OUTCOMES OF PATIENTS WITH HYPERTENSIVE HEART DISEASE AND HEART FAILURE WITH REDUCED EJECTION FRACTION (HFrEF) AT A TERTIARY CENTRE IN SOUTH AFRICA

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In fulfilment of

MASTER OF MEDICINE (MMED)

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DECLARATION

I, Darlene Boakye, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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DEDICATION

I dedicate this MMED to God, my parents Jonathan and Naomi Boakye and my siblings, Emmanuel, David and Mary-Ann Boakye.

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Above all, to God, He continues to perform modern day miracles and this is one of them.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACE-I	Angiotensin-converting enzyme inhibitor
BP	Blood pressure
CCF	Congestive cardiac failure
CMR	Cardiac magnetic resonance
CXR	Chest x-ray
DALYs	Disability-adjusted life years
ECG	Electrocardiogram
EF	Ejection fraction
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GFR	Glomerular filtration rate
GSH	Groote Schuur Hospital
HHD	Hypertensive heart disease
HIV	Human immunodeficiency virus
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IMHOTEP	African Cardiomyopathy and Myocarditis Registry Program
IVS	Interventricular septum
LA	Left atrial
LBBB	Left bundle branch block
LGE	Late gadelinioum enhancement
LV	Left ventricular

LVEDD	Left ventricular end diastolic dimension
LVEF	Left ventricular ejection fraction
LVPW	Left ventricular posterior wall
MRA	Mineralocorticoid receptor antagonist
NYHA	New York Heart Association Classification
RA	Right atrial
RAAS	Renin-angiotensin aldosterone system
RV	Right ventricular
RVSP	Right ventricular systolic pressure
SSA	Sub-Saharan Africa
SA	South Africa
TAPSE	Tricuspid annular plane systolic excursion
WHO	World Health Organization

ABSTRACT

Introduction. Hypertension is endemic in Sub-Saharan Africa and has been shown to be the leading cause of heart failure (HF) on the continent. Clinical observation suggests that hypertensive heart disease (HHD) is potentially reversible with medical therapy and that baseline characteristics and outcomes differ from other causes of HF.

Method. This was a single centre, retrospective hospital-based observational study of patients diagnosed with HF with reduced and mid-range ejection fraction (HFrEF and HFmrEF) secondary to HHD, seen at the Cardiomyopathy Clinic at Groote Schuur Hospital over a three-year period. Ethics approval was obtained (HREC REF 677/2018).

Results. A total of 59 patients were included, with an equal representation of both genders [female 49.2%]. The majority of patients were of mixed race [57.6%] and black African [39%] ethnicity. The mean age at presentation was 44 ±12.0 years. At baseline, 71.7% of patients had effort intolerance [NYHA Class II, 36.2%; Class III, 32.8%; Class IV, 1.7%] and the most common symptoms were dyspnoea [65.5%], pedal oedema [34.5%] and orthopnoea [29.3%]. A pre-existing diagnosis of hypertension was present in 66.8%, 30,5% had other co-morbidities (HIV, 5 [8.5%]; diabetes mellitus, 5 [8.5%]; chronic kidney disease, 5 [8.5%]) and 62% of women presented in the peripartum period. At baseline, the mean systolic and diastolic blood pressures were 130±20.1 and 81±12.8mmHg, respectively. Congestive HF was observed in 40.7% of cases despite being on medical therapy (loop diuretics [88.5%]; ACE-I [88.5%]; beta blocker [84.6%]; MRA [51.9%]). Atrial fibrillation [3.5%] and LBBB [10.5%] were infrequent. Left ventricular hypertrophy (LVH) was noted in 54.4% on ECG, and the mean QTc was prolonged [466±35ms]. On echocardiogram, mean wall thickness was normal [IVSd 1.0 [0.9-1.2]; LVPWd 1.1 [0.8-1.3], however, left atrial [4.4±0.9cm] and LV end-diastolic dimensions [LVEDD 6.4±0.8cm] were increased. LV ejection fraction (EF) was markedly impaired [29.9±10.4%]. At follow up, there was a significant ($p<0.05$) improvement in QTc ($p = 0.025$), LVEDD ($p = 0.022$) and LVEF ($p < 0.001$). Recovery of LVEF was observed in 86.5%

patients where repeat imaging was done [LVEF ≥ 50% in 45.9%; LVEF improved ≥10% in 40.5%]. 1- and 3-year transplant-free survival was 98.3% and 90.5%, respectively.

Conclusion. Most patients with HHD and impaired LVEF have a pre-existing history of hypertension and present with effort intolerance, congestion and mildly elevated or 'pseudonormal' blood pressures. Concentric LVH was not a prominent feature on echocardiogram and AF was infrequent. Despite severely impaired LVEF at baseline, mortality was lower than expected for HF patients and improvement in LVEF on therapy was observed in the majority of patients.

CHAPTER 1. Introduction and Literature Review

1.1. INTRODUCTION

Heart failure is a major cause of morbidity and mortality worldwide.[1] In 2014, 26 million individuals were affected globally[2] and to date this has increased to 64.3million.[3] It is estimated that approximately 6 million people in the United States have heart failure, this is projected to rise to 8 million by the year 2030. Studies conducted in other countries such as Spain, China, Germany and Italy; demonstrated a consistent rise in the prevalence of individuals diagnosed with heart failure.[2] To date there have been no formal statistics on the incidence or prevalence of heart failure in Sub-Saharan Africa (SSA).[2]

Heart failure (HF) is the most common manifestation of cardiovascular disease in hospitalized patients in Africa.[4] Unlike high income countries where ischaemic heart disease is predominant, the cardinal causes of heart failure in Sub-Saharan Africa (SSA) are hypertension, rheumatic heart disease, cardiomyopathies and infective causes.[1,5] The figure **(Figure 1.1)** below demonstrates the predominant causes of heart failure in SSA between the years of 1957-2010**.**[6,7] Furthermore, the average age of individuals presenting with HF in Africa is reported to be significantly lower when compared to individuals from high-income countries (median age of 55 years versus 66 – 70 years).[1] While there have been a number of studies on HF from Africa, there remains a paucity of published data on outcomes according to specific aetiologies of HF on the continent. Despite the fact that numerous studies have shown that hypertension is a leading cause of HF globally,[1,8] the current definition of hypertensive heart disease (HHD) fails to describe the full clinical spectrum of the disease, making diagnosing hypertensive heart disease difficult in the clinical setting.

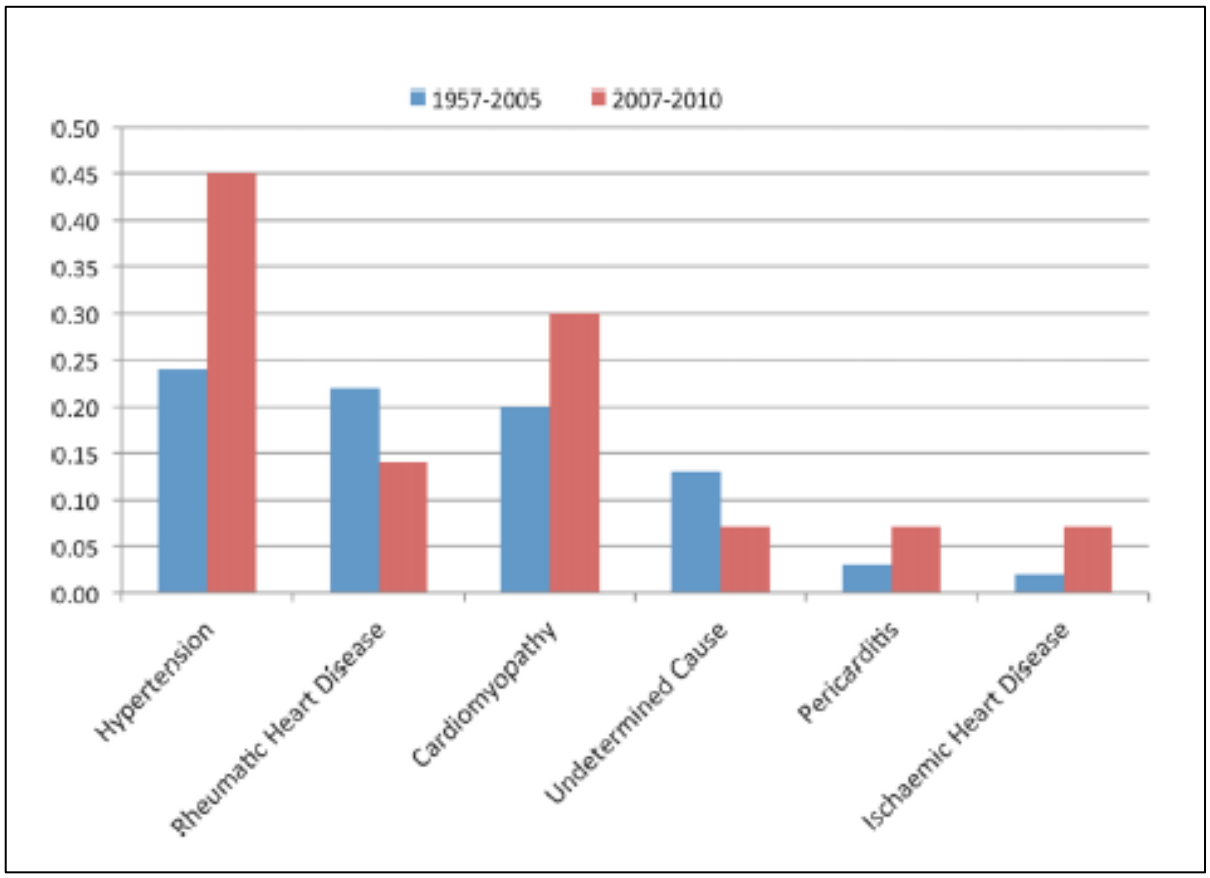

Figure 1.1 Predominant causes of heart failure in Africa between 1957-2010

(http://dx.doi.org/10.1136/heartjnl-2013-303592)

1.2. DEFINITION AND CLASSIFICATION OF HEART FAILURE

Heart failure is a clinical syndrome caused by structural and/or functional cardiac abnormalities resulting in reduced cardiac output and/or elevated intracardiac pressures. Evidence of an underlying cardiac abnormality is vital to the diagnosis of HF. The cardinal symptoms of heart failure include effort intolerence (breathlessness or fatigue on exertion), orthopnoea (breathlessness on lying supine), paroxysmal nocturnal dyspnoea (waking from sleep with breathlessness) and body swelling.[9]

Heart failure can be broadly classified into three different groups. Heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF). HFrEF is characterised by systolic

dysfunction with global reduction in the left ventricular ejection fraction (LVEF) of less than 40%.[10] Decreased LVEF in heart failure is usually a poor prognostic marker and an independent predictor of poor prognosis.[10] In contrast, HFpEF is characterised by impairment in left ventricular relaxation resulting in restricted filling of the left ventricle with preserved LVEF (LVEF ≥ 50%). HFpEF is usually a diagnosis of exclusion with the patients being elderly, female, obese and with a history of hypertension and atrial fibrillation.[10] HFmrEF represents a "grey area" where the LVEF is mid-range (LVEF 40-49%) and likely represent the early or recovery phase of HFrEF.[9]

1.3. EPIDEMIOLOGY AND DEFINITIONS OF HYPERTENSION

1.3.1. Global prevalence of hypertension

Hypertension is a principal risk factor for premature mortality and is currently the leading cause for disabilty-adjusted life years (DALYs).[11] Between 1990 and 2015, hypertension rose from the third commonest to the leading cause of DALY in both sexes **(Figure 1.2)**.[12] The prevalence of hypertension increased from 972 million people (26.4% of the gobal population) to 1.13 billion individuals (30-45% of global population) between 2000 and 2015, and currently accounts for 7.5 million deaths annually worldwide.[11,13,14] This increase has been attributed to the rise in the global population and ageing.[14] It is estimated that by 2025, 1.56 billion people globally will be living with hypertension. [11]

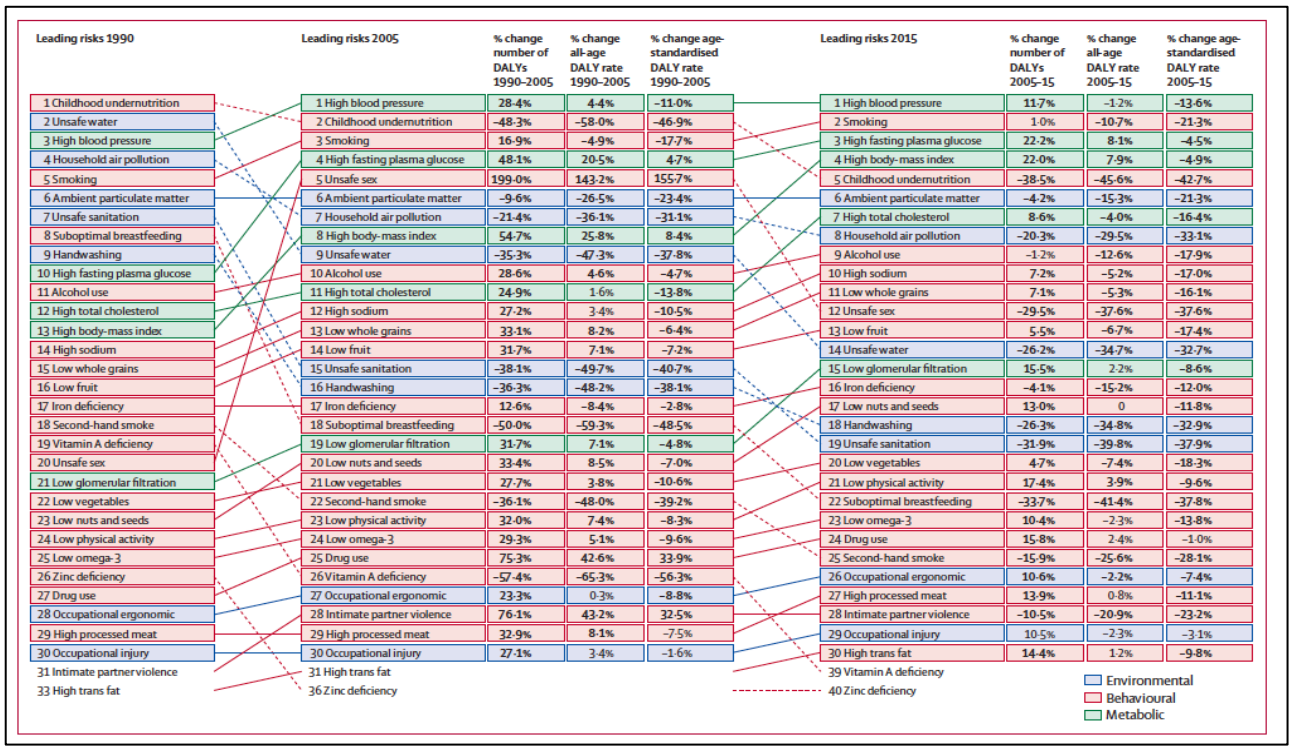

Figure 1.2 Top 30 leading risk factors for DALYs

(doi:10.1016/S0140-6736(15)00128-2)

1.3.2. Prevalence of hypertension in Sub-Saharan Africa

In contrast to most high income countries, Africa has shown an exponentional increase in the prevelance of hypertension compared to high-income-countries **(Figure 1.3).**[14,15] In the last 10 years, the rise of the prevalence of hypertension in SSA is greater than in any other continent. The variable prevalence of hypertension by region is thought to be related to diet, ethnic background and degree of urbanisation amongst others. [16]

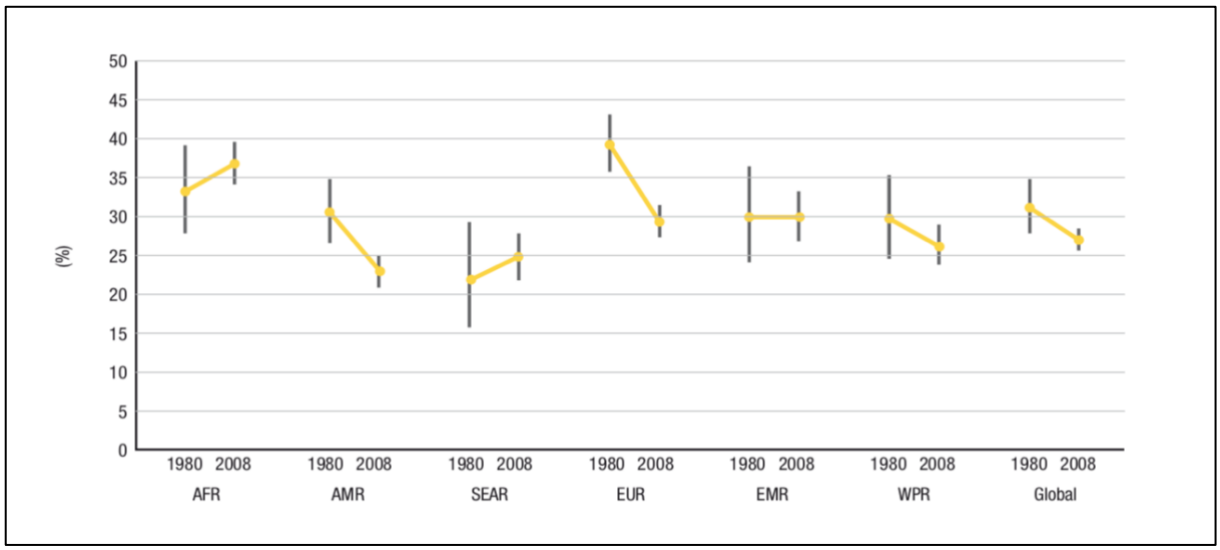

Figure 1.3 WHO launches the World Health Statistics 2012

(http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20175)

From limited published data, the estimated prevalence of hypertension in SSA is 46% of the adult population (older than the age of 25).[17] In South Africa (SA), between 1998 and 2008, the prevalence of hypertension rose from 21% to 77.3% in the older population.[18] In further studies, it was concluded the prevalance of hypertension in individuals with a mean age of 44 was 41.4%.[18] By 2025, the number of individuals with hypertension in SSA is expected to be 150 million.[19]

Despite the availability of anti-hypertensive treatment, optimal blood pressure control continues to be poor.[20] **Figure 1.4** below displays the increased percentage of individuals with uncontrolled hypertension.[20] At least 82% of individuals in SSA have untreated hypertension and 93% have uncontrolled hypertension.[21] In 2016, the documented percentage of hypertensive individuals taking their medication was less than 20%.[20] In South Africa, only 40% are reported to achieved favourable blood pressure readings.[22] This is thought to be multi-factorial with one of the reasons being that appropriate management and treatment of hypertension remains poor due to substandard health facilities.[23] This is being addressed in

SA by strengthening primary health care and adopting the World Health Organization (WHO) chronic disease model of care.[24]

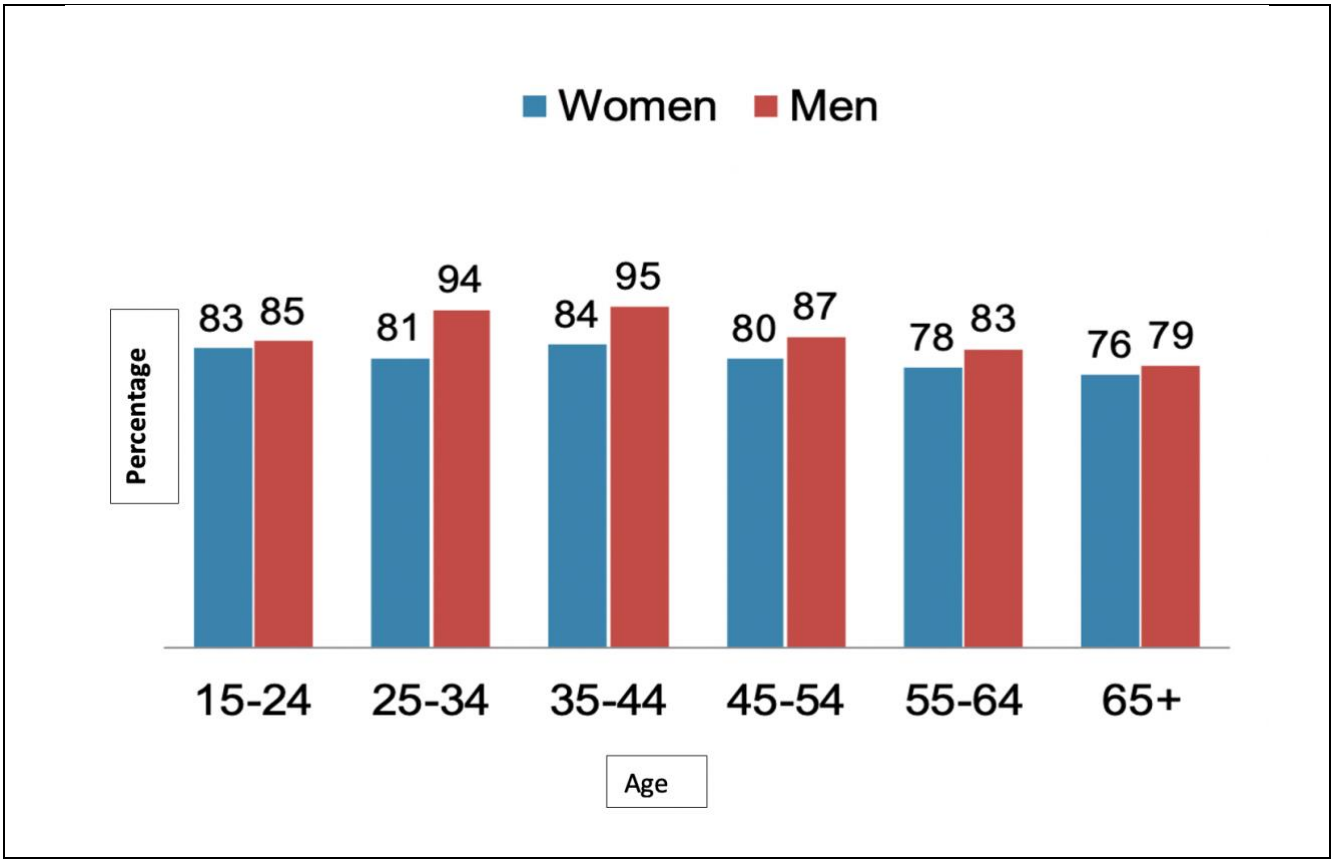

Figure 1.4 Percentage of patients with uncontrolled hypertension according to age, according to the South Africa Demographic and Health Survey 2016

(https://dhsprogram.com/pubs/pdf/FR337/FR337.pdf)

1.3.3. Definition of hypertension and blood pressure targets

According to the European Society of Cardiology (ESC), hypertension is defined as a systolic blood pressure (BP) of ≥ 140mmHg and/or a diastolic blood pressure of ≥ 90mmHg.[25] Hypertension can be further classified into three different categories:

- Grade 1 hypertension includes a systolic blood pressure of between 140-159 and/or a diastolic of 90-99
- Grade 2 hypertension includes a systolic of 160-179 and/or diastolic of 100-109
- Grade 3 hypertension includes a blood pressure of ≥ 180 and/or diastoic ≥ 110

Stratification of cardiovascular risk, events and other target organ damage is usually dependent on the blood pressure category.[25]

Importantly, the cut-off values defining hypertension vary according the clinical setting and the specific technique utilised to measure blood pressure. The most common diagnosis of hypertension is in an office or clinic setting, where hypertension is defined by a BP of ≥140 and/or ≥90 on at least 2 occasions 1-4 weeks apart. For 24-hour ambulatory blood pressure monitoring or home blood pressure monitoring, slightly lower blood pressure thresholds are used to diagnose hypertension (BP of ≥130 and ≥80 over 24 hours and ≥135 and ≥85 respectively).[26]

Randomised controlled trials have demonstrated that a decrease of 10mmHg systolic or 5mmHg diastolic values can reduce cardiovascular events by at least 20% and heart failure by 40%.[25] The latest ESC guidelines have advocated for lowering blood pressure to <140/90mmHg in all patients when therapy is commenced and if there are no adverse effects, to aim for a blood pressure reading of 130/80mmHg.[25] This recommendation is based on data from the SPRINT TRIAL, where a decrease in mortality and cardiovascular events with intensive blood pressure lowering was demonstrated. In non-diabetic patients younger than 65, a target systolic blood pressure between 120-129mmHg is advised.[25,27]

In addition, while rarely performed in hypertensive patients, fundoscopy does have a role in determining evidence of target organ damage and providing a prognostic estimation of microvascular changes and cardiovascular mortality. The main changes seen on fundoscopy consist of arteriolar attenuation, arteriovenous nipping, hemorrhages and optic disc swelling. Hypertensive retinopathy is seen in relation to elevated blood pressures and is one of the markers of hypertension. There is a correlation with hypertension and severity of retinopathy therefore fundoscopy examination may be useful in patients with hypertension.[28-34]

1.4. HYPERTENSIVE HEART DISEASE

1.4.1. Definitions of hypertensive heart disease

Although poorly understood, hypertensive heart disease (HHD) is a recognised complication of hypertension. The Framingham heart study (n = 5143) demonstrated that 91% of participants with hypertension developed hypertensive heart disease over a 20 year follow up period.[35] This observation lead to the identification of a number of key risk factors for the prevention of cardiovascular events.[36] While there is a paucity of data about the diagnostics, incidence, and prevalence of HHD in SSA, black Africans have been shown to be at risk of developing target organ damage (heart failure, cerebrovascular diseases and chronic kidney disease) from hypertension at a younger age than the mean age globally.[4] Earlier complications are thought to arise due to a number of factors, incluing genetic predisposition, late presentation and suboptimal treatment. [1]

The earliest defintions of HHD were released in 1966, describing a triad of:

1) Hypertension with left bundle branch block (LBBB) or LVH (left ventricular hypertrophy)
2) Hypertension with LVH or increased cardiac shadow on chest x-ray (CXR)
3) A previous history of hypertension or on treatment for hypertension with an enlarged cardiac shadow on CXR and/or LVH based on ECG (electrocardiogram). [37]

In 1993, the World Health Organization (WHO) classified hypertension into three stages based on target organ involvment, namely;

1) No target organ damage
2) Target organ damage either by LVH, retinopathy, proteinuria or ultrasound and/or radiological demonstration of atherosclerosis
3) Symptoms and signs of angina, heart failure or myocardial infarction. [38]

Although limited progress has been made on defining the syndrome, current consensus is that the following features may be present in HHD; left ventricular hypertrophy, systolic and/or diastolic dysfunction, and/or clinical heart failure.[25] There is, however, growing concern that the current definition of HHD fails to encompass the full spectrum of the various clinical presentations of this condition and fails to provide sufficient guidence in diagnosing HHD in the setting of systolic dysfunction. [39]

1.4.2. Pathophysiology of HHD

The mechanism of HHD relates to an increase in afterload with poor vessel compliance which is worsened by episodes of vasoconstriction as a result of sympathetic activation and raised peripheral resistance.[40] The development of LVH occurs secondary to an increased afterload where the cardiac myocytes attempt to adapt to the added stress on the left ventricle by increasing the total left ventricular mass. Activation of the renin-angiotensin aldosterone system (RAAS) sustains the ongoing development of LVH and myocardial fibrosis. [41]

Left ventricular hypertrophy is defined as an increase in cardiomyocyte size and left ventricular mass, and this can be divided into two main types; concentric and eccentric. Differentiating between the types of LVH has prognostic implications.[41] Persistent increased left ventricular stress may result in LVH, left ventricular diastolic and/or systolic dysfunction, arrythmias such as atrial fibrillation, and lastly heart failure.[25] LVH is one of the main markers of HHD and has been associated with increased morbidity and a two-fold increased in mortality in hypertensive cohorts.[42,43,44] Furthermore, regression of LVH has been associated with a decrease in cardiovascular morbidity and mortality.[45]

Increased peripheral vascular resistance and cardiac remodelling results in left ventricle dysfunction including left ventricular relaxation abnormalities and reduced ejection fraction.[35] Concentric LVH with left ventricular relaxation abnormalities may lead to heart failure with

preserved ejection failure.[35] Heart failure with reduced ejection fraction occurs in the setting of eccentric LVH, volume overload of the left ventricle, left ventriclular dilatation and systolic dysfunction.[35]

1.4.3. Clinical features of HHD

The clinical presentation of HHD may be varied depending on manifestation and stage of disease. In the literature, HHD has previously been classified by Iriarte et al in 1993 into four grades:

- Grade I: Asymptomatic with no evidence of LVH but with left ventricle diastolic dysfunction
- Grade II: Asymptomatic or in NYHA 1 (New York Heart Association Classification – grading system for severity of heart failure symptoms)[25] with LVH by echocardiographic features
- Grade III: Heart failure with preserved ejection fraction
- Grade IV: Left ventricle dilatation and heart failure with reduced ejection failure. [46]

Individuals with HHD may be asymptomatic initially and commonly only seek hospital attention late in the disease.[47-49] The commonest symptoms at presentation are dyspnoea, palpitations, orthopnoea, bilateral leg swelling, and fatigueabiltiy. Common clinical signs described in the literature include bipedal oedema, volume-loaded displaced apex, elevated jugular venous pressure, S3 and S4 gallop with features of pulmonary oedema with crackles.[21,44,50] According to published reports, approximately 50% of patients with hypertension will present with atrial fibrillation.[50] Late presentation leads to a poor prognosis with increased risk of cardiovascular morbidity and mortality. [47]

1.4.4. Diagnostic investigations to evaluate HHD

Electrocardiogram findings in HHD

An ECG is a key investigation that should be performed in all hypertensive individuals to determine the presence of LVH.[51] ECG is widely used due to its non-invasive, affordable and accessible nature.[52] The ESC/ESH (European Society of Cardiology/European Society of Hypertension) have emphasised 3 criteria used to determine LVH in a patient with hypertension:

1) Sokolow-Lyon criteria: SV1 and RV5 > 35mm
2) R wave in aVL ≥ 11mm
3) Cornell criteria: SV3 and RaVL >28mm in men and >20mm in women [25]

LVH is frequently associated with ST depression and T wave inversion in the lateral leads such as V5 and V6. This is known as a "strain pattern" and is associated with a poorer prognosis.[53]

Importantly, the sensitivity of detecting LVH on an ECG is low and averages between 10-30%.[54] The most commonly used criteria is the Sokolow-Lyon although the sensitivity is approximately 30%.[51] Obesity affects the detection of pathological LVH in using the Sokolow-Lyon criteria, decreasing its sensitivity to less than 10%. Cornell criteria showed no difference in detecting LVH between obese and non-obese patients and is the recommended criteria when assessing LVH in obese patients with hypertension.[55] Due to the variations in sensitivity of ECG findings, echocardiography and cardiac magnetic resonance imaging (CMR) are modalities that are better equipped to detect LVH. [52]

Echocardiogram findings in HHD

Echocardiogram is an imaging modality that provides details on left ventricular mass, aortic dimensions, atrial and ventricular chamber size, and systolic and diastolic function.[25] It is a simple, convenient and non-invasive method to determine the systolic function.[56] Features on

echocardiogram that are important in HHD include LV (left ventricular) mass, left atrial (LA) volume, left ventricular systolic and diastolic dyfunction.[50]

LA enlargement can preceed the development of LVH and this may be used as marker for the premature development of HHD.[40] The LIFE study demonstrated that LA enlargement is equivalent to the severity of LV diastolic dysfunction, and is strongly associated with LVH and impaired left ventricular diastolic function.[54,57] LA enlargement is not able to remodel as quickly as LVH with treatment and is an independent risk of atrial fibrillation, cerebrovascular accidents, heart failure and cardiovascular events. [56,58]

Diastolic dysfunction is an important marker of HHD and is present in over half of hypertensive patients. Left ventricular diastolic function is determined by evaluating left ventricular filling pressures.[59,60] The measurement E/A ratio includes E the peak velocity in early diastole, A the peak velocity in late diastole and deceleration time is important. [50] Once the E/A ratio is below 1, it shows an improvement in left ventricular diastolic dysfunction.[61] In severe hypertension, the E/A ratio can be "pseudonormal" which demonstrates restrictive physiology.[50] Lastly, prolonged deceleration time, isovelumetric relaxation time, E' and E/E' are other parameters used in the assessment of diastolic dysfunction. E/E' is useful in assessing the severity of diastolic dysfunction with a normal EF. [61,59] **Table 1.1** below illustrates the grading system of LV diastolic dusfunction in patients with reduced LVEF:[62]

Table 1.1 Grading diastolic dysfunction on echocardiogram

Diastolic dysfunction grade	Mitral inflow parameter	Other criteria
Grade I	E/A ≤0.8 + E ≤ 50cm/s	
Grade II	E/A ≤ 0.8 + E > 50cm/s or E/A > 0.8 - < 2	Two out of 3 criteria: Average E/E' > 14 TR velocity > 2.8m/s LA volume index > 34ml/m2
Grade III	E/A ≥2	Grade III diastolic dysfunction

Aortic root dilatation has been increasingly linked to hypertensive individuals. [63] This can also be used as an important variable in determining end organ damage as it also causes an increased cardiovascular risk. [64]

Lastly, a decreased LVEF is a poor prognostic marker. It can be easily assessed by the Simpson's method and this is the measurement of the ratio of the LV stroke volume over the end diastolic volume. A LVEF of >55% is the normal standard measurement used.[56]

Cardiac Magnetic Resonance Imaging

Over the last few years, CMR is now the best imaging modality to identify HHD and to assess therapeutic response.[65] CMR has excellent reproducibility and precision of LV mass is easily detected and is also useful in detecting late gadelinioum enhancement (LGE) which shows contrast build-up in regions of fibrosis or infarction. Approximately 50% of hypertensive patients have LGE which is associated with diastolic dysfunction.[60,66] Limitations on utilizing CMR in the African setting is cost and limited availability and expertise to evaluate CMR's with accuracy.[65,67]

1.4.5. Prognosis of HHD

Despite advances in medical therapy, advanced HF and NYHA Class IV are associated with a poor prognosis.[68] The 5 year mortality of HF is 50%, with half of these patients dying within the first year of diagnosis.[68] Other poor prognostic indices in HHD/HF include the presence of concentric LVH, LBBB, prolonged corrected QT on ECG, a depressed LVEF of <40%, enlarged LA, atrial fibrillation and anaemia.[43,56 ,69]

Studies have shown that patients hospitilised with HF in SSA are a decade or two younger compared to the mean age globally.[69] Just under 50% of individuals younger than 70 years of age are affected as compared to developed countries.[69]

1.5. RATIONALE FOR STUDY

Hypertension is endemic in Sub-Saharan Africa and has been shown to be the leading cause of HF on the continent.[1] It is not yet known which factors predict progression or recovery in HHD in our context. Clinical observation suggests that HHD is potentially reversible with medical therapy and that baseline characteristics and outcomes differ from other causes of HF [4,22,45] but there is a paucity of data to guide clinicians. Furthermore, the current definition of HHD fails to provide sufficient detail in diagnosing HHD in the setting of systolic dysfunction, where the blood pressure may be within the 'normal range' as a result of reduced cardiac output. Further clinical research in this field is highly relevant to improving patient outcomes.

The idea for this study came from the clinical observation that several patients referred to the cardiomyopathy clinic with "idopathic dilated cardiomyopathy" had 'unmasking' of underlying hypertension as their systolic function improved on treatment. The distinction between true dilated cardiomyopathy (which carries a poorer long-term prognosis) and HHD with HFrEF is highly relevant. Furthermore, improved definitions of HHD in the context of HFrEF, may prompt earlier detection of HHD with prompt initiation of treatment that may potentially decrease cardiovascular risk of morbidity and mortality.[22]

The study hypotheses on which this which this work is based, is that HHD with HFrEF is

1) a potentially reversible condition, and
2) in the context of heart failure and left ventricular systolic dysfunction, HHD may present with blood pressure readings within the normal range.

This study aims to:

1) identify specific baseline characteristics of a cohort of patients with HHD with HFrEF;
2) describe clinical characteristics that assist with the diagnosis of HHD with HFrEF; and

3) review outcomes and evaluate characteristics that are linked to poor prognosis of HHD with HFrEF in the African context.

CHAPTER 2. Methods

2.1. AIMS AND OBJECTIVES

We aimed to describe the baseline characteristics and report outcomes in patients diagnosed with heart failure with reduced ejection fraction secondary to HHD attending a tertiary centre in South Africa.

Primary Objectives:

1. Describe the baseline characteristics (demographic, clinical, electrocardiographic and echocardiographic) of patients diagnosed with HHD and HFrEF or HFmrEF, referred to the Cardiomyopathy Clinic at Groote Schuur Hospital (GSH)
2. Report outcomes of patients diagnosed with HHD and HFrEF or HFmrEF with a minimum follow-up of 6 months at tertiary care facility

Secondary Objectives:

1. Report on recovery of left ventricular dimensions and function in HHD with HFrEF or HFmrEF. Describe (if any) the features (demographic, clinical, electrocardiographic and echocardiographic) that may predict the recovery of left ventricular dimensions and function in this cohort

2.2. STUDY DESIGN

This study was a single-centre, retrospective hospital-based observational study of patients diagnosed with HFrEF or HFmrEF secondary to HHD, seen and followed-up at the Cardiomyopathy clinic at Groote Schuur Hospital over a three-year period (1 February 2015 – 31 January 2018).

2.2.1. Study population and patient eligibility

All patients referred to the Cardiomyopathy Clinic at GSH with a diagnosis of HFrEF or HFmrEF secondary to HHD were eligible for inclusion. The screening log for the African Cardiomyopathy and Myocarditis Registry Program (IMHOTEP – HREC 766/2014) initiated in February 2015 at Groote Schuur Hospital, was used to identify patients seen in the cardiomyopathy clinic who were excluded from IMHOTEP with a diagnosis of HHD. The definition of hypertensive heart disease utilized in this study was based on the guideline-derived definitions adopted by IMHOTEP.

Inclusion criteria:

- Age ≥ 18 years
- Diagnosis of heart failure according to the ESC definition; where heart failure is defined as a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and elevated intracardiac pressures at rest or during stress.[9]
- HFrEF defined by LVEF ≤ 40% and/or HFmrEF defined by LVEF 41-49%
- HHD as defined by the presence of hypertension with LV dysfunction based on the following definitions;[70]
    i. Blood pressure ≥ 160/100mmHg documented and confirmed at repeated measures
    ii. HHD was considered in patients with BP < 160/100 in the context of any of the following:
        - History of longstanding hypertension with dilated LV dimensions and severely impaired systolic function (LVEF ≤ 35%), regardless of blood pressure

- High normal (BP ≥130/85) or grade 1 hypertension (BP ≥ 140/90) in patients with systolic dysfunction and concentric LVH, particularly if on blood pressure lowering medications
- Evidence of hypertensive target organ damage – nephropathy (proteinuria, chronic kidney disease), retinopathy, LVH, small vessel disease

Exclusion criteria:

- Minors, age < 18 years
- Heart failure secondary to ischaemic heart disease, cardiomyopathy, valvular heart disease, pericardial disease, congenital heart disease, primary pulmonary hypertension or cor-pulmonale
- Insufficient baseline or follow-up information
- HHD with HF with preserved ejection fraction (HFpEF)

2.2.2. Primary and secondary endpoints

Primary endpoints

1. Death or transplantation

Secondary endpoints

1. Recovery of LV dimensions and function
    - Complete recovery of their LV function defined as normalisation of LVEF ≥ 50% at follow-up;
    - Partial recovery defined as a change in LVEF ≥10% from baseline LVEF, at the time of follow-up;
2. Stroke

2.3. DATA COLLECTION

Eligible participants were identified by reviewing cardiomyopathy clinic attendance records and the IMHOTEP screening log (patients excluded from IMHOTEP with a diagnosis of HHD were considered for inclusion). Data was obtained from the Groote Schuur Hospital medical folder and/or Cardiac Clinic buff folder.

The following parameters were evaluated at baseline and follow-up: demographics (age, gender and ethnicity), clinical features including history (symptoms and New York Heart Association (NYHA) Class at presentation) and examination findings, drug therapy, presence of co-morbidities, biochemistry, electrocardiographic and echocardiographic findings. Information on outcomes (vital status, hospitalization, and adverse events such as stroke) were obtained from hospital folder records, Clinicom, and/or by contacting the patient where necessary. Data was captured on an excel-based database. Data recorded on the database was anonymised, by assigning a study number to participants enrolled.

2.4. STATISTICAL ANALYSIS

Descriptive statistics were used to describe the study population. Categorical data was summarized in tables and reported as number and proportion. Chi-Squared tests of equal proportions was used to determine differences between categorical data. All continuous variables were tested for normal distribution using a histogram for visualization and Shapiro-Wilks test. Normally distributed data was reported as mean and standard deviation. Students' t-test (2 samples), ANOVA (more than 2 samples) and paired t-test (paired samples) were used to determine differences for normally distributed data. Non-normally distributed data was reported as mean and interquartile range. Wilcoxon sum rank (2 samples) and Kruskal-Wallace (more than 2 samples) were used to determine differences between non-normally distributed continuous data. Cox proportional hazards regression analysis was used to explore

the risk of adverse outcomes and Kaplan-Meier survival analysis has been used to report the survival. Univariate and multivariate logistic regression analysis was used to explore predictors for recovery of left ventricular function. All statistical tests were two-sided, at $\alpha = 0.05$. All statistical analysis was done using statistical software, IBM Statistical Package for the Social Sciences (SPSS), Version 27, 2020 in consultation with a statistician.

2.5. ETHICS AND SAFETY

Ethics approval (Appendix) was obtained from the University of Cape Town Human Ethics Committee prior to initiation of the study and was renewed annually for the duration of the study (HREC REF 677/2018). Institutional approval was granted by Groote Schuur Hospital prior to study initiation.

As this was a retrospective study and folder review, informed consent was not be taken from the participants. Waiver of informed consent was approved by the Human Research Ethics Committee at the University of Cape Town. As there was no intervention, this study posed minimal risk to the participants.

Ethical guidelines were followed throughout the period the study is conducted. Respect and confidentiality of all patient details was maintained, and clinical information has not been distributed or disclosed to the public. Each participant was assigned a unique study number at enrolment. Personal identifiers were not included on the database. Anonymity has been maintained in the presentation of results. The information and data analysed has been kept within the investigating team.

Any contact with patients was conducted by the research sister or the attending clinician working in the clinic. These staff members are known to the patients as they been working in the clinic for a number of years.

2.6. FINANCING AND INSURANCE

No financing or insurance was needed for this project as this study predominantly involved collection of data from hospital folders of patients seen in the Cardiomyopathy Clinic.

CHAPTER 3. Results

3.1. RECRUITEMENT

Over a 3-year period, a total of 88 patients attending the Cardiomyopathy Clinic at GSH, were identified as having HHD with heart failure (**Figure 3.1**). Nineteen patients were subsequently excluded from the analysis; insufficient data to confirm diagnosis (n=5) and HHD with HFpEF (n=14). Fifty-nine patients with a diagnosis of HHD with LVEF < 50% were included in the study analysis; 45 patients with HFrEF (LVEF ≤ 40%) and 14 patients with HFmrEF (LVEF 41-49%).

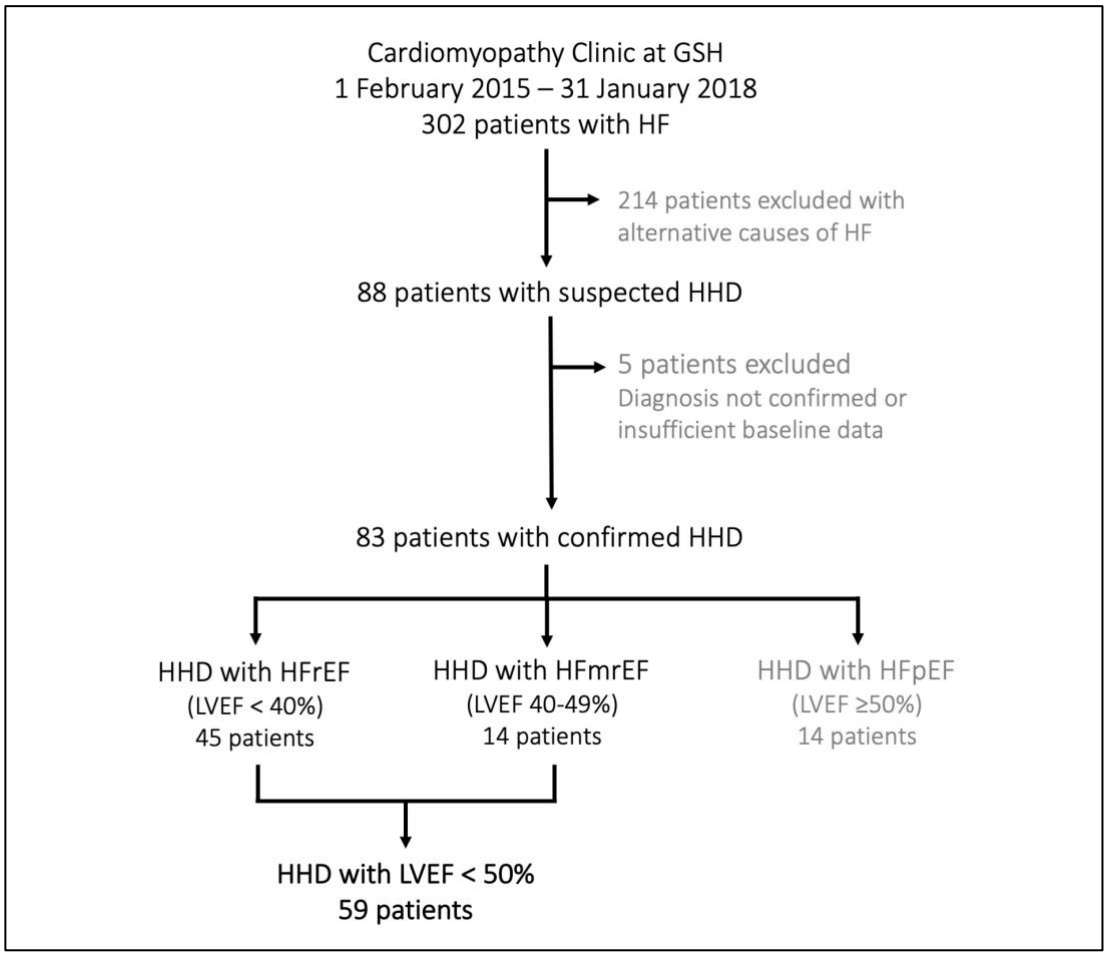

Figure 3.1 Recruitment of study participants

HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHD, hypertensive heart disease; LVEF, left ventricular ejection fraction.

3.2. BASELINE CHARACTERISTICS

Tables 3.1. and 3.2. outline the baseline characteristics of all 59 patients included in the analysis. The cohort had a similar distribution of males and females (49.2%), and most patients were of mixed race (57.6%), and black African participants (39%) ethnicity in keeping with local population demographics. The mean age of the cohort was 44.1 ±12 years with no statistical difference in age between males and females (p = 0.385). Thirty-nine patients (67.2%) presented with heart failure symptoms at baseline; the most common symptoms being dyspnoea (65.5%), followed by pedal oedema (34.5%), orthopnoea (29.3%), chest pain (21.4%), paroxysmal nocturnal dyspnoea (PND) (19%) and palpitations (17.2%). At baseline, 21 (36.2%) patients presented with NYHA Class II effort intolerance, 19 (32.8%) with Class III and only 1 (1.7%) with Class IV. Orthopnoea, PND and moderate-to-severe effort intolerance was more frequently observed in the HFrEF group compared with the HFmrEF group.

Sixty two percent of female patients were diagnosed with hypertensive heart disease and heart failure during the peripartum period. Of the 18 women diagnosed in the peripartum period, 4 had no prior diagnosis of hypertension, 6 had a new diagnosis of hypertension in the preceding year (i.e. during pregnancy or postpartum), and 3 had a history of longstanding hypertension. While a significant proportion of patients overall had a pre-existing diagnosis of hypertension at baseline (66.8%) **(Figure 3.2),** the majority of patients (n=41, 69.5%) had no other co-morbidities apart from hypertension. Additional co-morbidities were documented in 18 patients; diabetes, n=5 (8.5%); chronic renal disease, n=5 (8.5%); human immunodeficiency virus (HIV), n=5 (8.5%), chronic pulmonary disease, n=1 (1.7%) and autoimmune/connective tissue disease, n=1 (1.7%). Co-morbidities were more frequently observed in the HFrEF group compared to the HFmrEF, however, the difference was not statistically significant (p = 0.296). Most of the individuals were of sober habits, with 22% partaking in significant alcohol use and 10.2% participating in illicit drug use. Although there was a notable difference in alcohol consumption between the HFrEF and HFmrEF groups, it

was not statistically significant (p = 0.285). Thirty-one percent of individuals were recorded to be regular smokers.

Table 3.1 Baseline characteristics

Baseline characteristics	**ALL (n=59)**	**HFrEF (n=45)**	**HFmrEF (n=14)**
Female, *n (%)*	29 (49.2)	21 (46.7)	8 (57.1)
Ethnicity, *n (%)*			
Black African	23 (39.0)	19 (42.2)	4 (28.6)
Caucasian	2 (3.4)	2 (4.4)	0
Mixed race (coloured)	34 (57.6)	24 (53.3)	10 (71.4)
Age at presentation, *years*			
Mean age ±SD	44.1 ±12.0	44.1 ±11.9	44.1 ±12.8
Median age [IQR]	41.5 [35.4-51.3]	42.1 [35.3-51.1]	39.2 [35.8-58.6]
NYHA Class, *n (%)*			
NYHA Class I	17 (29.3)	11 (25.0)	6 (42.9)
NYHA Class II	21 (36.2)	15 (34.1)	6 (42.9)
NYHA Class III	19 (32.8)	17 (38.6)	2 (14.3)
NYHA Class IV	1 (1.7)	1 (2.3)	0
Cardiac symptoms at presentation, *n (%)*	39 (67.2)	32 (72.7)	7 (50.0)
Dyspnoea	38 (65.5)	30 (68.2)	8 (57.1)
Body swelling/oedema	20 (34.5)	16 (36.4)	4 (28.6)
Orthopnoea	17 (29.3)	17 (38.6)	0
Chest pain	14 (21.4)	11 (25.0)	3 (21.4)
Paroxysmal nocturnal dyspnoea	11 (19)	11 (25.0)	0
Palpitations	10 (17.2)	8 (18.2)	2 (14.3)
Presyncope/dizziness	6 (10.3)	4 (9.1)	2 (14.3)
Syncope	0	0	0
Diagnosis of HHD in peripartum period (females), *n (%)*	18/29 (62.1)	12/21 (57.1)	6/8 (75.0)
Previous diagnosis of hypertension	40 (66.8)	30 (66.7)	10 (71.4)
Number of additional co-morbidities (excluding hypertension)			
No Co-morbidities	41 (69.5)	29 (64.4)	12 (85.7)
1 additional co-morbidity	16 (27.1)	14 (31.1)	2 (14.3)
2 additional co-morbidities	2 (3.4)	2 (4.4)	0
Pre-existing co-morbidities, *n (%)*			
HIV	5 (8.5)	4 (8.9)	1 (7.1)
Atrial fibrillation	3 (5.1)	3 (6.7)	0
Diabetes [*mean* HBA1c ± SD]	5 (8.5) [10.0 ±2.0]	4 (8.9)	1 (7.1)
Chronic pulmonary disease	1 (1.7)	1 (2.2)	0
Chronic renal disease [*mean* GFR ±SD]	5 (8.5) [36.8 ±8.5]	5 (11.1)	0
Autoimmune/Connective tissue disease	1 (1.7)	1 (2.2)	0
Lifestyle/substance exposure, *n (%)*			
Alcohol (significant alcohol use)	13 (22.0)	12 (26.7)	1 (7.1)
Illicit drugs: methamphetamines/cocaine	6 (10.2)	5 (11.1)	1 (7.1)
Smoking	18 (30.5)	13 (28.9)	5 (35.7)

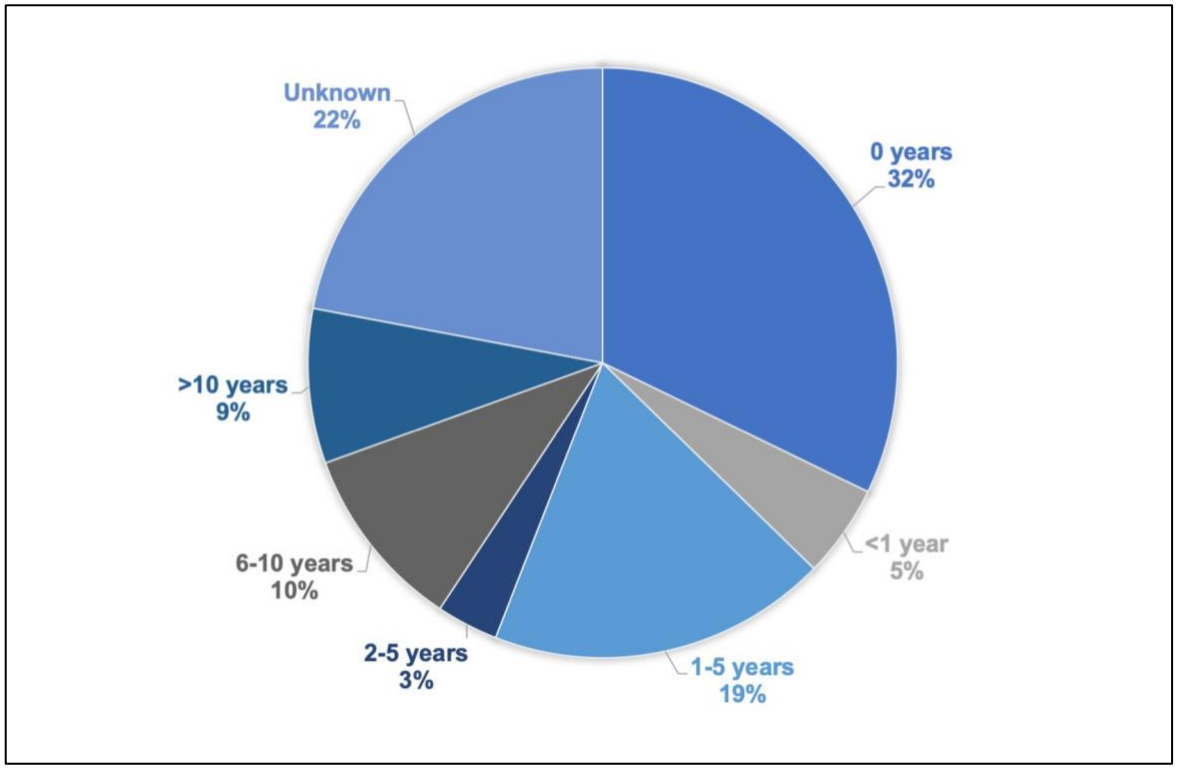

Figure 3.2 Duration of pre-existing hypertension in patients at baseline

Clinical examination findings **(Table 3.2)** at the first consultation showed a mean heart rate of 86 ±19.6 beats per minute. The mean systolic and diastolic blood pressure recorded at baseline were 130 ±20.1 mmHg and 81 ±12.8 mmHg, respectively, with no statistically significant difference in systolic blood pressure between HFrEF and HFmrEF ($p = 0.137$). Fundoscopy was performed in less than a third (30%) of cases at baseline, however, retinopathy was present in a fifth of patients where fundoscopy was performed. Signs of congestive cardiac failure on examination were present in less than half (40.7%) of patients at the first consultation. Out of the 59 patients in the cohort, there were only 52 patients who had treatment documented in their hospital record at baseline. The majority of patients were on a loop diuretic (88.5%), angiotensin-converting enzyme (ACE) inhibitors (88.5%), beta blockers (84.6%) and mineralocorticoid antagonist (MRA) (51.9%) at the time of the baseline consultation. Digoxin was not widely used, with 5 (9.6%) patients on it at baseline. Thiazide

diuretic and calcium channel blockers were prescribed in 3 (5.8%) and 2 (3.8%) of cases, respectively. Thirteen patients (25%) patients were on anti-platelet therapy at baseline.

Table 3.2 Baseline characteristics (continued)

Baseline characteristics	**ALL (n=59)**	**HFrEF (n=45)**	**HFmrEF (n=14)**
Examination at time of enrolment, *n (%)*			
Heart rate (beats/min), *mean ±SD*	86 ±19.6	89 ±21.0	78 ±12.7
Systolic blood pressure (mmHg), *mean ±SD*	130 ±20.1	128 ±20.5	137 ±17.6†
Diastolic blood pressure (mmHg), *mean ±SD*	81 ±12.8	81 ±13.7	82 ±9.8
Retinopathy reported$^{\Sigma}$	12 (20.3)	10 (22.2)	2 (14.3)
Congestive heart failure n (%)	24 (40.7)	21 (46.7)	3 (21.4)
BMI*	29.8 ±7.2	29.2 ±7.0	31.4 ±7.9
Medication at enrolment, *n (%)*			
Loop diuretic	46/52 (88.5)	35/40 (87.5)	11/12 (91.7)
Thiazide	3/52 (5.8)	3/40 (7.5)	0/12
Beta-blockers	44/52 (84.6)	34/40 (85.0)	10/12 (83.3)
ACE inhibitors/ARB	46/52 (88.5)	35/40 (87.5)	11/12 (91.7)
MRA	27/52 (51.9)	21/40 (52.5)	6/12 (50.0)
Digoxin	5/52 (9.6)	3/40 (7.5)	2/12 (16.7)
Calcium channel blockers	2/52 (3.8)	2/40 (5.0)	0/12
Anti-platelet therapy	13/52 (25.0)	11/40 (27.5)	2/12 (16.7)

†Independent T-test between groups (HFrEF and HFmrEF) for systolic blood pressure, p = 0.137.
$^{\Sigma}$Fundoscopy was not documented in majority of patients' clinical record, therefore, this number is likely an underestimation
*Body mass index may be influenced by presence of fluid overload, and should be interpreted with caution

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; MRA, mineralocorticoid antagonist.

3.3. BASELINE INVESTIGATIONS

Investigations performed prior to or at the time of the baseline consultation are indicated in **Table 3.3**.

Table 3.3 Investigations performed at baseline consultation

Investigations	ALL, n=59
Full blood count (FBC)	53 (89.8)
Creatinine, electrolytes and urea (CEU)	57 (96.6)
Thyroid function	37 (62.7)
Urinary protein: creatinine ratio	8 (13.6)
Electrocardiogram	57 (96.6)
Echocardiogram	54 (91.5)

Laboratory investigations (Table 3.4). Full blood counts were done on 89.8% of cases; mean haemoglobin and MCV were 12.7 ± 1.9 g/dl and 85.3 ± 5.9 f/l, respectively. Six patients had anaemia at baseline (majority normocytic); 4 patients were postpartum; 1 patient had a co-existing autoimmune condition and 1 patient was on anticoagulation therapy for atrial fibrillation. Renal function and electrolyte investigations were conducted in the vast majority (96.6%) of patients. Ten patients (17.5%) had renal dysfunction (estimated glomerular filtration rate [eGFR] < 60ml/min/1.73m^2) at baseline (9/10 from the HFrEF group); 5 patients previously diagnosed with chronic kidney disease (mean eGFR 36.8 ± 8.5 ml/min/1.73 m^2, and 5 patients with newly diagnosed renal dysfunction. Urine protein:creatinine ratio measurements were only performed in 8/59 (13.6%) of the patients, making it difficult to fully evaluate renal disease in this cohort. Mean sodium and median creatinine were 139 ±3.5 mmol/L and 81.9 umol/L (IQR 61.3-102). Mean HbA1C of those patients with diabetes (n=5) was 10.0 ±2.0 mmol/mol indicating poor diabetic control. Three patients had mild thyroid dysfunction.

Table 3.4 Laboratory investigations

Laboratory investigations	ALL (n=59)
Haemoglobin, mean ±SD (g/dL)	12.7 ±1.9 (12-15)
MCV, mean ±SD (fL)	85.3 ±5.9 (78.9 – 98.5)
Sodium, mean ±SD (mmol/L)	139.0 ±3.5 (136-145)
Creatinine, median [IQR] (umol/L)	81.9 [IQR 61.3-102.0] (49-90)

MCV, mean corpuscular volume.

Electrocardiogram (Table 3.5). Baseline electrocardiograms were available for analysis in 57/60 patients. The mean heart rate at baseline was 85 ±19.2 beats/minute. Sinus rhythm was noted in 96.5% of patients. Atrial fibrillation/flutter was present in 2 patients at baseline. The mean QRS duration was 98 ±21.1 milliseconds (ms) and the mean corrected QT interval was marginally increased in both males and females (QTc [male], 461.61 ±25.4; QTc [female] 469.8 ±42.8 [p = 0.380]). Left and right bundle branch block were present in 6 (10.5%) and 1 (1.8%) patients, respectively. Left atrial enlargement was seen in 22.8% of patients at presentation. LVH was present in 54.4% of cases and repolarization changes noted in 61.4%.

Table 3.5 Baseline electrocardiogram findings

Electrocardiogram	ALL, n=59	HFrEF, n=43	HFmrEF, n=14
Heart rate (bpm), *mean ±SD*	85 ±19.2	87 ±20.5	77 ±12.0
Rhythm			
Sinus rhythm, n (%)	55 (96.5)	4.0 (95.3)	14.0 (100.0)
Atrial fibrillation/flutter, n (%)	2 (3.5)	2.0 (4.7)	0
QRS			
QRS duration, *mean ±SD*	98 ±21.1	98 ±21.6	99 ±20.0
QTc*, mean ±SD	466 ±35.2	469 ±34.5	456 ±36.7
LBBB, n (%)	6 (10.5)	4 (9.3)	2 (14.3)
RBBB, n (%)	1 (1.8)	0	1 (7.1)
LA enlargement, n (%)	13 (22.8)	12.0 (27.9)	1.0 (7.1)
Left ventricular hypertrophy	31 (54.4)	24 (55.8)	7 (50)
Voltage (mm), mean ±SD	35.2 ±13.4	37.2 ±14	29.3 ±9.3
Cornell (mm), mean ±SD	24.5 ±10.1	25.7 ±10.2	21 ±8.9
Lead 1 (mm), mean ±SD [median, IQR]	8.4 ±4.3 [8(5-11)]	8.1 ±4.5	9.4 ±4.0
Repolarization changes , n (%)	35 (61.4)	28 (65.1)	7 (50.0)

*QTc [male], 461.61 ±25.4; QTc [female] 469.8 ±42.8 [p = 0.380]
LA, left atrial; LBBB, left bundle branch block; RBBB, right bundle branch block

Echocardiogram (Table 3.6.) Standard echocardiograms were performed on a total of 54/59 patients at baseline. On assessment of left heart study, the ascending aortic dimensions were within normal limits (mean diameter of 3.1 ±0.5cm). Mean left atrial diameter was increased (4.4±0.9 cm). The LV end diastolic dimensions (LVEDD) were increased (6.4 ±0.8 cm) and there was no statistical difference between the HRrEF and HFmrEF groups (p = 0.118). LVEF was markedly reduced (29.9 ±10.4 %) but as expected, there was a significant difference of between HFrEF and HFmrEF for LVEF (25.5 ±7.8 % versus 43.5 ±2.4 %, p <0.001) and fractional shortening (12.1 ±4.4 % versus 22.0 ±1.9 %, p <0.001). LVH was only present in 17 (32.1%) patients and the median measurements for LV wall thickness were within the normal range; interventricular septum (IVS) and left ventricular posterior wall (LVPW) thickness (median) in diastole were 1.0 [0.9-1.2] cm and 1.1 [0.8-1.3] cm respectively, with no significant differences between the groups (IVSd, p = 0.271; LVPWd, p = 0.493). Diastolic function was impaired; while the median E/A ratio was just below 2 (1.9 [0.9-3.1]), the mean E/E' was elevated (15.8 ±6.8). Functional mitral regurgitation was recorded in 81.5% of patients; the majority of patients had mild regurgitation (59.3%), and only a few patients had moderate (9.3%), moderate-to-severe (3.7%) and severe (9.3%) mitral regurgitation. Right atrial and ventricular dilation was reported in 37% and 33.3% of patients, respectively. RV (right ventricular) function was mildly impaired with a mean TAPSE of 14.9 ± 7.2 mm. Forty-four percent of patients had mild tricuspid regurgitation, and 9.3% and 13% had moderate and severe tricuspid regurgitation, respectively. The mean RV systolic pressure (RVSP) was 31±12 mmHg. Intra-cardiac thrombus and pericardial effusions were present in 4 (7.4%) and 12 (22.2%) cases respectively.

Table 3.6 Baseline echocardiogram findings

Baseline echocardiogram findings	**ALL, n=54**	**HFrEF, n = 41**	**HFmrEF, n = 13**
Aortic root (cm), *mean±SD*	3.1 ±0.5	3.1 ±0.6	3.1 ±0.5
LA dimension (cm), *mean±SD*	4.4 ±0.9	4.5 ±0.9	4.0 ±0.8
LV EDD (cm), *mean±SD*	6.4 ±0.8	6.5 ±0.8	6.1 ±0.7
LV fractional shortening, *mean ±SD*	14.2 ±5.7	12.1 ±4.4	22.0 ±1.9
LVEF (%), *mean ±SD*	29.9 ±10.4	25.5 ±7.8	43.5 ±2.4
LVH present, *n (%)*	17/53 (32.1)	11 (26.8)	6/12 (50.0)
LV wall thickness			
IVSd (cm), *median (IQR)*	1.0 [0.9-1.2]	1.0 [0.9-1.2]	1.1 [0.9-1.4]
IVS (systole) (cm), *median (IQR)*	1.2 [1.0-1.3]	1.1 [1.0-1.2]	1.5 [1.2-1.7]
LVPW (diastole) (cm), *median (IQR)*	1.1 [0.8-1.3]	1.0 [0.8-1.3]	1.1 [0.9-1.3]
LVPW (systole) (cm), *median (IQR)*	1.4 [1.2-1.7]	1.4 [1.2-1.6]	1.6 [1.4-1.9]
Diastolic function			
E/A, *median (IQR)*	1.9 [0.9-3.1]	1.9 [0.9-3.3]	1.5 [0.8-2.7]
E/E', *mean ±SD*	15.8 ±6.8	16.2 ±7.3	14.3 ±5.3
DCT, *mean ±SD*	158.4 ±65.1	151.6 ±69.9	173.9 ±52.3
Functional mitral regurgitation*, n (%)*	44 (81.5)	35 (85.4)	9 (69.2)
Mild MR	32 (59.3)	25 (61)	7 (53.8)
Moderate MR	5 (9.3)	3 (7.3)	2 (15.4)
Moderate – severe MR	2 (3.7)	2 (4.9)	0
Severe MR	5 (9.3)	5 (12.2)	0
RA dilatation*, *n (%)*	20 (37)	17 (41.5)	3 (23.1)
RV dilatation*, *n (%)*	18 (33.3)	14 (34.1)	4 (30.8)
TAPSE, *mean ±SD*	14.9 ±7.2	14.6 ±6.9	16.2 ±8.8
Functional tricuspid regurgitation, *n (%)*	36 (66.7)	33 (80.5)	3 (20.1)
Mild TR	24 (44.4)	21 (51.2)	3 (23.1)
Moderate TR	5 (9.3)	5 (12.2)	0
Severe TR	7 (13)	7 (17.1)	0
RVSP (mmHg), *mean ±SD*	31.1 ±12	31.6 ±12.3	27.8 ±10.3
Intra-cardiac thrombus, *n (%)*	4 (7.4)	4 (9.8)	0
Pericardial effusion*, *n (%)*	12 (22.2)	11 (26.8)	1 (7.7)

**Reported by operator, dimensions not always provided*

DCT, deceleration time; IVS, interventricular septum; LA, left atrium; LV, left ventricular; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall; MR, mitral regurgitation; RA, right atrial; RV, right ventricular; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

3.4. FOLLOW-UP

The follow-up and vital status of patients is represented in **Figure 3.3.** At the end of the study period, 6 patients had died, 1 patient underwent cardiac transplant, 14 patients continued follow-up in the cardiomyopathy clinic, 22 patients were discharged during the study period to follow-up at primary care facilities, and 16 patients had defaulted clinic follow-up on their own accord.

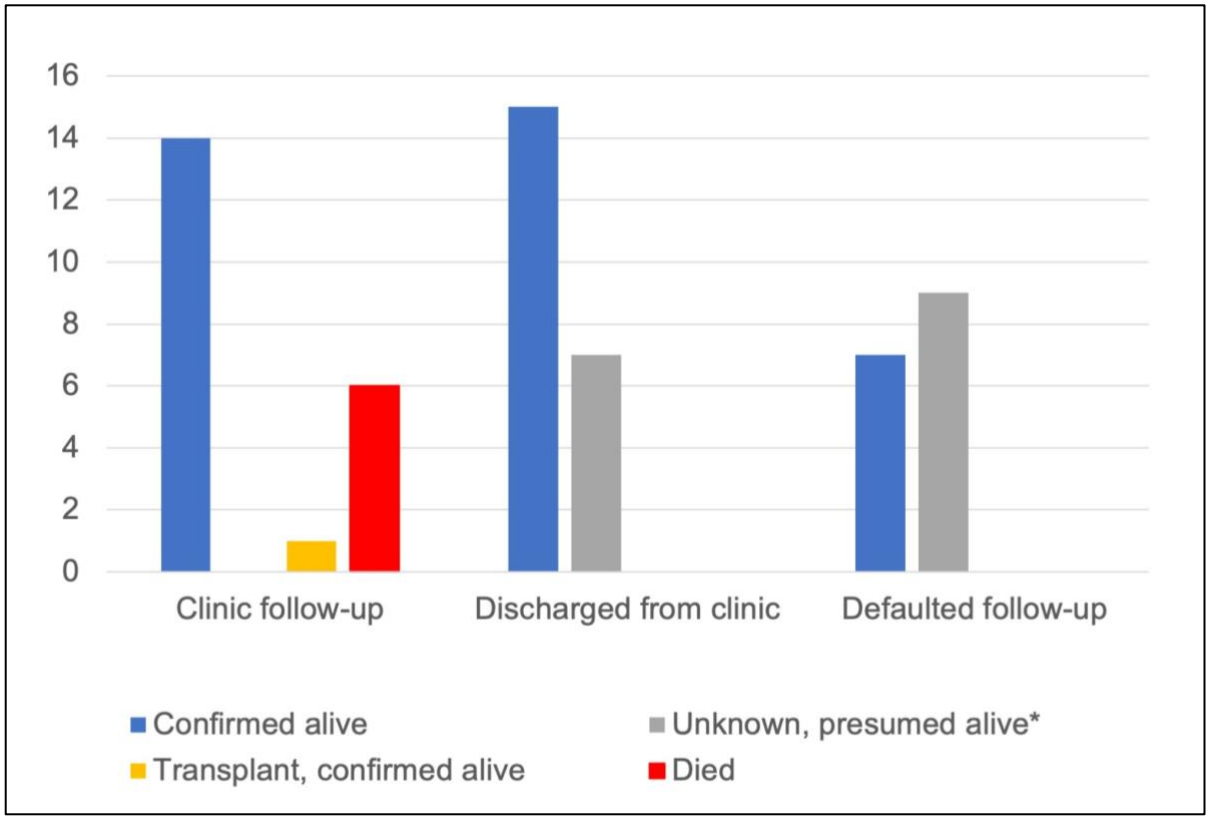

Figure 3.3 Follow-up and vital status of participants

*Unable to contact patient but no record of death (or clinic/hospital visits) in provincial health system database, *Clinicom,* at the end of follow-up period. Of note, all patients lost to follow-up had NYHA Class I and/or LVEF > 40% at their last review with the exception of one patient (NYHA Class II, LVEF 29%)

Follow-up data was collected for two visits within the study period; 53/59 patients were seen at follow-up 1 (F1) and 45/59 patients were seen at follow-up 2 (F2). The median times from baseline to follow-up 1 (F1) and follow-up 2 (F2), were 5.6 [IQR 3.0-6.9] months and 13.2 [IQR 9.1-15.7] months. Importantly, the vast majority of patients discharged from tertiary care or lost to follow-up were well (i.e. NYHA Class I and /or partial or complete recovery of LVEF), at their last clinic visit, therefore those followed-up, likely represent the more severe end of the spectrum of disease.

Clinical findings at follow-up 1 (F1) and follow-up 2 (F2) (Figure 3.4). A marked improvement in functional class was evident at follow-up, with an increasing proportion of patients reporting NYHA Class I effort tolerance (Baseline, 29.3%, F1, 52.8%; F2, 62.2%), and a corresponding decrease in the proportion of patients reporting heart failure symptoms at follow-up visits **(Figure 3.4 [A] and [B])**. Furthermore, there was a decrease in the number of patients presenting with clinical signs of congestive heart failure (CCF) as displayed in **Figure 3.4 [C]** (Baseline, 40.7%; F1, 17%; F2, 8.9%). Despite up-titration of medical therapy **(Figure 3.5)**, mean blood pressure remained relatively unchanged at follow-up, with systolic blood pressures 134 ±21.8 (paired sample T-test, p = 0.338) and 131 ± 21.2 mmHg (paired sample T-test, p = 0.634) on first and second follow up visits respectively **(Figure 3.4 [D])**.

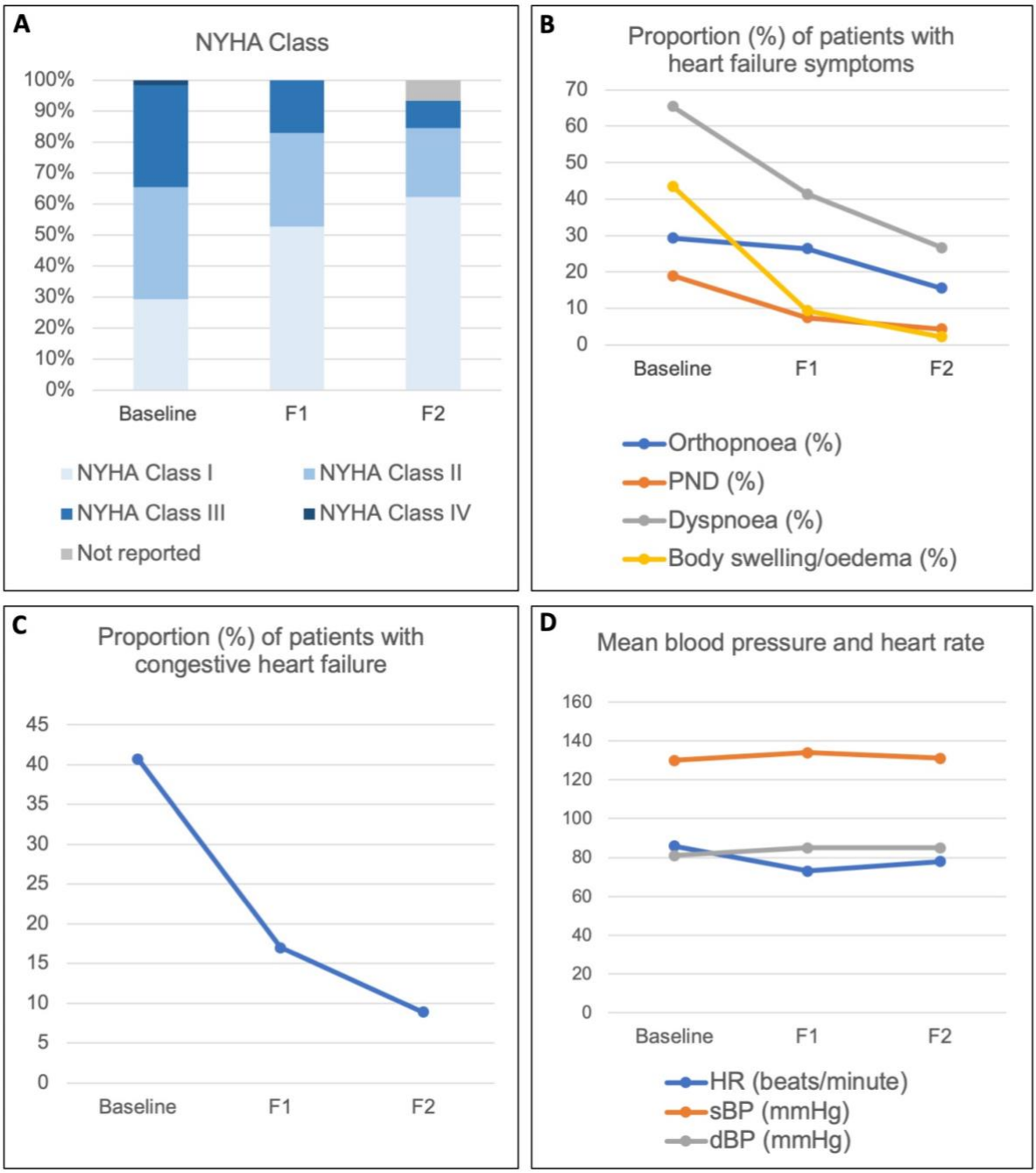

Figure 3.4 Symptoms and signs in patients at baseline and follow-up

(A) NYHA Class; (B) Proportion of patients with heart failure symptoms; (C) Proportion of patients with congestive heart failure; and (D) Mean blood pressure and heart rate

dBP, diastolic blood pressure; F1, follow-up 1; F2, follow-up 2; HR, heart rate; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnoea; sBP, systolic blood pressure.

Medical therapy (Figure 3.5). The majority of patients were on loop diuretics**,** beta-blockers, ACE-inhibitors and MRA's at follow-up with an increasing number of patients on

recommended doses for heart failure **(Figure 3.5 [C]).** There was a notable rise in the use of MRA's on follow up visits (baseline, 51.9%; F1, 83.3% and F2, 85.4%) but limited dose escalation. Hyperkalaemia was observed in 2 patients during the follow-up period. There was a small increase in the number of patients prescribed calcium channel blockers (12.5% - 22.0%) as well as an increase in mean dose prescribed at follow-up.

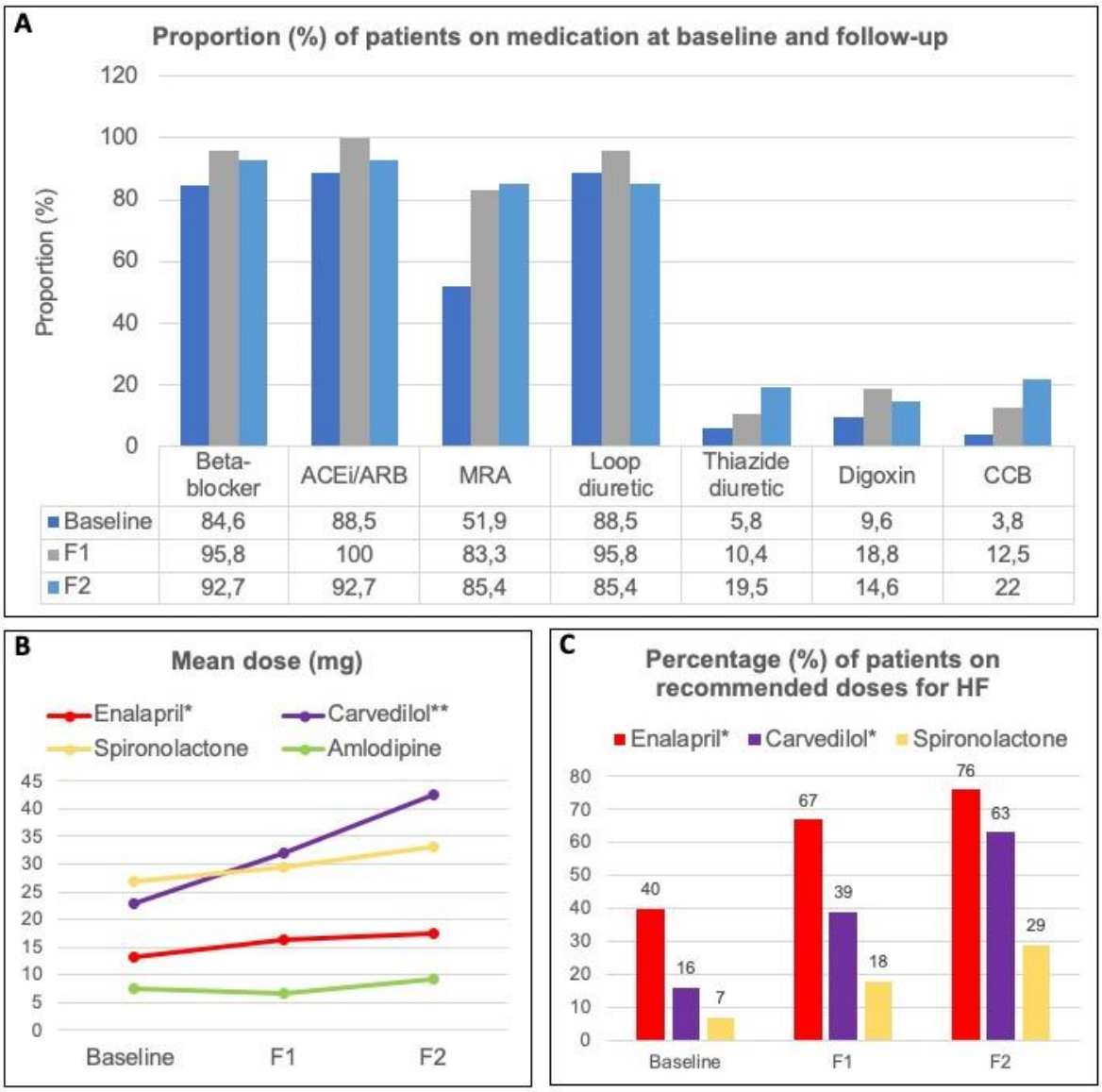

Figure 3.5 Medical therapy at baseline and follow-up

(A) Proportion of patients on medication at baseline and follow up; (B) Mean dose; (C) Percentage of patients on recommended doses for HF

*or equivalent dose of ACEi or ARB; **or equivalent dose of beta-blocker

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; F1, follow up 1; F2, follow up 2; MRA, mineralocorticoid antagonist.

Electrocardiogram. (Figure 3.6) The most notable change on ECG at follow-up was the progressive improvement of the corrected QT interval (baseline, 466 ±35.2ms, F1, 451.7 ± 39.2ms; F2, 449.2 ±36.6ms). This change in QTc over the follow-up period was significant (paired T-test comparing QTc at baseline and F1, p = 0.024; and baseline and F2, p 0.025). There were no other significant changes in the rest of the parameters. There was an apparent decline in some voltage parameters at follow-up, but these were not statistically significant. Two additional patients developed atrial fibrillation during follow-up.

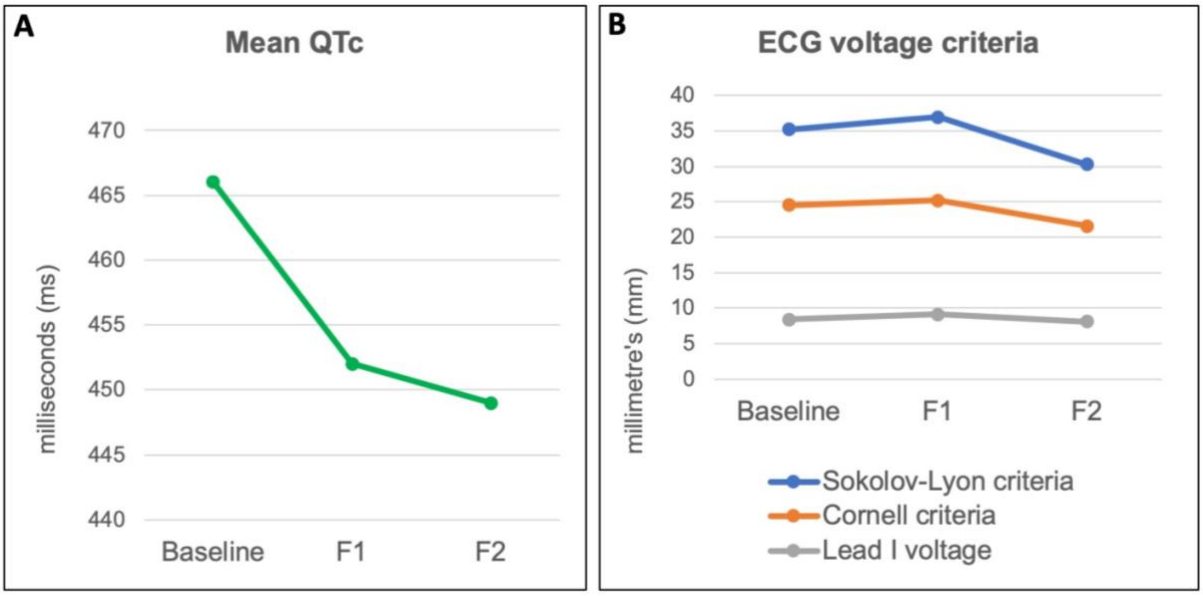

Figure 3.6 Echocardiogram findings for QTc and LVH criteria at baseline and follow-up

(A) Mean QTc; (B) ECG voltage criteria

Paired T-test comparing QTc at baseline and F1, p = 0.024; and baseline and F2, p 0.025

QTc, corrected QT interval.

Echocardiogram. Follow-up echocardiograms were done according to physician discretion and test availability. On the first follow-up, 28 patients had echocardiograms, and 27 patients on the second follow-up. There was an overall improvement in the LVEF (baseline, 29.9%, F1, 40%; F2, 44.3%), fractional shortening (baseline, 14.2 ±5.7; F1 21.9±7.9, F2, 23.0 ±7.8 ,

and TAPSE (baseline, 14.9 ±7.2; F, 16.8 ±5.6; F2, 18.4±4.1) **(Figure 3.7).** Left atrial and ventricular dimensions improved over the follow-up period, however, wall thickness remained relatively unchanged over follow-up. Paired T-tests indicated that changes in parameters between (1) baseline and F1, and/or (2) baseline and F2, were significant for LVEF (1) p<0.001) (2) p<0.001, fractional shortening (1) p<0.001 (2) p<0.001), LA dimensions (1) p = 0.007 (2) p = 0.064 and LV dimensions (1) p = 0.046 (2) p = 0.022, confirming reverse left ventricular remodeling in a significant number of patients in the cohort. While there was improvement in diastolic function parameters, these were not statically significant.

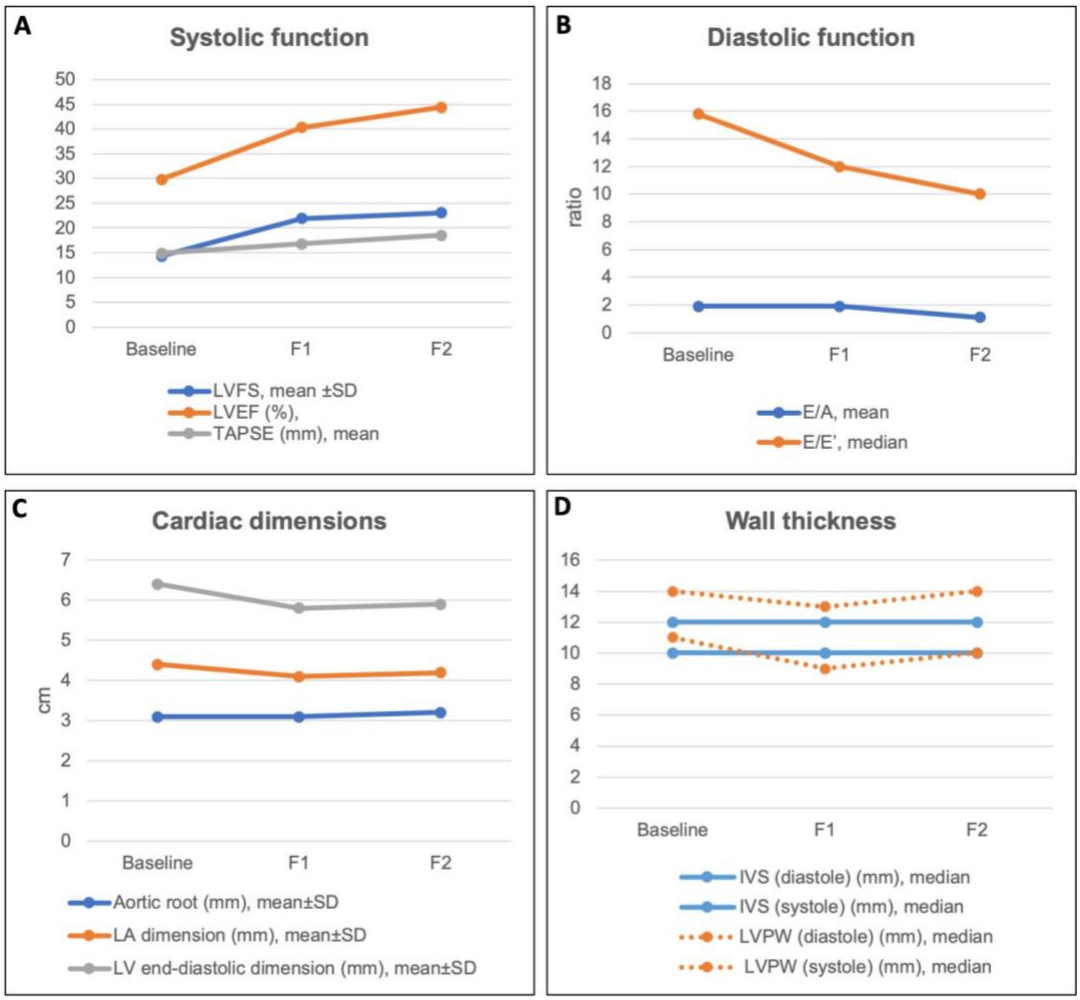

Figure 3.7 Echocardiographic findings at baseline and follow-up

(A) Systolic function; (B) Diastolic function; (C) Cardiac dimensions; (D) Wall thickness

F1, follow up 1; F2, follow up 2; IVS, interventricular septum; LA, left atrium; LV, left ventricular; LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening; LVPW, left ventricular posterior wall; TAPSE, tricuspid annular plane systolic excursion.

3.5. OUTCOMES

Survival. Patient outcomes over a median follow-up period of 3.0 [1.9-3.9] years are represented in **Figure 3.8**. During that time, 22 patients were discharged from the clinic (median duration of 9.0 [IQR 3.2-12.8] months from index presentation to discharge), 16 patients were lost to follow up, 14 patients were still undergoing follow up at the cardiomyopathy clinic, 6 patients died (3 patients died of decompensated HF; 1 patient died following a stroke; 2 patients died at home) and 1 patient underwent cardiac transplantation (hypertensive vascular changes confirmed on histology). Transplant-free survival at 1-year and 3-years, was 98% and 90%, respectively. There was no statistically significant difference in transplant-free survival between HFrEF and HFmrEF (log rank, p = 0.586), however, there was a significant difference in transplant-free survival between those patients with no additional co-morbidities (apart from hypertension), and those with additional comorbidities (log rank, p=0.024) **(Figure 3.9).**

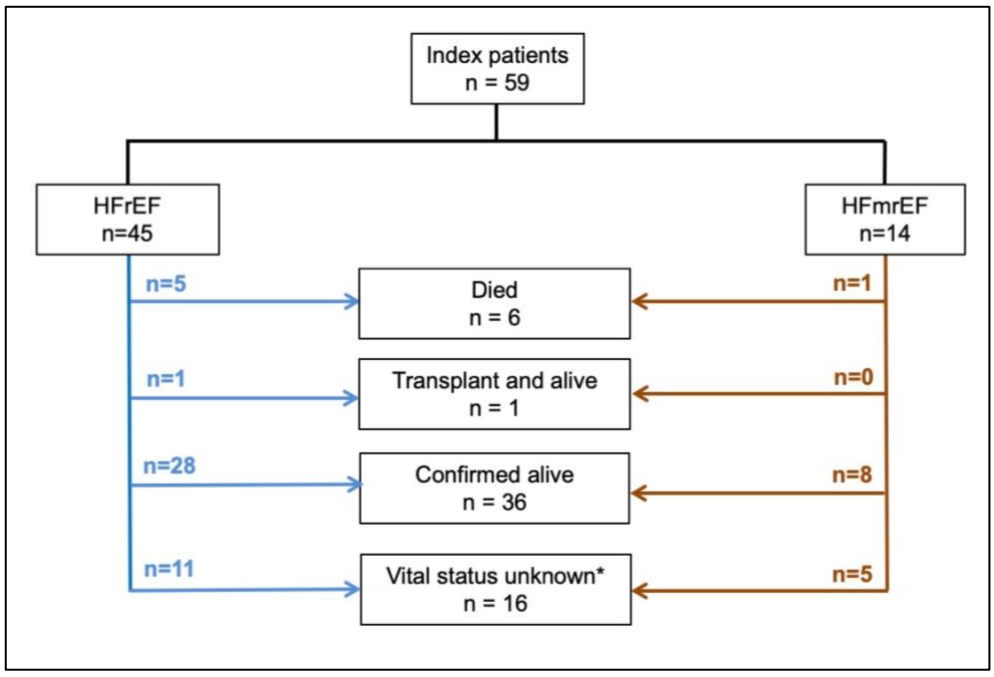

Figure 3.8 Survival outcomes

*Presumed alive; unable to contact patient but no record of death (or clinic/hospital visits) in provincial health system database, *Clinicom,* at the end of follow-up period.

HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction

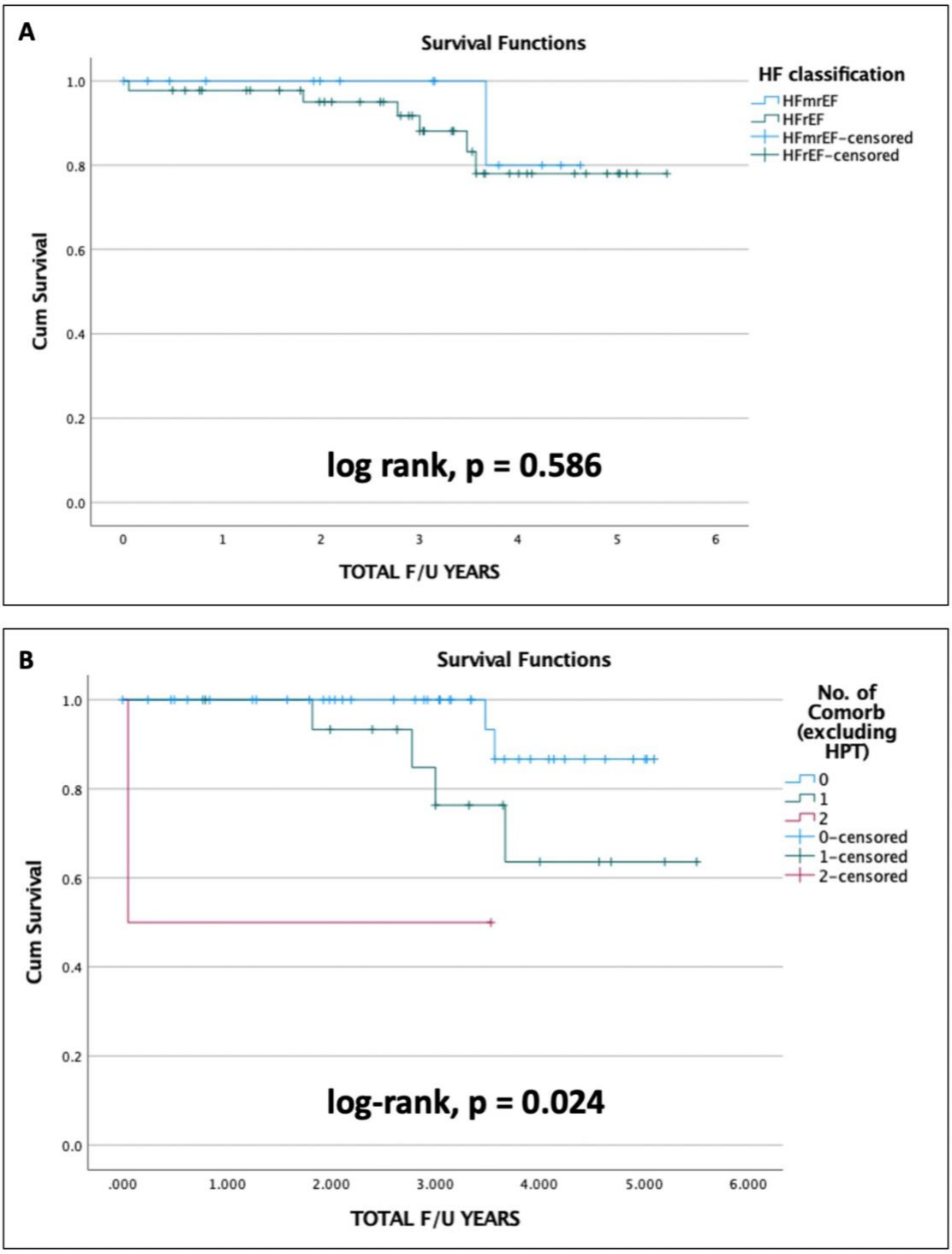

Figure 3.9 Kaplan-Meier transplant-free survival analysis

(A) HFrEF versus HFmrEF and (B) Number of co-existing co-morbidities in addition to hypertension

HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction

Recovery

Figure 3.10 indicates recovery of LV function within the cohort. Thirty-seven patients underwent repeat echocardiographic assessment within the follow-up period. Recovery of LVEF was observed in 86.5% patients where repeat imaging was done; 17 (45.9%) patients had complete recovery of their LV function (defined as LVEF ≥ 50%); 15 (40.5%) showed partial recovery (defined as LVEF improvement of ≥10%); and 5 patients had no recovery of their LV function.

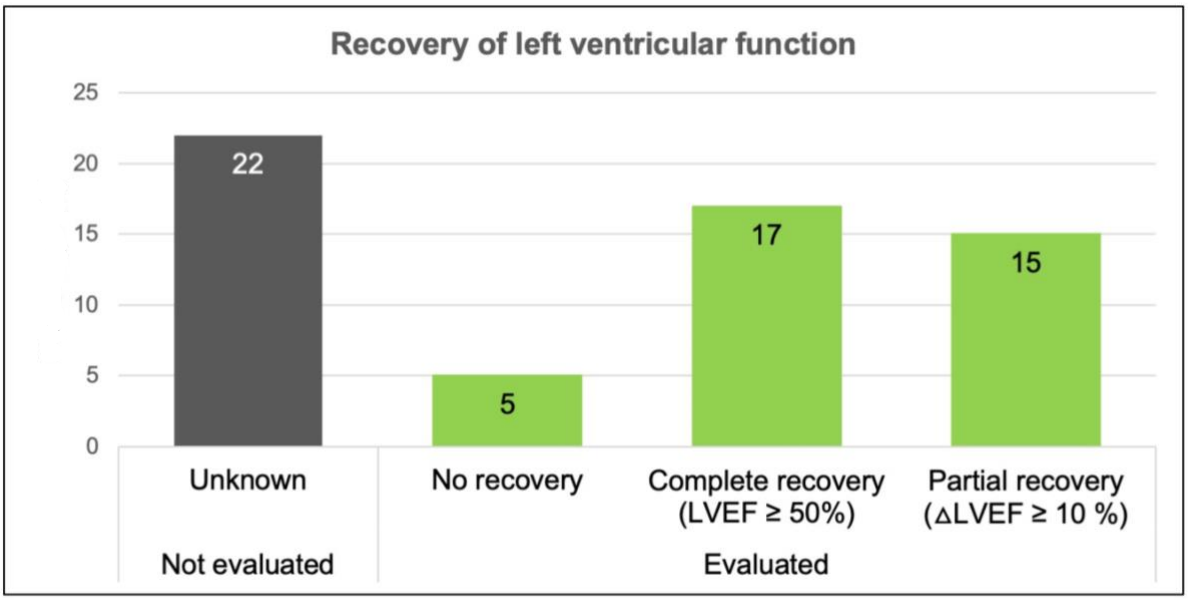

Figure 3.10 Recovery of left ventricular function

LVEF, left ventricular function

CHAPTER 4. Discussion and Conclusion

4.1. DISCUSSION

There is limited research available on HHD with heart failure and reduced (or mid-range) ejection fraction from an African perspective. Most studies that have investigated the characteristics of individuals with HHD are from American, European and Asian countries. This study contributes to the current literature and provides useful information on the nature of HHD and the severity of the disease within a South African context.

The primary aims of this study were to describe specific baseline characteristics and outcomes of South African patients presenting with HHD with HFrEF or HFmrEF. HHD with HFrEF or HFmrEF is seen in all ethnic groups in South Africa, and the predominance of patients with mixed race and black African ancestry is representative of the regional population. The mean age of presentation with heart failure in our cohort was significantly younger than what has been reported globally (44 ±12 years versus 70 years).[36] This finding is consistent with prevalence data showing that 44.1% of individuals below the age of 50 have hypertension in South Africa.[18] Although not explored in this study, earlier onset of heart failure in individuals has socioeconomic relevance, affecting national productivity due to disability and premature death.[4] The most common symptoms at presentation were dyspnoea and oedema, similar to what has been described in other studies from West Africa[47,48] and the majority of patients presented with either NYHA class II or III effort intolerance.

A significant proportion of women in this cohort presented with heart failure during the peripartum period. Gestational hypertension is an important contributor to maternal mortality in Africa[43] and appears to be a key risk factor for the development of HHD with HFrEF and HFmrEF in our female population. Overall, more than two-thirds of patients seen had a pre-

existing diagnosis of hypertension at baseline presentation with heart failure. Despite the frequency of pre-existing hypertension, the vast majority of patients had no additional co-morbidities. Although infrequent, diabetes, chronic renal disease and HIV were the most common co-morbidities seen in our cohort, and an increase in the number of co-morbidities appears to be a risk factor for premature death. Although difficult to interpret in the setting of congestive heart failure, the majority of patients in this cohort were overweight, an observation that was not significantly altered by the resolution of congestion at follow-up, and has been as described in other South African studies on hypertension.[18,71] Although infrequent, anaemia was seen in a few patients, particularly in the postpartum period. As iron deficiency and anaemia are associated with worse clinical outcomes[72] and may be a precipitant for decompensated heart failure, addressing anaemia and iron deficiency in patients with hypertension, in addition to blood pressure control, may help to mitigate subsequent decompensation. Contrary to what has been reported in other cohorts[50] atrial fibrillation was an infrequent finding at baseline or at follow-up in this group of patients.

The diagnosis of HHD in the context of impaired systolic function is challenging, and blood pressure readings at baseline may not accurately reflect underlying hypertension. Pseudo-normal readings in the context of HFrEF may be attributed to decreased cardiac output and the effects of therapy, including hypovolemia secondary to loop diuretic use and vasodilation.[73] Of note, there may be differences in BP readings based on the presentation of heart failure. It has been shown that that patients that present with acute decompensated chronic heart failure are usually able to maintain their blood pressure based on the compensatory mechanisms. New onset acute heart failure does not produce the appropriate feedback mechanisms to preserve the blood pressure.[74] In our study, mean systolic blood pressure at baseline presentation with heart failure was only marginally elevated, and ranged from 88 to 172 mmHg. Despite the variation in blood pressure measurements at baseline, the presence of hypertension and/or TOD was confirmed in all patients during follow-up, indicating that the modified criteria for diagnosis of HHD utilized in the study may be clinically useful. While there

is a linear association between raised blood pressure and cardiovascular disease[75], lower blood pressures in the context of HFrEF may not necessarily reflect reduced risk. There are no clear guidelines on BP targets for patients with HHD and heart failure.[9] Optimization of therapy in HHD with HFrEF or HFmrEF is currently based of general heart failure guidelines, and is not tailored specifically to blood pressure targets. This may be relevant in patients that present with elevated blood pressures and heart failure, and in those patients that recover their LV function on anti-failure therapy with subsequent unmasking of underlying hypertension.

The detection of LVH was not a prominent finding across this cohort; less than a third of patients had LVH on echocardiogram and the median wall thickness across the cohort was within the normal range. This challenges traditional definitions for HHD where LVH has been included as an important criteria.[25] In contrast to dilated cardiomyopathy where wall thinning is frequently observed (Kraus, S. 2019. Ph.D. Thesis. UCT), LV wall thickness may be normal or, less frequently, increased in HHD. Regression of LVH in patients with hypertension is associated with a reduction of target organ damage associated with hypertension.[76] The pseudo-normalisation of blood pressure in HHD with HFrEF, in conjunction with other factors such as younger age and lack of co-morbidities, may possibly account for lower rates of LVH and target organ damage in our cohort, although this has not been proven in this study. The degree of target organ damage is difficult to accurately report as fundoscopy, urine dipstick and urine protein creatinine ratios were not done (or not recorded) in the vast majority of patients at clinic visits. Routine evaluation of the non-cardiac TOD should be conducted in all patients with heart failure secondary to HHD, regardless of blood pressure readings. Urine protein:creatinine ratio may also be helpful in distinguishing between hypertensive renal disease (TOD) or primary chronic kidney disease, and cardiorenal syndrome in patients with HHD and heart failure. Although renal dysfunction was seen in less than a fifth of patients at presentation, univariate and multivariate logistical regression analysis indicates that an abnormal baseline creatinine is associated with lower rates of complete recovery at follow-up.

Most patients were initiated on appropriate therapy for HF but were on suboptimal doses at baseline. The proportion of patients on optimal drug doses for heart failure did increase substantially over the follow-up period, however, 24% and 37% of patients were still on sub-optimal doses of ACE-inhibitors and beta-blockers at the second follow-up (13.2 [IQR 9.1-15.7] months). Despite this, the rate of mortality or transplantation was low for a heart failure cohort and a significant number of patients had partial or complete recovery of their LVEF. Ideally, the ACE-I should have been up-titrated to optimal doses prior to the addition of calcium channel blockers as this has no effect on mortality or survival. Studies have shown that ACE-I and beta blockers improve left ventricular volume, hypertrophy and LVEF.[77-79] Reverse remodeling, specifically regression of LVH and improvement of left ventricular dimensions and LVEF, has a proven positive outcome on mortality,[80] therefore, optimisation of heart failure therapy would likely improve outcomes and recovery rates even further. Transplant-free survival was surprisingly good (98.3% and 90.5% at 1- and 3-years, respectively), in comparison to outcomes reported in heart failure studies conducted in Sub-Saharan Africa, despite hypertension being identified as the leading cause for heart failure in these cohorts.[1,8,81] Overall survival was good in this cohort although there was no statistically significant survival difference between HFrEF and HFmrEF.

It is not yet fully known what causes a particular subset of patients with hypertension develop HHD with HFrEF, nor why the cardiac insult appears to be so severe compared to other organ involvement. Contributing factors, such as increased alcohol intake, pregnancy, co-morbidities such as Diabetes Mellitus and HIV, and genetic predisposition, may possibly render the myocardium more vulnerable and further research is necessary to better understand the relationship between hypertension and these factors.

4.2. LIMITATIONS

The main limitations of this study were that it was retrospective and observational, and subject to selection bias. As patients were recruited from a tertiary institution in Cape Town, this cohort likely represents the more severe end of the disease spectrum. As repeat imaging was only conducted in those requiring follow-up at the tertiary care facility, the rates of recovery may be underestimated. Furthermore, the cohort size was small, making it difficult to reliably predict factors associated with recovery or adverse outcomes. Due to the retrospective nature of the study, follow-up periods varied with a number of patients being discharged or lost to follow-up, and vital status could not be confirmed in all patients. Despite the above-mentioned limitations, this study provides real world data on clinical manifestations, treatment and outcomes of patients with HHD. A number of health care gaps have been identified, namely; improvements could be made to better optimize therapy in the first year after diagnosis with heart failure, and fundoscopy and urinary protein assessments should be done routinely in all patients with HHD.

4.3. CONCLUSION

Hypertension is endemic in Sub-Saharan Africa and has been shown to be the leading cause of heart failure on the continent. In this study, patients with HHD and impaired ventricular function were younger and had better outcomes compared to HF from all causes. Most presented with effort intolerance, congestion and mildly elevated or ‘pseudonormal’ blood pressures. The majority of patients had a prior diagnosis of hypertension and a significant proportion of women presented with heart failure in the peripartum period. Additional co-morbidities were uncommon, however, were associated with worse clinical outcomes. Concentric LVH was not a prominent feature on echocardiogram and AF was infrequent. Despite severely impaired LVEF at baseline, mortality was lower than expected for HF patients and improvement in LVEF on therapy was observed in the majority of patients, suggesting

that hypertensive heart disease is potentially reversible with medical therapy. However, larger prospective studies would be necessary in order to confirm these observations and provide more robust data on outcomes and possible predictors of mortality and morbidity in HHD.

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APPENDIX

List of appendix documents

Appendix A – Human Research Ethics Committee Approval

Appendix B - Institutional Approval

APPENDIX A – Human Research Ethics Committee Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arlefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

21 November 2018

HREC REF: 677/2018

Dr S Kraus
c/o Ms V Francis
J52-15
UCT Clinical Research Unit
OMB

Dear Dr Kraus

PROJECT TITLE: OUTCOMES OF PATIENTS WITH HYPERTENSIVE HEART DISEASE AND HEART FAILURE WITH REDUCED EJECTION FRACTION (HFrEF) AT A TERTIARY CENTRE IN SOUTH AFRICA- (MMed Candidate - Dr D. Boakye)

Thank you for your response letter dated 08 November 2018, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Darlene Boakye will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

APPENDIX – Institutional Approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
E-mail : Bernadette.Eick@westerncape.gov.za

Dr S. Kraus
UCT CLINICAL RESEARCH UNIT

E-mail: Darlene.Boakye@uct.ac.za / s.kraus@uct.ac.za

Dear Dr Kraus,

RESEARCH PROJECT: Outcomes Of Patients With Hypersensitive Heart Disease And Heart Failure With Reduced Ejection Fraction (HFrEF) At A Tertiary Centre In South Africa (Mmed. Dr Darlene Boakye)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 November 2019, subject to the approval of Professor N. Ntusi: Head Department of Medicine.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Kindly submit a copy of the publication or report to this office on completion of the research.

I would like to wish you every success with the project.

Yours sincerely

Signature Removed

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 26 February 2019

C.C. Mr. L. Naidoo
Dr. H. Aziz
Professor N. Ntusi

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