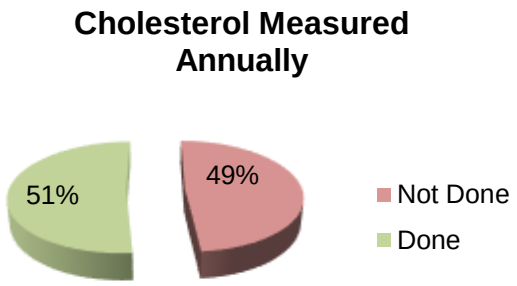

Figure 47: Cholesterol measured annually

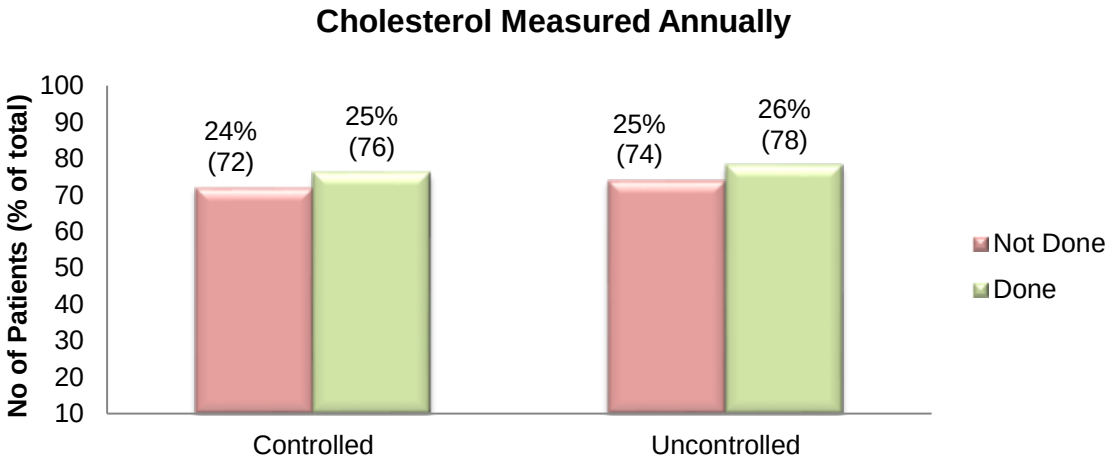

Figure 48: Cholesterol measured annually (controlled and uncontrolled BP)

3.7.5 Electrocardiogram (ECG)

A resting ECG was not performed annually on any patient attending the clinic.

3.8 Therapy

The relationship between the number and class of anti-hypertensive drugs is assessed against different variables. A total of 12 classes of drugs are assessed as recommended by the 2011 SAHG.

3.8.1 Number of drugs in each Grade of Hypertension

A total of 103 hypertensive patients with normal BP were on ≥ 3 anti-hypertensive agents. Of these 103 patients, 43 were prescribed 3 drugs and 40 were using 4 drugs. Between stages 1 to stage 3, a total of 5 patients were still prescribed ≤ 2 agents.

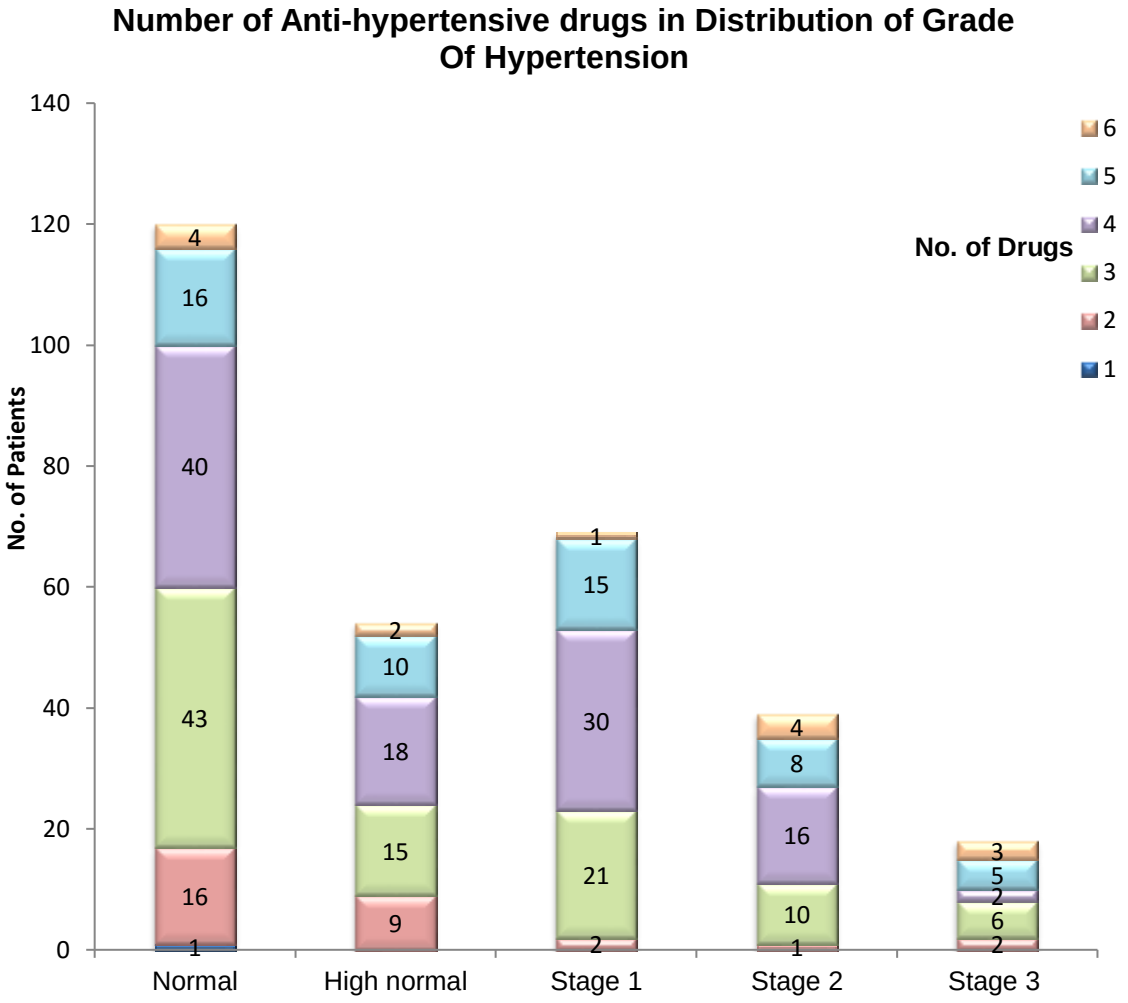

Figure 49: Number of anti-hypertensive drugs in distribution of grade of hypertension

3.8.2 Number of drugs in Controlled and Uncontrolled Hypertension

Within the controlled group of hypertensive patients, 85% (n=126) were prescribed ≥3 drugs. In the uncontrolled group, 94% (n=143) were using ≥ 3 anti-hypertensive agents, whilst 6% (n=9) were still prescribed 2 agents.

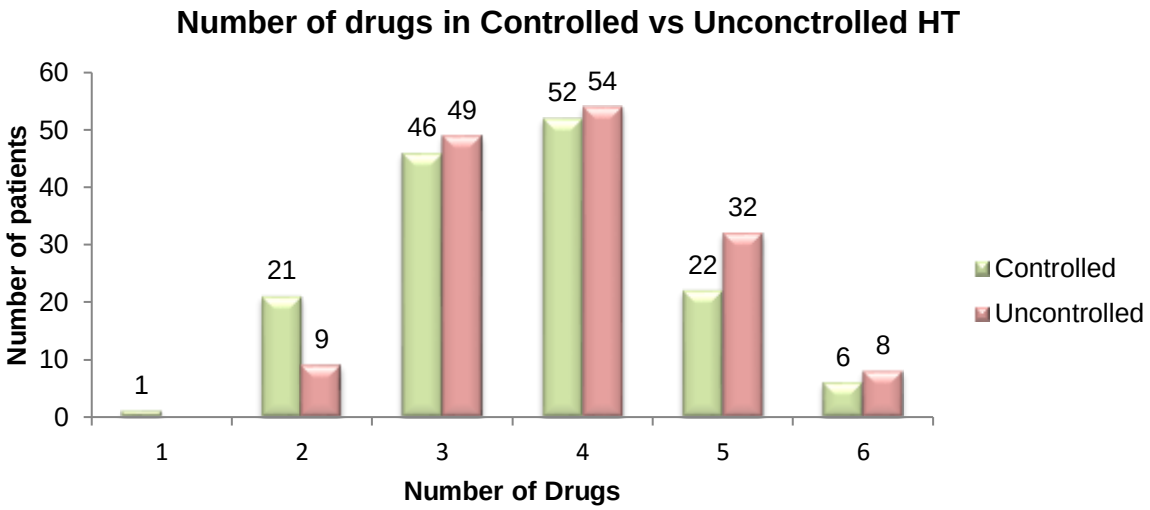

Figure 50: Number of drugs in controlled vs uncontrolled HT

3.8.3 Number of drugs in different Races

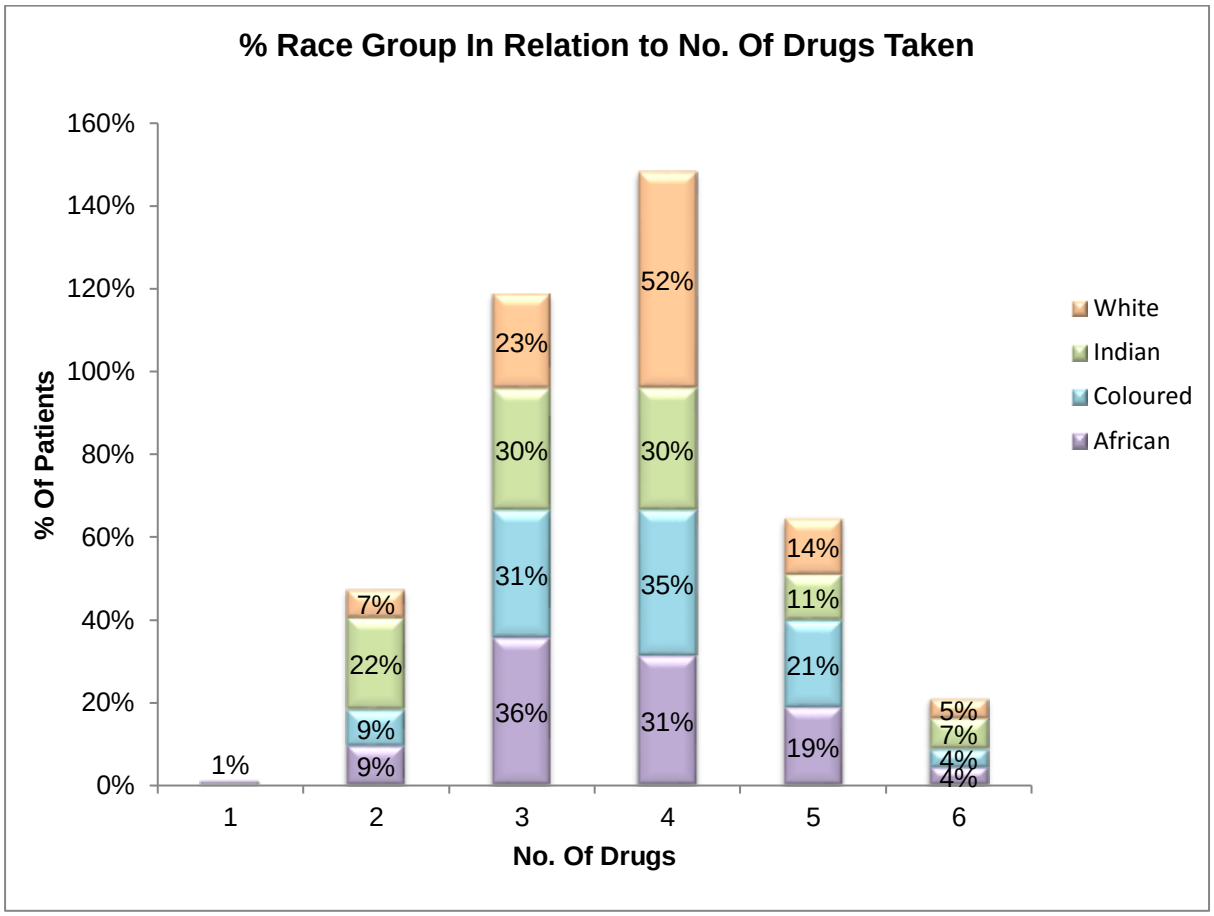

Figure 51: Percentage of race group in relation to number of drugs taken

3.8.4.1 Class of drugs in Controlled and Uncontrolled Hypertension

The use of thiazide diuretics was significantly higher in the controlled hypertensive group, 24% (n=36) compared to the uncontrolled group, 20% (n=31), (p-value 0.01). The use of all classes of diuretics, except for the loop diuretic, was prescribed more frequently in the controlled group than the uncontrolled group. The use loop diuretics and beta blockers were significantly higher in the uncontrolled hypertensive group compared to the controlled BP group (p-value 0.009; p-value 0.001) respectively.

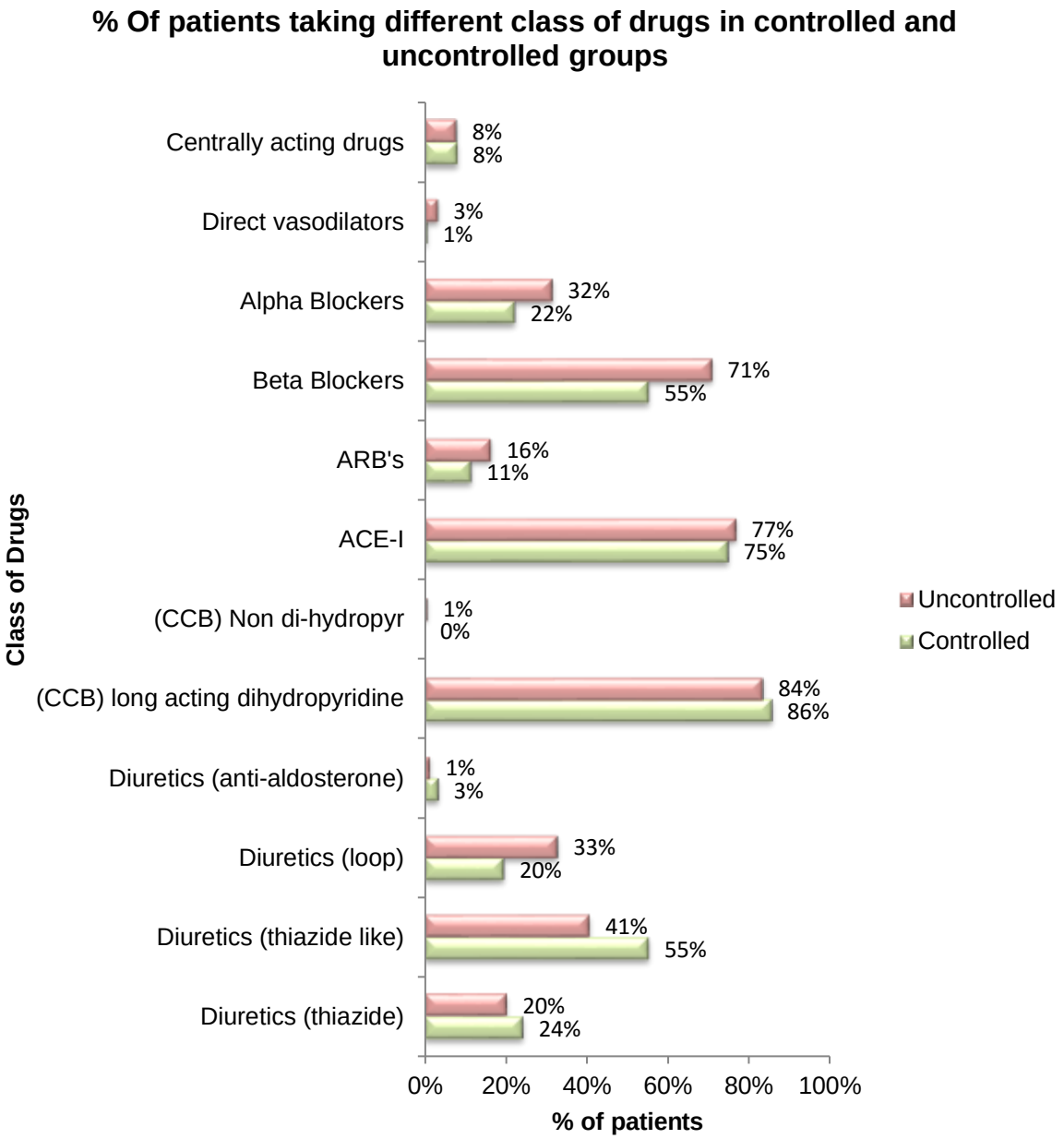

Figure 52: Percentage of patients taking different class of drugs in controlled and uncontrolled groups

3.8.4.2 Significant differences between class of drugs in the controlled and uncontrolled groups

Table 23: Significant differences between class of drugs in the controlled and uncontrolled groups

		Levene's Test for Equality of Variances		t-test for equality of means
		F	Sig.	Sig. (2-tailed)
Thiazide *	Equal variances assumed	54,77	0,001	0,001
	Equal variances not assumed			0,001
Diuretics Loop*	Equal variances assumed	28,44	0,001	0,009
	Equal variances not assumed			0,009
Diuretics (anti-aldosterone)	Equal variances assumed	5,69	0,01	0,23
	Equal variances not assumed			0,24
CCB long Acting (Dihydropyridine)	Equal variances assumed	1,17	0,27	0,58
	Equal variances not assumed			0,58
CCB (Non-dihydropyridine)	Equal variances assumed	3,95	0,04	0,32
	Equal variances not assumed			0,31
ACE-I	Equal variances assumed	0,63	0,42	0,69
	Equal variances not assumed			0,69
ARB	Equal variances assumed	6,23	0,01	0,21
	Equal variances not assumed			0,21
Beta Blocker*	Equal variances assumed	22,62	0,001	0,00
	Equal variances not assumed			0,00
Alpha Blocker	Equal variances assumed	13,28	0,001	0,07
	Equal variances not assumed			0,07
Direct Vasodilators	Equal variances assumed	10,85	0,001	0,10
	Equal variances not assumed			0,10
Centrally Acting drugs	Equal variances assumed	0,018	0,89	0,94
	Equal variances not assumed			0,94

* Significant differences in these classes of drugs

3.8.5 Class of drug in different Races

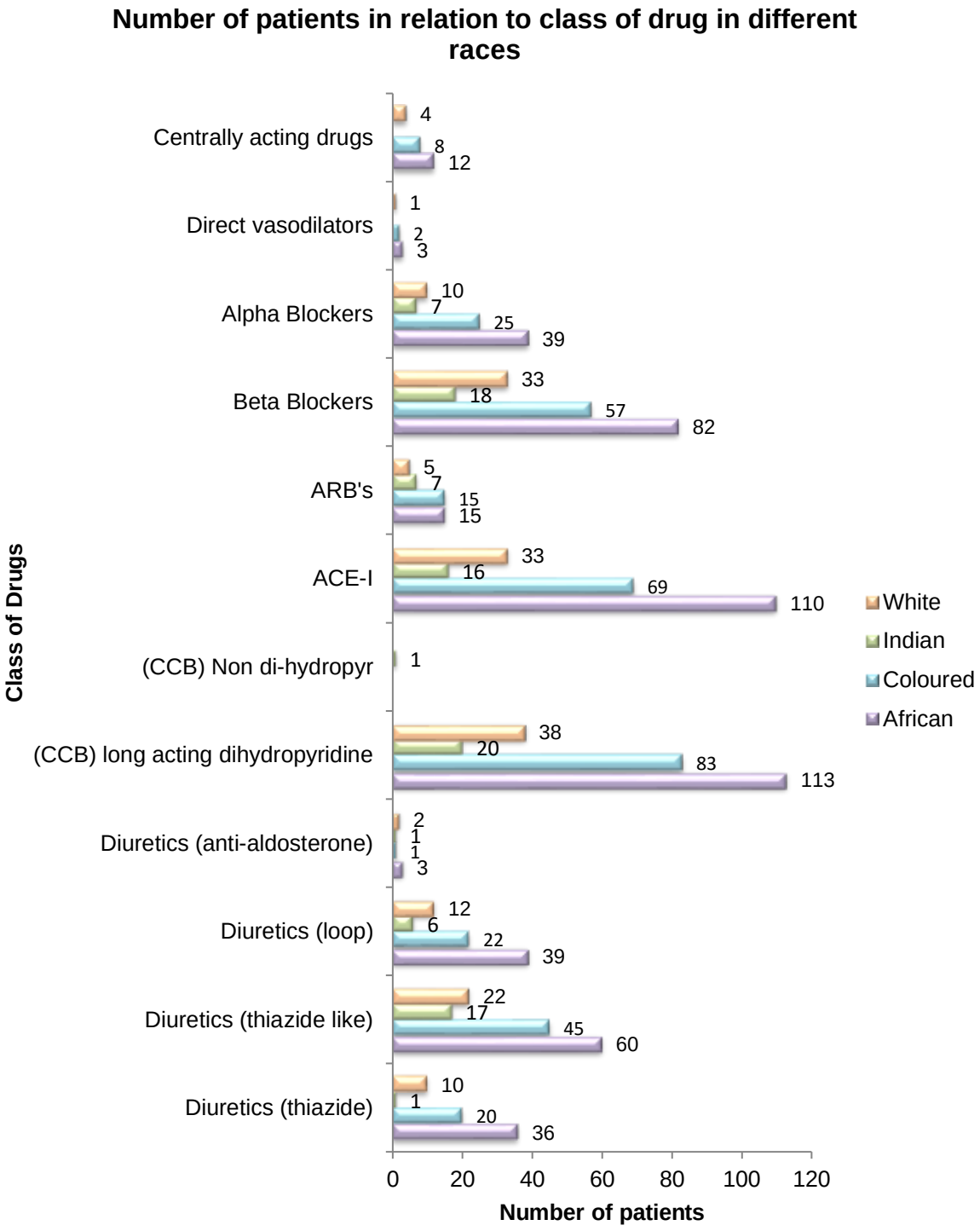

Figure 53: Number of patients in relation to class of drug in different races

3.8.6 Class of drug in Hypertensive Diabetic patients

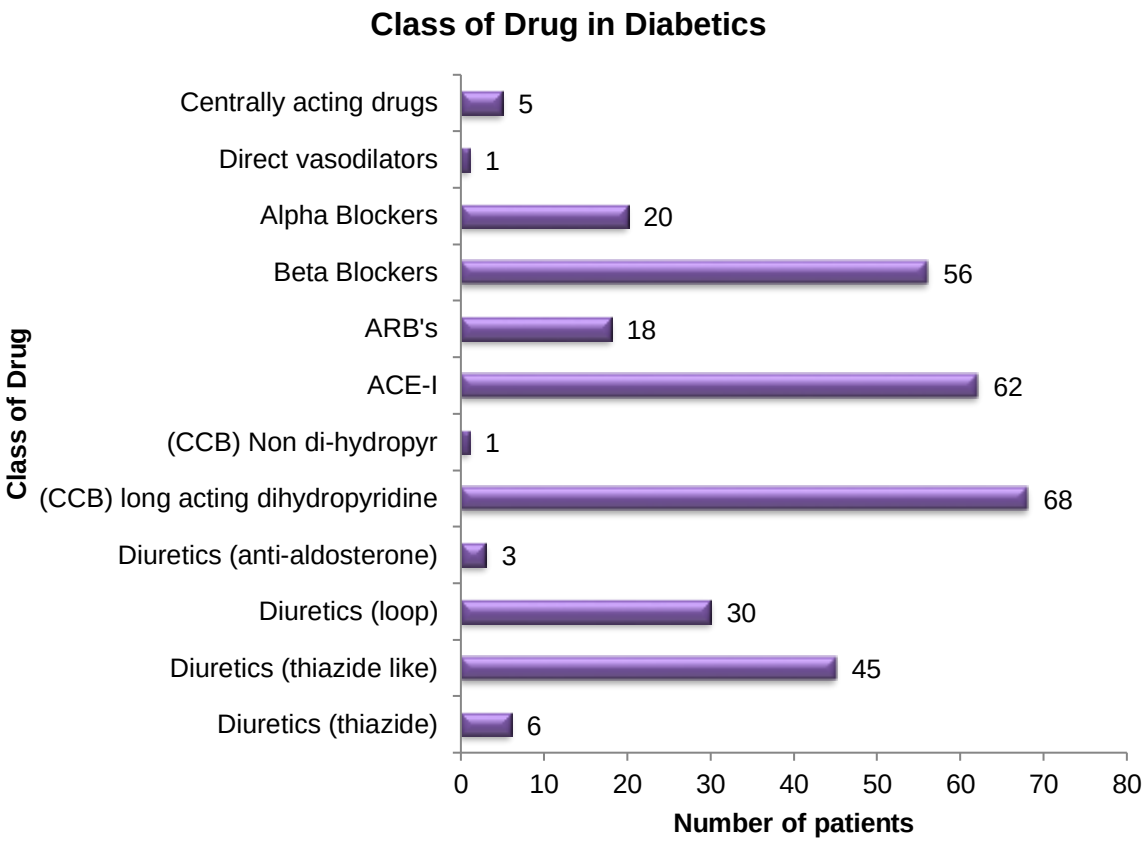

Figure 54: Class of drug in Diabetics

3.8.7 Class of drug in Resistant Hypertension

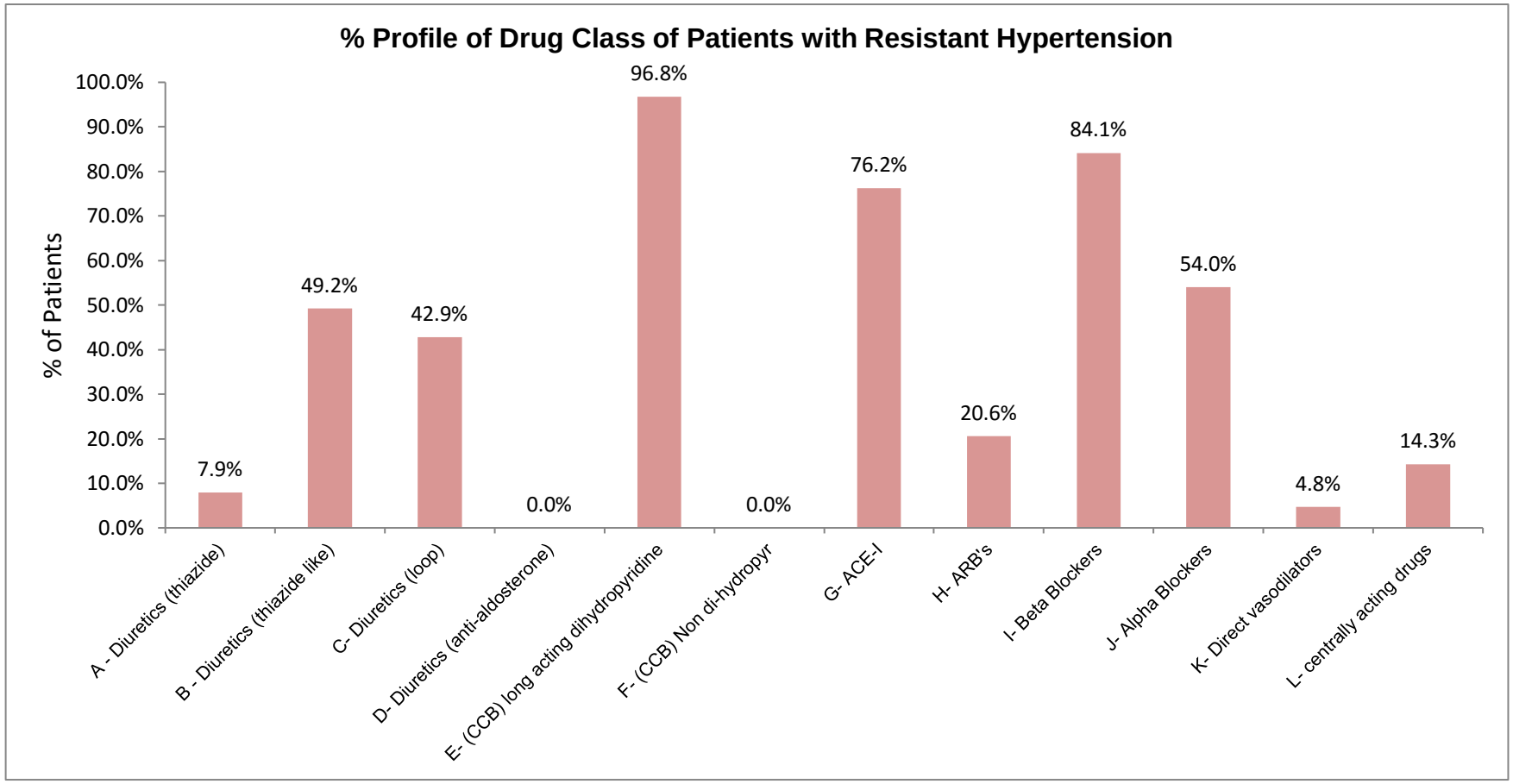

Figure 55: Percentage profile of drug class of patients with Resistant Hypertension

3.9 Follow up

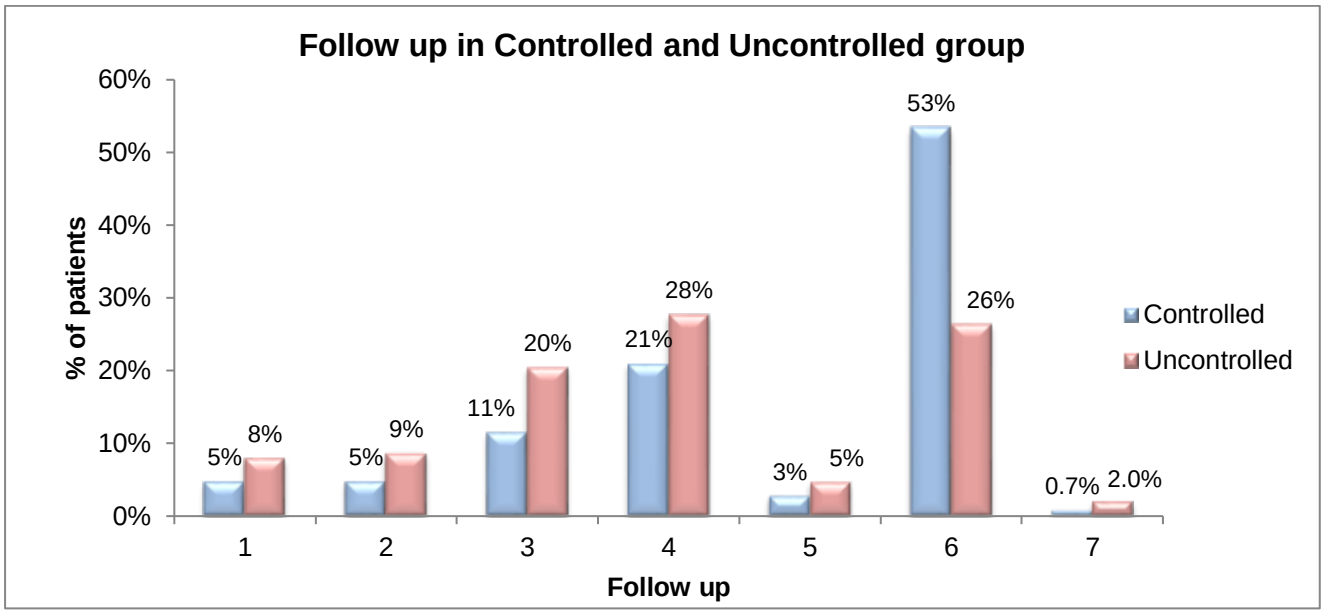

Figure 56: Follow up in controlled and uncontrolled group

3.10 Variables associated with significant differences between controlled and uncontrolled groups

Table 24: Variables associated with significant differences between controlled and uncontrolled groups

Variable	Mean Controlled	Mean uncontrolled	p-value
Age > 65 years	61.65	64.68	0.03
Systolic BP (mm/hg)	119.67	154.28	0.001
Diastolic BP (mm/hg)	70.91	85.11	0.001
Triglycerides (mmol/l)	1.49	1.75	0.02
Serum Creatinine (umol/l)	82.35	101.65	0.01
eGFR (ml/min/1.73m2)	72.70	64.96	0.001
Glucose (mmol/l)	6.55	7.10	0.04
Number of Drugs	3.62	3.88	0.03
Proteinuria	1.12	1.51	0.001

Of all the significant variables, the following 2 variables were significant for Odds Ratio. The Odds Ratio is indicated in brackets:

a. Glucose (1.681) CI [1.039,2.719]
b. Proteinuria (5.660) CI[0.992; 32.279]

The chi-square for the Odds Ratio is 368.265, which is significant ($p<0.05$), indicating that the predictor variables can be predicted better than other variables

The pseudo R-square of Cox and Snell is 0.709, which indicates that for uncontrolled BP 70.9% can be predicted by the variables.

CHAPTER 4: DISCUSSION

4.1 Demographics

The median age of hypertensive patients in this study population was 63 years with 59% older than 60 years. This is consistent with both national and international statistics provided by SADHS and NHANES databases.

The gender ratio was approximately 2.5:1 in favour of females. This trend was reproduced in a local study carried out at a primary health care facility within the same province (Onwukwe, 2012). However, data from the SADHS shows a comparable HT prevalence between males and females, whilst international data from the NHANES survey favours a male predominance. The increased prevalence of females in the index study does not necessarily imply that females are more susceptible to HT but rather that women may have superior health seeking behaviour. A South African study highlighted this association in both rural and urban women with a further conclusion that women had greater knowledge on health and compliance to therapy than men (Greeff et al, 2012).

Africans had the highest prevalence of hypertension, in both males and females, as compared to other racial groups. This is in contrast to national data published by the SADHS, whereby the highest prevalence of HT in both sexes was in the White race. However, most international and national data show an increased prevalence of HT amongst African Americans and Black Africans (Kramer et al, 2004; Opie & Seedat, 2005). The major difference is seen in urban Blacks rather than rural Blacks, thus emphasizing the influence of urbanisation and environment on BP. The difference in results could also be attributed to the fact that the current study was conducted in a public hospital, thus servicing the middle to low income population group, which in SA is predominantly Black.

4.2 Target BP and co- morbidities

The study revealed that only 49% of the study population achieved target BP. This data is comparable to international data published by the NHANES survey in the USA, where approximately 52% of patients were controlled. However, the NHANES survey was a national survey and thus does not address BP control at a community or tertiary level of health care. South African data regarding target BP control varies between 33 to 40% and majority of these studies were representative of hypertensive patients at a PHC setting (Rayner, 2010; Brand et al, 2013; Steyn et al, 1999; Steyn et al, 2008). The sample population from these studies is a good representation of the current study population as it was carried out within a comparative demographic drainage area, with the exception that most of these studies were conducted at a PHC setting. One particular study conducted at a PHC facility within a comparable representative area of the index study, showed a greater achievement in target BP, with control amongst 57% of the subjects (Onwukwe, 2012). The current study represents control of BP at a specialised HT clinic compared to a PHC facility, where resources and expertise are lacking. On the other hand, a specialised HT clinic is designed to manage hypertensive patients that require further expertise based on the presence of co-morbidities, TOD and resistant HT. This is evident in the current study where the prevalence of known diabetes, dyslipidaemia, TOD and CKD is 28%, 66%, 5%, and 11% respectively. Thus, the sample population between a PHC facility and a tertiary centre is expected to be very different, which could possibly explain the higher rate of target BP achievement at the PHC setting. The high prevalence of uncontrolled BP implies a greater risk of microvascular and macrovascular complications with an associated increase in CV morbidity and mortality as evidenced by data from the trials discussed in the

literature review. This highlights a system failure at numerous levels of care within the tertiary care facility.

4.3 Blood Pressure control and severity of hypertension

4.3.1 BP control with age

Uncontrolled HT was significantly higher in the age group greater than 65 years. This is in conformity with the literature, where approximately 20% of the elderly have controlled BP (Chobanian et al, 2003; Human & Pavlik, 2002). It is important to recognise the implications of poor BP control in this age group so that measures are taken to improve control. There is a three to four-fold increase in CVD risk in older compared to younger individuals (Chobanian et al, 2003). The possible explanations for this poor control are numerous and should always be considered when managing patients. They include patient and physician related factors. Patient related factors include ISH; increasing co-morbidities with poor functional status; poor accessibility to health care facilities; lack of social support systems; and poor compliance to therapy related to lack of education or polypharmacy. Physician related factors are vital to recognise as these are predominantly secondary to the failure of setting appropriate targets due to the misconception that BP control in the elderly require different targets. There is no convincing evidence to support the inaccurate assumption that aggressive BP control is associated with an increased risk of morbidity, unless DBP is <60mmHg (Chobanian et al, 2003). Thus, data from numerous studies has provided sufficient evidence to support the direct relationship between SBP reduction in subjects over 80 years and a reduction in CV morbidity and mortality from macrovascular disease. Most of the studies achieved a SBP of ±145mmHg. One study in particular, the FEVER study, showed an additional benefit in reduction of CV events with SBP less than 140 compared to 145mmHg (SHEP

Cooperative Research Group, 1991; Staessen et al, 1997; Gueyffier et al, 1999; Beckett et al, 2008; Zhang et al, 2011). In general, control of SBP is associated with a control in DBP (Chobanian et al, 2003).

The total control of DBP was 20% greater than SBP. MRFIT study highlights the importance of an elevated SBP compared to a DBP as a negative predictor of mortality in CAD. Thus, identifying this group of patients is important in improving outcomes. The current study showed a significantly higher rate of ISH in the age group older than 60 years as compared to those between 30 and 60 years of age. This data is comparable to international data whereby ISH is prevalent in approximately two-thirds of hypertensive patients older than 60, increasing to almost 100% in those older than 75 years (Chobanian et al, 2003). The increasing prevalence of ISH with age has been well described in the literature and can be attributed to the stiffening of large arteries with a decrease in capacitive compliance. However, arterial capacitive compliance has been shown to be significantly lower in ISH than with essential hypertension even in age matched groups (Coylewright et al, 2008). Thus, the role of other factors contributing towards ISH, become important to explore. The SAHG describes an association between diabetes and ISH, but the literature is limited regarding the relationship between the two conditions. A possible explanation is the added decrease in vascular compliance associated with DM. The current study revealed that 85% of diabetic patients with ISH were over 60 years. However, further analysis failed to show that these two variables were dependent on each other. The probable explanation for this is that the study was not designed to assess diabetes and thus was not powered adequately for assessing this association. Furthermore, the current study established a significant difference in the prevalence of ISH between females and males, with a greater prevalence in the

former. A plausible explanation for this is menopause. There is conflicting data regarding the increase in prevalence of HT with menopause, with numerous studies attributing this relationship to age and other CV risk factors. On the contrary, there is also evidence that illustrates gender differences in BP, whereby pre-menopausal women have lower BP than age related men, with women showing higher rates of HT than men with age. This implies that age and sex hormones are contributory factors. In addition, increased arterial stiffness coincides with menopause and it has been shown to be associated with an increase in carotid-femoral pulse wave velocity after adjustments for age and other CV risk factors (Beltran et al, 2001; Coylewright et al, 2008). This may provide a possible explanation for the greater rise in SBP in post-menopausal women. A further association was found between racial groups and ISH, with a significant difference between Africans compared to Coloureds and Whites, with a higher prevalence in Africans. The reason for this trend is unclear but genetic differences have been postulated to account for these findings. The data from this study thus exposes areas of potential future research.

4.3.2 BP control with gender and race

The distribution of gender amongst those who failed to achieve target BP favoured a female distribution (52%) compared to males (47%). However, these differences were not shown to be significant. Both national and local data show contrasting results, whereby females are more controlled than men. The differing results could be attributed to the smaller male sample size.

The most uncontrolled racial group was the African race. However, this is not a true reflection of racial distribution of control as Africans are also the most prevalent race amongst the study population. An individualised assessment of BP control within each race showed that the Coloured race were the most poorly controlled (55%),

followed by the Whites (52%), Africans (49%) and Indians (41%). In addition, the Coloured race also displayed the greatest propensity to develop severe (grade 3) HT. This is in contrast to most studies that show an increased severity and poorer control of HT predominantly in Blacks (Onwukwe, 2012; Fiscell & Holt, 2008). Since the current study is a retrospective review, the lack of data regarding the socio-economic status, including level of education, employment and income as well as social habits provides a challenge to draw conclusions and associations from this data. A multivariate regression analysis, conducted in a large South African cross-sectional study, designed to assess the prevalence and associated factors in subjects older than 50 years, revealed that being Coloured was associated with higher rates of HT secondary to socio-demographic factors (Peltzer & Phaswana-Mafuya, 2013). Another study conducted in Cape Town, almost 20 years ago, showed that Coloureds had the second highest prevalence of DM after Indians. A recent 2012 study, confirmed that the prevalence of DM and the MS were still increasingly prevalent in this racial group, with an associated increase in CVD. Furthermore, MS was more prevalent in female subjects secondary to increased central obesity (Erasmus et al, 2012). This confirms an increase in clustering of CV risk factors within the Coloured group. Thus, a possible explanation for the increased severity and poor BP control within the Coloured group could be secondary to associated co-morbidities and CV risk factors. In the current study, the subgroup analysis showed a trend towards an increased prevalence of DM and uncontrolled BP, with a 10% greater prevalence in this subgroup. However, this difference did not reach statistical significance, as the study was not designed to analyse this. In addition, the retrospective design of the study did not allow for the glycaemic status to be determined in all subjects. However, an important association was established

between the level of glucose and BP. There was a statistically significant increase in glucose in the uncontrolled subgroup, whereby the odds of having uncontrolled BP was 1.7 times higher with an elevated glucose level. The literature shows that HT is the most frequent component constituting the MS, but there is a gap in the literature regarding the prevalence of uncontrolled BP in the MS, providing an opportunity for research within this area. MS is also associated with a five-fold increased risk of developing type 2 DM.

4.3.3 BP control and diabetes

In the index study, DM was co-morbid with HT in only 28% of subjects, with a female predominance. The HDS study also showed a gender distribution of DM in HT favouring females, with a prevalence of 39%. The lower prevalence in the current study could partly be attributable to the fact that the glycaemic status was unknown in 18% of subjects. The failure of the healthcare facility and staff to comply with SAHG is highlighted by this, with the implication of inadequate care. Without an annual glucose assessment, CV risk assessment is incomplete with a resultant increased risk of CVE. The literature clearly describes a synergistic effect on the rate of CVE with co-morbid DM in HT. Furthermore, target BP is lower in patients with DM, thus highlighting suboptimal care within this undiagnosed group of patients.

4.3.4 BP control in obesity and dyslipidaemia

The literature associates the increased prevalence of co-morbid DM and MS in females with HT to an increase in central obesity. The WHO and SADHS have shown an increase in BMI amongst females. In the current study, abdominal circumference was not measured but BMI was used as a measure of obesity. However, BMI could not be calculated in 52% of the study population. Data from those in whom a BMI was measured showed that 66% of females within the

uncontrolled group were obese as compared to 35% of males. There was a significantly higher association of obesity in the uncontrolled hypertensive patients.

The proven independent association between obesity and the increased risk of CVD are highlighted by numerous studies as discussed in the literature review. The INTERHEART study showed a 40% increase in the risk of MI (Yusuf et al, 2004). Therefore, the role of lifestyle modification is the cornerstone of BP control. The noncompliance to guidelines, by not adequately assessing glycaemic status and BMI in all hypertensive patients, infers that an inadequate risk assessment and management thereof are current deficits at our clinic.

The NHANES II study showed a consistent association with central obesity and hypertriglyceridemia. In the uncontrolled subgroup, there was significantly higher triglyceride levels compared to the controlled BP group. The likely cause for this is the increased BMI within the uncontrolled HT subjects. Data from the current study did not show a linear correlation between obesity and elevated triglycerides, but there was a trend to higher triglyceride levels with an increase in BMI. The failure to prove a linear correlation between these variables can be attributed to the retrospective nature of the study, whereby BMI was unknown in 51% of patients with elevated triglycerides. Although central obesity was not measured in the study, the increased BMI associated with hypertriglyceridemia implies that the subjects with increased BMI most probably had increased central obesity. This equates to an increase in CV risk being missed by the attending physician. Using the SAHG criteria for dyslipidaemia, two thirds of the sample population had dyslipidaemia, with a 10% greater prevalence in the uncontrolled BP group. The literature confirms a strong association between HT and dyslipidaemia, with dyslipidaemia being a predictor of HT and CVD. The relationship with CV mortality is a continuously graded one. A high

LDL and a decreased HDL are independent risk factors for CV mortality. From the current study population, 47% and 53% of patients failed to achieve target LDL and HDL respectively. This data once again highlights the increased CV risk posed by abnormal lipids within the study population.

4.4 Target Organ Damage

A significant increase in serum creatinine with an associated significant decrease in eGFR was observed in the uncontrolled hypertensive group. The data from this study is comparable to the INSIGHT study with regard to the prevalence of elevated serum creatinine but there was almost a four-fold increase in the prevalence of eGFR less than 60ml/min in the index study. The difference in the eGFR results could be secondary to age and ethnic differences of the participants. Urine dipstick did not show a correlation to the observed creatinine-based decline in renal function. Only 10 subjects had a urine dipstick ≥ 2+ proteinuria. A possible explanation could include operator error and accuracy of the urine reagent sticks. Another plausible explanation is based on the premise that the urine reagent strips used at the HT clinic can only detect protein if albuminuria exceeds 300mg/day. Thus, microalbuminuria (albumin 30-300mg/day) would be missed on these standard reagent strips. For this reason, the SAHG recommend an annual urine sample to be tested for microalbuminuria. This will detect glomerular disease, as this is the underlying mechanism of hypertensive nephrosclerosis. Microalbuminuria was only tested for in seven subjects. Instead, a spot urine P: Cr was tested in only four of the ten hypertensive patients with proteinuria on urine dipstick. However, 34% of all the hypertensive patients had a urine P: Cr despite no indication. Of these limited patients with proteinuria on urine dipstick, two thirds were diabetic. Thus, although the sample is small, there is a suggestion that proteinuria is more prevalent in

hypertensive patients with DM. Furthermore, analysis of this limited data showed that the odds of BP remaining uncontrolled are 5.6 times higher when urine protein exceeded ≥2+. This data implies that subclinical kidney damage is not being detected in these high risk patients and once again infers an inadequate CV risk assessment. Within the current study, no significant ethnic differences were noted in the prevalence of CKD. The data from the current study is in contrast to other studies which describes an increased prevalence of CKD within the African population.

4.5 Compliance to guidelines

The failure of the staff at the HT clinic to comply with SAHG is demonstrated in numerous areas of assessment. None of the patients had assessment of central obesity, but components of general obesity were the preferred choice. Measures of central obesity are considered to be superior to BMI in predicting CVD risk based on the premise that increased visceral adipose tissue is associated with multiple metabolic abnormalities. Despite weight being measured at each visit in 97% of patients, BMI could only be calculated in 47%, due to the unavailability of height measurements. An important point to consider is that during this retrospective audit, all files did not have a documented calculated BMI, which leaves the observer to assume that more than likely it was not measured. The fact that BMI could be measured in only 47% of subjects represents inadequate therapy, as lifestyle modification cannot be encouraged if BMI is not monitored.

It is routine for the nursing staff to perform a urine dipstick at each visit, but the staff failed to conduct further investigations on the 31 abnormal urine dipstick results and test for microalbuminuria. This highlights the lack of training of the clinic staff. A solution for this would be to have adequate training and protocols in place for the nursing staff.

Of the annual recommended blood investigations, the most distressing is the failure of a documented glucose level in 61% of the patients. As discussed earlier, this implies inadequate CV risk assessment, but it also has significant implications for control of BP and associated complications. In addition, failure to test annual creatinine level in 46% of the subjects implies the probability of targeting an incorrect BP and missing TOD.

An annual lipogram was performed in 51% of patients, despite the guidelines recommending a full lipogram when the TC exceeds 5.1mmol/l. This again shows lack of training and awareness by the staff members of the SAHG.

An ECG was not done annually on any patient attending the facility. Due to the retrospective nature of the study, the possibility of the ECG missing from the file is a plausible explanation, but bearing in mind that this could not be the case in all records, suggests that the ECG was not recorded. For this reason, the failure to assess LVH, an important indicator of TOD, once again highlights the lack of compliance to national guidelines.

The implications of this data are distressing, as the failure to optimise BP at a tertiary level could also reflect the possibility of poor control at a PHC level as well.

4.6 Therapy

A significant difference was noted between the number of drugs used between the controlled and uncontrolled subgroups, with a greater number of drugs used in the uncontrolled group. This is an expected result as uncontrolled patients require a dose titration or addition of a drug, once non-adherence has been excluded. However, further analysis of therapy revealed that there were six subjects with stage

1 to 3 HT that were still prescribed ≤ 2 agents. Despite the small number of these patients, it still represents the failure of appropriate escalation of therapy.

An analysis of therapy demonstrated that diuretics constituted 25% of all antihypertensive agents prescribed. Two thirds of all antihypertensive drugs prescribed belonged to one of the three first line drug classes. These included a thiazide or thiazide like diuretic, ACE-I, ARB, and CCB. Data from the SADHS showed that almost half of all antihypertensive medication prescribed was a type of diuretic. A significant difference was noted in the controlled and uncontrolled subgroups regarding the use of three classes of drugs. There were a significantly higher number of patients in the controlled group on a diuretic, specifically a thiazide like diuretic. The use of loop diuretics and beta blockers were greater in the uncontrolled group. The assumption that use of a thiazide diuretic is associated with better control of blood pressure should be interpreted with great caution as multiple variables influence BP control. Ethnic differences with antihypertensive drug prescriptions exist predominantly in Blacks, with a recommendation of the combination use of a diuretic with a CCB. Within the study, the largest proportion of CCB and diuretic was prescribed to Black patients. This could be interpreted as physicians' compliance to guideline recommendations. However, these results must be interpreted with care as the African population did constitute the largest proportion of the sample. In the current study, no significant racial difference was noted in antihypertensive use in the controlled and uncontrolled groups.

Another specialised area of antihypertensive drug prescriptions is amongst diabetics. The well described diabetogenic effect of a thiazide diuretic and BB is currently met with conflicting data. Current data show that a thiazide diuretic is safe to use in a diabetic, whilst a BB still carries a risk of worsening diabetes. The most important

drug to be prescribed in a diabetic with microalbuminuria is an ACE-I. This highlights the importance of screening for proteinuria in order to provide goal-directed therapy. Unfortunately, the current study revealed that screening for nephropathy by testing urine for proteinuria using a urine P: Cr, was conducted in less than two thirds of diabetics, and urine microalbuminuria was tested in only seven patients. Of the total antihypertensive drugs prescribed in diabetics, ACE-I/ARB constituted 25%, BB 17% and thiazide diuretics 16%. The drug used most in diabetic patients was a CCB. The infrequent use of a thiazide diuretic in diabetic patients is most likely secondary to the false assumption of its diabetogenic properties.

Due to the retrospective nature of the study, an accurate evaluation of resistant HT could not be performed as patient adherence and lifestyle modification could not be determined. The data categorising resistant HT is based on the SAHG definition using current therapy prescribed. In the current study, 21% of subjects met the definition of resistant HT, and in whom fourth line drugs were infrequently prescribed. None of these patients were prescribed an aldosterone antagonist, as is supported by the ASPIRANT trial. There was no significant gender or racial differences noted in this subgroup. Most importantly, these patients were inadequately followed up.

4.7 Follow up

In order to achieve target BP, goals need to be set by both the patient and the physician. One way of ensuring these goals are met is through appropriately timed follow up visits. Although the SAHG does not have stringent follow up guidelines, the rule of three to six monthly follow up, once target BP is achieved, is quite clearly outlined within the guideline. In approximately 80% of uncontrolled patients follow up was scheduled only after three months. There was a significant difference between the follow up scheduled dates in the controlled and uncontrolled subgroups. This

inappropriate follow up does not allow the necessary dose titration or stepwise increase in therapy, thus further worsening BP control and associated complications.

In summary, the results of the study showed that HT was more prevalent in the African race, with a greater distribution in females and the elderly, specifically in those older than 60 years. A significant contribution to HT in those over 60 years was related to ISH. Just over half of the patients did not achieve target BP despite being managed in a specialist clinic. Resistant HT was prevalent in approximately one quarter of the patients, although lifestyle and adherence could not be assessed. Variables that were significantly higher in the uncontrolled BP subgroup were as follows: age over 65 years; increased BMI with an associated hypertriglyceridemia; elevated serum creatinine with a corresponding low eGFR and proteinuria. Of these significant variables, a strong correlation was found between uncontrolled BP and increased BMI, elevated glucose and proteinuria. In addition, the uncontrolled subgroup showed a trend towards an increased prevalence of DM. Furthermore, thiazide diuretics were prescribed more in the controlled group with loop diuretics used more in the uncontrolled group, probably secondary to reduced eGFR. There was greater use of CCB and diuretics in Africans, as per recommendations by the SAHG and thus showed compliance by physicians to therapy guidelines. The staff at the specialist clinic failed to comply with the following aspects of the guidelines:

a) assessing central obesity;
b) BMI review;
c) Urinalysis and microalbuminuria assessment;
d) Proteinuria testing.

None of the patients had adequate TOD assessment in that an ECG was not carried out annually on any of the participants. Poor follow up scheduling was significantly

higher in the uncontrolled group thus implying that failure of achieving BP targets is not only secondary to patient related factors.

4.8 STUDY LIMITATIONS

a) Observer Bias / Measurement Bias:

   a. Being a retrospective clinical audit, data collection relies on accuracy of written record, thus the following important data was not readily available:

      i. BMI could not be calculated on all patients as weight and height were not routinely recorded;

      ii. Factors influencing lifestyle modification such as total sodium intake, alcohol intake, exercise and smoking habits were not documented;

      iii. Presence of certain co-morbidities: congestive heart failure

   b. BP at the Hypertension Clinic is measured using an automated device. Accuracy of BP measurement is affected by both patient related factors and observer errors;

   c. Measuring BP in the clinical setting is confounded by 'white coat' hypertension, whereby higher BP's are recorded due to anxiety experienced by the patient;

   d. Using a single BP recording to assess target BP control, instead of multiple readings over time, poses a risk of misclassification of BP control.

b) Selection Sampling Bias:

   a. The study population only includes patients attending the HJH Hypertension Clinic, and thus the sample is not representative of the entire population. In addition, a large volume of hypertensive patients attend the general medical out-patient clinic, thus the results from this study are not a reflection of all hypertensive patients at HJH;
   b. The routine investigations carried out at this specialized clinic do not take place at other medical out-patient departments thus the study may be an over-representation of compliance to National Hypertension Guidelines.

c) Confounding bias:

   a. Socio demographic factors, lifestyle modification, adherence to therapy and other patient related variables that have an effect on outcome measures could not be evaluated due to the retrospective nature of the study.

4.9 STUDY STRENGTHS

a) The blood results are standardised and are obtained from the same laboratory (NHLS);
b) Data was collected from patients' records by a single researcher. This ensured that the data was collected in a standardised manner using data collection sheets and thus likely to be more reliable.

CHAPTER 5: CONCLUSION

I have shown that the total number of patients achieving target BP, as recommended by the SAHG, at a specialised HT clinic is suboptimal. This can be attributed to both patient, physician and facility related factors.

Certain variables were significantly higher in the uncontrolled BP group. The non-modifiable risk factor that was significantly higher in the uncontrolled subgroup was age ≥ 65 years. Modifiable risk factors that were significantly increased in the uncontrolled subgroup included specific co-morbidities such as hyperglycaemia, dyslipidaemia (specifically hypertriglyceridemia), and obesity as measured by BMI. Other variables that were significantly higher in the uncontrolled group included serum creatinine with a calculated eGFR and proteinuria. If these major risk factors are assessed and targeted early in the management of the hypertensive patient, better control in BP can be achieved. On the contrary, failing to recognise and target these risk factors will lead to TOD.

Compliance to guidelines regarding routine investigations was clearly suboptimal. Should these improve, there should be concomitant improvement of control of BP, and possible early detection of TOD. Thus, the concept of clinical inertia is important. Clinical inertia refers to the failure of physicians to modify patient's therapy despite them not meeting therapeutic targets. The most common reasons for clinical inertia are assuming patient non-compliance or white coat HT. This is usually an easier option for the physician instead of investigating the other possibilities of poor control and appropriate escalation of therapy.

If both patient and physician-related factors are always kept in mind in patients with uncontrolled BP, the chances of targeting the problem appropriately will be much

higher. Thus, to improve BP control, there should be checklists for both the nurses and physicians to serve as reminder of the recommended investigations and therapeutic targets.

FUTURE INTERVENTIONS AND STUDIES

a) Firstly, strategies directed at educating the nursing staff, so as to improve compliance to guidelines, will be strongly recommended to the management of the HJH HT clinic. These will include protocols for nursing staff ensuring baseline investigations are performed as per SAHG recommendations. In addition, nursing staff should be trained as to when they should investigate an abnormal urine dipstick, thus avoiding the situation of discarding a urine sample.

b) Secondly, interventional strategies directed at improving physicians' compliance to guidelines should be instituted. These include two tick sheets that are designed separately: one for the first visit and the other for each follow up visit (Appendix F). The admission visit should have detailed risk stratification for major CV risk and an assessment of TOD and ACC. Each visit should have a tick sheet for the routine investigations as well as lifestyle modification, therapy and side effects.

c) Future studies aimed at addressing the significant associations that were found in the current study will prove to be informative. Of all the significant variables associated with uncontrolled BP, only two were found to be significantly correlated hyperglycaemia and proteinuria. Thus, interventional studies should target these two variables, in assessing if there is an associated improvement in BP control and CV mortality.

d) The increased prevalence of ISH in postmenopausal females is oestrogen related. The deficiency in the literature regarding this association provides an area for further research.

Reference list

Adler, A. I., Stratton, I. M., Neil, H. A. W., et al. (2000). Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. British Medical Journal, 321(7258): 412-419.

Alberti, K. G. M. M., Eckel, R. H., Grundy, S. M., et al. (2009). Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation, 120(16): 1640-1645.

Amod, A., Ascott-Evans, B.H., Berg, G.I., et al. (2012). The 2012 SEMDSA Guideline for the Management of Type 2 Diabetes (Revised). Journal of Endocrinology, Metabolism and Diabetes of South Africa; 2012; 17(2 Supplement 1): S1-S95. Available:http://www.semdsa.org.za/images/2012_SEMDSA_Guideline_July_FINAL.pdf [Accessed 19. 08. 2014]

Anderson, R. J., O'Brien, M., MaWhinney, S., et al. (2000). Mild renal failure is associated with adverse outcome after cardiac valve surgery. American Journal of Kidney Diseases; 35(6): 1127-1134.

Antikainen, R., Grodzicki, T., Palmer, A. J., et al. (2003). The determinants of left ventricular hypertrophy defined by Sokolow–Lyon criteria in untreated hypertensive patients. Journal of human hypertension; 17(3): 159-164.

Appel, L. J., Wright Jr, J. T., Greene, T., et al. (2010). Intensive blood-pressure control in hypertensive chronic kidney disease. New England Journal of Medicine; 363(10): 918-929.

Asia Pacific Cohort Studies Collaboration. (2006). Central obesity and risk of cardiovascular disease in the Asia Pacific Region. Asia Pacific Journal of Clinical Nutrition; 15(3): 287-292.

Assmann, G., Cullen, P., & Schulte, H. (1998). The Munster Heart Study (PROCAM). Results of follow-up at 8 years. European heart journal; 19: A2-11.

Assmann, G., Schulte, H., von Eckardstein, A., et al. (1996). High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. Atherosclerosis; 124: S11-S20.

Atkinson, B. L., & Y. Veriava. South African hypertension guideline 2006: PART 2. South African Medical Journal; 96 (2006): 337-362.

Bakris, G. L., Sarafidis, P. A., Weir, M. R., et al. (2010). Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. Lancet; 375(9721): 1173-1181.

Beckett, N. S., Peters, R., Fletcher, A. E., et al. (2008). Treatment of hypertension in patients 80 years of age or older. New England Journal of Medicine; 358(18): 1887-1898.

Beltran, A., McVeigh, G., Morgan, D., et al. (2001). Arterial compliance abnormalities in isolated systolic hypertension. American journal of hypertension; 14(10): 1007-1011.

Benner, J. S., Erhardt, L., Flammer, M., et al. (2008). A novel programme to evaluate and communicate 10-year risk of CHD reduces predicted risk and improves patients' modifiable risk factor profile. International journal of clinical practice; 62(10): 1484-1498.

Bigazzi, R., Bianchi, S., Baldari, D., et al. (1998). Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. Journal of hypertension; 16(9): 1325-1333.

Birtwhistle, R. V., Godwin, M. S., Delva, M. D., et al. (2004). Randomised equivalence trial comparing three month and six month follow up of patients with hypertension by family practitioners. British Medical Journal; 328(7433): 204.

Blood Pressure Lowering Treatment Trialists' Collaboration. (2003). Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet; 362(9395): 1527-1535.

Brand, M., Woodiwiss, A. J., Michel, F., et al. (2013). Chronic diseases are not being managed effectively in either high-risk or low-risk populations in South Africa. South African Medical Journal; 103(12): 938-941.

Cardio-Sis Study Group. (2008). Randomized study of traditional versus aggressive systolic blood pressure control: rationale, design and characteristics of the study population. Journal of human hypertension; 22(4): 243-251.

Carretero, O. A., & Oparil, S. (2000). Essential hypertension part I: definition and etiology. Circulation; 101(3): 329-335.

Chobanian, A. V., Bakris, G. L., Black, H. R., et al. (2003). "The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report." Journal of the American Medical Association; 289(19): 2560-2571.

Ciobanu, A., Magda, S., Cinteza, M., et al. (2007). A comparison of Indapamide SR 1.5 mg with hydrochlorothiazide 25 mg, in combination with an ACE-inhibitor, in patients with hypertension and diabetes: The AISHA study. Maedica-a Journal of Clinical Medicine, 2(4): 307.

Cohn, J. N., & Tognoni, G. (2001). A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. New England Journal of Medicine: 345(23): 1667-1675.

Coylewright, M., Reckelhoff, J. F., et al. (2008). Menopause and hypertension: an age-old debate. Hypertension; 51(4): 952-959.

Cushman, W. C., Evans, G. W., Byington, R. P., et al. (2010). Effects of intensive blood-pressure control in type 2 diabetes mellitus. New England journal of medicine; 362(17): 1575-1585

Davis, B. R., Cutler, J. A., & Gordon, D. J. (2002). Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Anti-hypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). Journal of the American Medical Association; 288(23): 2981-2997.

Davis, T. M., Millns, H., Stratton, I. M., et al. (1999). Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 29. Archives of internal medicine; 159(10): 1097-1103.

de Koning, L., Merchant, A. T., Pogue, J., & Anand, S. S. (2007). Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. European heart journal; 28(7): 850-856.

de Leeuw, P. W., Ruilope, L. M., Palmer, C. R., Brown, M. J., Castaigne, A., Mancia, G., ... & Wagener, G. (2004). Clinical significance of renal function in hypertensive patients at high risk: results from the INSIGHT trial. Archives of internal medicine; 164(22): 2459-2464.

Dennison, C. R., Peer, N., Lombard, C. J., et al. (2007). Cardiovascular risk and Co-morbid conditions among Black South Africans with hypertension in public and private primary care settings: The HiHi Study. Ethnicity & disease; 17(3): 477-483.

Department of Health. 2007. South Africa Demographic and Health Survey 2003. Pretoria: Medical Research Council.

Devereux, R. B., Wachtell, K., Gerdts, E., et al. (2004). Prognostic significance of left ventricular mass change during treatment of hypertension. Journal of the American Medical Association; 292(19): 2350-2356.

Domino, F. J., & Kaplan, N. M. (2010). Overview of hypertension in adults.

Available: http://www.uptodate.com/contents/overview-of-hypertension-in-adults [Accessed 19.08.2014]

Ehret, G. B. (2010). Genome-wide association studies: contribution of genomics to understanding blood pressure and essential hypertension. Current hypertension reports; 12(1): 17-25.

Eknoyan, G., & Levin, N. W. (2002). K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. American Journal of Kidney Diseases; 39(2 Suppl 1): S1-266.

Elliott, W. J. (2008). What factors contribute to the inadequate control of elevated blood pressure?. Journal of Clinical Hypertension; 10(Suppl.1): 20-26.

Erasmus, R. T., Soita, D. J., Hassan, M. S., et al. (2012). High prevalence of diabetes mellitus and metabolic syndrome in a South African coloured population: Baseline data of a study in Bellville, Cape Town. South African Medical Journal; 102(11): 841-844.

Estacio, R. O., Jeffers, B. W., Gifford, N., et al. (2000). Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care; 23: B54-64.

Fiscella, K., & Holt, K. (2008). Racial disparity in hypertension control: tallying the death toll. The Annals of Family Medicine; 6(6): 497-502.

Flack, J. M., Neaton, J. D., Daniels, B., et al. (1993). Ethnicity and renal disease: lessons from the multiple risk factor intervention trial and the treatment of mild hypertension study. American journal of kidney diseases; 21(4): 31-40.

Flack, J. M., Sica, D. A., Bakris, G., et al. (2010). Management of High Blood Pressure in Blacks an Update of the International Society on Hypertension in Blacks Consensus Statement. Hypertension; 56(5): 780-800.

Franklin, S. S., Gustin, W., Wong, N. D., et al. (1997). Hemodynamic patterns of age-related changes in blood pressure The Framingham Heart Study. Circulation; 96(1): 308-315.

Franklin, S. S., Jacobs, M. J., Wong, N. D., et al. (2001). Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensive analysis based on National Health and Nutrition Examination Survey (NHANES) III. Hypertension; 37(3): 869-874.

Franklin, S. S., Larson, M. G., Khan, S. A., et al. (2001). Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation; 103(9): 1245-1249.

Gelber, R. P., Gaziano, J. M., Orav, E. J., et al. (2008). Measures of obesity and cardiovascular risk among men and women. Journal of the American College of Cardiology; 52(8): 605-615.

Genovese G, Friedman DJ, Ross MD et al. Association of Trypanolytic ApoL1 variants with kidney disease in African Americans. Science 2010; 329(5993):841-845

Gerstein, H. C., Mann, J. F., Yi, Q., et al. (2001). Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. Journal of the American Medical Association; 286(4): 421-426.

Greeff, M., Kruger, A., & Van der Hoeven, M. (2012). Differences in health care seeking behaviour between rural and urban communities in South Africa. International journal of equity health; 11: 31-39

Gress, T. W., Nieto, F. J., Shahar, E., et al. (2000). Hypertension and anti-hypertensive therapy as risk factors for type 2 diabetes mellitus. New England Journal of Medicine; 342(13): 905-912.

Gueyffier, F., Bulpitt, C., Boissel, J. P., et al. (1999). Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. Lancet; 353(9155): 793-796.

Hair, J. F. Black, W., C., Babin, B., J., et al. (2010). Multivariate data analysis. 7th ed. Pearson Prentice Hall: New Jersey.

Haller, H., Ito, S., Izzo Jr, J. L., et al. (2011). Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. New England Journal of Medicine; 364(10): 907-917.

Halperin, R. O., Sesso, H. D., Ma, J., et al. (2006). Dyslipidemia and the risk of incident hypertension in men. Hypertension; 47(1): 45-50.

Hansson, L., Zanchetti, A., Carruthers, S. G., et al. (1998). Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet; 351(9118): 1755-1762.

Hillege, H. L., Fidler, V., Diercks, G. F., et al. (2002). Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation; 106(14): 1777-1782.

Howard, B. V., Ruotolo, G., & Robbins, D. C. (2003). Obesity and dyslipidemia. Endocrinology and metabolism clinics of North America; 32(4): 855-867.

Hulley, S. B., Rosenman, R. H., Bawol, R. D., et al. (1980). Epidemiology as a guide to clinical decisions. The association between triglyceride and coronary heart disease. New England Journal of Medicine; 302(25): 1383-1389.

Huxley, R., Mendis, S., Zheleznyakov, E., et al. (2009). Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk—a review of the literature. European Journal of Clinical Nutrition; 64(1): 16-22.

Hyman, D. J., & Pavlik, V. N. (2002). Poor hypertension control: let's stop blaming the patients. Cleveland Clinic Journal of Medicine, 69(10), 793-799.

Jamerson, K., Weber, M. A., Bakris, G. L., et al. (2008). Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. New England Journal of Medicine; 359(23): 2417-2428.

James, P. A., Oparil, S., Carter, B. L., et al. (2014). 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Journal of the American Medical Association; 311(5): 507-520.

Jensen, J. S., Feldt-Rasmussen, B., Strandgaard, S., et al. (2000). Arterial hypertension, microalbuminuria, and risk of ischemic heart disease. Hypertension; 35(4): 898-903.

Jermendy, G., Horváth, T., Littvay, L., et al. (2011). Effect of genetic and environmental influences on cardio metabolic risk factors: a twin study. Cardiovascular Diabetology; 10: 96-103.

Kannel, W. B. (1991). Left ventricular hypertrophy as a risk factor: the Framingham experience. Journal of hypertension; 9: S3-S9.

Kannel, W. B., & McGee, D. L. (1979). Diabetes and cardiovascular disease: the Framingham study. Journal of the American Association; 241(19): 2035-2038.

Kaplan, N. M., Bakris, G. L., & Forman, J. P. (2009). Genetic factors in the pathogenesis of primary essential hypertension. Update for patients. Available: http://www.uptodate.com/contents/genetic-factors-in-the-pathogenesis-of-primary-essential-hypertension [Accessed 19.08.2014]

Kearney, P. M., Whelton, M., Reynolds, K., et al. (2005). Global burden of hypertension: analysis of worldwide data. Lancet; 365(9455): 217-223.

Keil, J., E., Sutherland, S., E., Knapp, R., G., et al. (1993).Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardio-vascular and diabetic complications. Journal of Hypertension; 11: 309–317

Ker JA (2006). Essential hypertension. CME 2006;24:176-182

Klahr, S., Levey, A. S., Beck, G. J., et al. (1994). The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. New England Journal of Medicine; 330(13): 877-884.

Køber, L., Torp-Pedersen, C., Carlsen, J. E., et al. (1995). A clinical trial of the angiotensin-converting–enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. New England Journal of Medicine; 333(25): 1670-1676.

Kramer, H., Han, C., Post, W., et al. (2004). Racial/ethnic differences in hypertension and hypertension treatment and control in the multi-ethnic study of atherosclerosis (MESA). American journal of hypertension; 17(10): 963-970.

Krum, H., Skiba, M., & Gilbert, R. E. (2003). Comparative metabolic effects of hydrochlorothiazide and indapamide in hypertensive diabetic patients receiving ACE inhibitor therapy. Diabetic medicine; 20(9): 708-712.

Kunz, R., Friedrich, C., Wolbers, M., & Mann, J. F. (2008). Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin–angiotensin system on proteinuria in renal disease. Annals of internal medicine; 148(1): 30-48.

Kupper, N., Willemsen, G., Riese, H., et al. (2005). Heritability of daytime ambulatory blood pressure in an extended twin design. Hypertension; 45(1): 80-85.

Law, M. R., Morris, J. K., & Wald, N. J. (2009). Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. British medical journal; 338: 1665-1683.

Lee, C. M. Y., Huxley, R. R., Wildman, R. P., & Woodward, M. (2008). Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. Journal of clinical epidemiology; 61(7): 646-653.

Leeder, S., Raymond, S., Greenberg, H., et al. (2004). A race against time: The Challenge of Cardiovascular Disease in Developing Countries. The Centre for Global Health and Economic Development.

Levy, D., Salomon, M., D'Agostino, R. B., et al. (1994). Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. Circulation; 90(4): 1786-1793.

Lewington, S., Clarke, R., Qizilbash, N, Peto, R. & Collins, R. (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet; 360: 1903-1913.

Lewis, E. J., Hunsicker, L. G., Bain, et al. (1993). The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. New England journal of medicine; 329(20): 1456-1462.

Lewis, E. J., Hunsicker, L. G., Clarke, W. R., et al. (2001). Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. New England Journal of Medicine; 345(12): 851-860.

Liu, L., Zhang, Y., Liu, G., et al. (2005). The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. Journal of hypertension; 23(12): 2157-2172.

Lorell, B. H., & Carabello, B. A. (2000). Left ventricular hypertrophy pathogenesis, detection, and prognosis. Circulation; 102(4): 470-479.

Luft, F. C. (2001). Twins in cardiovascular genetic research. Hypertension; 37(2): 350-356.

Mabin, T., Sapoval, M., Cabane, V., et al. (2012). First experience with endovascular ultrasound renal denervation for the treatment of resistant hypertension. EuroIntervention; 8(1): 57-61.

Madhur, M. S. & Maron, D. J (2013). Hypertension Author: Meena S Madhur, MD, PhD; Chief Editor: David J Maron, MD, FACC, FAHA MEDSCAPE

Mampuya, W. M. (2012). Cardiac rehabilitation past, present and future: an overview. Cardiovascular diagnosis and therapy; 2(1): 38.

Mancia, G., Bombelli, M., Corrao, G., et al. (2007). Metabolic Syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) Study Daily Life Blood Pressure, Cardiac Damage, and Prognosis. Hypertension; 49(1): 40-47.

Mancia, G., Fagard, R., Narkiewicz, K., et al. (2013). 2013 ESH/ESC Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). European Heart Journal; 34(28): 2159-2219.

Manjunath, G., Tighiouart, H., Coresh, J., et al. (2003). Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney international; 63(3): 1121-1129.

Manjunath, G., Tighiouart, H., Ibrahim, H., et al. (2003). Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. Journal of the American College of Cardiology; 41(1): 47-55.

Maritz, F. J. (1995). Dyslipidaemia in South Africa. In: Krisela, S., Fourie, J., Temple, N. (eds.). Chronic diseases of lifestyle in South Africa since 1995-2005. Cape Town: Technical Reports; 97-108.

Mathew, J., Sleight, P., Lonn, E., et al. (2001). Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. Circulation; 104(14): 1615-1621.

Matsushita, K., van der Velde, M., Astor, B. C., et al. (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality: a collaborative meta-analysis of general population cohorts. Lancet; 375(9731): 2073.

McMurray, J., Östergren, J., Pfeffer, M., et al. (2003). Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM) programme. European journal of heart failure; 5(3): 261-270.

Moosa, M.R., Naiker, S., Naiker, I., et al,. 2004. South African Renal Society chronic dialysis guidelines. Durban: South African Renal Society.

Mulrow, C. D., Chiquette, E., Angel, L., et al. (1998). Dieting to reduce body weight for controlling hypertension in adults. Cochrane database of systematic reviews; 4: CD000484.

Naicker, J. (2012). Glomerular filtration rate (GFR) and estimation of the GFR (eGFR) in adults. Continuing Medical Education; 30(7): 235-237.

Naicker, S. (2003). End-stage renal disease in sub-Saharan and South Africa. Kidney International; 63: S119-S122.

Naicker, S. (2013). End-stage renal disease in Sub-Saharan Africa. Kidney International Supplements; 3(2): 161-163.

National Clinical Guideline Centre. Hypertension: Clinical management of primary hypertension in adults. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Aug. 36 p. (Clinical guideline; no. 127). Available: http://www.guideline.gov/content.aspx?id=34824 [Accessed 19.08.2014]

National Heart Lung and Blood Institute. (2002). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III): final report. Circulation; 106(25): 3143.

Neaton, J. D., & Wentworth, D. (1992). Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease overall findings and differences by age for 316099 white men. Archives of internal medicine; 152(1): 56-64.

Neter, J. E., Stam, B. E., Kok, F. J., et al. (2003). Influence of weight reduction on blood pressure a meta-analysis of randomized controlled trials. Hypertension; 42(5): 878-884.

Ntusi, N. B. (2011). Dismal management of hypertension at primary level: does it reflect a failure of patients, a failure of the system or a failure of doctors?: editorial. Cardiovascular journal of Africa; 22(4): 172-174.

Ntyintyane, L. M., Panz, V. R., Raal, F. J., & Gill, G. V. (2005). Metabolic syndrome, undiagnosed diabetes mellitus and insulin resistance are highly prevalent in urbanised South African blacks with coronary artery disease. Cardiovascular journal of South Africa; 17(2): 50-55.

Nyamdorj, R. (2008). BMI compared with central obesity indicators in relation to diabetes and hypertension in Asians. Obesity; 16(7): 1622-1635.

Obesity in Asia Collaboration. (2008). Is central obesity a better discriminator of the risk of hypertension than body mass index in ethnically diverse populations?. Journal of hypertension; 26(2): 169-177.

Okin, P. M., Devereux, R. B., Jern, S., et al. (2004). Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. Journal of the American medical association; 292(19): 2343-2349.

Okonofua, E. C., Simpson, K. N., Jesri, A., et al. (2006). Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension; 47(3): 345-351.

Onwukwe, S., C., & Omole, O., B. (2012). Drug therapy, lifestyle modification and blood pressure control in a primary care facility, south of Johannesburg, South Africa: an audit of hypertension management. South African Family Practice; 54(2): 156-161.

Opie, L. H., & Seedat, Y. K. (2005). Hypertension in sub-Saharan African populations. Circulation; 112(23): 3562-3568.

Palaniappan, L., Carnethon, M. R., Wang, Y., et al. (2004). Predictors of the incident metabolic syndrome in adults the insulin resistance atherosclerosis study. Diabetes Care; 27(3): 788-793.

Park, Y. W., Zhu, S., Palaniappan, L., et al. (2003). The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. Archives of internal medicine; 163(4): 427-436.

Parving, H. H., Brenner, B. M., McMurray, J. J., et al. (2012). Cardio renal end points in a trial of aliskiren for type 2 diabetes. New England Journal of Medicine; 367(23): 2204-2213.

Parving, H. H., Lehnert, H., Bröchner-Mortensen, J., et al. (2001). The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. New England Journal of Medicine; 345(12): 870-878.

Patel, A. (2007). Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet; 370(9590): 829-840.

Peltzer, K., & Phaswana-Mafuya, N. (2013). Hypertension and associated factors in older adults in South Africa: cardiovascular topics. Cardiovascular journal of Africa; 24(3): 66-71.

Pestana, J. A., Steyn, K., Leiman, A., & Hartzenberg, G. M. (1996). The direct and indirect costs of cardiovascular disease in South Africa in 1991. South African medical journal; 86(6): 679-684.

Pewsner, D., Jüni, P., Egger, M., et al. (2007). Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. British medical journal; 335(7622): 711.

Pfeffer, M. A., Sacks, F. M., Moyé, L. A., et al. (1999). Influence of baseline lipids on effectiveness of pravastatin in the CARE trial. Journal of the American College of Cardiology; 33(1): 125-130.

Pierdomenico, S. D., & Cuccurullo, F. (2010). Risk reduction after regression of echocardiographic left ventricular hypertrophy in hypertension: a meta-analysis .American journal of hypertension; 23(8): 876-881.

Pitt, B., Zannad, F., Remme, W. J., et al. (1999). The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New England Journal of Medicine; 341(10): 709-717.

Rayner, B. (2010). Hypertension: detection and management in South Africa. Nephron Clinical Practice; 116(4): c269-c273.

Rayner, B., & Becker, P. (2006). The prevalence of microalbuminuria and ECG left ventricular hypertrophy in hypertensive patients in private practices in South Africa. Cardiovascular journal of South Africa; 17(5): 245-249.

Reboldi, G., Angeli, F., de Simone, G., et al. (2014). Tight versus standard blood pressure control in patients with hypertension with and without cardiovascular disease. Hypertension; 63(3): 475-482.

Reinecke, H., Trey, T., Matzkies, F., et al. (2003). Grade of chronic renal failure, and acute and long-term outcome after percutaneous coronary interventions. Kidney international; 63(2): 696-701.

Ritz, E., & Bakris, G. (2009). World Kidney Day: hypertension and chronic kidney disease. Lancet; 373(9670): 1157-1158.

Ruggenenti, P., Fassi, A., Ilieva, A. P., et al. (2004). Preventing microalbuminuria in type 2 diabetes. New England Journal of Medicine; 351(19): 1941-1951.

Ruggenenti, P., Fassi, A., Ilieva, A. P., et al. (2011). Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: the BENEDICT-B randomized trial. Journal of hypertension; 29(2): 207-216.

Ruggenenti, P., Perna, A., Loriga, G., et al. (2005). Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. Lancet; 365(9463): 939-946.

Ruilope, L. M., Salvetti, A., Jamerson, K., et al. (2001). Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. Journal of the American Society of Nephrology; 12(2): 218-225.

Sample size calculator. Raosoft®[homepage on the Internet]. c2004 [cited 2010 March 13]. Available from: http://www.raosoft.com/samplesize.html

Sarnak, M. J., Greene, T., Wang, X., et al. (2005). The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. Annals of Internal Medicine; 142(5): 342-351.

Sarnak, M. J., Levey, A. S., Schoolwerth, A. C., et al. (2003). Kidney disease as a risk factor for development of cardiovascular disease a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation; 108(17): 2154-2169.

Sarwar, N., Danesh, J., Eiriksdottir, G., et al. (2007). Triglycerides and the risk of coronary heart disease 10 158 incident cases among 262 525 participants in 29 western prospective studies. Circulation; 115(4): 450-458.

Sassard, J., Bataillard, A., & McIntyre, H. (2005). An overview of the pharmacology and clinical efficacy of indapamide sustained release. Fundamental & clinical pharmacology; 19(6): 637-645.

Schillaci, G., Verdecchia, P., Porcellati, C., et al. (2000). Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. Hypertension; 35(2): 580-586.

Schoeman, H., S. (2009). A cross-sectional study of blood pressure control in hypertensive patients in general practice (the I-TARGET study). Cardiovascular Journal of Africa; 20:224–227.

Schrader, J., Lüders, S., Kulschewski, A., et al. (2005). Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention principal results of a prospective randomized controlled study (MOSES). Stroke; 36(6): 1218-1224.

Schrier, R. W., Estacio, R. O., Esler, A., & Mehler, P. (2002). Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney international; 61(3): 1086-1097.

Sciarretta, S., Valenti, V., Tocci, G., et al. (2010). Association of renal damage with cardiovascular diseases is independent of individual cardiovascular risk profile in hypertension: data from the Italy-Developing Education and awareness on Micro Albuminuria in patients with hypertensive Disease study. Journal of hypertension; 28(2): 251-258.

Seedat, Y. K., & Rayner, B. L. (2012). South African Hypertension Guideline 2011. South African Medical Journal; 102(1): 60-62.

Sehestedt, T., Jeppesen, J., Hansen, T. W., et al. (2010). Risk prediction is improved by adding markers of subclinical organ damage to SCORE. European heart journal; 31(7): 883-891.

SHEP Cooperative Research Group. (1991). Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Journal of the american medical ssociation; 265(24): 3255-3264.

Shulman, N. B., Ford, C. E., Hall, W. D., et al. (1989). Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. Hypertension; 13(Suppl 5): I80.

Solvd Investigators. (1991). Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. New england journal of medicine; 325: 293-302.

South African Medical Research Council. (2003). South Africa demographic and health survey 2003. Available: http://www.mrc.ac.za/bod/sadhs.htm [Accessed 15.10. 2014]

South African Medical Research Council. (1998). South Africa Demographic and Health Survey – 1998. Available: http://www.hst.org.za/sites/default/files/SADHS_1998_Full.pdf [Accessed 19.08.2014]

South African Renal Society. (2014). Recommendations for the Early Detection and Management of CKD. Available: http://www.sarenalsociety.org/guidelines/CKD_SARSdocument1.pdf [Accessed 19.08. 2014]

Sowers, J. R., & Bakris, G. L. (2000). Antihypertensive therapy and the risk of type 2 diabetes mellitus. New england journal of medicine; 342(13): 969.

Staessen, J. A., & Jiguang, W. (2001). Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet; 358(9287): 1033-1041.

Staessen, J. A., Fagard, R., Thijs, L., et al. (1997). Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet; 350(9080): 757-764.

Stamler, J., Wentworth, D., & Neaton, J. D. (1986). Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded?: Findings in 356 222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). Journal of the american medical association; 256(20): 2823-2828.

Steyn, K., Gaziano, T. A., Bradshaw, D., et al. (2001). Hypertension in South African adults: results from the Demographic and Health Survey, 1998. Journal of hypertension; 19(10): 1717-1725.

Steyn, K., Goldberg, Y. P., Kotze, M. J., et al. (1996). Estimation of the prevalence of familial hypercholesterolaemia in a rural Afrikaner community by direct screening for three Afrikaner founder low density lipoprotein receptor gene mutations. Human genetics; 98(4): 479-484.

Steyn, K., Levitt, D., Patel, M., et al. (2008). Hypertension and diabetes: poor care for patients at community health centres. South African Medical Journal; 98(8): 618-622.

Steyn, K., Levitt, N., Fourie, J., et al. (1998). Treatment status and experiences of hypertension patients at a large health center in Cape Town. Ethnicity & disease; 9(3): 441-450.

The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. (1993). Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet; 342(8875): 821-828.

The Heart Outcomes Prevention Evaluation (HOPE) Study investigators. (2000). Effects of ramipril on cardiovascular and microvascular outcomes in MICROHOPE substudy. Lancet; 355:253–259.

UK Prospective Diabetes Study Group. (1998). Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. British medical journal; 317(7160): 703.

Václavík, J., Sedlák, R., Plachý, M., et al. (2011). Addition of Spironolactone in Patients with Resistant Arterial Hypertension (ASPIRANT) a randomized, double-blind, placebo-controlled trial. Hypertension; 57(6): 1069-1075.

Van den Hoogen, P. C., Feskens, E. J., Nagelkerke, N. J., et al. (2000). The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. New england journal of medicine; 342(1): 1-8.

Van Rooyen, J. M., Kruger, H. S., Huisman, H. W., et al. (2000). An epidemiological study of hypertension and its determinants in a population in transition: the THUSA study. Journal of human hypertension; 14(12): 779-787.

Vasan, R. S., Larson, M. G., Leip, E. P., et al. (2001). Impact of high-normal blood pressure on the risk of cardiovascular disease. New england journal of medicine; 345(18): 1291-1297.

Vassalotti, J. A., Stevens, L. A., & Levey, A. S. (2007). Testing for chronic kidney disease: a position statement from the National Kidney Foundation. American journal of kidney diseases; 50(2): 169-180.

Vazquez, G., Duval, S., Jacobs, D.R. Jr., Silventoinen, K. (2007). Comparison of Body Mass Index, Waist Circumference, and Waist/Hip Ratio in Predicting Incident Diabetes: A Meta-Analysis. Epidemiologic reviews; 29:115-128.

Verdecchia, P., Reboldi, G., Angeli, F., et al. (2005). Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. Hypertension; 46(2): 386-392.

Verdecchia, P., Schillaci, G., Borgioni, C., et al. (1998). Prognostic significance of serial changes in left ventricular mass in essential hypertension. Circulation; 97(1): 48-54.

Viazzi, F., Leoncini, G., Conti, N., et al. (2010). Combined effect of albuminuria and estimated glomerular filtration rate on cardiovascular events and all-cause mortality in uncomplicated hypertensive patients. Journal of hypertension; 28(4): 848-855.

Volpe, M., Battistoni, A., Tocci, G., et al. (2012). Cardiovascular risk assessment beyond systemic coronary risk estimation: a role for organ damage markers. Journal of hypertension; 30(6): 1056-1064.

Wachtell, K., Olsen, M. H., Dahlöf, B., et al. (2002). Micro albuminuria in hypertensive patients with electrocardiographic left ventricular hypertrophy: the LIFE study. Journal of hypertension; 20(3): 405-412.

Walker, A. R. P., Walker, B. F., Manetsi, B., et al. (1990). Obesity in black women in Soweto, South Africa: minimal effects on hypertension, hyperlipidaemia and hyperglycaemia. Journal of the royal society for the promotion of health; 110(3): 101-103.

Wilson, P. W., Garrison, R. J., Castelli, W. P., et al. (1980). Prevalence of coronary heart disease in the Framingham Offspring Study: role of lipoprotein cholesterols. American journal of cardiology; 46(4): 649-654.

Wilson, P. W., Kannel, W. B., Silbershatz, H., & D'Agostino, R. B. (1999). Clustering of metabolic factors and coronary heart disease. Archives of internal medicine; 159(10): 1104-1109.

Wison, S., Foo, K., Cunningham, J., et al. (2003). Renal function and risk stratification in acute coronary syndromes. American journal of cardiology; 91(9): 1051-1054.

World Health Organization. (2008). Global Health Observatory. Available: http://www.who.int/gho/ncd/risk_factors/overweight [Accessed 19.08.2014]

World Health Organization. (2013). A global brief on hypertension. Available: http://www.who.int/ [Accessed 19.08.2014]

World Health Organization. (2011). Waist circumference and waist-hip ratio: Report of a WHO expert consultation, Geneva, 8-11 December 2008.

Wright Jr, J. T., Bakris, G., Greene, T., et al. (2002). Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. Journal of the american medical association; 288(19): 2421-2431.

Wuehl, E., Trivelli, A., Picca, S., et al. (2009). Strict blood-pressure control and progression of renal failure in children. New england journal of medicine; 361(17): 1639-1650.

Yusuf, S., Diener, H. C., Sacco, R. L., et al. (2008). Telmisartan to prevent recurrent stroke and cardiovascular events. New england journal of medicine; 359(12): 1225-1237.

Yusuf, S., Hawken, S., Ôunpuu, S., et al. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet; 364(9438): 937-952.

Yusuf, S., Teo, K., Anderson, C., et al. (2008). Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet; 372(9644): 1174-1183.

Zanchetti, A., Grassi, G., & Mancia, G. (2009). When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. Journal of hypertension; 27(5): 923-934.

Zhang, Y., Zhang, X., Liu, L., & Zanchetti, A. (2011). Is a systolic blood pressure target< 140 mmHg indicated in all hypertensives? Subgroup analyses of findings from the randomized FEVER trial. European heart journal; 32(12): 1500-1508.

APPENDIX & ADDENDUM:

Appendix A: Data collection sheet

Appendix B : Ethics clearance certificate

Appendix C: Permission letter, Superintendent, Dr Hlongwane

Appendix D: Permission letter, Head of Department, Internal Medicine, Dr Chita

Appendix E: Permission letter, Head of Hypertension Clinic, Dr Radev

Appendix F: Recommended hypertension clinic checklist and clerking sheet

Addendum

Appendix A: Data Collection:

Allocated Study Number: ----------

DEMOGRAPHICS:

Age	
Sex	
Race	

Hypertension Guidelines:

	Guidelines	Yes	No	Actual measurement
Blood pressure				
BMI	Every visit			
Body weight				
Height				
Abdominal Obesity	Every visit			
Waist circumference				
Waist-to-hip ratio				
Urine dipstick				
Protein	Every visit			
Blood	Yearly if normal			
Sugar	Repeat @next visit if abnormal on first			
Microalbuminuria				
Blood tests	First visit then yearly			
Creatinine	Yearly if normal			
Potassium	Yearly if normal			
Glucose(fasting)	Yearly if normal			
Random total cholesterol	Yearly if normal			
ECG(resting)	Yearly if normal			

Therapy:

Number of antihypertensive drugs	
Names of classes of drugs	

Comorbidities:

	Yes	No
Diabetes		
Dyslipidaemia		

APPENDIX B

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Farzahna Mohamed

CLEARANCE CERTIFICATE	**M120948**
PROJECT	A Retrospective Review of Hypertension Control at Helen Joseph Hospital Over a 3 Year Period
INVESTIGATORS	Dr Farzahna Mohamed.
DEPARTMENT	Department of Internal Medicine/Cardiology
DATE CONSIDERED	28/09/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 28/09/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Z Bayat

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX C

19 June2012

To whom it may concern:

Re: Research Project

Title: A retrospective review of hypertension control at Helen Joseph Hospital over a 3 month period

Investigator: Dr Farzahna Mohamed

This confirms that permission has been granted to the above doctor to conduct the above study at this hospital for degree purposes. The study is a retrospective clinical audit and descriptive study which entails analysis patient's records. The above doctor will have access to the medical records of the selected individuals. She has assured us of the anonymity of the data collection.

There will be no added financial cost to patients or the hospital.

Thank you,

Dr NL Hlongwane
Superintendent
Helen Joseph Hospital

APPENDIX D

19 June 2012

To whom it may concern:

Re: Research Project

Title: A retrospective review of hypertension control at Helen Joseph Hospital over a 3 month period

Investigator: Dr Farzahna Mohamed

This confirms that permission has been granted to the above doctor to conduct the above study at this hospital for degree purposes. The study is a retrospective clinical audit and descriptive study which entails analysis patient's records. The above doctor will have access to the medical records of the selected individuals. She has assured us of the anonymity of the data collection.

There will be no added financial cost to patients or the hospital.

Thank you,

Dr Chita
Acting Head of Department
Internal Medicine
Helen Joseph Hospital

APPENDIX E

19 June 2012

To whom it may concern:

Re: Research Project

Title: A retrospective review of hypertension control at Helen Joseph Hospital over a 3 month period

Investigator: Dr Farzahna Mohamed

This confirms that permission has been granted to the above doctor to conduct the above study at this hospital for degree purposes. The study is a retrospective clinical audit and descriptive study which entails analysis patient's records. The above doctor will have access to the medical records of the selected individuals. She has assured us of the anonymity of the data collection.

There will be no added financial cost to patients or the hospital.

Thank you,

Dr Radev
Head of Hypertension Clinic
Internal Medicine
Helen Joseph Hospital

APPENDIX F

Hypertension Clinic

Name: _____ **Hospital No:** _____

Sex: M F **Race:** B W I C **Height:** _____

Year of Diagnosis: _____ **Co-morbidities:** _____

_____

Major Risk Factors, Target Organ Damage & Complications (Tick Sheet)

Major Risk factors		***TOD***		***Complications***	
Level of SBP & DBP		LVH: ECG Sokolow- Lyon >35mm		Coronary Heart Disease	
Smoking		Urine Microalbuminuria		Heart failure	
Dyslipidaemia (mmol/l): -TC > 5.1, or -LDL > 3, or -HDL < 1 (men) -HDL <1.2 (female)				Chronic Kidney Disease: -macroalbuminuria -eGFR< 60 ml/min	
Diabetes mellitus				Stroke or TIA	
Men > 55 years				Peripheral Arterial Disease	
Women > 65 years				Advanced retinopathy -Haemorrhages -Exudates/Papilloedema	
Family history of early CVD: -Men < 55 years -Women <65 years					
Waist circumference : -Men ≥ 102cm -Women ≥ 88 cm					

Routine investigations: (Tick Sheet)

Investigation	***Clinic frequency***	***Comments***	
Body weight - BMI or WC	Every Visit	Target < 25 kg/m²	
Urine dipstick -Protein -Blood -Sugar	First visit Yearly if normal Repeat @next visit if abnormal	Abnormal dipstick: -Proteinuria ≥ 2+ -Haematuria ≥1+	
Microalbuminuria	First visit then yearly		
Blood tests -Creatinine (eGFR) -Potassium -Glucose (fasting) -Total cholesterol -Uric acid	All tests: Yearly if normal	↓Potassium(1^0aldosteronism / diuretics) -Hba1c / OGTT if 6.1-7.1mmol/l -TC > 5.1mmol/l – fasting lipogram - ↑ UA is C/I to diuretics	
ECG	Yearly if normal		

Date of Visit	Date of Visit	Date of Visit
Weight **BMI**	**Weight** **BMI**	**Weight** **BMI**
Urine Dipstick	**Urine Dipstick**	**Urine Dipstick**
BP (sitting) **BP (standing)**	**BP (sitting)** **BP (standing)**	**BP (sitting)** **BP (standing)**
Hx:	**Hx**	**Hx**
Exam	**Exam**	**Exam**
Plan	**Plan**	**Plan**

ADDENDUM

1. The study was conducted over a 3 month period from January to March 2012. The study objectives were designed to determine the number of patients in who target blood pressure was achieved in accordance with the 2011, fifth SAHG. Since the write up of this study, the sixth hypertension guideline has been published in 2014. The following revisions were made:
    a. Normal BP (mmHg) is now classified as an SBP < 120 or DBP < 90. Optimal BP is a new category defined as an SBP 120-129 or DBP 80-84. There is no change in the definitions of grade 1-3 HT and thus did not impact the results of the study.
    b. ISH has now been defined in the new guidelines, and is in keeping with the ESC definition of a SBP ≥ 140 with a DBP < 90. Patients in the study were classified with ISH using these criteria.
    c. The new guidelines recommend commencing drug therapy in all patients with grade 2 HT. The 2011 guidelines recommended a 3-6 month trial of lifestyle modification prior to initiating drug therapy, in those with moderate CV risk.
    d. Goals of therapy have been simplified in the 2014 SAHG, whereby a universal goal of antihypertensive treatment is a BP <140/90mmHg, regardless of CV risk and co-morbidities. This study classified target BP as per the 2011 SAHG criteria, whereby a BP goal of <130/80mmHg was recommended in high risk patients.
    e. The 2014 SAHG do not support the JNC 8 recommendations for a higher target BP < 150/90mmHg for persons > 60 years of age, without diabetes and CKD, but endorse this target in patients > 80 years of age. The study

used the 2011 SAHG recommendations for target BP in classifying the study participants.

2. Since the write up of this study, the results of the SPRINT trial were published in November 2015. The purpose of this trial was to assess if intensive BP control (SBP < 120mmHg) was superior to the commonly recommended target BP (SBP <140mmHg). All participants were > 50 years of age, with ≥ 1 CV risk factor, excluding diabetes. Of these participants, 28% were > 75 years of age. Intensive BP control was associated with a significantly lower rate of fatal and non-fatal CVE and death. However, adverse events including hypotension, syncope and electrolyte abnormalities were higher in the intensive group. This study may be one of many studies that may influence the future recommendations on target BP in the elderly.