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Management of Heart Failure at Chris Hani Baragwanath Academic Hospital

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Masters in Medicine in the branch of Internal Medicine

Johannesburg, 2016

i. Declaration

I, Piyush Meel, do hereby declare that this research report is my own original, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine at the University of Witwatersrand, Johannesburg. I further declare that this has not been previously submitted for any other examination or degree at this or any other university.

(Signed) _____

10 June 2016.

ii. Abstract

Heart failure with a reduced ejection fraction (HFrEF) is defined as heart failure with an ejection fraction of less than or equal to 45%. Guideline-based treatment of HFrEF has a significant impact on morbidity and mortality. Therefore, the adequacy of pharmacological treatment of HFrEF at the Chris Hani Baragwanath Academic Hospital (CHBAH) Medical Outpatients Department (MOPD) was assessed retrospectively between 2013 and 2014. In addition, the prevalence of aetiologies, comorbidities and complications of HFrEF were determined.

Mean age of 299 patients was 53 ± 15.4 (55% females). 67.1% received beta blockers, 76.9% received angiotensin converting enzyme inhibitors, 94% received furosemide and 65% received spironolactone. None were on hydralazine and isosorbide dinitrate combination therapy. Hypertensive heart disease, human Immunodeficiency virus associated cardiomyopathy, idiopathic dilated cardiomyopathy and diabetes were the aetiology of HFrEF in 65%, 23%, 13% and 10.4% of patients, respectively.

In conclusion, treatment of HFrEF was found to be suboptimal. Dissemination of national HF guidelines, doctors' education and improved organisation of care are potential solutions to effect improvement of service and patient care.

iii. Acknowledgments

I would like to thank Dr. Nirvarthi Maharaj for her guidance in this work. I would also like to thank my wife and family for their constant support.

iv. Contents

i. Declaration i

ii. Abstract ii

iii. Acknowledgement..... iii

v. List of figures..... vii

vi. List of tables..... viii

vii. List of abbreviations ix

1. Background of heart failure 1

1.1 Introduction 1

1.2 Definition 1

1.3 Burden of heart failure..... 2

1.4 Aetiologies of heart failure..... 4

1.4.1 Coronary artery disease 6

1.4.2 Hypertensive heart disease 9

1.4.3 Diabetes mellitus 9

1.4.4 Cardiomyopathies..... 10

1.4.5 Valvular heart disease 14

1.4.6 Thyroid disease..... 15

1.5 Pathophysiology of heart failure 16
1.5.1 Left ventricular dysfunction 16
1.5.2 Compensatory mechanism 17
1.6 Complications of heart failure 18
1.6.1 Arrhythmias 18
1.6.2 Stroke 19
1.6.3 Anaemia 19
1.6.4 Chronic inflammation 21
1.6.5 Electrolyte abnormalities 21
1.6.6 Cardio-renal syndrome 23
1.6.7 Venous and pulmonary thromboembolism 23
1.6.8 Other pulmonary complications of heart failure 24
1.6.9 Gastrointestinal complications, muscle wasting and exercise intolerance 24
1.7 Therapy of heart failure 25
1.7.1 Pharmacological therapy 25
1.7.2 Other agents including newer and experimental therapies 28
1.7.3 Non-pharmacological therapy 31
2. Objectives of the study 33
2.1 Primary objective 33
2.2 Secondary objectives 34

3. Methodology 34
3.1 Design 34
3.2 Duration 34
3.3 Patient selection 34
3.3.1 Inclusion criteria 35
3.4 Data capturing sheet 36
3.5 Data analysis 36
3.6 Ethics 36
4. Results 36
4.1 Patient characteristics 36
4.2 Aetiologies of HFrEF 40
4.3 Co-morbidities of heart failure 42
4.4 Complications of heart failure 43
4.5 Pharmacological therapy 44
5 Discussion 49
6 Study limitations 69
7 Conclusion 69
8 Appendix 71
9 References 76

v. List of figures

Figure 1 Age and sex distribution of patients with heart failure with reduced ejection fraction (HFrEF) 39

Figure 2 Aetiologies of heart failure with reduced ejection fraction (HFrEF)..... 40

Figure 3 Co-morbidites in patients with heart failure with reduced ejection fraction (HFrEF) 42

Figure 4 Complications of heart failure with reduced ejection fraction (HFrEF)..... 44

Figure 5 Pharmacological treatment of heart failure with reduced ejection fraction (HFrEF) 46

Figure 6 Anti-remodelling therapy in patients with heart failure with reduced ejection fraction (HFrEF) 47

vi. List of Tables

Table 1 Baseline characteristic of patients with heart failure with reduced ejection fraction (HFrEF) 38

Table 2 Distribution of various aetiologies according to age groups 41

Table 3 Medications and dosages..... 48

Table 8.1 Laboratory values according to national health laboratory service 71

vii. List of abbreviations

ACE	Angiotensin converting enzyme
ACEI	Angiotensin converting enzyme inhibitor
AHeFT	African-American Heart Failure Trial
AIDS	Acquired immune deficiency syndrome
ARB	Angiotensin receptor blocker
ARF	Acute rheumatic fever
ARV	Anti-retroviral
BMI	Body mass index
CAD	Coronary artery disease
CHBAH	Chris Hani Baragwanath Academic Hospital
CIBIS II	Cardiac Insufficiency Bisoprolol Study
CKD	Chronic kidney disease
CMO	Cardiomyopathy
CO	Cardiac output
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
CRP	C-reactive protein

CRT	Cardiac resynchronization therapy
CVD	Cardiovascular disease
DCMO	Dilated cardiomyopathy
DM	Diabetes mellitus
DVT	Deep venous thrombosis
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
Hb	Haemoglobin
HeFSSA	Heart Failure Society of South Africa
HF	Heart failure
HFpEF	Heart failure with a preserved ejection fraction
HFrEF	Heart failure with a reduced ejection fraction
HHD	Hypertensive heart disease
H-ISDN	Hydralazine and isosorbide dinitrate
HIV	Human immune deficiency virus
HIV-CMO	Human immune deficiency virus Associated cardiomyopathy

ICD	Implantable cardioverter-defibrillator
IDCMO	Idiopathic dilated cardiomyopathy
IHD	Ischaemic heart disease
LCZ696	Valsartan/Sacubitril
LV	Left ventricular
LVH	Left ventricular hypertrophy
MAP	Mean arterial pressure
MOPD	Medical Outpatients Department
MRA	Mineralocorticoid receptor antagonists
NHLS	National Health Laboratory Service
NYHA	New York Heart Association
PDE5	Phosphodiesterase Type 5
PE	Pulmonary embolism
PPCMO	Peripartum cardiomyopathy
PHC	Primary health care
RAAS	Renin angiotensin aldosterone system
SA	South Africa

SD	Standard deviation
SNS	Sympathetic nervous system
SOLVD	Studies of left ventricular dysfunction
SSA	Sub-Saharan Africa
SV	Stroke volume
TB	Tuberculosis
TPR	Total peripheral resistance
US	United States
VHD	Valvular heart disease
V-HeFT	Vasodilator-Heart Failure Trial
WHO	World Health Organisation

1 Background

1.1 Introduction

Heart failure (HF) is a major cause of morbidity and mortality worldwide and places a tremendous burden on the patient physically, psychologically and socially (Bleumink et al 2004, Lloyd-jones et al 2002, McMurray et al 2002, McMurray et al 1998). In addition, it is associated with huge economic cost to health care (McMurray et al 2002). Despite the existence of comprehensive, well-written national and international guidelines on HF, their use has been shown to be inadequate in Sub-Saharan Africa (SSA), including South Africa (SA), as well as in Europe and America (Damasceno et al 2012, Rywik et al 2008, Komajda et al 2003, Cleland et al 2002). This present study, dealing with patients diagnosed with HF at Chris Hani Baragwanath Academic Hospital (CHBAH), was conducted in an effort to characterise and compare the quality of pharmacological treatment of the disease in relation to the latest European Society of Cardiology (ESC) chronic HF guidelines and the Heart Failure Society of South Africa (HeFSSA) guidelines (McMurray et al 2012, Mpe et al 2013). Secondary aims were to characterise the aetiologies, comorbidities and complications of the cohort.

1.2 Definitions

HF is defined clinically as a syndrome whereby patients experience typical symptoms (e.g. breathlessness, ankle swelling and fatigue) and signs (e.g. raised jugular venous pressure, pulmonary crackles, S3 and displaced apex beat) resulting from an abnormality of cardiac structure and/or function (McMurray et al 2012). HF may be broadly divided into HF with a reduced ejection fraction (HFrEF) of 35% or less and HF with a preserved ejection fraction (HFpEF) of 50% or more. Patients who have an

ejection fraction (EF) of between 35% and 50% constitute a 'grey area', but have at least mild systolic dysfunction (Mann et al 2014). For the purposes of this study all patients with HF with an EF of less than or equal to 45% were considered. The reason for this is that a number of medications are recommended by guidelines for treatment of patients with an EF between 35% and 45% as their use has been shown to be beneficial (McMurray et al 2012). The New York Heart Association (NYHA) functional classification is used to describe the severity of HF. Patients with NYHA class I are asymptomatic and those with NYHA class II have mild symptoms, whereas those with NYHA class III and IV have moderate and severe symptoms, respectively (McMurray et al 2012).

1.3 Burden of heart failure

More than 20 million people suffer from HF worldwide and it is the commonest cause of hospitalisation of people older than age 65 (Bleumink et al 2004, Lloyd-Jones et al 2002, McMurray et al 1998). Both the prevalence and incidence of HF have increased over time and correlate directly with aging of the population (Bleumink et al 2004, Lloyd-Jones et al 2002). A number of studies propose the prevalence of congestive HF as being 3-20 cases per 1000 of the population, with a surge to more than 100 cases per 1000 of the population in people with an aged 65 years or more. On the whole, it is estimated that congestive HF affects 1-3% of the general population and 10% of elderly people. The Framingham and Rochester studies have indicated the overall incidence of HF to be 0.1-0.2%, with a 50% increase in incidence occurring every ten years of life (McMurray et al 2002). The lifetime risk of the development of HF in both sexes is one in five (Bui et al 2011).

Fewer people are dying of acute coronary events, hence survive to develop chronic cardiovascular disease (CVD) and HF, resulting in an increase in the incidence of the latter. A decrease in HF related to coronary artery disease may be attributable to the more frequent use of thrombolytic therapy and revascularisation techniques. The prognosis of HF has improved and so has the life expectancy of the elderly living with the disease in western populations (Cowie et al 1997). Compared to the developed world, data on the prevalence and incidence of HF in Africa and the developing world is scarce. Hospital-based studies are the main sources of such information; these estimate that CVD is responsible for 7-10% of all medical admissions to African medical institutions with HF accounting for 3-7% of this figure (Ntusi et al 2009).

The Framingham Heart Study reported that once a diagnosis of HF had been established, only 25% of men and 38% of women survived for five years (Cowie et al 1997). According to the Framingham study, the increasing age of HF patients is associated with an increase in the mortality rate, with a 27% and 61% increase in mortality rate per decade of life in males and females, respectively (Kannel et al 1994). Case fatality rates from congestive HF in some western countries are in the region of 15% per annum, compared to rates ranging from 9-12.5 % in African countries, although the latter figure may be misleading as a result of insufficient data (Kengne et al 2008, McMurray et al 2002). Half of all deaths affecting HF patients are sudden. This mode of death is five times more common in these people compared to the general population (Cowie et al 1997, Kannel et al 1994).

Patients affected by HF typically have a high readmission rate (Cowie et al 1997). HF is the leading cause of admission to hospital in patients older than 65, and it is responsible

for about 5% of all medical admissions in most nations. Congestive HF admission rates seem to be increasing gradually in the developed world, especially among the elderly. In general, annual admissions were between 10 and 40 admissions per 10 000 of the population in 1990 and rose to more than 75 admissions per 10 000 of the population in those aged 65 or more during that period. Less than 1% of the United Kingdom population was hospitalised annually for HF in the 1990s (McMurray et al 2002). In SSA the disease has been reported to be the fifth to sixth most common cause of admission in the general internal medicine wards. In Zimbabwe HF accounts for 6% of all hospital admissions (Kengne et al 2008).

HF is also a profound burden economically, as it is the commonest cause of hospitalisation in patients aged 65 or above, and is the second most common cardiovascular cause of physician outpatient visits in the United States (US) (McMurray et al 2002). In 1989, in the US, $8 billion was spent in the treatment of HF (Kannel et al 1994). Patients with HF are reported to have an extremely poor quality of life, with a significant impact on their activities of daily living, sexual activity and social interrelationships (McMurray et al 2002).

1.4 Aetiologies of Heart Failure

In western countries coronary artery disease (CAD) is the predominant cause of HF. In the US it has been shown that male sex, physical inactivity, cigarette smoking, increased body mass index (BMI), lower educational status, diabetes, hypertension, valvular heart disease (VHD), and CAD are all independently associated with an increased risk of congestive HF (He et al, 2001). In the developed world, VHD is a much less common cause of HF than previously (Cowie et al 1997). Rheumatic VHD and

cardiac manifestations of some communicable diseases, human immunodeficiency virus (HIV) infection and tuberculosis (TB), in particular, are much more common in the developing world (Ntusi et al 2009, Damasceno et al 2007). The bulk of HF cases in SSA occur as a result of non-ischaemic pathology and comprise mainly of rheumatic VHD, hypertensive heart disease (HHD) and cardiomyopathy (CMO), which are responsible for two thirds of cases in most studies (Ntusi et al 2009). Cor pulmonale, largely as a result of post-tuberculous destructive lung disease and pericarditis chiefly due TB causes 20% of cases of HF (Damasceno et al 2007). More than 30 million people in Africa are affected by HIV, which predisposes patients to HIV-related CMO and tuberculous pericarditis, both conditions that play an important role in the aetiology of HF in SSA (Ntusi et al 2009).

Data on HF in SA is limited; however, one study conducted at CHBAH established that in 844 cases of HF the commonest aetiologies were HHD (33%), idiopathic dilated cardiomyopathy (IDCMO) (28%), right HF (27%), ischaemic CMO (9%) and VHD (8%) (Stewart et al 2008). Of note was a lower incidence of ischaemic heart disease (IHD) in black people, which the study largely represented. This finding was consistent with other studies indicating the low incidence of IHD in black Africans (Ntusi et al 2009, Damasceno et al 2007, Walker et al 1997). Another study conducted in Kenya, which was based on echocardiography findings, concluded that HF was primarily the result of rheumatic heart disease (32%), followed by dilated cardiomyopathy (DCMO) (25%) and HHD (17%). IHD in this study was found to be an uncommon contributor in the aetiology of HF, corresponding to 2% of the total cases (Damasceno et al 2007). Lastly,

hyperthyroidism and hypothyroidism may also be associated with HF, as discussed below.

1.4.1 Coronary artery disease

CAD is the leading cause of HF in developed countries and smoking, diabetes, hypertension and obesity are the main risk factors for CAD (He et al 2001, Gheorghiade et al 1998, Kannel et al 1994). CAD is associated with a four times higher risk of the development of HF. It is estimated that between 14% and 20% of patients will develop HF within five to six years after experiencing a myocardial infarction (Mosterd et al 1997). The disease will manifest itself in some fashion in every fifth man and every 17th woman by the age of 60. Important determinants in the acquisition of this disease include hypertension, an increase in the total to high density lipoprotein cholesterol ratio, cigarette smoking, excess weight, elevated blood sugar levels, stress and electrocardiographic abnormalities (Castelli et al 1984). In 2006, CAD caused 425 425 deaths in the US and it was responsible for 1 of every 6 deaths. In the US, one person has a coronary event every 25 seconds and one death occurs every minute as a result of a coronary event (Go et al 2013).

Data in most developing countries has not been gathered adequately; however, CAD incidence rates have been estimated at 98 per 100 000 in China, 199 per 100 000 in 1990 in India and 166 per 100 000 in the Middle East. An estimated 58% of the worldwide CAD mortality affected the developing world in 1990, and mortality and

morbidity rates in the regions mentioned above are projected to double from 1990 to 2020. During this period it is predicted that there will be an increase of 120% in CAD mortality for women in the developing world, and the corresponding figure forecast for men is 137% (Okrainec et al 2004).

As indicated previously, CAD in Africa remains comparatively uncommon. CAD contributes to 6% of CVD in the South African black population and CAD mortality is reported to be only 0.2% (Bertrand 1995). In 1994, a mere 36 patients were diagnosed with CAD at CHBAH, which serves a population of 3 million people who reside in Soweto. The population consists of predominantly black South Africans. However, among South Africans of European and Asian ancestry CAD was the major cause of death (165.3 and 101.2 per 100 000 of the populations, respectively) (Walker et al 1997).

Hypertension is perhaps the strongest risk factor in the African context and has been reported to affect 10-30% of Africans (Onen 2013). Furthermore, hypertensive patients run more than twice the risk of CAD compared to normotensive individuals (Lip et al 2000). The increasing prevalence of IHD in diabetic patients in SSA has been attributed to westernisation of lifestyles. Among native African diabetic patients, IHD still remains considerably less prevalent compared to patients of European ancestry. This may be due to the shortage of traditional risk factors associated with IHD among African diabetics (Ntusi et al 2009).

The presence of a more favourable lipid profile, characterised by low total cholesterol and increased high density lipoprotein cholesterol levels, may be responsible for protecting black South Africans against IHD. This was indicated in the Transition of

Health during Urbanisation of South Africa study (Onen 2013). In contrast, another study conducted in Bloemfontein reported that the serum cholesterol level in black Africans had increased considerably. This particular study indicated that cholesterol levels were similar to levels in Mediterranean populations (Walker et al 1997).

Weight and increased truncal obesity are recognised as important risk factors for the development of CAD (Onen 2013, Steyn et al 2006). Black women were found to be the most overweight and obese (prevalence of 58.5%) in a sample of 7 726 South African women between the ages of 15 and 95 years. On the other hand, in a sample of 5401 South African men between the ages of 15 and 95 years, white men were recognised to have the highest prevalence of raised BMI and obesity (54.5%) (Steyn et al 2006).

Cigarette smoking is associated with a one and a half times increased risk of development of CAD compared to the risk run by non-smokers (Castelli 1984). The prevalence of smoking in SA is estimated at 16.2% (Shisana et al 2013). Exercise has been associated with decreased risk of development of CAD (Castelli 1984). Levels of physical fitness among South African populations seem to be inversely proportional to the economic status of the areas they inhabit (Shisana et al 2013).

Acute myocardial infarction causes necrosis of myocytes of the affected area(s) of a ventricle, which results in inadequate diastolic relaxation and systolic contraction. The myocardial scarring associated with this initial insult leads to local dysfunction and remodelling in remote areas of the left ventricle which is detrimental to ventricular function (Pazos-López et al 2011). The risk of HF is substantially increased in the event of ongoing dilatation of the left ventricle, within a month of the occurrence of a

myocardial infarction (Cowie et al 1997). Constantly reduced blood perfusion secondary to chronic severe coronary stenosis may lead to poor myocardial function. Furthermore, several arrhythmias such as atrial fibrillation and atrial flutter can deteriorate cardiac function in patients with CAD (Pazos-López et al 2011).

1.4.2 Hypertensive heart disease

The commonest cause of HF, according to the Framingham study, was hypertension; however, its significance in western countries is on the decline (Cowie et al 1997). In rural areas of West Africa, 30-40% of people aged 65 and above have hypertension, compared to 50% of semi-urban dwellers (Onen 2013). In 2000 hypertension affected about 80 million patients in SSA and it is predicted that in 2025 150 million people will have the disease (Twagirumukiza et al 2011). In most of Africa, HHD complicated by HF is a critical health problem (Ntusi et al 2009). Congestive HF as a consequence of HHD developed in 16% of black patients in a study which took place in the 1970s and analysed the prevalence of cardiac complications in 1 000 South African patients in a period of seven years (Seedat et al 1976). The Heart of Soweto study, discussed previously, also indicated HHD as the commonest cause of HF at CHBAH (Stewart et al 2008).

1.4.3 Diabetes mellitus

Type 2 diabetes mellitus (DM) is responsible for over 90% of cases of diabetes, and hence is the predominant form of the disease (Ntusi et al 2009). In 2011 the prevalence of diabetes in SSA was 14.7 million (4.02% of 366 million worldwide) and it is predicted to rise to 28 million by 2030 (Onen 2013). The chief cause of death in Type 1 diabetics

is HF, and numerous studies indicate that up to 25% of HF patients have diabetes (Kengne et al 2008, Rodrigues et al 1995). Approximately 50% of patients admitted for HF had diabetes in the Heart Failure in Israel Survey (Kengne et al 2008). In diabetics, pathological changes occur at the level of cardiac myocytes which are the result of chronic hyperglycaemia, insulin resistance and the deposition of collagen and other glycation end-products in the myocardium (Bell 2003, Bell 1995). These changes eventually result in diabetic cardiomyopathy with increased myocardial stiffness and early diastolic dysfunction (Factor et al 1980). Furthermore, patients with diabetic cardiomyopathy have a predisposition to hypertensive complications of the heart, and an increased mortality rate following acute myocardial infarction and subsequent development of HF (Jaffe et al 1984, Factor et al 1980).

1.4.4 Cardiomyopathies

When the muscle of the heart is structurally or functionally abnormal, in the absence of CAD, hypertension, valvular disease and congenital heart disease sufficient to explain the myocardial abnormality witnessed, it is termed a CMO (Elliott et al 2008). In Africa, CMO may be regarded as endemic or non-endemic. DCMO, post-partum cardiomyopathy (PPCMO), and endomyocardial fibrosis can be regarded as endemic, whereas hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy and HIV cardiomyopathy (HIV-CMO) are regarded as non-endemic (Ntusi et al 2009).

CMOs present a massive problem in Africa because of their high prevalence in communities burdened by poverty and destitution, difficulties in diagnosis mainly as a

result of lack of resources and adequate expertise and often the absence of effective intervention. Furthermore, they are associated with high mortality. The presence of impaired systolic function and left ventricular (LV) dilatation in the absence of a recognisable cause is termed IDCMO. Along with HHD and rheumatic heart disease it ranks as one of the chief causes of HF in Africa. DCM is responsible for 10-17% of all cardiac diseases identified at autopsy in Uganda and South Africa (Sliwa et al 2005). Despite a lack of population-based epidemiological studies in SSA, hospital data indicates that DCMO is the cause of HF in 20% of admissions to African hospitals for the disease (Ntusi et al 2009). It is usually diagnosed in the third and fourth decades of life, and is twice as prevalent in men as in women (Sliwa et al 2005). Furthermore, once patients are symptomatic, DCMO is associated with a four-year mortality of 34% (Ntusi et al 2009). Despite an unknown aetiology, DCMO is thought to be the end result of myocardial injury secondary to several insults, including haemodynamic, infective, immunologic, toxic and genetic factors. Possible causes of DCMO in Africans include 'burnt-out' hypertension, infection and myocarditis, autoimmunity, metabolic factors including iron overload and, lastly, pregnancy (Sliwa et al 2005).

It is often difficult to differentiate between DCMO and burnt-out HHD (Mokhobo 1980, Brockington et al 1976). This is because a percentage of patients with DCMO on index presentation demonstrate a hypertensive blood pressure reading; on the contrary, patients with HHD and marked systolic dysfunction may have normal blood pressure at the outset (Lawal et al 1988, Mokhobo 1980). In addition, features of hypertensive target organ damage, such as hypertensive nephropathy, may not be clinically appreciable (Mokhobo 1980).

Infections with Toxoplasma gondii, Coxsackievirus B and African trypanosomiasis have been studied in various African countries and have been implicated in the pathogenesis of myocarditis and subsequent development of DCMO (Sliwa et al 2005). It has been acknowledged since 1986 that HIV infection may be associated with a CMO. HF resulting from HIV-CMO bears a poor prognosis and a high mortality rate, especially among patients who are not on highly active antiretroviral (ARV) therapy (Ntusi et al 2009). Global systolic dysfunction with or without LV dilatation is characteristic of HIV-CMO (Magula et al 2003). It is not well understood how HIV infection is associated with HF (Butt et al 2011). Possible mechanisms include comorbidities associated with HIV infection (e.g. heavy alcohol consumption), ARV therapy with a resultant increased risk of coronary heart disease and subsequent HF, nutritional deficiencies, direct cardiotoxic effects of certain ARVs, myocarditis and immunologic damage to the myocardium (Butt et al 2011, Sliwa et al 2005).

Ongoing HIV replication seems to play an important role in the development of HF and a person with an HIV-1 ribonucleic acid level higher than 500 copies/ml has a significantly increased risk of the disease. Among HIV-infected people heavy alcohol consumption is more prevalent; which is a known risk factor for HF (Butt et al 2011). The use of potent ARV medication is associated with an increase in cardiovascular risk factors, including hyperlipidaemia, insulin resistance and truncal obesity. Thus, as HIV-positive people survive longer on ARV medication, CVD could become substantially more prevalent (Kamin et al 2005). A dose-dependent skeletal myopathy with associated cardiac dysfunction may occur with the use of zidovudine; this resolves when the drug is discontinued (Butt et al 2011).

In autopsy studies of acquired immunodeficiency syndrome (AIDS) patients, myocarditis is present in up to 50%. In HIV-infected people, myocarditis, myocardial dysfunction and HF may result from secondary infection of the heart by various pathogens. Cytomegalovirus, acid-fast bacilli, Toxoplasma gondii, Candida species, Histoplasma capsulatum, Cryptococcus neoformans, and Staphylococcus aureus have been isolated in the myocardium of HIV-infected patients (Butt et al 2011). In a prospective study carried out in Zimbabwe it was shown that 50% of acutely ill hospitalised patients who were HIV positive had cardiac abnormalities demonstrated on echocardiography. These abnormalities consisted of LV dysfunction, cardiomyopathy and pericardial effusion (22%, 9% and 19 %, respectively) (Ntusi et al 2009).

Immune hyperactivation, generation of anti-myocardial antibodies and subsequent myocardial inflammation and damage in response to endemic infections such as tryanosomiasis and viral infections are thought to result from an imbalance between helper and suppressor T cells. This was demonstrated in a Kenyan study (Sliwa et al 2005).

Chronic alcohol use has been strongly linked to the subsequent development of DCMO and has been reported to be a contributory agent in up to 45% of patients with the disease in Africa (Sliwa et al 2005). In some parts of Africa, excess iron from the consumption of iron-rich beer may be involved in the pathogenesis of DCMO (Swift 1996). This has been called Bantu haemosiderosis and is a potentially reversible condition (Sliwa et al 2005). Finally, thiamine and vitamin B6 deficiency are well-known causes of DCMO, with the former being present in up to 4% of alcoholic patients with HF (Tobias et al, 1989).

PPCMO is a type of DCMO that presents with clinical features of HF during the last month of pregnancy or within five months of the postpartum period. Autoimmunity caused by chimerism of hematopoietic progenitor cells from the foetus to the mother, myocarditis, and the haemodynamic stress of pregnancy have been proposed as aetiological agents in the pathogenesis of PPCMO (Elliott et al 2008). The worldwide incidence of PPCMO varies, with an incidence of 1 in 15 000 deliveries in the US compared to an incidence of 1 in 1000 deliveries in SA. Zaria, a province in Nigeria, has an incidence of 1 in 100 deliveries, the world's highest. This high rate has been associated with the consumption of Kanwa by women in the area (Sliwa et al 2005). Women affected by PPCMO have a better survival rate than patients with IDCMO, with a greater rate of spontaneous recovery of LV function. In addition, HIV co-infection has not been demonstrated to affect the outcome of patients with PPCMO. In a prospective South African study that included 100 patients with PPCMO, 15% died, and 23% recovered normal LV function after six months of optimal medical therapy (Ntusi et al 2009). After 25 years of follow-up of patients with PPCMO in Nigeria, the latest mortality rate found was 42% (Ford et al 1998).

1.4.5 Valvular heart disease

According to the World Health Organisation (WHO), acute rheumatic fever (ARF) and consequent rheumatic heart disease affect about 15.6 million people globally. Group A streptococcal infection of the pharynx precedes the development of acute rheumatic fever, which causes an inflammatory reaction in multiple organs, including the heart. This may eventually lead to fibrosis and damage of the heart valves, which in the long term leads to altered haemodynamics, cardiac remodelling and HF (Sliwa et al 2010).

The primary cause of VHD in SSA is infectious disease, comprising infective endocarditis and ARF (Ntusi et al 2009). In contrast to the developed world where VHD occurs in the elderly, in SSA it occurs commonly in young people, including school children (Sliwa et al 2010, Ntusi et al 2009). In SSA, RHD is responsible for 17-43% of all CVD and is associated with an alarmingly high annual mortality rate and morbidity (Ntusi et al 2009).

In a large study conducted between 2006 and 2007 at CHBAH, 960 patients (24%) from a total of 4005 new patients with HF were found to have valvular abnormalities. The majority of patients were women (59%) and black Africans (90%). Structural VHD affected 481 patients (51%) and 439 patients (46%) had functional VHD. Among those patients affected with structural VHD, 344 (36%) had newly diagnosed rheumatic heart disease and 101 (11%) had degenerative VHD. The main causes of functional VHD were right HF/pulmonary hypertension, IDCMO, PPCMO, hypertensive and ischaemic CMO (Sliwa et al 2010).

1.4.6 Thyroid disease

HF from hyperthyroidism is usually a consequence of tachycardia-mediated CMO. It has been reported that elderly patients with pre-existing hypertension or with risk factors for coronary heart disease, such as smoking and diabetes, are more vulnerable to the injurious haemodynamic effects of hyperthyroidism and the development of HF. Furthermore, atrial fibrillation has been found to be an independent risk factor for the development of HF and its onset could lead to deterioration of cardiac function (Siu et al 2007).

LV diastolic dysfunction is the most consistent abnormality in patients with overt hypothyroidism. LV systolic function is, however, only minimally affected as evidenced by mildly decreased values of ejection fraction (EF) and stroke volume (SV) (Crowley et al 1997, Wieshammer et al 1989). In the elderly overt hypothyroidism may be particularly hazardous and could often result in frank cardiac decompensation and congestive HF. Cardiac hypertrophy and interstitial fibrosis occur with aging and may intrinsically account for diastolic dysfunction and reduced cardiovascular performance (Fazio et al 2004).

1.5 Pathophysiology of heart failure

The clinical syndrome of HF represents the sum of many anatomic, functional, and biological alterations that interact together in a complex network and in different genetic and environmental backgrounds over a sustained period of time. The pathogenesis and progression of HF occur through various potential mechanisms, which interact within a spectrum (Jessup et al 2003). Proposed mechanisms include the cardio-circulatory and cardio-renal models. At some point during the course of HF, the disease will progress independently of the patient's haemodynamic status. This emphasises the role of other underlying pathological mechanisms, particularly a neuro-hormonal model that describes the progression of HF secondary to the overexpression of biologically active molecules that are toxic to the heart and circulation (Mann 1999).

1.5.1 Left ventricular dysfunction

HF may be considered a progressive disorder that occurs after an index event either damages the heart muscle, resulting in a loss of functioning cardiac myocytes, or alternatively interferes with the ability of the myocardium to generate force, which prevents the heart from contracting normally. This index event may occur suddenly, as in the case of a myocardial infarction, or it may have a gradual onset, as occurs in conditions associated with haemodynamic pressure or volume overloading. This initial insult results in a decline in pumping capacity of the heart. However, the majority of patients will remain asymptomatic or minimally symptomatic at this stage and will usually develop symptoms only after the dysfunction has been present for some time (Mann 1999). Many compensatory mechanisms become activated in the setting of cardiac injury or depressed cardiac output (CO) and seem capable of maintaining and regulating LV function for a period of days to months to years (Jessup et al 2003, Mann 1999). This may explain why patients with LV dysfunction may remain asymptomatic for a considerable amount of time (Mann 1999).

1.5.2 Compensatory mechanisms

Patients with HF have decreased CO, which in turn leads to a decrease in mean arterial pressure (MAP) and therefore decreased tissue perfusion. The body attempts to maintain adequate tissue perfusion and compensates in order to normalise MAP using multiple mechanisms including the Frank–Starling mechanism, neuro-hormonal activation and ventricular remodelling. Although initially these mechanisms are protective, their long-term effects serve to worsen HF in a vicious cycle (Kemp et al 2012).

The Frank–Starling mechanism represents the intrinsic capability of the heart to respond to an enhanced preload with an increase in force development (Weil et al 1998). It plays an important compensatory role in the early stages of HF; however, its role in end stage HF is controversial, with contradictory findings reported in studies (Kemp et al 2012, Weil et al 1998, Schwinger et al 1994).

Neuro-hormonal activation plays an important role in the maintenance of MAP and in compensation during early stages of HF. It also stimulates sodium and water retention, which maximizes SV and increases CO via the Frank–Starling mechanism. Activation of the sympathetic nervous system (SNS) and release of catecholamines (norepinephrine and epinephrine) occur in response to decreased MAP seen in HF. This activation causes peripheral vasoconstriction, in addition to having direct chronotropic and inotropic effects on the heart. MAP increases in response to the increased SV and total peripheral resistance (TPR). Activation of the renin–angiotensin–aldosterone system (RAAS) occurs, which leads to vasoconstriction, sodium retention and thirst stimulation. The end outcome of the activation of this particular neuro-hormonal system is to stimulate release of norepinephrine and vasopressin, enhance sodium reabsorption and increase contractility. Activation of these neuro-hormonal systems is important for compensation during early stage HF; however, in the long term it leads to ventricular remodelling with further deterioration of myocardial function (Kemp et al 2012).

Remodelling is a process whereby chronic haemodynamic stresses on the heart lead to alterations in the size, shape, structure and function of the ventricle. As remodelling occurs, the entire geometry of the heart changes, as it becomes less elliptical and more spherical. This is a compensatory mechanism of the failing heart, which enlarges in

order to increase ventricular volume and, therefore, a greater SV and higher CO despite a decreased EF. The remodelling process in HF is progressive and eventually becomes deleterious. Progressive ventricular enlargement and hypertrophy lead to increased wall tension and fibrosis, which ultimately worsen cardiac contractility (Kemp et al 2012, Mann 1999).

1.6 Complications of heart failure

The complications of HF include arrhythmias, stroke, anaemia, chronic inflammation, electrolyte abnormalities, cardio-renal syndrome, venous and pulmonary thromboembolism and additional complications affecting the respiratory system. Muscle weakness and gastrointestinal problems may also complicate HF.

1.6.1 Arrhythmias

Tachyarrhythmias, which may complicate HF, include atrial arrhythmias such as atrial fibrillation, atrial flutter and atrial tachycardia or arrhythmias that are of ventricular origin (Lip et al 2015). About a third (range 10-50%) of HF patients are affected by atrial fibrillation and its prevalence increases with the severity of HF (Watson et al 2000). The precise prevalence of atrial flutter and atrial tachycardia is uncertain; however, it is estimated that about 30% of HF patients have non-sustained atrial tachycardias. Malignant ventricular arrhythmias including sustained and non-sustained ventricular tachycardia, are frequent in advanced HF and are commonly assumed to be the cause of sudden death in HF. Bradyarrhythmias may also complicate HF and may be precipitated by drugs such as digoxin and beta-blockers, or electrolyte disturbances (Lip et al 2015).

1.6.2 Stroke

It is estimated that 10-24% of stroke patients have HF, and HF is thought to be the probable cause of stoke in 9% of all patients (Haeusler et al 2011). About 82% of all strokes are cardio-embolic and most cases occur secondary to thrombus formation due to atrial fibrillation or LV hypokinesia (Lip et al 2015, Haeusler et al 2011). HF may also be associated with hypotension and a hypercoagulable state, which may also increase the risk of stroke (Haeusler et al 2011).

1.6.3 Anaemia

Anaemia in HF is associated with increased hospitalisations and mortality. Various criteria have been used to classify patients as anaemic; however, the most commonly accepted definition is that of the WHO (haemoglobin [Hb] 13g/dl or 12g/dl in women) (Felker et al 2004). In a meta-analysis of 34 published studies involving 153 180 patients with HF, the prevalence of anaemia was reported to be 37.2% (Shah et al 2013). The prevalence of anaemia seems to correlate with the severity of HF and has been reported to be as high as 79% in patients with NYHA functional class IV. Although the pathophysiology of anaemia in HF is not entirely clear, there are several possible mechanisms by which HF could lead to its development (Felker et al 2004).

These include haemodilution, renal dysfunction, chronic inflammation, decreased perfusion to the bone marrow, malnutrition due to right HF and drug therapy (such as angiotensin-converting enzyme inhibitors). One of the features of HF is an expansion in plasma volume, thus anaemia may occur as a result of dilution rather than an actual reduction in red blood cell mass. In patients with HF, chronic kidney disease (CKD) and anaemia rank as some of the most common comorbidities. In advanced renal failure there is a decrease in circulating erythropoietin levels with a resultant decline in

erythrocyte production and Hb levels (Shah et al 2013, Felker et al 2004). Patients with end-stage renal disease and anaemia are susceptible to the development of cardiac complications including LV hypertrophy (LVH), LV dilatation and HF (Virani et al 2008, Horwich et al 2002).

Chronic inflammation plays a role in the development of anaemia in HF. In patients with substantial symptoms of HF, elevated levels of pro-inflammatory cytokines promote iron storage by the reticuloendothelial system, lead to reduced erythropoietin production and bone marrow resistance to erythropoietin, and, finally, result in hepatic hepcidin production which eventually prevents release of stored iron (Shah et al 2013, Felker et al 2004). Erythropoeisis is suppressed by angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). A decrease in Hb concentration to 0.3g/dL may occur with their use. This is due to the antagonism of a reduction in angiotensin II mediated renal hypoxia, which serves as a stimulus for erythropoietin production (Shah et al 2013).

1.6.4 Chronic inflammation

Plasma C-reactive protein (CRP) is frequently raised in HF, as demonstrated by multiple small studies, and elevated levels may be associated with the subsequent development of the disease. In one study, baseline CRP levels were measured in 4 202 patients with HF and were found to be raised compared to the general population. Furthermore, increased levels of CRP correlated with the severity of HF and were an independent marker of mortality and morbidity (Anand et al 2005). CRP can potentially aggravate HF through several processes including cytokine production through activation of the

complement system which results in myocyte necrosis and promotion of LV remodelling (Park et al 2014, Anand et al 2005).

1.6.5 Electrolyte abnormalities

Electrolyte abnormalities are a common complication of congestive HF (Leier et al 1994). They occur as a result of activation of the renin-aldosterone axis, renal dysfunction, exaggerated sympathetic activity with consequent rise in neuro-hormones such as catecholamines, and an increase in other substances (Kjeldsen 2010, Leier et al 1994). Furthermore, drug therapy, especially diuretics, can have detrimental effects on electrolyte balance (Cooper et al 1999). Electrolyte disturbances in people with a normal heart may have little adverse effect, but in the context of LV dysfunction may trigger malignant arrhythmias and even death (Kjeldsen 2010, Cooper et al 1999, Leier et al 1994).

Hyponatremia in HF develops as a result of multiple mechanisms, including the impaired ability of the kidney to excrete dilute urine as a result of diminished CO, activation of the sympathetic nervous system and renin-angiotensin-aldosterone axis and diuretic therapy, especially with thiazides. Hyponatremia usually indicates the severity of HF and may be associated with a poorer prognosis (Leier et al 1994).

Hypokalemia is generally defined as a serum potassium concentration that is lower than 3.5 mmol/L. Hypokalemia has been shown to be an independent risk factor for reduced survival in patients with HF (Kjeldsen 2010). The pathophysiological processes that occur in chronic congestive HF, described above, provide the ideal situation for the development of hypokalemia and its catastrophic complications (dysrhythmias, cardiac

arrest and death). Hypokalemia develops as a result of various mechanisms in CHF, including activation of the RAAS with associated increased potassium excretion though the action of aldosterone, diuretic therapy, mild respiratory or metabolic alkalosis (often secondary to diuretics) and magnesium depletion (Kjeldsen 2010, Leier et al 1994). Hyperkalemia can have clinical consequences as lethal as those of hypokalemia. Among the most common clinical reasons for the development of life-threatening hyperkalemia are inattention to complications of therapy (e.g., renal dysfunction), prescription of unacceptably large doses of a potassium-sparing diuretic or other medications that contributes to hyperkalemia and failure to discontinue the oral potassium supplement or potassium-sparing diuretic once hypokalemia has been corrected (Juurlink et al 2004, Leier et al 1994).

The development of hypomagnesemia and whole body magnesium depletion occurs as a result of the pathophysiologic milieu of congestive HF. Hypomagnesemia is thought to be arrhythmogenic and probably increases the risk of morbidity and mortality in some pathological conditions such as digitalis toxicity, prolonged QT interval and acute myocardial infarction. Furthermore, it often co-exists with and contributes to the development of resistant hypokalemia (Leier et al 1994).

1.6.6 Cardio-renal syndrome

The presence of CKD significantly increase the risk of developing congestive HF, and the coexistence of both diseases is associated with markedly increased mortality. Both CKD and congestive HF are diseases that have bidirectional effects on each other (i.e. each disease has an effect on the progression of the other) (Shiba et al 2011,

Silverberg et al 2004). Many proposed mechanisms of cardio-renal interaction are involved in the development of cardio-renal syndrome (Shiba et al 2011). These include factors that are common to both the kidney and the heart, including traditional cardiovascular risk factors, inflammation, release of humorally mediated factors, toxins and genetic risk factors, among others. In addition, there are organ-specific factors, including decreased CO with renal hypoperfusion, sodium and water retention with consequent hypertension, anaemia, brain natriuretic peptide, and electrolyte and acid-base imbalances (Shiba et al 2011, Silverberg et al 2004).

1.6.7 Venous and pulmonary thromboembolism

HF is an important and independent risk factor for venous thromboembolism. The prevalence of pulmonary embolism (PE) in HF patients ranges from 0.9% to 39%, whereas that of deep vein thrombosis (DVT) ranges from 10% to 59% (Dean et al 2010). Predisposing factors include immobility, LV systolic impairment and the existence of a possible chronic inflammatory state in HF (Dean et al 2010, Watson et al 2000).

1.6.8 Other pulmonary complications of heart failure

In addition to PE, other complications of the respiratory system that may occur in HF include pulmonary oedema, pulmonary hypertension, disorders of breathing during sleep and pneumonia (Figueroa et al 2006, Gehlbach et al 2004, Corrales-Medina et al 2013). Sleep disorders in HF are obstructive sleep apnoea and/or Cheyne-Stokes respiration/central sleep apnoea. These disorders have been reported to affect 40-50% of out-patients with chronic mild HF (Figueroa et al 2006).

1.6.9 Gastrointestinal complications, muscle wasting and exercise intolerance

Oedema of the absorptive mucosa and intestinal bacterial overgrowth may occur as a result of structural and functional abnormalities of the gastrointestinal tract in HF. These abnormalities further result in cardiac cachexia, anaemia and systemic inflammatory activation (Romeiro et al 2012). HF may also result in ischaemic hepatitis and chronic hepatic congestion, which lead to impaired hepatic function (Fouad et al 2014, Møller et al 2013). Muscle wasting occurs commonly in HF and is associated with reduced exercise capacity and muscle strength (Fülster et al 2013). An increased ratio of ventilation to carbon dioxide production and poor lung compliance related to pulmonary congestion also lead to exercise intolerance (Gehlbach et al 2004).

1.7 Therapy of heart failure

1.7.1 Pharmacological therapy

Two classes of drugs, namely ACEIs and beta blockers have become the mainstay of therapy to delay or stop the progression of cardiac dysfunction and improve mortality in HF. Even while these agents are underused in the treatment of HF, new classes of agents have been added that show an impact on mortality, increasing the complexity of optimal pharmacological therapy. These include ARBs, mineralocorticoid receptor antagonists (MRAs) and the combination of hydralazine and an oral nitrate (H-ISDN). All drugs used in the treatment of HF are used in conjunction with diuretics to eliminate

symptoms and signs of fluid overload (McMurray et al 2012). No randomised control trial has, however, demonstrated a reduction in mortality with their use.

Carvedilol, bisoprolol and metoprolol were all associated with fewer hospitalisations and significant mortality reduction in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), Cardiac Insufficiency Bisoprolol Study (CIBIS II) and Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trials, respectively. It is unclear whether this benefit will occur with use of other agents in the beta blocker class, as there is insufficient evidence. In the above mentioned trials most patients (>90%) were also concurrently on ACEIs, therefore the beneficial effects may not be so pronounced when beta blockers are used individually (McMurray et al 2012). A time-dependent 'biological' amelioration in intrinsic systolic function occurs with antiadrenergic treatment, which reverses some of the underlying abnormalities of HF (Bristow et al 1996). Optimum benefit seems to be related to the extent of beta blockade, although it is recommended that dose titration be individualised (Gullestad et al 2005a, Wikstrand et al 2002). The starting dose of carvedilol, a drug commonly used in the setting of this study, is 3.125 mg twice daily, with the target dose being 25 to 50 mg twice daily, depending on the patient's weight (McMurray et al 2012). Carvedilol has more holistic antiadrenergic properties and additional supplementary favourable properties, which may account for its larger effect on survival in comparison to second- generation compounds (Bristow et al 1996).

ACEI use in all classes of HF has been shown to reduce mortality; although controversial, it is recommended that maximal tolerated doses be used for optimum benefit (SOLVD Investigators 1992, CONSENSUS Trial Study Group 1987). The target

dose of enalapril, for example, is 20 mg twice daily (Kostis et al 1994). It is still recommended that ACEIs be used in black patients, although some trials have questioned their benefit in this patient group (Shekelle et al 2003). ARBs have been recommended for patients unable to tolerate ACEIs because of cough, and have been demonstrated to be equally effective or slightly inferior in mortality reduction and hospitalisation rate (Jong et al 2002).

ACEIs and beta blockers are powerful therapies, which result in a 25% to 40% reduction in mortality and hospitalisations for HF. This reduction is noted across all functional classes and degrees of LV dysfunction. The order of HF therapy has caused considerable debate previously; however, there appears to be general agreement now that it is safe and effective to initiate treatment with an ACEI or a beta blocker (Fang 2005).

MRAs have been demonstrated to reduce mortality and hospitalisation and are recommended in Class II HF with EF<30% or Class III-IV HF with EF<35% that does not improve with the combination of ACEI and beta blocker therapy (McMurray et al 2012). Doses of between 12.5 mg and 25 mg daily are effective in halting the effects of aldosterone, but may be increased to 50 mg in more severe cases of HF (Pitt et al 1999, RALES Investigators 1996). It is imperative to monitor potassium levels regularly with the use of MRAs (McMurray et al 2012).

Mortality and morbidity reduction with MRA therapy occurs as a result of aldosterone antagonism. Aldosterone increases sodium retention and potassium loss, causes myocardial and vascular fibrosis and baroreceptor dysfunction. These processes are

detrimental to the pathogenesis of HF, its progression and the risk of sudden cardiac death secondary to ventricular arrhythmias. Hence MRAs can be considered to be cardio-protective (Pitt et al 1999).

ACEIs in black patients were found to be less beneficial compared to H-ISDN in terms of mortality, as demonstrated by the Vasodilator-Heart Failure Trial (V-HeFT) trials. The reduced efficacy of angiotensin converting enzyme (ACE) inhibition in blacks appears to be related in part to a less active renin-angiotensin system in them (Carson et al 1999). The beneficial effect of H-ISDN was confirmed with the African-American Heart Failure Trial (A-HeFT) trial, which involved African-American patients with class III to IV HF who were on standard HF therapy (Taylor et al 2004). Therapy was also associated with a significant improvement in quality of life, improvement in symptoms and decreased hospitalisation. It is thus recommended that H-ISDN be considered as an alternative to an ACEI or ARB, if neither is tolerated, for the treatment of class II-IV HF patients with an EF≤45% and dilated LV (or EF≤35%) to prevent hospitalisation and the risk of premature death. Patients must also receive a beta blocker and an MRA. The prescription of this combination of drugs must also be considered in patients with an EF≤45% and an NYHA class between II-IV who have persistent symptoms despite treatment with a beta blocker, ACEI (or ARB) and an MRA (McMurray et al 2012).

The use of digoxin may be considered in HF patients with NYHA class II-IV and an EF≤45% who continue to have symptoms despite treatment with and ACEI (or ARB), beta blocker and an MRA, to reduce the risk of hospitalisation. It may also be considered in NYHA class II-IV HF patients to decrease the risk of hospitalisation in patients with an EF≤45% who are unable to tolerate a beta blocker (McMurray et al

2012). Its use has demonstrated a significant impact on hospitalisation rate but not on overall mortality (DIGITALIS Investigation Group 1997).

Ivabradine should be considered in addition to an ACEI, beta blocker and an MRA in patients with a heart rate ≥70 per minute despite adequate beta blockade. It has been proven to reduce hospitalisation and mortality in patients with systolic HF (McMurray 2012).

1.7.2 Other agents including newer and experimental therapies

N-3 polyunsaturated fatty acid therapy has been shown to reduce morbidity and mortality associated with HF as a result of decreased vascular resistance, improvement in LV diastolic function, reduced incidence of hypertensive ventricular hypertrophy and, finally, diminished vasoconstrictive responses to angiotensin II (Tavazzi et al 2008).

In patients with HF secondary to DCMO, immunoglobulin G and immuno-adsorption therapy may improve cardiac function through modification of the humoral and cellular inflammatory processes in the myocardium (Gullestad et al 2001, Staudt et al 2001).

Tolvaptan, a selective vasopressin V2 receptor antagonist, has been shown to normalise serum sodium levels in patients with hypervolemic hyponatremia secondary to congestive HF who have been on chronic diuretic therapy (Gheorghiade et al 2003). Hyponatremia in congestive HF is a poor prognostic indicator and therapy with tolvaptan will perhaps improve the outcomes of patients in this specific setting.

Multiple endogenous vasoactive peptides, namely natriuretic peptides, bradykinin and adrenomedullin are catabolised by the neutral endopeptidase, Neprilysin. Neprilysin

inhibition results in elevation of these peptides, antagonising the adverse effects of neuro-hormonal over-activation, which include vasoconstriction, sodium retention and pathological remodelling. In a large double-blinded randomised control trial involving 8442 patients with HF, Valsartan/sacubitril (LCZ696), which comprises the neprilysin inhibitor sacubitril and the ARB valsartan, was compared to the ACEI, enalapril. Patients included in the trial had class II, III or IV HF with an EF≤40%. Patients were randomised to either those that would receive LCZ696 at a dose of 200 mg bd or those that would receive enalapril at a dose of 10 mg bd. Importantly, the drugs were be given to their respective groups in addition to other recommended therapy for HF. The primary composite outcome was death from cardiovascular causes or hospitalisation for HF. The inhibition of both the angiotensin II Receptor and neprilysin with LCZ696 was found to be more effective than ACE inhibition with enalapril in reducing the risk of death from cardiovascular causes and hospitalisation of HF. In addition, LCZ696 was more effective in reducing death from any cause and was associated with a greater improvement in symptoms associated with HF and less physical limitation. These advantages of LCZ696 were highly significant and clinically important, and indicate that in patients with HF combined angiotensin receptor and neprilysin inhibition is superior to inhibition of the renin-angiotensin system alone (McMurray et al 2014).

Thalidomide can mitigate adverse myocardial remodelling and ameliorate LV function in congestive HF through its immunomodulatory properties (Gullestad et al 2005b). Adrenomedullin is a novel hypotensive peptide, acquired from human pheochromocytoma which acts as a circulating hormone and has a role in the regulation of volume and pressure homeostasis in congestive HF. Further research is needed to

determine the potential benefits of adrenomedullin therapy in congestive HF (Nicholls et al 2003). In patients with HF secondary to DCMO related to chronic viral infections, antiviral interferon may result in virus elimination and prevent progression of LV dysfunction (Daliento et al 2003, Kühl et al 2003).

Phosphodiesterase type 5 inhibitors (PDE5I) inhibit ergoreflex, which is characteristically exaggerated in patients with HF and plays a role in the deterioration of symptoms. Sildenafil, a selective PDE5I, increases nitric oxide bioavailability and efficacy in addition to modulation of exercise muscle signalling and reflex capacity neurogenic vasoconstriction. These actions, in turn, result in improved vascular responsiveness and ventilator efficiency, reduced pulmonary vascular resistance, increased exercise capacity and better health of patients with chronic LV systolic HF (Guazzi et al 2007).

Testosterone appears to be useful in the treatment of HF. In HF affecting both sexes, deficiencies in testosterone and anabolic hormone occur frequently and are independent risk markers for decreased exercise capacity and poor prognosis. Testosterone use also aids in the development of increased muscle mass which may increase endurance and decrease muscle fatigue in patients with HF. Improved baroreceptor sensitivity, elevation of Hb level, immunosuppression and the anti-inflammatory action of testosterone are additional ways by which this substance boosts exercise capacity and enhances the functional status of patients with HF (Toma et al 2012).

1.7.3 Non-pharmacological therapy of heart failure

The aim of management of HF is the provision of sustained, quality care of patients which involves participation of the hospital and the community within a continuum. Patients must join a multidisciplinary-care management programme in order to decrease the risk of HF hospitalisation. This programme would further consist of a cardiac rehabilitation programme, regular patient education and psychosocial support. It would also require adequate collaboration between doctors, nurses and allied health professionals (i.e. pharmacists, dietitians, physiotherapists, psychologists, social worker and primary care doctors).

Patients should be educated about HF as a disease, symptom monitoring and self-care, medication (i.e. indications, doses and side effects) and the importance of adherence to medication. Self-care behaviour would include the recognition of signs and symptoms, daily weighing, avoidance of excessive fluid intake and limitation of alcohol consumption. Recognition of worsening symptoms and signs would allow the patient to increase diuretic dose when necessary, and prompt them to seek medical care. Counselling should be offered as necessary with attention to the psychosocial aspects of HF (McMurray et al 2012).

Regular and structured exercise training is a vital part of cardiac rehabilitation and is currently recommended for stable NYHA class I-III HF patients. It improves exercise capacity, symptoms and quality of life of HF patients. In addition, it may reduce hospitalisation and mortality rate of HF. Prior to initiating exercise training, it is important to establish that the HF patient is clinically stable and all contraindications have been excluded through tests such as a stressing electrocardiogram and symptom limited exercise test. Exercise prescriptions for HF patients must be individualised, as there is

no universal agreement between various exercise regimens. Important factors to consider when prescribing an exercise regimen are behavioural characteristics, personal goals and choices. Regular endurance aerobic exercise is the cornerstone of exercise training in HF and is recommended in patients with HF to improve functional capacity and symptoms (McMurray et al 2012, Piepoli et al 2011). Resistance/strength training and respiratory training may also complement aerobic exercise depending on the individual needs of the patient (McMurray et al 2012, Piepoli et al 2011).

Implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) are significant developments in the management of HF. ICDs reduce the risk of sudden death from ventricular arrhythmias and bradyarrhythmias in patients with HF. They currently are indicated for the primary and secondary prevention of sudden cardiac death in patients with HF who meet specific criteria. CRT is indicated in certain HF patients who fulfill specific criteria in relation to QRS duration and morphology, EF and functional status. Further information regarding the exact indications for these therapies may be obtained from the ESC and HeFFSA guidelines (McMurray et al 2012, Mpe et al 2012).

It is important to note that the development and maintenance of an effective, structured and multidisciplinary cardiac rehabilitation programme, as described above may not be possible at CHBAH. This is because of the enormous problems that the hospital is facing, including tremendous shortage of staff, huge patient burden, stress among all levels of staff, poor organization, low health budget and poor resources (Landman et al 2001). In addition, patients are often from a poor socioeconomic background and may not be able to afford the financial cost that participation in such a programme would

demand from them. Despite all these problems, there are still a large number of hard working, staff members with outstanding commitment to patient care from various disciplines at CHBH (Von Holdt et al 1997). Thus, it is hoped in the current situation, that various members of staff by the application of the principles of cardiac rehabilitation can ease the burden of patients with HF by working in close collaboration in this resource limited environment.

2. Objectives of the study

2.1 Primary objective

The primary aim of this study was to characterise the quality of pharmacological management of HFrEF at CHBAH Medical Outpatients Department (MOPD) and to establish whether it was in accordance with current HeFFSA and ESC guidelines. For the purposes of this study, HFrEF was considered as HF with an EF≤45%.

2.2 Secondary objectives

The secondary objectives of the study were to determine the prevalence of the aetiologies, comorbidities and complications of HFrEF at the MOPD at CHBAH.

3. Methodology

3.1 Design

This was a single-centre, retrospective study which was conducted at CHBAH MOPD.

3.2 Duration

This study was conducted from 1 August 2013 to 31 August 2014.

3.3 Patient selection

The MOPD at CHBAH accepts new referrals for medical conditions from peripheral clinics and hospitals in Soweto and surrounding areas. Patients that are admitted to the medical wards at CHBAH for medical conditions, including HFrEF, are also subsequently followed up at MOPD. A significant number of HFrEF cases, however, are reviewed at the specialist cardiology clinic, depending on the complexity of the case at initial diagnosis as judged by the attending cardiologist or cardiology fellow in training. The management of HFrEF was expected to be poorer at MOPD in comparison to the specialist cardiology clinic based on multiple studies, which justified its preferential selection as the setting of this study (Rynik et al 2008, Komajda 2003, Mckee et al 2003). The sample size for this study was calculated based on the prevalence of HFrEF in a 2006 study conducted at CHBAH which was 47% (Stewart et al 2008). The calculated sample size was 383 patients with HFrEF. Due to time constraints and resource limitations, a convenient sample of 299 patients with HF with EF≤45% was selected. This sample size was comparable to that of similar studies conducted in Kenya and Ghana (Owusu 2007, Oyoo et al 1999). Files of MOPD patients were obtained from the MOPD records department at CHBAH and analysed until 299 patients

with documented HF and an echocardiogram proven EF of less than or equal to 45% had been obtained.

3.3.1 Inclusion criteria

a) EF ≤45% confirmed on echocardiogram
b) Previous diagnosis of HF
c) Age> 18 years

3.4 Data-capturing sheet

Relevant parameters including patient demographics (age, sex and race), vital signs (blood pressure and pulse), EF, aetiology of HF, the presence of any complications and/or co-morbidities and prescribed medications, were recorded in a data sheet. The data recorded reflected information documented by doctors whom the patients had consulted. In terms of the vital signs and medication prescriptions, the data was obtained from the patients' last (i.e., the most recent) MOPD visit. Information on patient demographics, presence of complications and/or co-morbidities and previous hospitalisations was largely obtained from the last MOPD visit, but if this information was not documented adequately, it was obtained from previous consultations and other relevant documents in the files. A documented history of previous hospital admission for HF was recorded in the data capturing sheet. Laboratory parameters that were recorded included the values of Hb, potassium, sodium, CRP and estimated glomerular filtration rate (eGFR). Laboratory data was collected from 'Labtrak,' the online results program provided by the National Health Laboratory Service (NHLS). This data

reflected the latest results of every patient that were available online during the period of the study.

3.5 Data analysis

A study number was allocated to each participant. A separate data sheet correlated names with a study number. All data captured was recorded in Microsoft Excel sheets. Data analysis was performed with Statistica version 12.5 series 0414 for Windows. The continuous variables were expressed as mean ± standard deviation (SD) or median. The categorical data was expressed as percentage.

3.6 Ethics

This retrospective study was approved by the Ethics Committee of the University of the Witwatersrand (Clearance number M140862).

4. Results

4.1 Patient Characteristics

The characteristics of the patients are presented in Table 1. The members of the study group were aged between 21-92 years, with a mean age of 53 ±15.4. There were 135 males and 164 females. A large number of females developed HFrEF at a younger age compared to their male counterparts, with a minimum age of 21 years and a mean age of 52.2 while the minimum age of males was 24, with a mean age of 54.1. The age and sex distribution of the patients is shown in Figure 1. Females had the highest incidence of HFrEF among all groups, except for the age group between 41 and 60 years, where

males had a higher incidence. Blacks (95.3%) were the majority of patients with HFrEF followed by coloreds (3.3%). Whites and Indians accounted for only two patients (0.7%). The mean systolic and diastolic blood pressures were 134.9 ± 16.6 and 76.8 ± 12.8, respectively. The mean pulse rate was 74.2 ± 8.4. The mean LV EF was 30.9 ± 9.75. Of the total study group, 290 patients (96.98%) had a history of previous hospital admission for HF.

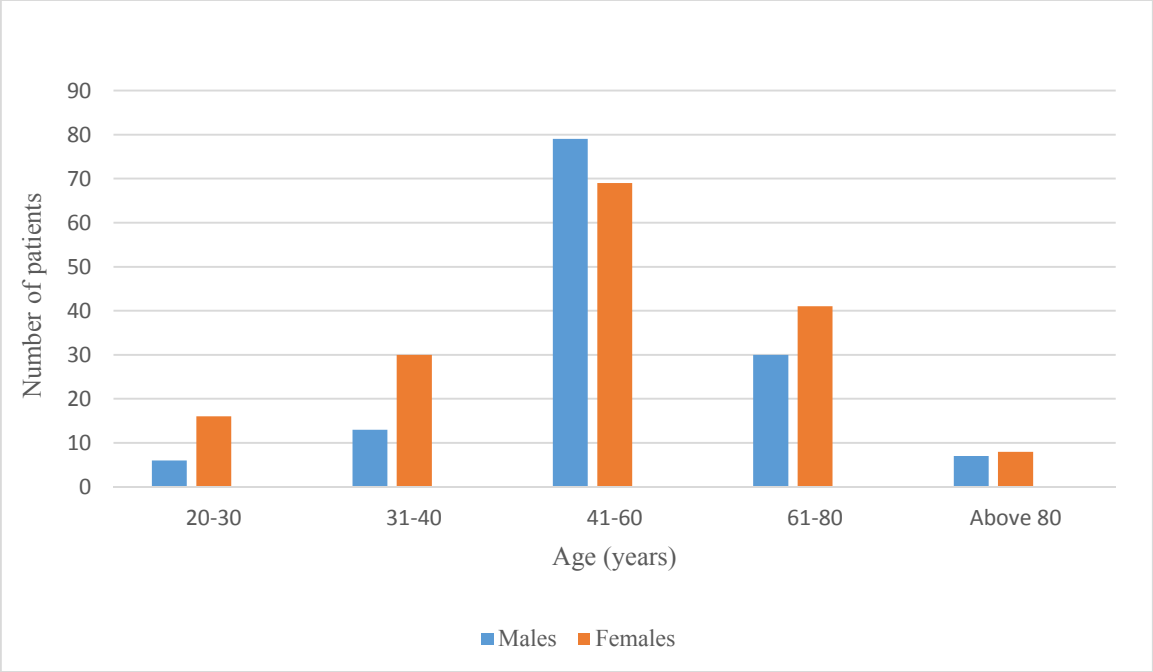
Table 1: Baseline characteristics of patients with heart failure with reduced ejection fraction (HFrEF)

N = 299 (Total)	**Number (percentage)**
Patient characteristics	
Age* (Years)	53 ± 15.4
Sex	
Male	135 (45)
Female	164 (55)
Race	
Black	285 (95.3)
Coloured	10 (3.3)
Indian	2 (0.7)
White	2 (0.7)
Clinical parameters	
Systolic blood pressure* (mmHg)	134.9 ± 16.6
Diastolic blood pressure* (mmHg)	76.8 ± 12.8
Pulse rate* (beats/minute)	74.2 ± 8.4
Left ventricular ejection fraction* (%)	30.9 ± 9.75

Previous hospital admission for heart failure	290 (96.98)

Data expressed as mean ± SD

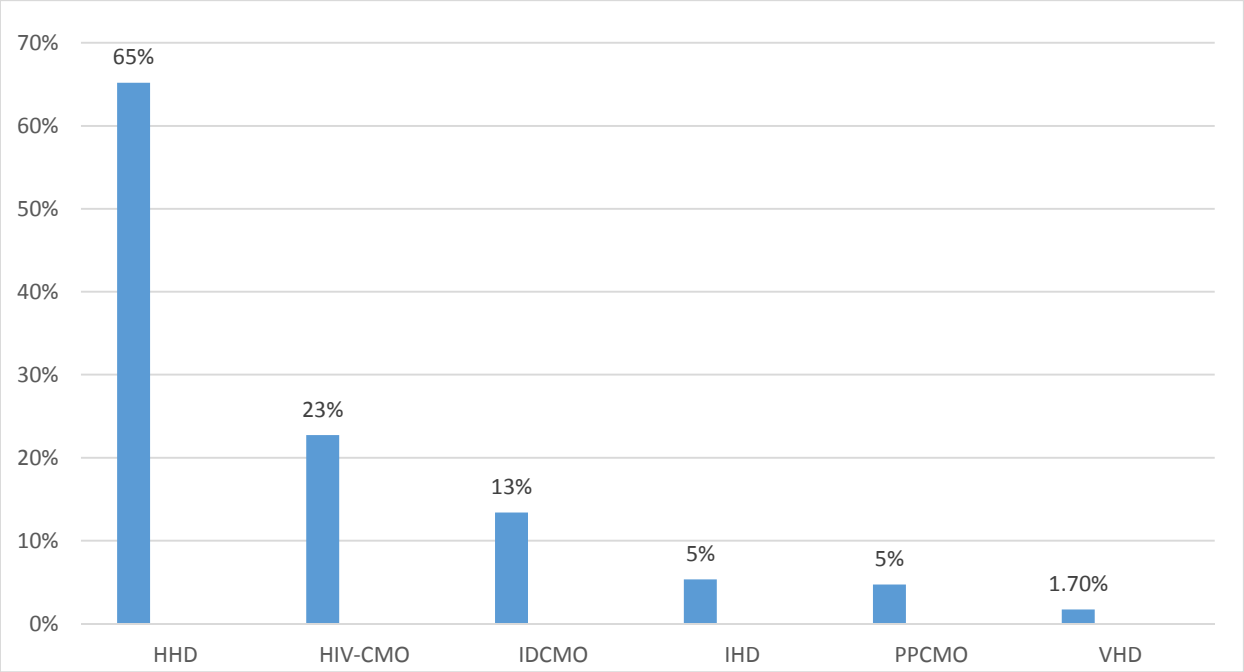
Figure 1: Age and sex distribution of patients with heart failure with reduced ejection fraction (HFrEF)



4.2 Aetiologies of HFrEF

As illustrated in Figure 2, HHD was the cause of HFrEF in the majority of the patients, affecting 196 of the total number of 299 patients, followed by, HIV-CMO, IDCMO, IHD, PPCMO, and, finally, VHD. The leading causes of HFrEF among young black women in the 20-30 age group were PPCMO and HHD. This was followed by IDCMO and HIV-CMO, as depicted in Table 2.

Figure 2: Aetiologies of heart failure with reduced ejection fraction (HFrEF)



HHD = Hypertensive heart disease, HIV-CMO = Human immunodeficiency virus associated cardiomyopathy, IDCMO = Idiopathic dilated cardiomyopathy, IHD = Ischaemic heart disease, PPCMO = Peripartum cardiomyopathy, VHD = Valvular heart disease

Table 2: Distribution of various aetiologies according to age groups. Note that the total number of patients equated to 338, as some patients had combinations of two different aetiologies

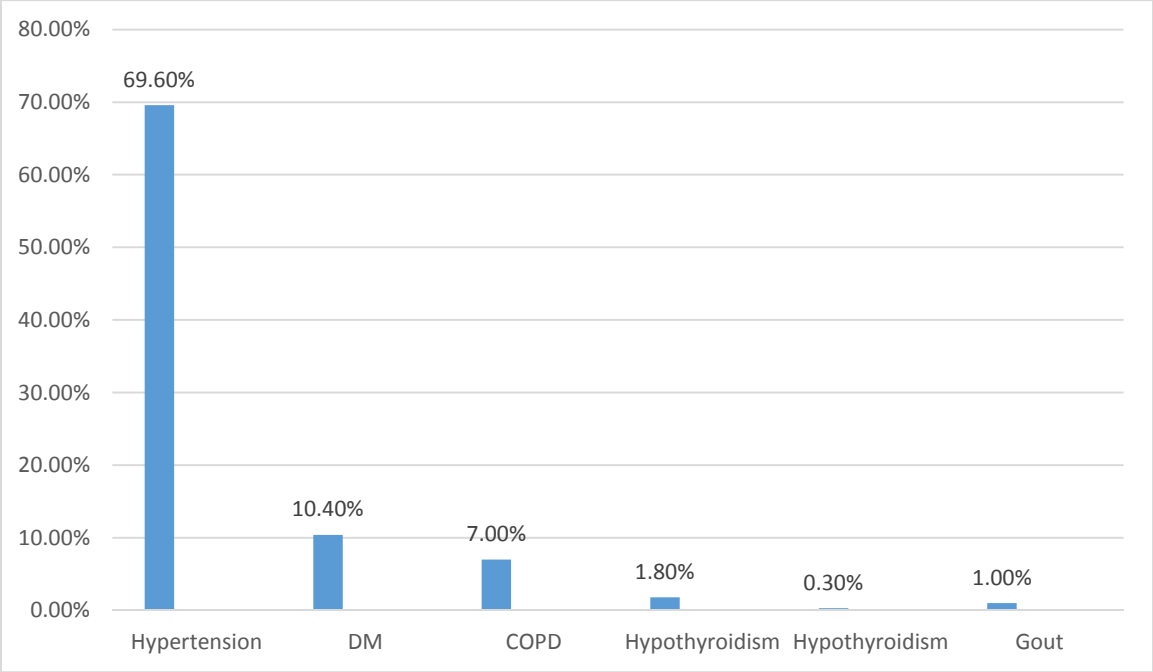
Age Group	Sex	Aetiology					
		HHD	DCMO	IHD	HIV-CMO	PPCM	VHD
20-30	F M	6 2	1 2	1 0	3 3	6 0	0 0
31-40	F M	10 7	2 4	2 0	16 4	6 0	0 0
41-60	F M	43 53	7 12	5 4	19 19	2 0	3 1
61-80	F M	36 25	6 5	1 2	1 3	0 0	1 0
Above 80	F M	7 6	0 1	1 0	0 0	0 0	0 0

HHD = Hypertensive heart disease, HIV-CMO = Human immunodeficiency virus associated cardiomyopathy, IDCMO = Idiopathic dilated cardiomyopathy, IHD = Ischaemic heart disease, PPCMO = Peripartum cardiomyopathy, VHD = Valvular heart disease

4.3 Co-morbidities

The distribution of the various co-morbidities in patients with HFrEF is indicated in Figure 3. Hypertension affected 197 patients with HFrEF of the total study group. Other co-morbidities included DM, chronic obstructive pulmonary disease, gout and thyroid disease.

Figure 3: Co-morbidities in patients with heart failure with reduced ejection fraction (HFrEF)

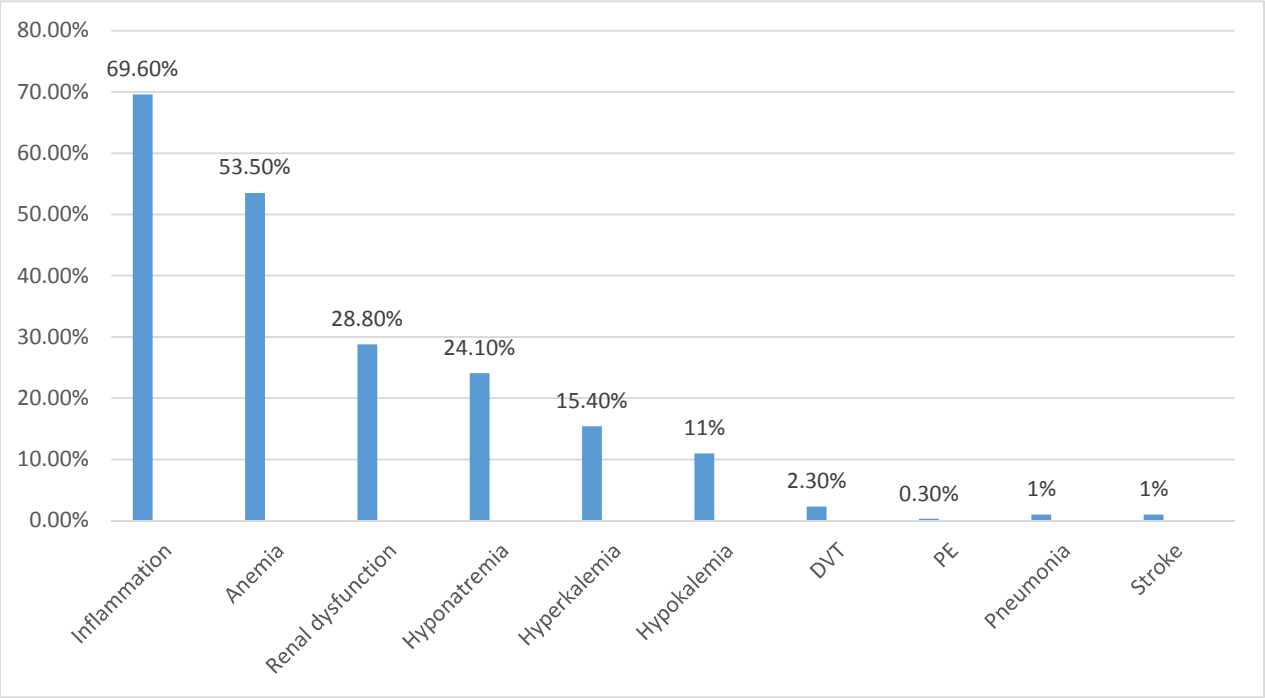


COPD = Chronic obstructive pulmonary disease, DM = Diabetes mellitus

4.4 Complications of HFrEF

The complications of HFrEF are depicted in Figure 4. The normal values of relevant blood tests as defined by the NHLS are indicated in Table 8.1 (Appendix). The presence of inflammation was defined by a CRP level of more than 5 mg/L. One hundred and eighty one of the 299 patients had a CRP result, therefore, the proportion of patients with an elevated level of CRP was calculated accordingly. Of the 181 patients with a CRP result, 126 had an elevated CRP. Anemia was defined by a haemoglobin level of less than 14.3 g/dL for men and less than 12.1g/dL for women. Anaemia was present among 160 of the total study group. Hyponatremia was defined by a sodium level of less than 136 mmol/L and affected 72 patients. Hypokalemia was defined as a potassium level less than 3.5 mmol/L whereas hyperkalemia indicated a potassium level of more than 5.1 mmol/L. Hypokalemia and hyperkalemia affected 33 and 46 patients, respectively. The definition of renal dysfunction was an eGFR of less than 60 ml/min/1.73m^2 according to the Modification of Diet in Renal Disease formula. Renal dysfunction was present in 86 patients. A diagnosis of DVT was made among seven patients previously, while one patient had a history of PE. The number of patients previously diagnosed with pneumonia and stroke were three in each case.

Figure 4: Complications of heart failure with reduced ejection fraction (HFrEF)



DVT= Deep vein thrombosis, PE= Pulmonary embolism

4.5 Pharmacological therapy

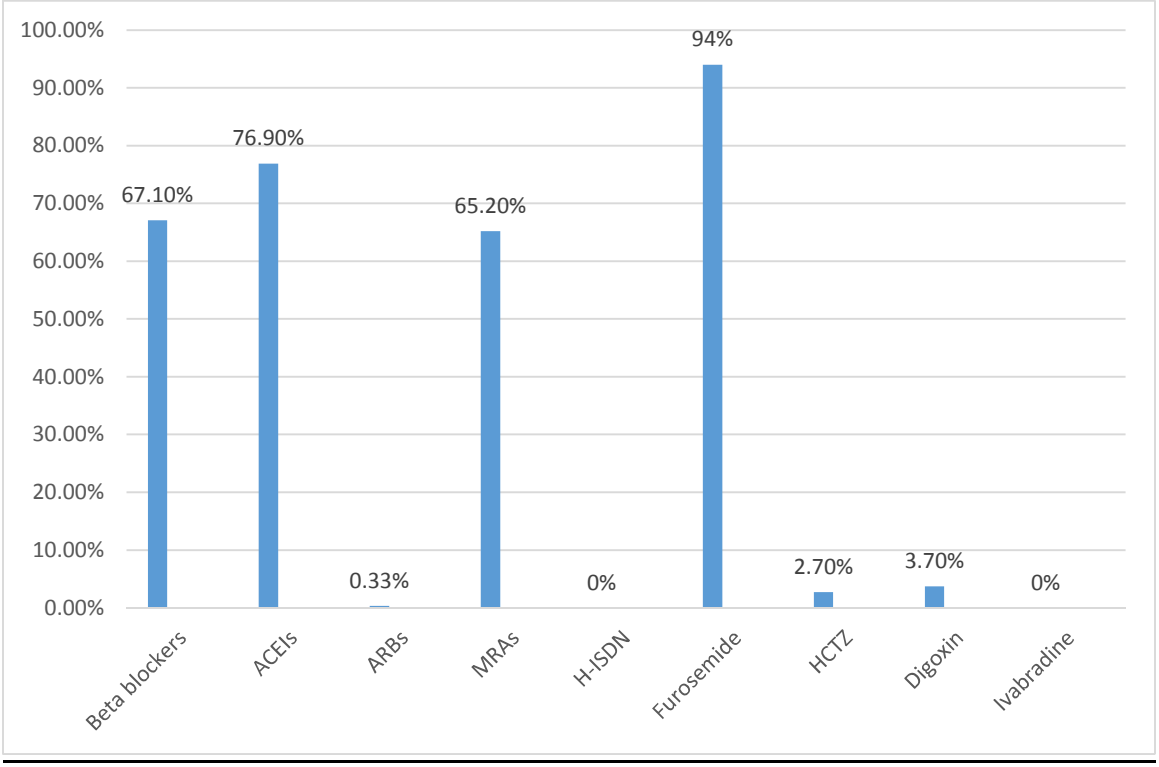
Figures 5 and 6 depict the distribution of the various drugs and drug combinations used in the treatment of HFrEF. Table 3 depicts the distribution of the various classes of drugs used in the treatment of HFrEF with their respective doses.

Two hundred and eighty-one (93.97%) patients of the total 299 patients with HFrEF were on furosemide, whereas only eight (2.67%) were on hydrochlorothiazide. The mean dosage of furosemide was 83.79 ± 85.04 and the median calculated to be 243.79.

Carvedilol was used in 191 patients (63.87%) in contrast to atenolol which was used in only 10 patients (3.3%). The mean carvedilol dose was 12.4 ± 11.7. The ACE inhibitor perindopril was prescribed in 179 patients (59.8%), while enalapril, a drug belonging to the same class, was used in 51 (17.05%) patients. Mean dosages of perindopril and enalapril were 4.06 ± 1.66 and 12.2 ± 8.26, respectively. The MRA antagonist spironolactone was used to treat HFrEF in 195 patients (65.2%), with a mean dose of 24.2 ± 8.9.

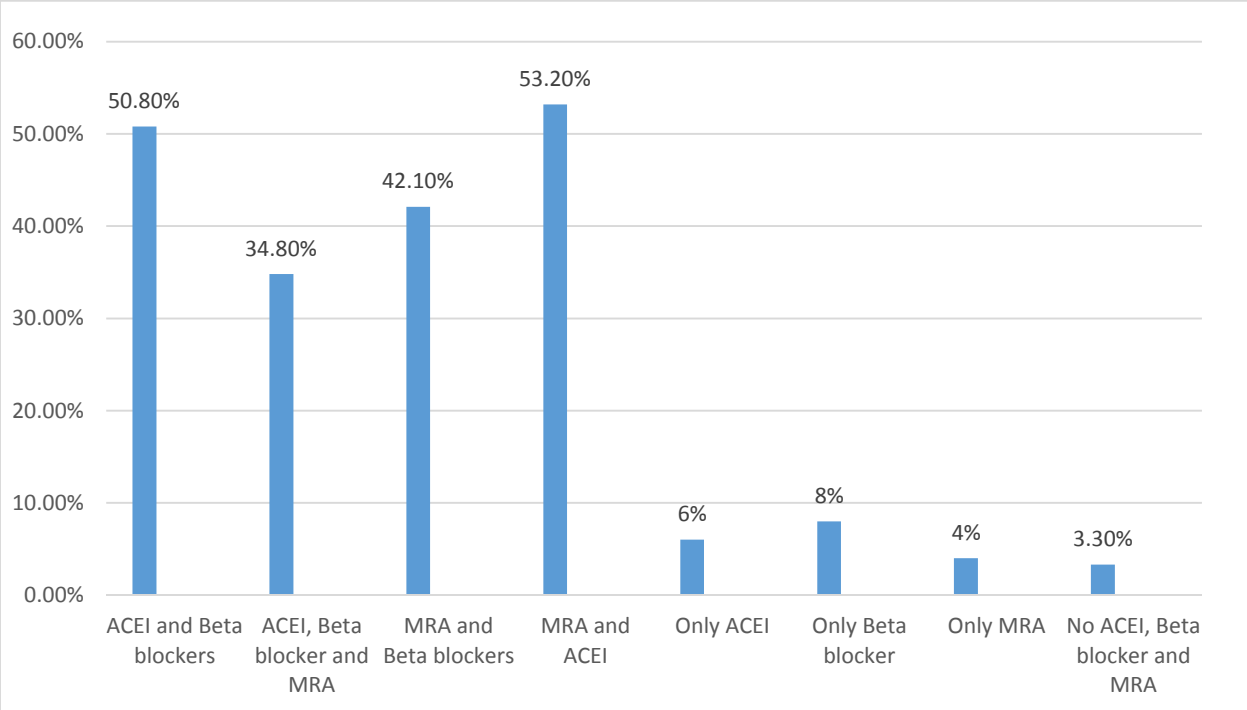
One (0.33%) patient was treated with telmisartan, the angiotensin receptor blocker. Digoxin was employed as treatment in 11 patients (3.67%). Hydralazine and ivabradine were not used as therapy of HFrEF in any patient.

Figure 5: Pharmacological treatment of heart failure with reduced ejection fraction (HFrEF)



ACEIs = Angiotensin converting enzyme inhibitors, ARBs = Angiotensin receptor blockers, MRAs = Mineralocorticoid receptor antagonists, H-ISDN = Hydralazine and isosorbide dinitrate, HCTZ = Hydrochlorothiazide

Figure 6: Anti-remodelling therapy in patients with heart failure with reduced ejection fraction (HFrEF)



ACEI= Angiotensin converting enzyme inhibitors, MRA=Mineralocorticoid receptor antagonists

Table 3: Medication and dosages

Medication	**Number (percentage)**	**Dosage (mean ± SD)**	**Dosage (median and range)**
Beta-blockers			
Atenolol	10 (3.3)	41.25 ± 25.03	37.5 (12.5-100)
Carvedilol	191 (63.87)	12.4 ± 11.7	6.25 (3.125-50)
ACEI /ARB			
Perindopril	179 (59.8)	4.06 ± 1.66	4 (2-12)
Enalapril	51 (17.05)	12.2 ± 8.26	10 (2.5-40)
Telmisartan	1 (0.33)	80	80
MRA			
Spironolactone	195 (65.2)	24.2 ± 8.9	25 (12.5-100)
Hydralazine and isosorbide mononitrate			
Hydralazine	0		
Isosorbide Mononitrate	12 (4)	11.25 ± 4.3	10 (5-20)
Diuretics			

Furosemide	281 (94)	83.79 ± 85.04	243.79 (20-1000)
Hydrochlorothiazide	8 (2.7)	15.6 ± 5.78	12.5 (12.5-25)
Digitalis glycosides			
Digoxin	11 (3.7)	0.13 ± 0.03	0.12 (0.12-0.25)
Other			
Ivabradine	0		

ACEI=Angiotensin converting enzyme inhibitor, ARB=Angiotensin receptor blocker, MRA=Mineralocorticoid receptor antagonist

5. Discussion

The mean age of male and female patients with HFrEF was 52.2 and 54.1 years, respectively. These findings were similar to those reported in the Heart of Soweto study cohort, as well as those indicated in other African studies (Stewart et al 2008; Owusu 2007; Oyoo et al 1999). Notably, compared to western populations in which HF affects mainly individuals above the age of 65, the mean age of patients in African countries, including SA, is significantly lower (Bui et al 2011; Stewart et al 2008; Owusu 2007; Oyoo et al 1999).

This difference may reflect the overall lower average life expectancy of South Africans and the impact of the HIV epidemic in delaying population growth (Albert 2008). Other factors that have a major impact on the health and life expectancy of South Africans

include dysfunction of the public health system, poverty, low levels of education, lifestyle factors (e.g. smoking, physical inactivity and alcohol consumption), and socio-cultural and environmental factors (Bradshaw 2008, Puoane et al 2008, Bradshaw et al 2001). The public health care system in SA is overburdened and has limited resources, resulting in significant under-diagnosis and inadequate treatment of chronic non-communicable diseases, which are known risk factors for the development of HF (e.g. hypertension, DM and hyperlipidaemia). Furthermore, nurses at peripheral care clinics in SA have been reported to lack skills to comprehensively manage such chronic non-communicable diseases (Puoane et al 2008). The progression of these conditions, which often co-exist in patients may eventually lead to the complication of HF. In addition, because of the resource limitations of the public health system, HF patients do not have access to life-saving treatments such as ICDs and CRT.

The variation in life expectancy between African and western countries may also be a result of differences in aetiologies and demographics of HF between economically disparate areas of the world (Owusu 2007). Rheumatic heart disease affects an alarming number of children and young adults in developing countries including SA, and HHD affects a significant number of young black women (Sliwa et al 2014, Sliwa et al 2014). The earlier occurrence of these diseases among these populations may lead to an earlier presentation with the clinical syndrome of HF. This is in stark contrast to the incidence of the disease in the increasingly elderly populations of developed countries as a result in advances in the treatment of IHD, which is the chief cause of HF among them (Cowie et al 1997).

Not surprisingly, the majority of patients with HFrEF were black (95.3%) because this represents the population, by far, to which CHBAH caters for geographical reasons (Walker et al 1997). Coloureds, Indians and whites represented a small minority of the patients in the current study. Women, particularly black women (153 out of 164), were the majority of patients with HFrEF in the current study, consistent with the findings of the Heart of Soweto study (Stewart et al 2008). This is in contrast to the incidence of HF in developed countries, where there is a significant predominance of males with the disease (Bui et al 2011).

HHD, IDCMO and HIV-CMO were the major causes of HFrEF in this study, while PPCMO, IHD and VHD were less important aetiologies. It is important to note, however, that this may not be a true representation of the various aetiologies of HFrEF at CHBAH as most patients with cardiac diseases are seen at the specialist cardiology clinic.

HHD has been found to be an important cause and among the commonest ones of HF in many African countries, including SA (Ntusi et al 2009; Stewart et al 2008; Damasceno et al 2007). High blood pressure is responsible for a high burden of disease in SA (including morbidity and mortality) (Shisana et al 2013). Blacks, which formed the predominant ethnic group in this study are considerably more affected by and experience more severe hypertension compared to other ethnicities (Onen 2013; Ntusi et al 2009; Ferdinand et al 2007; Opie et al 2005). Furthermore, they also experience early onset hypertension (Kengne et al 2008).

A large systematic review of 25 studies that were conducted in SSA between 1987 and 2004 indicated that the prevalence of hypertension was between 13% and 48% and that

hypertension placed a significant burden on women of African descent (Sliwa et al 2014). In 2003, it was reported that in SA only 18% of hypertensive men and 22% of hypertensive women had their blood pressure controlled (Puoane et al 2008). HHD (65%) accounted for the largest number of cases of HFrEF in this study. Although primarily affecting patients between the ages of 41 and 80 in this study, HHD was the cause of HF in a significant number of young patients. The majority of patients with HHD in this study were black women (27%) and 5.4% of this group were between the ages of 21 and 40. HHD was also found to be common among black women in the Heart of Soweto study and tended to affect them at a relatively young age (Sliwa et al 2014). In this study, among patients with HHD as a cause of HFrEF, the disease was a complication of hypertension in about 93% of the total number of hypertensive patients. This study highlights the important role of hypertension in the aetiology of HHD and subsequent HFrEF.

IDCMO and HIV-CMO were the other major causes of HFrEF in this study and their importance in this regard has been reported in multiple other studies in Africa as well as SA (Ntusi et al 2009; Damasceno et al 2007; Stewart et al 2008). Despite the fact that the aetiologies of IDCMO are to a great extent unknown, 'burnt-out' hypertension, infection, immunological factors and chronic alcohol use, as previously mentioned, are potential aetiologies, with the latter thought to be contributory in up to 45% of DCMO cases in Africa (Sliwa et al 2005). Chronic alcohol consumption may be an important cause of DCMO in South Africa, as according to a 2011 WHO report the consumption rate in the country is among the highest per capita in the world. It has been reported that 9-10 litres of pure alcohol are consumed per person annually in SA (Seggie 2012).

HIV-CMO has been reported to be the foremost cause of cardiac disease in acutely ill hospitalised patients with HIV infection (Magula et al 2003). Furthermore, HIV is reported to play an independent and important role in the development of HF (Butt et al 2011). PPCMO and IHD affected an almost equal number of patients as a cause of HF in this study. PPCMO is an important cause of HF in SA and other African countries (Ntusi et al 2009, Sliwa et al 2005). All patients affected by PPCMO in this study were black. This finding is in agreement with reports that the disease may be more common in black women, but it is confounded by the fact that the women may be of poor socioeconomic status, which is associated with an increased risk of PPCMO (Sliwa et al 2005). It may also reflect the large predominance of black patients in this study. The majority of patients in the study with IHD were black, which may reflect the possible changing epidemiology of modifiable risk factors associated with urbanisation, education and a higher income level among black Africans (Ntusi et al 2009).

Primary VHD, a disease that many experienced practitioners feel is not managed well in SA, usually presents as a complication of acute rheumatic fever and plays a major role in the development of HF in the country (Sliwa et al 2010, Commerford 2005,). Its incidence as an aetiology of HFrEF in this study was very low, probably because most patients with VHD that are seen at the MOPD are promptly referred to the specialist cardiology clinic for further management.

Hypertension, DM and COPD were the major comorbidities in this study. Thyroid disease and gout were present in a minority. Hypertension has been discussed previously. According to one large study involving 8,231 diabetic patients and 8,845 non-diabetic patients, those that were affected by diabetes had a rate of developing

congestive HF 2.5 times that were non diabetic patients (30.9 vs. 12.4 cases per 1,000 person-years). In addition to the high prevalence of DM in HF patients, it is associated with a worse functional status and prognosis (McMurray et al 2012, Nichols et al 2004)). Data on the quality of diabetic control in SA is relatively little, however, studies conducted in the Tshwane district revealed a high prevalence of poor diabetic care and poor glycaemic control (Webb et al 2015, Westaway et al 2008). The presence of COPD in HF patients is associated with worse functional status and a worse prognosis (McMurray et al 2012).

Inflammation, anaemia, renal dysfunction and electrolyte disturbances were the major complications of HFrEF identified in this study. Inflammation, as indicated by a raised CRP level, has been shown to have a direct relation with the progression of HF (Anand et al 2005). Anaemia was found to be a much more common comorbidity in this study compared to the findings of the Heart of Soweto study (41% vs 10%) (Stewart et al 2008). It is associated with greater severity of HF and increased morbidity and mortality (Shah et al 2013, Felker et al 2004). The incidence of renal dysfunction in this study was similar to that of the Heart of Soweto study (28.8 vs. 25%) (Stewart et al 2008). Its presence is associated with increased mortality in HF (Shiba et al 2011, Silverberg et al 2004). Hyponatremia was the most common electrolyte abnormality observed in the study. It is associated with increased severity of HF and contributes among other factors to a poor prognosis. Venous and pulmonary thromboembolism, stroke and pneumonia affected a minority of patients and may all occur as a complication of HF, as discussed previously.

It is evident from the results of the current study that pharmacological management of HFrEF is suboptimal and does not comply with the latest ESC or HeFSSA guidelines on the management of the disease. The HeFSSA guidelines have, in essence, been derived from the ESC guidelines and have been endorsed by HeFSSA (Mpe et al 2013). Both guidelines recommend that all patients with LV dysfunction, regardless of NYHA class, receive both ACEI and beta blockers (McMurray et al 2012, Mpe et al 2013). Unless contraindicated, it would be expected that all patients that satisfied the inclusion criteria (i.e. had HFrEF) would have received a beta blocker and an ACEI as minimum therapy. However, this was not the case, as only 201 (67.2%) and 230 (76.9%) patients were treated with beta blockers and ACEIs, respectively. It was discovered that only 50.8% of patients received the combination of an ACEI and a beta-blocker. Furthermore, 6% of patients received ACE inhibitors exclusively without any other anti-remodelling therapy, and 8% of patients received only beta blockers. This was of concern, as the roles of ACE inhibitors and beta blockers in the treatment of HFrEF are complementary and both medications must be started promptly soon after diagnosis (McMurray et al 2012). However, there is benefit, albeit less, in the use of an ACEI without use of a beta blocker in the treatment of HFrEF, as the Studies of Left Ventricular Dysfunction (SOLVD) and Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trials demonstrated, where the use of beta blockers was less than 10% (Solvd Investigators 1992, Consensus Trial Study Group 1987). Furthermore, it has been shown in a study that although ACEIs and beta blockers, when used in the treatment of HFrEF, is each associated with a decrease in 24-month mortality when used individually, there is a more significant incremental reduction in

mortality in the same period when they are used in combination (Fonarow et al 2012). It is important to note, however, that in the SOLVD trial the benefits of ACEI were in addition to those rendered by the MRA, spironolactone, which all patients received (McMurray et al 2012). The combination of an MRA and ACEI was used in 53.2 patients in this study, whereas the combination of an ACEI, beta- blocker and MRA was used in 34.80% of patients.

In the treatment of HFrEF according to the ESC and HeFSSA guidelines, an MRA is added to conventional treatment (i.e. ACEI and beta blocker) when there is no improvement in symptoms in a patient with an EF ≤ 35% in order to reduce the risk of HF hospitalisation and premature death (McMurray et al 2012). It is possible that patients who were not prescribed spironolactone were well controlled on a combination of an ACE inhibitor and a beta blocker and did not require further anti-remodelling therapy. No major trials have been conducted that studied the role of MRAs as an anti-remodelling drug when used without either an ACE inhibitor or beta-blocker, or both, in the treatment of HFrEF (McMurray et al 2012). Therefore, the use of MRAs as the only anti-remodelling therapy among 4% of patients in this study is unjustified.

Although the beneficial effects of ACEIs are thought to be a class effect, the efficacy of perindopril has not been demonstrated in any randomised control trials in the treatment of HFrEF. In this study perindopril was used remarkably more than enalapril (59.8% vs. 17%), despite this fact. It was also concerning that the ACEI that was used most did not have well-defined maximum recommended doses for the treatment of HFrEF because of the lack of investigational RCTs in this regard. In addition, among the relatively small

number of patients who did receive enalapril, the mean dose was suboptimal (12.2 ± 8.26 mg) and much less than the recommended target dose to obtain substantial benefit for patients with HFrEF (McMurray et al 2012).

Carvedilol was the predominant beta blocker used in this study, while a minority of patients were receiving atenolol. The mean dose of carvedilol was also substantially lower than the recommended maximum doses (50-100 mg daily) for optimum benefit in HF (McMurray et al 2012). The beneficial effect of atenolol in the treatment of HFrEF has not been investigated prospectively in any large RCT, although one retrospective study involving 11 326 patients suggests that it has an effect on mortality similar to carvedilol (Go et al 2009).

The prescribed dose of spironolactone (24.2 ± 8.9 mg) for treatment of patients in this study was acceptable according to ESC recommendations; however, the maximum dose can be as high as 50 mg daily. Telmisartan, an ARB, was used in one patient, perhaps in order to avoid the chronic cough associated with the use of ACE inhibitors (McMurray et al 2012). The loop diuretic, furosemide, was very commonly used to relieve symptoms of congestion, with a mean dose of 83.79 ± 85.04.

Despite the vast amount of evidence, including the landmark A-HeFT and V-HeFT trials, on the beneficial effects of using a combination of H-ISDN in black patients with HF, this strategy was not employed in any patient in this study. Isosorbide dinitrate was used without hydralazine in 4% of patients, despite lack of evidence of a beneficial role of this practice in the treatment of HF. Furthermore, the dose of this drug that was used was markedly suboptimal (11.25 ± 4.3 mg) (McMurray et al 2012).

Digoxin was used in 11 patients (3.67%) with HF, none of whom had associated atrial fibrillation. This may have been practised in order to improve clinical status and reduce symptoms. As mentioned previously, digoxin plays no role in improving mortality in patients with HF, but does reduce the hospitalisation rate and patient symptomatology (McMurray et al 2012; DIGITALIS Investigation Group 1997). Ivabradine was not used in any patient, probably because its use at CHBAH is restricted to cardiologists and requires their motivation.

ACEIs and beta adrenergic antagonists are strongly recommended by the ESC and HeFSSA guidelines because of the large number of clinical trials that support their efficacy (McMurray et al 2012, Swedberg et al 2005). Despite this, many patients with congestive HF do not receive these and other guideline recommended medications they require or receive suboptimal doses because doctors do no adopt or apply treatment guidelines (Komajda et al 2005, Swedberg et al 2005, Komajda et al 2003, Cleland et al 2002). Even in well-resourced settings, guideline-based medications are being inadequately or insufficiently utilised for the management of HF, as indicated by a large number of studies conducted in Europe and America (Rywik et al 2008, Swedberg et al 2005). In the IMPROVEMENT study, which was a survey involving 15 European countries and 1 363 physicians, it was shown that ACE inhibitors and beta blockers were prescribed to only 60% and 34% of patients, respectively. Furthermore, only 20% received these drugs in combination and doses of the medication were 50% of the target doses recommended by the ESC guidelines (Cleland et al 2002). The EuroHeart Failure Survey, which involved the analysis of discharge summaries of 11 304 patients from 24 ESC countries, also revealed that the prescriptions of evidence-based

medications, including ACEIs and beta blockers, were unacceptably infrequent. Furthermore, the doses of these medications, especially those of beta blockers, were suboptimal (Komajda et al 2003).

The findings of the present study are similar to multiple other studies conducted in African countries, including SA, that have reported that guideline-based treatment of HF is suboptimal (Bloomfield et al 2013, Damasceno et al 2012, Ruf et al 2010, Owusu 2007, Adewole et al 1996). In the Heart of Soweto study 84% of patients received beta-blockers, a considerably higher percentage than what was prescribed to patients in this study, while 74% of patients received ACEI, a figure similar to what was obtained in this study (Ruf et al 2010). The higher use of these medications in the Heart of Soweto study may be attributable to expert care, as the patients were seen at the specialist cardiology clinic. The Sub-Saharan Survey of Heart Failure study was a large, prospective multicentre survey of 1 006 patients admitted with acute HF at multiple hospitals in nine different countries in SSA. It reported that upon discharge 80% of patients received an ACEI or ARB, and the same number of patients received the medication at one and six months of follow-up. Furthermore, only a strikingly low 30% of patients were prescribed a beta blocker upon discharge and fewer than 50% received the medication on review at six months. In the same study, it was shown that fewer than 10% of patients received the combination of hydralazine and nitrates in addition to standard anti-remodelling therapy with a beta-blocker, ACEI, and an MRA (Damasceno et al 2012). A retrospective Nigerian study also showed that the use of ACEIs for patients with HF remained generally very low, despite the observation that prescriptions of the drugs increased from 32% in 1992 to 65% in 1994 (Adewole et al 1996). A study

involving 100 patients in a Ghanaian hospital demonstrated that ACEIs and beta-blockers were underutilised among all NYHA classes of HF (Owusu 2007). A similar trend was observed in a study from Cameroon, which demonstrated that between 1998 and 2001 only 20% of patients with HF were prescribed beta-blockers (Bloomfield et al 2013).

There are numerous barriers to the adequate adoption and implementation of evidence-based management guidelines. These include doctors' prescribing patterns, relationships between healthcare professionals and patients and the role of the pharmaceutical industry (Swedberg et al 2005). Important factors that influence the prescribing patterns of doctors in the treatment of HF include the patient's age and sex, presence of co-morbidities and the area of specialty and experience of the doctor. In addition, other specific aspects include contraindications to the use of a particular drug, drug side effects, underestimation of the morbidity and mortality of HF, underestimation of the extent of the benefit of guideline-based HF medication, intolerance of a medication, low blood pressure and the severity of HF (Rywik et al 2008, Swedberg et al 2005, Komajda et al 2003, Mckee et al 2003, Cleland et al 2002,). Many doctors have a fear and apprehension of guideline-recommended medications because of their potential to cause adverse effects upon commencement and to worsen the condition of the patient. This is a concern particularly for elderly patients who are often sensitive to the introduction of drugs and their subsequent titration (Swedberg et al 2005). Elderly patients also have a high incidence of comorbid conditions (renal failure, diabetes and stroke) and are often victims of polypharmacy. This places them at substantial risk of drug toxicities, drug-drug interactions and non-adherence (Swedberg et al 2005,

Higashi et al 2004). In particular, the development of electrolyte disturbances such as hyperkalemia, often precipitated by the combined administration of an ACEI and an MRA, is a concern among doctors (Mckee et al 2003). It is not surprising therefore that elderly patients are prescribed potentially beneficial medications to a much more limited extent than younger patients. Doctors may also feel that evidence of the benefits of certain medications in this population is not strong enough, as elderly patients are inadequately represented in clinical trials (Higashi et al 2004). Furthermore, doctors are often not familiar with important evidence-based treatment guidelines and this may result in their failure to prescribe appropriate medication for HF (Swedberg et al 2005).

Among those doctors that are mindful of current HF management guidelines, implementation of knowledge in effective care may not be adequate, as the IMPROVEMENT survey demonstrated (Cleland et al 2002). This discrepancy may be due to cynicism of doctors about guidelines, their use of medications with which they or their patients feel more comfortable and/or the poor organisation of health services at their institution (Swedberg et al 2005, Cleland et al 2002). Clinical experience and area of specialisation are also factors that seem to influence the prescribing patterns of doctors and studies have shown that the rate of prescription of evidence-based medication for HF is significantly higher among cardiologists compared to non-cardiologists (Rynik et al 2008, Komajda 2003, Mckee et al 2003). The pharmaceutical industry and patients' demands for specific medications also have an influence on the prescription of doctors. Doctors are often led into incorrect prescribing by pharmaceutical advertising, which promotes drugs that have no scientific basis for their use (Stevenson et al 1999, Avorn et al 1982).

The South African public health system currently has major challenges in the provision of adequate medical care. At CHBAH major problems include ineffective management, enormous patient burden, lack of communication between employees and their supervisors, undersupply of medication and resources, a low health care budget, a huge shortage of doctors and high levels of stress and low morale among doctors (Von Holdt et al 2007, Landman et al 2001). The Primary Health Care (PHC) centres in the communities have also been reported as dysfunctional, with problems similar to those of CHBAH, in addition to the lack of skilled staff (Puoane et al 2008). Therefore, it is possible that guideline-based treatment of HF at CHBAH is inadequate and the management of chronic diseases such as hypertension and DM, which can result in the complication of HF, at the PHC level is inadequate. This would translate in increased referrals to CHBAH of patients with HF.

The lack of stewardship in the different segments of the health sector has a negative impact on the provision of a good health care service (Coovadia et al 2009). Management of public hospitals in South Africa, including that of CHBAH, has been reported to be dysfunctional, fragmented, bureaucratic and authoritarian. It is vital that management and clinical processes are integrated so that hospitals function more effectively in terms of optimal resource allocation and clinical outcomes. Unfortunately, most public hospital managers in SA have little clinical background (Von Holdt et al 2007).

An audit of CHBAH conducted in 2001 revealed that 50% of staff felt that communication between employees and their supervisors was less than optimal (Landman et al 2001). It is therefore possible that junior doctors (i.e. interns, medical

officers and junior registrars) do not seek advice regarding patient management from their seniors at the MOPD. Junior doctors often do not have experience in the management of many conditions, including HF, and therefore it is important to consult a senior when required. It has been shown that doctors regard training and experience as one of the main factors influencing their prescribing patterns (Swedberg et al 2005).

It has been reported that 67% of staff felt that the climate at CHBAH was one of a hospital under significant stress because of heavy workloads (Landman et al 2001). Levels of stress among CHBAH interns were also significant, according to a study conducted in 2005, which cited long working hours, a heavy workload and decreased quality of care as important sources of stress among these junior doctors (Sun et al 2008). The organisational values of the hospital have also been reported not to be ideal, as the sentiment of 'serving the greatest number of patients' was found to be more popular than a good work ethic (57.6% vs. 18.6%) (Landman et al 2001). As a result of very large patient numbers at CHBAH and the associated enormous pressure, time constraints and high levels of stress that interns, the prime working force of doctors at CHBAH, experience, it is highly probable that guideline-recommended therapy for patients is not being implemented (Sun et al 2008, Landman et al 2001). In a 2001 audit of CHBAH, it was also revealed that 83.1% of staff interviewed felt that there was a huge shortage of staff at CHBAH and 67% were of the opinion that patients received sub-standard care because of the very large patient numbers (Landman et al 2001). It is therefore possible that a large number of patients have to be seen by relatively few 'stressed out' junior doctors, who have fewer consultants to advise them when required. Quality patient care may thus be compromised.

The unavailability or undersupply of many medications is also a major problem at CHBAH as well as other public hospitals in South Africa. It was reported that in 2001 51% of staff at CHBAH verbalised that there was an undersupply of medications, and the main reasons for this were a low health budget and the HIV/AIDS pandemic (Landman et al 2001). It is thus possible that many effective guideline-based medications for the treatment of HF are not always available or are in constant short supply. The unavailability of these medications may therefore preclude their use by doctors. Lastly, as a result of the low health care budget, easy access to information on evidence-based medicine, in the form of online medical databases and software, national and international guidelines and medical journals, may not be available at CHBAH.

Important steps need to be taken to ensure that the management of HF and many other chronic diseases at CHBAH is of the highest standard despite limited resources. This would require the institution of strong, assertive management and a change in the prescribing patterns of doctors. CHBAH is reportedly the largest hospital in the southern hemisphere and is faced with a magnitude of problems, including staff shortages, poor conditions of service, staff-reported substandard levels of care and poor organisation (Landman et al 2001). Drastic sustainable solutions need to be implemented, the detailed description of which is beyond the scope of this study. Some of the recommendations made in the 2001 ethical audit of CHBAH included the development of strong leadership, management expertise and professionalism, collaboration of CHBAH with the private sector and academia, a change in management style and organisational culture, constructive communication and participation in decision-making

among staff, an increased budget allocation, adequate supply of medication and an urgent review of staff numbers (Landman et al 2001). In addition, it would be advisable for people with a clinical background to be appointed as hospital managers to enable the hospital to function more effectively (Van Holdt et al 2007).

Other important steps in the adequate management of HF at CHBAH would be the widespread dissemination of HeFFSA guidelines, education of doctors with emphasis on evidence-based medicine, comprehensive discharge summaries, regular audits with attention to clinical outcomes and integration of care. Extensive dissemination of evidence-based guidelines, organised management programmes and education may improve the prescribing patterns of doctors in the treatment of HF (Swedberg et al 2005, Cleland et al 2002). Collaboration between the cardiology and internal medicine departments at CHBAH may improve the care of HF patients at the CHBH MOPD through evidence-based education. It has been shown that cardiologists seem to prescribe relevant evidence-based treatment to HF patients significantly more often than do generalists or doctors who are experts in other areas (Mckee et al 2003). Doctors at CHBAH should ensure that upon discharge of HF patients that were admitted to hospital, comprehensive discharge summaries with clear follow-up instructions are documented, as this can improve outpatient care and the doctor-patient relationship and effect a reduction in the risk of rehospitalisation (Swedberg et al 2005). The institution of regular audits and development of registries that would record the clinical information of patients would facilitate the investigation, treatment and allocation of resources for the management of HF (Ponikowski et al 2014, Swedberg et al 2005). ‘Point of care’ online resources, mobile devices and applications may be an effective method to enhance

patient care among junior doctors in an MOPD with a shortage of consultants and a large patient burden (Ventola 2014, Schwartz et al 2003). Lastly, the development of 'HF checklists', which would include necessary parameters such as patient compliance with medication, NYHA functional class, patient vital signs, important clinical signs (peripheral oedema, crackles, third heart sound), symptomatic and anti-remodelling therapy and chemistry results, may be very helpful, as they would require clinicians to document comprehensively. Checklists have the potential to improve patient outcomes by establishing a standard of knowledge and aid in achieving evidence-based best practices and quality care (Winters et al 2009).

This study highlights the important roles of non-communicable (i.e. DM, hypertension, IHD, PPCMO) and communicable (i.e. HIV, rheumatic fever) diseases in the aetiology of HF in SA. Non-communicable diseases such as DM and hypertension, which can be complicated by HF in the long-term, are infrequently diagnosed and inadequately managed at South African public facilities, particularly Primary Health Care (PHC) facilities. Solutions that have been attempted to improve the management of chronic non-communicable disease include the development of policies and guidelines (i.e. food-based dietary guidelines, tobacco and alcohol control) and integrated community-based programmes that encourage risk factor reduction and community participation. Other solutions that have been proposed include the institution of a more improved, comprehensive training programme for nurses and doctors, with an emphasis on human resource management, and the development of infrastructure that encourages good health (Puoane et al, 2008). It is vital that the chronic diseases and risk factors associated with the development of HF are managed well at the PHC level in order to

prevent the disease. Adequate management of risk factors would decrease the prevalence of HF in the community, and thus, decrease the number of patients referred with HF to CHBAH, an already over-burdened institution.

Inadequate screening, treatment and control of hypertension in SSA may all contribute to the high prevalence of HHD. Hypertension is a readily identifiable condition, which can be treated with relatively inexpensive medication, including thiazides and dihydropiridine calcium antagonists, which in particular are very efficacious in black Africans. The use of these agents may lead to the regression of LVH, which is associated with HHD and its progression (Sliwa et al 2014). In the management of diabetes, socio-emotional support of patients and education of doctors who treat this disease has been found to be beneficial (Van zyl et al 2005, Westaway et al 2005). Early diagnosis and prevention of modifiable risk factors for CHF, including tight glucose control and blood pressure control, are imperative to prevent occurrence of the disease (McMurray et al 2012, Nichols et al 2004).

Steps that can be taken by the medical department at CHBAH in order to improve the treatment of non-communicable diseases, such as hypertension and diabetes, include the institution of community and PHC out-reach programmes, and tele-medicine conferences. Out-reach programmes would require that senior registrars and consultants in the department of Internal Medicine, would visit PHC centres on a weekly basis and would provide evidence-based care for patients, in addition to educating and empowering the nurses and doctors in these institutions in this regard. The out-reach programme must provide this service for PHC centres in and around Soweto, which are the predominant areas that CHBAH provides health-care for. The use of tele-medicine

to improve medical care at PHCs may be an option, however, it has been reported that this service is not cost-effective, as it is under-utilized, and is associated with multiple technical and organizational challenges (Gulube et al 2001).

Measures that can be taken in order to prevent HIV infection in the community are similar to those described for non-communicable diseases (i.e. education of care-givers and community, policy and guideline development and effective community campaigns), with an emphasis on sexual behavior, condom use and compliance to medication among those patients that have the disease. Primary and secondary prevention, prevention of overcrowded living conditions and education of the community are important in the prevention of acute rheumatic fever. Primary prophylaxis (i.e. institution of antibiotics within nine days of onset of sore throat) is the cornerstone of primary prevention, however, is difficult to achieve as it is dependent on patient help-seeking behavior (Long et al 2012). Over-crowded living conditions are closely associated with poverty. The Reconstruction and Development Programme, a South African government project established in 1994 which is involved in the development of low-cost housing for mainly poor communities, may have a role in alleviating the crowded conditions associated with the development of acute rheumatic fever. Education of communities, especially of children, about the symptoms and signs of acute rheumatic fever, and when to seek medical care, may also assist in primary prevention. Further measures that have been recommended in order to prevent and manage the acute rheumatic fever include registry-based disease notification and secondary prophylaxis programmes, as well as echocardiographic screening (Sliwa et al 2010).

6. Study Limitations

As this was a retrospective observational study, there were significant limitations. The accuracy of the data collected was dependent on the quality and thoroughness of documentation by doctors. Also, the prescribing patterns of doctors at CHBAH MOPD may have changed since the period that this study investigated. As a result of poor and inconsistent documentation, the distribution of the varying severities of HF expressed according to the NYHA functional class could not be analysed and correlated with the treatment that patients received. Comprehensive and accurate information on the frequency and timing of hospital admissions of patients with HF could also not be obtained, which precluded the use of this parameter as a marker of adequacy of HF treatment. Lastly, in cases where vital evidence-based HF medications were not prescribed, the reasons for their omission were not consistently or sufficiently documented. The reasons for not prescribing these medications would have provided valuable insight and understanding of the prescribing patterns among the doctors at the medical outpatients department at CHBH. Further research is required in this regard.

7. Conclusion

In conclusion, it has been demonstrated in the current study that the pharmacological management of HFrEF at the CHBH medical outpatient department is suboptimal and is

not in accordance with the HeFSSA or the ESC guidelines. The reasons for the prescribing patterns of doctors are not clear and need to be investigated further. The main aetiologies of HF in this study were similar to those in the Heart of Soweto Study, namely HHD and IDCMO. Major complications included inflammation, anaemia and renal dysfunction. Measures to improve the management of HF at the CHBAH MOPD include widespread dissemination of HF guidelines, education of doctors, improved organisation of care, institution of checklists, and collaboration between the internal medicine and cardiology departments. Furthermore, control of risk factors and communicable and non-communicable diseases that lead to the development of HF and its progression needs to be achieved. This may be accomplished by the development of strong policies and guidelines, CHBAH out-reach programmes, education and empowerment of the community and strengthening of PHC centres, with emphasis on training and education of nurses.

8. Appendix

Table 8.1: Laboratory normal values according to National Health Laboratory Service

Parameters	**NHLS normal range**
Sodium	136-145 mmol/L
Potassium	3.5-5.1 mmol/L
C-Reactive Protien	0-5 mg/L
eGFR	>60 ml/min/1.73m^2
Haemoglobin Men Women	 >14.3 g/dL >12.1 g/dL

Data capturing sheet

Patient Demographics

Age:

Sex:

Race:

Pulse:

Blood pressure:

Study number:

Aetiology

Hypertensive heart disease (HHD)	
Idiopathic dilated cardiomyopathy (IDCMO)	
HIV-associated cardiomyopathy (HIV-CMO)	
Ischaemic heart disease (IHD)	
Valvular heart disease (VHD)	
Other	

Co-Morbidities/risk factors

Hypertension	
Diabetes	

Thyroid disease	
Other	

Laboratory blood tests/complications

Blood Test	**Result**
Haemoglobin (Hb)	
Sodium (Na)	
Potassium (K)	
Estimated glomerular filtration rate (eGFR)	
C-Reactive Protein (CRP)	
Deep vein thrombosis/pulmonary embolism	
Other	

Pharmacological Therapy

Class of drug	**Specific drug**	**Dosage**
Beta blocker		
Angiotensin Converting Enzyme Inhibitor (ACE)		
Mineralocorticoid Receptor Antagonist (MRA)		
Angiotensin Receptor Blocker (ARB)		
Loop diuretic		
	Digoxin	
	Hydralazine	
	Isosorbide dinitrate	
	Ivabradine	

Ethics clearance certificate

R14/49 Dr P Meel

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140862

NAME: (Principal Investigator) Dr P Meel

DEPARTMENT: Internal Medicine
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE: Management of Heart Failure at Chris Hani Baragwanath Academic Hospital

DATE CONSIDERED: 29/08/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr Nirthi Maharaj

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 09/10/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

Date 29/08/14

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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