Clinical Characteristics, Causes, Adherence to Heart Failure Treatment Guidelines and Mortality of Patients with Acute Heart Failure: the Groote Schuur Hospital Experience

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Student number: SZYPAT001

Submitted to the University of Cape Town

In partial fulfilment of the requirements for the degree of

Master of Medicine (Medicine) (MMed (Med))

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of submission: 12 March 2016

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Declaration

I, **Patryk Zygmunt Szymanski**, 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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Acknowledgements

I would like to acknowledge the following persons for their contributions and support to this dissertation:

Sisters Dee Isaacs and Veronica Francis for help with the recruitment of patients and collection of data for this study.

Ms Imelda Booysen at Groote Schuur Hospital's Records Department for obtaining all the folders for review.

Groote Schuur Pharmacy for providing medication transcripts.

Ms Janine Saaiman for compiling all the study patients' personal details into a contact database.

Mr Lwazi Mhlanti for the development of the database and data capturing.

Professors Bongani Mayosi, Karen Sliwa and Peter Raubenheimer for assistance with the development of the study protocol.

Ms Zameka Ndzotyana for assistance with the administrative processes of the master's degree.

Professor Motasim Badri and Artur Szostak for their assistance with the statistical analysis of this study.

The Discovery Foundation for granting financial support.

Lastly, Professor Bongani Mayosi for his vision, continued guidance, support and patience. It has been a privilege working under your supervision. You have shown me that anything is possible.

Dedication

To my parents for always believing in me and to Madzia who showed me that it is possible to eat an elephant as long as one takes one bite at a time.

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Abbreviations

ACE	Angiotensin converting enzyme
ADHERE	Acute Decompensated Heart Failure National Registry
A-HeFT	African-American Heart Failure Trial
AHF	Acute heart failure
B-AHEF	Bi Treatment With Hydralazine/Nitrates Versus Placebo in Africans Admitted With Acute Heart Failure study
BOLD	Burden of Obstructive Lung Disease
CIBIS II	The Cardiac Insufficiency Bisoprolol Study II
DCM	Dilated cardiomyopathy
DIG	Digitalis Investigation Group
DM	Diabetes mellitus
EHFS I/II	EuroHeart Failure Survey I/II
EMF	Endomyocardial fibrosis
ESC	European Society of Cardiology
HAART	Highly active antiretroviral therapy
HF	Heart failure
HIV	Human immunodeficiency virus
IHD	Ischaemic heart disease
IMPI	Investigation of the Management of Pericarditis study
MERIT HF	Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure study
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure study
PPCM	Peripartum cardiomyopathy
RALES	Randomized Aldactone Evaluation Study

RHD	Rheumatic heart disease
RHF	Right heart failure
sSA	Sub-Saharan Africa
SOLVD	Studies of Left Ventricular Dysfunction
TaHeF	Tanzania Heart Failure study
THESUS-HF	The Sub-Saharan Africa Survey of Heart Failure
TB	Tuberculosis
V-HeFT I/II	Vasodilator Heart Failure Trial I/II

Abstract

Background

There is limited information on acute heart failure (AHF) and the treatment thereof in sub-Saharan Africa. Therefore, the aim of this study was to describe the clinical characteristics, causes, adherence to heart failure (HF) treatment guidelines and mortality of patients presenting to Groote Schuur Hospital with acute heart failure (AHF)**.**

Methods

This is a sub-study of The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF). This sub-study is a prospective and observational survey that focused on the enrolment and follow-up of additional patients with AHF presenting to Groote Schuur Hospital entered into the existing registry, following the publication of the primary paper of THESUS-HF in 2012. The patients were classified into prevalent (or existing) or incident (or new) cases of heart failure.

Results

Of the 119 patients included, 69 (58%) were female and the mean (SD) age was 49.9 (16.3) years. Prevalent cases were mostly of mixed ancestry (63.3%) with more hypertension (70%), diabetes mellitus (36.7%), hyperlipidaemia (33.3%) and ischaemic heart disease (36.7%) than incident cases. The main causes of heart failure were cardiomyopathy (20.2%), ischaemic heart disease (IHD) (19.3%) and rheumatic valvular heart disease (RHD) (18.5%). Most patients received renin-angiotensin system blockers and loop diuretics on discharge. There was a low rate of β-blocker, aldosterone antagonist and digoxin use. Rehospitalisation at 180 days occurred in 25.2%. In-hospital mortality was 8.4 % and the case fatality rate at six months was 26.1%.

Conclusion

In Cape Town the main causes of AHF are cardiomyopathy, IHD and RHD. AHF affects a young population and is associated with a high rate of rehospitalisation and mortality. There is a serious under-use of β-blockers, aldosterone antagonists and digoxin. An emphasis on the rigorous application of treatment guidelines is needed in order to reduce re-admission and mortality.

Literature Review

Introduction

Heart failure (HF) is a worldwide phenomenon that affects millions of people yearly and carries a high mortality. In the US 5.8 million people are affected with HF and the worldwide prevalence is estimated to be >23 million people.[1,2] The past three decades have seen a rise in the research associated with HF. Large multicentre studies from USA (e.g., ADHERE) and Europe (e.g., EHFS II) have provided a greater insight into the aetiology, treatment and outcomes of patients with HF in the developed world.[3,4] Clinical trials such as SOLVD, MERIT-HF, CIBIS-II and COPERNICUS have helped to establish ACE-inhibitors and beta-blockers as cornerstones in the treatment of the disease.[5–8]

Despite these advances, there are still many unanswered questions. The causes of HF and demographics of the patients suffering thereof are not uniformly distributed and great geographic variance exists. Observational studies from sub-Saharan Africa (sSA) show that hypertension, rheumatic heart disease (RHD) and idiopathic cardiomyopathies are the main causes of heart failure in a significantly younger group of patients when compared to those of developed countries.[9–11] Furthermore, the epidemiological transition due to the movement of people from rural areas to urban centres in search of work and education is resulting in lifestyle changes that in turn are contributing to an increase in cardiovascular diseases.[12–14] There is a growing body of knowledge on HF in sSA, however there is a paucity of data regarding the treatment and outcomes of patients with acute heart failure (AHF). This study aims to address this need though examining the treatment and outcomes of patients presenting to a tertiary level hospital in Cape Town, South Africa.

This literature review will focus on the available body of evidence relating to HF – the causes, treatment and outcomes, with a special focus on sSA. A PubMed search was performed using the terms “acute” or “chronic heart failure”, “cardiomyopathy” “valvular heart disease”, “treatment of heart failure”, “outcomes of heart failure” “tuberculosis” and “HIV” from January 1, 1980, through November 30, 2015. The reference lists of the relevant articles and reviews on the subject were consulted. Only

studies published in English were retrieved, and articles with important insights about the epidemiology, aetiology, treatment and outcomes of HF in Africa and internationally are cited.

Incidence and demographics

The advancement and improvement of medical care of endemic and emerging diseases has allowed for an increase in the number of older people in the population. This group of patients has a high risk of developing HF.[15] This has lead to HF becoming a great public health problem in the developed world and is associated with large numbers of hospitalisations, high mortality and an increased burden on financial and physical resources.[3,15] Analysis of Framingham Study data found that the prevalence of HF was high, affecting about 1% of people in their 50's and then rising with age affecting 10% of people in their 80's. The annual incidence was also found to increase with age. In the 45 to 54 year age group, the incidence of HF was 0.2%, rising to 4.0% in men 85 to 94 years.[16] Clinical drug trials have provided detailed information on the natural history of HF, however these trials studied a highly selected group of patients.[15] Until recently, there were no multicentre prospective epidemiological studies describing HF in the general population.

The first of these studies, the EuroHeart Failure Survey programme (EHFS I), undertaken between 2000 and 2001 enrolled 11 327 patients from 115 hospitals in 24 countries in Europe.[15] The aim of this study was to investigate whether patients with known or presumed heart failure were being managed in accordance with the European Society of Cardiology (ESC) guidelines. This study was followed up with EFHS II in 2006 which enrolled 3 580 patients from Northern Europe (3.5%), Western Europe (20.4%), Central Europe (34.4%) and Mediterranean Europe (42.4%).[4] The aims of this study were to assess the aetiology and precipitating factors of acute heart failure (AHF), the patient characteristics for acute new-onset HF and acute decompensated chronic HF, as well as for clinical groups classified according to ESC AHF guidelines.

In 2005 the Acute Decompensated Heart Failure National Registry (ADHERE) was published.[3] This observational study from the USA enrolled 105 388 patients from 274 hospitals and is the largest epidemiological study to date. The Organized Program

to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) study collected data on 48 612 patients hospitalised for HF at 259 hospitals in the USA.[17] These large epidemiological studies have provided great insight into the demographics, causes, treatment and natural history of HF in the developed world.

In the developing world, improved control of infectious and nutritional disorders along with epidemiological transition have increased the risk of cardiovascular disease.[13,18,19] Considering this increased burden of cardiovascular disease, a review of published data on HF in developing countries by Mendez and Cowrie in 2001 found no published population-based studies of HF.[14] Information on the epidemiology of HF in sSA is mostly gained from hospital-based studies, showing that CVD accounts for 7–10% of all medical admissions to African hospitals, with heart failure contributing to 3–7% of these admissions.[11]

Four prospective hospital-based observational studies from the sub-continent stand out. The first is the Heart of Soweto Study, which was published in 2008, and enrolled 844 patients presenting with *de novo* HF to Chris Hani Baragwanath Hospital in Soweto, South Africa.[9] This was followed by the Sub-Saharan Africa Survey of Heart Failure (THESUS–HF) published in 2012, which is the largest multicentre study to date, with 1006 patients from 9 African countries.[10] More recently the Abeokuta Heart Failure Clinical Registry from Nigeria described 452 consecutive patients presenting with AHF to the only tertiary hospital in Abeokuta, while the prospective Tanzania Heart Failure (TaHeF) study examined 427 patients and the predictors of heart failure.[20,21]

These studies along with a handful of smaller retrospective analyses have added to the volume of knowledge regarding HF in sSA. When comparing the data from the above-mentioned registries, certain epidemiological and demographic differences between USA, Europe and Africa are revealed. Firstly, the mean age of patients with HF in USA and Europe is between 70-73 years.[3,15,22] This contrasts greatly with sSA, where the patients are between the ages of 42-59 years.[9,10,20] This evidence discloses a younger population of patients, who are in the socio-economic prime of their lives.

The proportion of women affected with HF in the developed world ranges from 39-65%.[3,4,22] In sSA, the proportion of affected women compared to men varies by region. Nigeria has a lower proportion of female patients than males when compared to South Africa and the East African countries of Kenya and Uganda.[9,10,20,23] The proportion of affected males compared to females of 40-60% is similar when comparing the developed world to sSA.[3,4,10,20]

Diabetes mellitus (DM), hypertension and ischaemic heart disease (IHD) account for the majority of the risk factors predisposing to the development of HF in developed countries.[3,15,24,25] In sSA hypertension, cardiomyopathy and RHD are the main predisposing factors.[26]) In recent years there has been an increase in the incidence of DM, dyslipidaemia and obesity.[27]) This is thought to be most likely due to movement of people from rural areas to the cities in search of work, resulting in a change in diet and lifestyle.[13,28] Considering this transition, the incidence of IHD remains low and this may be partly due to under reporting and a lack of resources to further investigate patients presenting to health care services with invasive diagnostic tests such as coronary angiography.[26,29]

Human immunodeficiency virus (HIV) infection affects 30 million people worldwide with sSA carrying the majority of the disease burden (22 million people).[30] The 2014 WHO Global Tuberculosis report estimates that in 2013, 9 million people developed tuberculosis (TB). Almost one third (29%) of TB infections occurred in sSA with over 50% of TB cases co-infected with HIV.[31] In rural South Africa HIV and TB are the leading causes of death in patients under the age of 65.[32] HIV/TB co-infection has been recognised as an important risk factor for the development of HF in sSA and this further contributes to the relatively young age of patients with HF.[30,33,34]

Considering the differences in age, sex and risk factors for HF when comparing developed countries with sSA, it is interesting to note that African-Americans share similar characteristics with sub-Saharan Africans. Racial differences in the demographics, causes and outcomes of HF have been noticed in the USA. A study conducted at the Cook County Hospital in Chicago studied 301 black patients with HF.[35] Published in 1996, this study showed a younger population (56 years) with a high incidence of hypertension and low incidence of myocardial infarction. These

observations have been further confirmed by post-hoc sub-group analysis of African-Americans compared to their Caucasian counterparts in the SOLVD, DIG, OPTIME-CHF, RALES and OPTIMIZE-HF studies.[36–40] A possible explanation for this disparity may lie in the pathophysiology of HF in African-Americans underpinned by differences in neurohormonal responses and genomic variances.[40–42]

Aetiology

HF is a clinical syndrome recognised by the constellation of symptoms and signs of poor effort tolerance and fluid retention as a result of neurohormonal responses to cardiac dysfunction.[43] Its causes are varied and differ in different parts of the world.

Cardiomyopathy, RHD and hypertension are considered to be the major causes of HF accounting for 75.5% of cases in sSA.[10,25,40,41] In developed countries IHD alone or in conjunction with hypertension, atrial fibrillation and DM constitute the commonest causes of HF, with dilated cardiomyopathy (DCM) in the minority.[3,15,24]

Cardiomyopathy accounts for 30% of cases of HF in adult Africans.[26,46] DCM, peripartum cardiomyopathy (PPCM) and endomyocardial fibrosis (EMF) are endemic to sSA.(47) DCM carries a 4 year mortality of 34%.[48] In African patients the aetiological factors that have been studied include undiagnosed hypertension, autoimmune disease, iron overload, alcohol abuse, myocarditis, pregnancy and nutritional deficiencies.[47] Familial and genetic associations such as HLA-DR1 and DRw10 antigens, reported in South African patients, have furthered the understanding of the pathogenesis of unexplained DCM.[49–51]

The THESUS-HF study showed that 7.7% of HF was due to PPCM.[26] This disorder of unknown cause occurs in the last month of pregnancy and the following 5 months postpartum.[52] African race along with gestational hypertension and multiparity are some of the risk factors associated with the development of PPCM.[53] Recent evidence also suggests a familial and genetic predisposition to its development. [51,54] When compared to idiopathic DCM, patients with PPCM have a better survival and a higher rate of spontaneous recovery.[53,55]

EMF is a form of restrictive cardiomyopathy caused by fibrosis in the mural endocardium resulting in the restriction of ventricular diastole and entrapment of the papillary muscles of the atrioventricular valves.[46] In Uganda it accounts for 20% of HF cases and is considered to be the most common form of heart disease.[56] The pathogenesis remains unknown. It is suggested that an interplay between the environment (geography, social circumstances and infective agents) and the host (diet, eosinophilia) may be the basis for this pathology.[46,56] The prognosis of EMF is poor even with medical treatment.[46]

In developing countries RHD is the most common cause of acquired heart disease in children, adolescents and young adults.[57] A study conducted to detect RHD in scholars aged between 4-24 years in South Africa and Ethiopia using echocardiographic screening showed a prevalence of 20.2 cases per 1000 and 31 cases per 1000 respectively.[58] The high mortality of RHD is well illustrated by the clinical outcomes of South African patients included in THESUS-HF, which showed an initial in-hospital mortality of 17.5%, a 60-day mortality of 24.8% and a180-day mortality of 35.4%.[57]

HIV-associated cardiomyopathy is characterised by global systolic functional impairment with or without left ventricular dilatation.[59] The exact prevalence in Africa is not clear. The Heart of Soweto Study found HIV-associated cardiomyopathy to be the most common cause (38%) of *de novo* HF in patients with HIV.[33] Other studies have described the prevalence to range from 5-57% in people living with HIV.[30] The prognosis is poor without highly active antiretroviral therapy (HAART).[30,59] HIV and its direct effect on the myocardium along with its effect on the immune system are the proposed mechanisms for the pathogenesis of the cardiomyopathy.[60] HIV-immunosuppression-related myocarditis due to opportunistic infections such as TB have also been implicated.[33,34,61,62]

TB pericarditis accounts for the most common type of pericardial disease worldwide.[63] In sSA, TB accounts for > 90% of pericardial effusions in the HIV infected population.[30] Furthermore, the prevalence of myopericarditis in TB pericarditis has been described to be 53% in a patient cohort from Cape Town.[34] Constriction is a common and serious complication of TB pericarditis.[63]

Antituberculosis therapy, pericardiocentesis and pericardiectomy are used to treat TB pericarditis and its complications, yet despite these interventions, the mortality remains high especially in patients co-infected with HIV.[63,64]

Right heart failure (RHF) accounts for a very small proportion of HF in the developed world, amounting to only 3.2%.[4] This contrasts considerably with findings in Africa where in urban South Africa 28% of HF cases were due to RHF.[65] The BOLD study reported that South Africa has a high prevalence of chronic obstructive airways disease.[66]) The reason for these observations is multifactorial and potentially represents the sequelae of urbanisation.[28,67] Exposure to pollution, dust from mining, smoking, and the use of solid fuel heaters, along with HIV and TB, both important risk factors for RHF, contribute to the increasing prevalence of airways disease and its complications.[30,33,65]

Treatment

The development of a number of international registries in the past decade have provided invaluable epidemiological and clinical information aiding in the management of HF.[68] Current guidelines for the diagnosis and management of HF advocate the use of ACE-inhibitors, β-blockers and mineralocorticoid antagonists for symptomatic and mortality benefit.[69,70] Diuretics and digoxin are used for symptom control while digoxin use aids in decreasing HF hospitalization.[71] Despite these advances, evidence from high-income countries shows sub-optimal adherence to medical recommendations.[72–74]

Little is known regarding the treatment practices of HF in sSA. The THESUS-HF registry in sSA notes three important observations regarding the management of HF. Firstly, there was a high incidence of the use of aspirin in patients with non-ischaemic HF, while the use of the hydralazine hydrochloride and nitrates combination, shown to be effective in patients of African decent, was hardly used.[10,75] β-blockers were only used in 50% of patients at six months of follow-up.[10]

Retrospective post-hoc analysis of the SOLVD trial suggests a lesser response to ACE-inhibitor in African-Americans and an increase in the rate of hospitalisations.[41] V-

HeFT I studied the effect of the vasodilator combination of isosorbide dinitrate and hydralazine on HF, finding that it has no clinical benefit in their Caucasian population. However, in the African-American group it showed a significant survival benefit, suggesting that nitric oxide may play a pivotal role in the pathogenesis of HF in this group.[76] Following this trial, V-HeFT II was designed in order to test two therapies, namely that of the nitrates and hydralazine combination and the ACE-inhibitor, enalapril. A comparison of outcomes between Caucasians and African-Americans once again shows a significant benefit of ACE-inhibitors over vasodilator therapy in the Caucasian group. In the African-American group there was no difference in benefit between the two therapies.[77] Conclusions from the A-HeFT study state that the addition of a fixed dose of isosorbide dinitrate and hydralazine to the standard therapy for HF is effective and increases survival in African-American patients suffering from advanced HF.[75] The therapeutic benefit of the nitrate and hydralazine combination in sub-Saharan Africans is unknown and is currently being investigated in a prospective, placebo-controlled, double-blinded, randomised study comparing treatment with hydralazine/isosorbide dinitrate versus placebo in addition to standard care in 500 African patients admitted with acute heart failure and left ventricular dysfunction (B-AHEF).[29]

In contrast to the developed world, the high prevalence of HIV and TB and their cardiovascular manifestations add another dimension to the treatment of HF in sSA. There is a paucity of evidence regarding the treatment of HIV in patients with HF, and whether the early introduction of HAART in these patients changes the outcome of HF is unknown.[10,30] With regards to the treatment of TB pericardial disease, the IMPI trial examined the use of prednisolone as an adjunctive therapy to TB therapy. The results showed that prednisolone did not have a significant effect on the combined outcome of death from all causes, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis. However, the study did demonstrate that the use of adjunctive glucocorticoids reduces the incidences of pericardial constriction and hospitalisation. These beneficial effects are similar in both HIV-positive and HIV-negative patients. There was however an increase in the incidence of HIV-associated malignancies in immunosuppressed patients. [78]

Pharmacological therapy forms the cornerstones of HF treatment. However, evidence from the developed world shows that despite appropriate prescribing of medication, patient education and adherence to therapy, lifestyle and behavioural changes contribute significantly to re-hospitalization and long-term outcomes in HF patients.[79,80] This has prompted the development of HF management programs utilizing a multidisciplinary approach in order to educate patients and their carers about HF, provide support with regards to diet, risk factor modification and adherence to therapy, along with early recognition of decompensating HF.[79,80] The implementation of these strategies has aided in reducing mortality and re-hospitalisation, improving quality of life and decreasing healthcare costs.[81,82]

Information regarding medication adherence, self-care behaviour and knowledge about HF in Africa is scarce.[74] A study of urban Africans in Soweto, South Africa, showed that individual medication adherence ranged from 64-79%, behavioural adherence varied from 2.5-98% and that treatment knowledge was poor with half of the patients unable to name medication side-effects or their functions.[74]

Considering the current understanding of HF in Africa, specific areas of management have been highlighted. These include prevention and management of risk factors associated with HF in the African context, improved adherence to current treatment recommendations, long-term treatment and follow-up of PPCM, family screening for cardiomyopathy in patients with unexplained DCM and increasing research into treatments for HF including nitrate/hydralazine combination, digoxin, bromocriptine and pentoxifylline.[29]

Outcome

HF is one of the most common causes of admission to hospital and carries with it poor outcomes worldwide.[3,4,83,84] The Framingham study shows that after receiving the diagnosis of HF, the one year and five year survival rates are 57% and 25% respectively for men, and 64% and 38% respectively for women.[85] The ADHERE, EHFS II and OPTIMIZE-HF registries showed an in-hospital mortality of 3.8-6.7%.[3,4,17] *De novo* HF and patients treated in intensive care unit (ICU) had poorer outcomes, while hypertensive heart disease had the best outcome.[3,4] With regards to

outcomes, OPTIMIZE-HF reported 8.6% mortality at 90 days with a median time to death of 42 days.[17] The length of stay described in these registries varied from 3-14 days, with a clear distinction between Europe and USA, at 11 days and 4.3 days respectively.[3,4] This may represent differing practices and access to specialist opinion thus affecting outcome, depending on the hospitals to which patients are admitted.[86]

The limited data from sSA show similar in-hospital mortality, at 3.8% and 4.2% in the Nigerian AHF registry and THESUS-HF, respectively.[10,20] This similarity in outcomes is of interest considering the demographic and aetiological differences between the developed world and sSA. This suggests that once HF occurs, its progression is independent of the patient characteristics.[10] Despite the similar outcomes, the causes of HF leading to death are different with endemic causes such as DCM, PPCM and EMF accounting for the majority of deaths.[10] However, epidemiological transition with changes in diet and socio-economic context in many of the developing countries may see non-endemic causes of HF increase the burden of disease and mortality.[13,14,28,87] Length of stay in studies from sSA are longer than those reported in high income countries.[10,20] Sub-analysis of predictors and outcomes of 60-day readmission or death and 180-day mortality of the THESUS-HF study shows that the main predictors for adverse outcomes in sSA are similar to the rest of the world. Exceptions to this include the effect of HIV status on mortality and the lack of prediction by sodium on readmission and deaths.(88)

Conclusion

The increasing prevalence of HF in the developed world is setting great health and social challenges.[15,18,89] In USA alone, it is estimated that $12.7 billion per annum is spent on the in-patient management of HF.[89] The development of large multicentre registries in the USA and Europe has provided great insight into the aetiology, treatment, and outcome of HF.[3,15,73] Furthermore, the development of strategies aimed at prevention, improved adherence to treatment and long-term monitoring of HF show promising results.[80–82]

In Africa, improvements in the control of communicable diseases and malnutrition along with population migration to urban centres underpins the increase of

cardiovascular disease, which is becoming a significant cause of morbidity and mortality.[90] In 2008 communicable, maternal, perinatal and nutritional conditions accounted for the majority of deaths in South Africa. However, cardiovascular disease was the main cause of death amongst non-communicable diseases.[12] There is still a lack of information on HF in Africa and in order to tackle this increasing public health problem, further epidemiological, etiological and treatment information is needed in order to develop health policies for the diagnosis, management, prevention and control of HF.[14,18,47,91] Finally, given the contemporary understanding of HF in sSA, certain areas of research have been suggested, including clinical trials on fixed-dose isosorbide dinitrate/hydralazine combination and bromocriptine, the study of coronary artery disease as a cause of HF and examining the use of molecular genetic testing in the diagnosis and management of cardiomyopathies.[29]

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Journal ready manuscript

Clinical Characteristics, Causes, Adherence to Heart Failure Treatment Guidelines and Mortality of Patients with Acute Heart Failure: the Groote Schuur Hospital Experience

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Abstract

Background

There is limited information on acute heart failure (AHF) and the treatment thereof in sub-Saharan Africa. Therefore, the aim of this study was to describe the clinical characteristics, causes, adherence to heart failure (HF) treatment guidelines and mortality of patients presenting to Groote Schuur Hospital with acute heart failure (AHF)**.**

Methods

This is a sub-study of The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF). This sub-study is a prospective and observational survey that focused on the enrolment and follow-up of additional patients with AHF presenting to Groote Schuur Hospital entered into the existing registry, following the publication of the primary paper of THESUS-HF in 2012. The patients were classified into prevalent (or existing) or incident (or new) cases of heart failure.

Results

Of the 119 patients included, 69 (58%) were female and the mean (SD) age was 49.9 (16.3) years. Prevalent cases were mostly of mixed ancestry (63.3%) with more hypertension (70%), diabetes mellitus (36.7%), hyperlipidaemia (33.3%) and ischaemic heart disease (36.7%) than incident cases. The main causes of heart failure were cardiomyopathy (20.2%), ischaemic heart disease (IHD) (19.3%) and rheumatic valvular heart disease (RHD) (18.5%). Most patients received renin-angiotensin system blockers and loop diuretics on discharge. There was a low rate of β-blocker, aldosterone antagonist and digoxin use. Rehospitalisation at 180 days occurred in 25.2%. In-hospital mortality was 8.4 % and the case fatality rate at six months was 26.1%.

Conclusion

In Cape Town the main causes of AHF are cardiomyopathy, IHD and RHD. AHF affects a young population and is associated with a high rate of rehospitalisation and mortality. There is a serious under-use of β-blockers, aldosterone antagonists and digoxin. An emphasis on the rigorous application of treatment guidelines is needed in order to reduce re-admission and mortality.

Introduction

Heart failure (HF) is a worldwide phenomenon that affects millions of people yearly and carries a high mortality. In the US, 5.8 million people are affected by HF and worldwide >23 million people are thought to be affected.[1,2] The past three decades have seen a rise in the research on HF. Large multicentre studies from USA (e.g., ADHERE) and Europe (e.g., EHFS II) have provided a greater insight into the aetiology, treatment and outcomes of patients with HF in the developed world.[3,4]

Observational studies from sub-Saharan Africa (sSA) show that hypertension, rheumatic valvular heart disease and idiopathic cardiomyopathies are the main causes of HF affecting a young population.[5–7] This epidemiological pattern is strikingly different from that of the developed world where a much older population suffer from HF, with ischaemic heart disease (IHD) the primary cause.[3,4] Despite these differences, the epidemiological transition is resulting in the rise of diabetes mellitus (DM), hypertension and IHD in sSA.[7,8] In 2008 communicable, maternal, perinatal and nutritional conditions accounted for the majority of deaths in South Africa. However, cardiovascular disease was the main cause of death amongst non-communicable diseases.[9]

There is limited information on the use of evidence-based interventions and outcome of HF in Africa. Contemporary epidemiological, aetiological and treatment information is needed in order to develop appropriate health policies for the diagnosis, management, prevention and control of HF in Africa. [11,12]

This study aimed to explore the treatment practices of doctors and outcomes of patients with congestive or acute heart failure (AHF) at Groote Schuur Hospital, a tertiary level academic institution in Cape Town, South Africa that serves as a referral hospital for 5 million people. Furthermore, the clinical features and causes of heart failure were explored.

Methods

Study design and clinical setting

This is a sub-study of The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF), a prospective, multicentre, observational survey of patients with AHF admitted to 12 university hospitals in 9 countries.[6] The sub-study that is reported here is based on the enrolment of additional patients with AHF followed up in the existing

THESUS-HF registry presenting to Groote Schuur Hospital. Patients with AHF (incident (i.e., *de novo*) or prevalent (i.e., decompensation of previously diagnosed heart failure)) were added to the registry following the publication of the primary paper of THESUS-HF in 2012.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are the same as the criteria published in the THESUS-HF study.[6] Briefly, patients older than 12 years with the diagnosis of AHF based on clinical evaluation and confirmed by echocardiography were enrolled. The exclusion criteria were acute ST-elevation myocardial infarction, known severe renal failure (patients undergoing dialysis or creatinine >350 μmol/L), nephrotic syndrome, hepatic failure or other causes of hypoalbuminaemia.

Case definition and data collection

The diagnosis of HF was based on finding the clinical syndrome of effort intolerance (i.e., shortness of breath, dyspnoea, and / or fatigue) associated with features of fluid retention (i.e., peripheral oedema, orthopnoea, paroxysmal nocturnal dyspnoea, raised jugular venous pressure, pulmonary oedema, and / or tender hepatomegaly) in the presence of clinical signs of cardiac dysfunction (i.e., low blood pressure, displaced apex, presence of third heart sound). The presence of cardiac dysfunction was confirmed by echocardiography performed by a trained echocardiographer. The cause of HF was based on information obtained from the history, physical examination, echocardiography, and special aetiological investigations interpreted by the admitting team on the index admission. Where no cause for HF was stated the research team determined the aetiology from the given data.

For this study, consecutive patients that were enrolled into the Groote Schuur Hospital THESUS-HF registry from 1 June 2012 to 31 May 2014 (24 months) with more than 90% completed data were selected. The THESUS-HF registry holds the basic clinical information as determined by the clinical history and previous medical records, along with an echocardiogram report confirming the diagnosis of HF. Furthermore, patients were followed up for 180 days to document their clinical outcomes of rehospitalisation and death. Their baseline demographic and clinical information, echocardiographic findings, treatment and clinical outcomes were entered onto a data capture sheet by the research nurse and echocardiographer. Outstanding demographic, clinical,

treatment and outcomes data were collected through folder review, pharmacy records and telephonic consultations with the study participants. All completed data capture sheets were entered into the THESUS-HF database.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) and ROOT.[12] Normally distributed continuous data are presented as the mean with standard deviation, and non-Gaussian distributed variables as the median plus range. Categorical data are presented as percentages. Case fatality rate was calculated at discharge and at six months of follow-up.

Ethics

The University of Cape Town Human Research Ethics Committee granted ethics approval for this study (Ethics number: REC REF: 579/2014). All patients entered into the THESUS-HF registry gave written informed consent.

Results

Baseline patient characteristics on admission

One hundred and twenty patients were enrolled in the THESUS–HF registry at Groote Schuur Hospital between 1 June 2012 and 31 May 2014. One patient was excluded due to missing clinical details. **Table 1** shows the baseline clinical characteristics for the total cohort (119 patients) and compares the incident cases (first presentations) with the prevalent cases (recurrent presentations). The mean (SD) age of the cohort was 49.9 (16.3) years. Sixty-nine (58%) patients were female and the predominant population groups were black African (n=59 [49.6%]) and mixed ancestry (n=54 [45.4%]).

The prevalent cases were more likely to be people of mixed ancestry with more hypertension, DM, hyperlipidaemia, IHD, pericardial disease, cardiomyopathy and a higher New York Heart Association (NYHA) functional class than incident cases.

Table 1. Baseline Clinical Characteristics of 119 Patients with Acute Heart Failure at Groote Schuur Hospital

Characteristics	All cases (N=119)	Incident cases (N=89)	Prevalent cases (N=30)	P value
Age, y				
Mean (SD)	49.9 (16.3)	48.6 (16.2)	53.7 (16.4)	.143
Sex, No. (%)				.349
Female	69 (58.0)	53 (59.6)	16 (53.3)	
Male	50 (42.0)	36 (40.4)	14 (46.7)	
Race, No. (%)				.005
African	59 (49.6)	51 (57.3)	8 (26.7)	
Caucasian	4 (3.4)	3 (3.4)	1 (3.3)	
Mixed ancestry	54 (45.4)	35 (39.3)	19 (63.3)	
Asian	2 (1.7)	0 (0)	2 (6.7)	
No. of AHF admissions in last 12 months, No. (%)				Not applicable
0	89 (74.8)	89 (100)		
1	22 (18.5)		22 (73.3)	
2	4 (3.4)		4 (13.3)	
3	4 (3.4)		4 (13.3)	
Hypertension, No. (%)	58 (48.7)	37 (41.6)	21 (70.0)	.006
Diabetes mellitus, No. (%)	26 (21.8)	15 (16.9)	11 (36.7)	.025
Smoking, No. (%)	46 (38.7)	31 (34.8)	15 (50)	.105
Hyperlipidaemia, No. (%)	13 (10.9)	3 (3.4)	10 (33.3)	<.001
Ischaemic heart disease, No. (%)	17 (14.3)	6 (6.7)	11 (36.7)	<.001
Atrial fibrillation, No. (%)	6 (5.0)	5 (5.6)	1 (3.3)	.526
Stroke, No. (%)	5 (4.2)	3 (3.4)	2 (6.7)	.372
Pericardial disease, No. (%)	3 (2.5)	0 (0)	3 (10)	.015
Valvular heart disease, No (%)	12 (10.1)	10 (11.2)	2 (6.7)	.374
Cardiomyopathy, No. (%)	11 (9.2)	4 (4.5)	7 (23.3)	.005
Cor Pulmonale, No. (%)	7 (5.9)	3 (3.4)	4 (13.3)	.066
HIV, No. (%)	14 (11.8)	10 (11.2)	4 (13.3)	.490
PVD, No. (%)	2 (1.7)	2 (2.2)	0 (0)	.558
NYHA, No. (%)				<.001
I	23 (23.7)	23 (34.3)	0 (0)	
II	20 (20.6)	17 (25.4)	3 (10)	
III	44 (45.4)	24 (35.8)	20 (66.7)	
IV	10 (10.3)	3 (4.5)	7 (23.3)	
Body mass index				
Mean (SD)	27.4 (9.8)	27.6 (10.5)	26.7 (7.6)	.680
Systolic blood pressure, mm Hg				
Mean (SD)	134.6 (33.2)	137.4 (32.9)	126.3 (33.3)	.115
Diastolic blood pressure, mm Hg				
Mean (SD)	81.9 (22.5)	82.4 (23.3)	80.5 (20.1)	.688

Heart rate, bpm				
Mean (SD)	102.5 (22.7)	102.7 (24.3)	101.9 (17.3)	.865
Respiratory rate, BPM				
Mean (SD)	22.8 (5.3)	23.0 (5.7)	22.0 (3.5)	.370
Oedema, No. (%)				.762
0	37 (31.1)	27 (30.3)	10 (33.3)	
1+	1 (0.8)	1 (1.1)	0 (0)	
2+	21 (17.6)	17 (19.1)	4 (13.3)	
3+	60 (50.4)	44 (49.4)	16 (53.3)	
Pulmonary oedema, No. (%)				.038
0	46 (38.7)	33 (37.1)	13 (43.3)	
1	4 (3.4)	2 (2.2)	2 (6.7)	
2	28 (23.5)	26 (29.2)	2 (6.7)	
3	41 (34.5)	28 (31.5)	13 (43.3)	
LVEF, %				
Mean (SD)	34.1 (16.9)	35.9 (17.4)	28.2 (14.0)	.085
Creatinine, µmol/dL				
Mean (SD)	109.7 (75.4)	110.2 (83.9)	108.4 (43.5)	.912
Urea, mmol/L				
Mean (SD)	10.2 (7.5)	9.7 (7.2)	11.6 (8.3)	.250
Sodium				
Mean (SD)	136.9 (6.3)	137.0 (6.6)	136.9 (5.7)	.943
Haemoglobin, g/dL				
Mean (SD)	12.3 (2.6)	12.1 (2.7)	12.7 (2.4)	.329
White cell count, No./µL				
Mean (SD)	9.7 (4.5)	9.8 (4.5)	9.2 (4.5)	.482

Abbreviations: AHF, acute heart failure; HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class; PVD, peripheral vascular disease

Oedema:

0: Complete absence of skin indentation with mild digital pressure in all dependent areas

1+: Indentation of skin that resolves over 10-15 seconds

2+: Indentation of skin is easily created with limited pressure and disappears slowly (15-30 seconds or more)

3+: Large areas of indentation easily produced and slow to resolve (> 30 seconds)

Pulmonary oedema:

0: No rales heard after clearing cough

1: Moist or dry rales heard in lower ⅓ of one or both lung fields that persist after cough

2: Moist or dry rales heard throughout the lower half to ⅔ of one or both lungs

3: Moist or dry rales heard throughout both lung fields

Causes of heart failure

The main causes of HF were cardiomyopathy (n=24 [20.2%]), IHD (n=23 [19.3%]) and valvular heart disease (n=22 [18.5%]). Hypertension accounted for 10.1% (n=12) of the cohort. Due to the small sample size, cardiomyopathy represents the cumulative

causes of cardiomyopathy, and includes PPCM, idiopathic DCM and HIV cardiomyopathy. **Figure 1** shows the causes of heart failure including other causes. The other causes included toxins, arrhythmias, and Grave's disease.

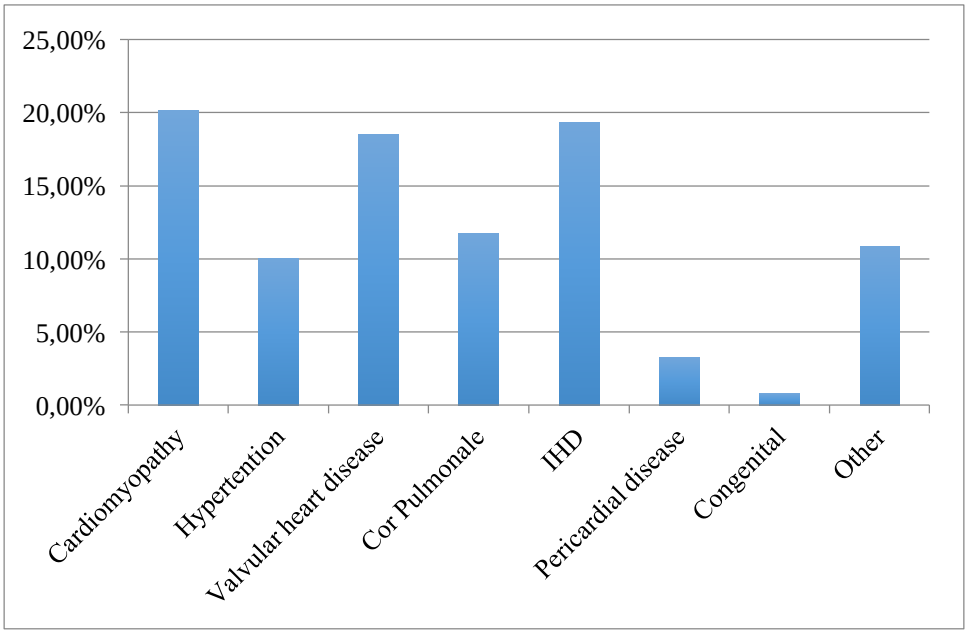

Figure 1 Causes of heart failure

Therapies for heart failure: Admission and discharge/day 7 admission

Intravenous loop (IV) diuretics were the most commonly used IV therapy on admission (n=94 [79%]), while renin-angiotensin system blockers were the most commonly used oral treatment (n=70 [59.3%]). Mechanical ventilation and dobutamine were used in only 0.9% (n=1) and 1.7% (n=2) of cases respectively. Renin-angiotensin system blockers (73.0% [n=81]), loop diuretics (74.6% [n=82]) and β-blockers (42.7% [n=47]) were most commonly issued on discharge. On discharge only 26.1% (n=15) received aldosterone antagonists and 15.5% (n=17) digoxin. IV dopamine, IV digoxin and oral hydralazine were never prescribed. **Table 3** shows the IV and oral therapies used in incident and prevalent cases.

Table 3. Prescribed Medication on Admission and Discharge or Day 7 Admission

Treatment	All Cases		Incident Cases		Prevalent Cases	
	Admission (No/%)	**Discharge/ D7 (No/%)**	**Admission (No/%)**	**Discharge/ D7 (No/%)**	**Admission (No/%)**	**Discharge/ D7 (No/%)**
Nitrates (IV)	4 (3.5)	0 (0.0)	3 (3.5)	0 (0.0)	1 (3.3)	0 (0.0)
Furosemide (IV)	94 (79.0)	20 (18.0)	71 (79.8)	13 (15.9)	23 (76.7)	7 (24.1)
Dobutamine	2 (1.7)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Mechanical ventilation	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)
ACE inhibitor/ARB	70 (59.3)	81 (73.0)	48 (54.5)	57 (69.5)	22 (73.3)	24 (82.8)
Loop diuretics	24 (20.7)	82 (74.6)	17 (19.8)	60 (74.1)	7 (23.3)	22 (75.9)
Beta blockers	21 (18.3)	47 (42.7)	13 (15.3)	32 (39.5)	8 (26.7)	15 (51.7)
Digoxin	15 (13.2)	17 (15.5)	9 (10.6)	12 (14.8)	6 (20.7)	5 (17.2)
Nitrates	4 (3.5)	9 (8.2)	3 (3.5)	4 (4.9)	1 (3.3)	5 (17.2)
Aldosterone antagonists	15 (12.9)	29 (26.1)	9 (10.5)	19 (23.2)	6 (20.0)	10 (34.5)
Simvastatin	36 (30.8)	36 (32.4)	21 (24.1)	21 (25.6)	15 (50.0)	15 (51.7)
Aspirin	30 (25.6)	32 (28.8)	19 (21.8)	19 (23.2)	11 (36.7)	13 (44.8)
All anticoagulation	45 (38.5)	32 (28.8)	32 (36.8)	26 (31.7)	13 (43.3)	6 (20.7)

Anticoagulation: warfarin, heparin, enoxaparin

Length of stay, rehospitalisation, and case fatality rate

The mean length of stay in hospital for all cases was 9.2 days (SD=12.2) with a median of 6 days (range: 1-109 days). Rehospitalisation at 180 days occurred in 25.2% (n=30) of the total cohort. Twelve patients (10.1%) were lost to follow-up. The reasons for this included no reply to telephonic calls (n=11) and one patient left for another province. The rate of death during hospital admission was 8.4 % (10 of 119 patients) and case fatality rate at six months was 26.1% (31 of 119 patients).

Discussion

The main findings of this study include a relatively young population suffering from HF, with prevalent cases more likely to have DM, HT, IHD and more advanced disease. Furthermore, cardiomyopathy, IHD and rheumatic valvular heart disease account for the majority of causes of HF. There is an under-use of β-blockers, aldosterone antagonists and digoxin. Finally, there was high rehospitalisation and mortality rates.

The mean age of patients with AHF is 49.9 years and 58% are female. These findings are similar to what has been observed in other registries from sSA.[5,6,13,14] This is significant as it demonstrates that HF in Cape Town affects the bread-winner generation, rather than the elderly as has been noted in the developed world.[3,4]

Secondly there is a difference in the clinical characteristics between patients with new-onset disease and those with a previous diagnosis of HF. The patients with prevalent disease are mostly from the mixed ancestry community. This may be representative of Cape Town's population demographics where the mixed ancestry community constitute the largest group in the Western Cape.[15] Furthermore those with prevalent disease have more hypertension, DM, hyperlipidaemia and IHD. Finally, their baseline NYHA functional class is higher possibly indicating a group of patients with more advanced HF, which may reflect sub-optimal treatment of HF along with poor follow-up and education regarding HF.

In sSA hypertension, RHD and the endemic cardiomyopathies account for the majority of HF cases.[6] In this study, cardiomyopathy, IHD and rheumatic valvular heart disease are the leading causes of AHF in Cape Town, accounting for 60% of cases referred to tertiary care. Of interest is the high prevalence of IHD. Observational studies from sSA state the incidence of IHD as a cause of HF to be between 0.4-9%.[5,6,13,14] In this study 19.3% of patients were diagnosed with an ischaemic cause of heart failure. One of the possible reasons for the disparity in observations may be due to the effects of urbanisation. It has been shown in the literature that movement of people from rural areas to urban centres results in a change in diet and lifestyle predisposing to the development of IHD.[7,8] Another reason may be the availability of a specialist cardiology service to this study cohort, which may have allowed for better

diagnostic tests (angiography and echocardiography) resulting in the increased diagnosis of IHD. Hypertensive HF is less prevalent in this study than is described in other studies from sSA. The reason for this is not clear, and requires further investigation.

The rate of β-blocker use was low in this study, 42.7%, when compared with EHFS II (61%) but similar to rates of use observed in the Tanzania Heart Failure (TaHeF) study (42%) and THESUS-HF (50%).[4,6,16] The low rate of β-blocker use may be due to the severity of HF treated. In this cohort over half of the patients presented with NYHA functional class of III and IV combined. On discharge 26.1% of patients received aldosterone antagonists and 15.5% received digoxin. This is considerably lower than has been described in the rest of sSA, where aldosterone and digoxin are prescribed in 60-75% and 31-72% of cases respectively.[5,6,13,14] The side-effect profiles, potential drug interactions and close monitoring of these therapies in a population group where compliance to follow-up and access to specialist care is sub-optimal may explain their limited use. Hydralazine use was low possibly because of its limited availability at Groote Schuur Hospital, and also known low use by physicians in sub-Saharan Africa.[13} In this study 28.8% of patients were discharged with aspirin. This is far less than is described in THESUS-HF, where more than 50% of patients were discharged on aspirin despite the low prevalence of ischaemic HF.[6] This study shows a population with a high prevalence of IHD. Whether the use of aspirin in this study is in keeping with the prevalence of IHD as identified in this cohort, needs to be further evaluated.

The mean length of stay was 9.2 days and is similar to the number of admission days described in studies from developed nations and sSA.[4–6,13] The six-month readmission rate was 25.2%. The reasons for this high re-admission rate may be three fold. Firstly, sub-optimal adherence to evidence based treatments may be resulting in high re-admission rates. Gaps in the patients' understanding of HF and importance of treatment follow up and lifestyle adherence may be a further contributory factor. And finally, hospital bed pressure may lead to premature discharge of HF patients. The in-hospital and six month mortality rates were 8.4% and 26.1% respectively. This is higher than is described in the rest of sSA. THESUS-HF, the largest multicentre study on HF to date, reported an in-hospital mortality of 4.2% and a six month mortality of 17.8%.[6] These high mortality rates may be due to the different aetiological pattern in

Cape Town with a significant contribution of IHD, and a lower prevalence of hypertension as the primary cause of AHF. There was also a low adherence to life saving medications such as β-blockers and aldosterone inhibitors. These observations stress the importance of adhering to evidence based treatment guidelines. Furthermore, the management of HF is complex and requires a multidisciplinary approach encompassing routine follow-up with patient education, optimisation of treatment and social support.[16]

This study has a number of limitations. The sample size was small and may underrepresent the causes of HF. A second limitation was that rehospitalisation to other institutions may not have been documented in all cases. Furthermore, only admission and discharge treatment practices are described in this study. It may be that the use of aldosterone and β-blockers as well as other HF treatment may have increased during ambulatory care in the community. There is also lack of data on HF survival benefit drug dosages used. Finally, 10.1% of the patient cohort was lost to follow up which may have contributed to an under-estimate of the case fatality rate in this study.

Conclusion

This study provides important insights into the demographics, causes, treatment and outcomes of patients with AHF in Cape Town. It confirms observations noted in earlier sSA HF studies showing that a young adult population is affected by HF. Cardiomyopathy, IHD and rheumatic valvular heart disease account for 60% of cases AHF. However, of concern is the high prevalence of IHD in this cohort, the highest reported thus far in sSA. Furthermore, there is a serious under-use of β-blockers, aldosterone antagonists and digoxin. The high re-admission rate and six month mortality may be a reflection of the sub-optimal adherence to evidence based treatment guidelines. There needs to be an emphasis on the rigorous application of treatment guidelines in order to reduce re-admission and mortality associated with AHF in Cape Town.

Acknowledgements

We thank Sisters Dee Isaacs and Veronica Francis for help with the recruitment of patients and collection data for this study. We would also like to thank Mr Lwazi Mhlanti for the development of the database and data capturing. The study was funded by the Discovery Foundation (through an MMed Fellowship to PS), the Lily and Ernst

Hausmann Research Trust, the South African Medical Research Council, and AstraZeneca. We also acknowledge the THESUS-HF Consortium (Drs G Cotter, A Damasceno, and K Sliwa) for permission to conduct the sub-study in Cape Town.

Competing interests

The authors declare that have no competing interests.

Authors' contributions

PS drafted the manuscript and managed the data collection. MB performed the data analysis and assisted with data preparation for statistical analysis. BMM supervised the study and was a major contributor to the study design and final manuscript.

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UNIVERSITY OF CAPE TOWN
YUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

THE SUb-Saharan Africa Survey of Heart Failure – THESUS-HF

in collaboration with the Departments of Medicine of GF Jooste Hospital and Groote Schuur Hospital

Tel/fax 021 690 1053 **email: nschrued@pgwc.gov.za**
Department of Medicine **Principal investigator: Prof BM Mayosi**

INFORMED CONSENT FORM AND STATEMENT

Dear Mr/Mrs./Ms .....

Explanation and purpose of the research:

You have been admitted to hospital with the diagnosis of heart failure. The information surrounding the characteristics, causes, treatment and short term outcome of acute heart failure in Africa is largely unknown.

We are doing an observational study researching these aspects of acute heart failure in order to improve our knowledge and future care of patients with acute heart failure.

We would like to know if you would like to participate in the study to help us improve our knowledge about the condition of acute heart failure.

Procedure and duration:

The study will entail us asking you a few questions relating to your health and symptoms, examining you and doing a specialized test on the heart called an echocardiogram (ECHO) and recording all this information on a special case report form. This echocardiogram uses sound waves to give us a picture and movie of the heart and will not be painful.

We will repeat the examination for the first two days after admission and on the 7th day or day of discharge to review your progress and to record this information. We would like to gather other relevant information from your file and record this on the case report form.

We will not require any special blood tests or be testing any medicines at any time. We will not be taking over your treatment from your admitting doctor while you are in hospital.

We would like to contact you in between one (1) months and one (1) year's time via telephone to enquire about your progress. If you are re-admitted to hospital during this time we would like to access the information from your file relating to your re-admission.

Possible risks:

The only risk to you is the breach of confidentiality by the investigators collecting the information. However we will not be putting your name or contact information on the case report form and you will only be assigned a unique study patient number.

Any publications of the information and study findings will not contain identifying data and only the study patient number will be used. The contact information and identifying details for follow up will be safeguarded by the investigators to reduce the risk of breach of confidentiality.

Possible benefits:

The benefit to you is getting a specialized assessment and test of your heart (ECHO). If further specialized care for your heart condition is required based on the accepted standard of practice, you will be referred to Groote Schuur Hospital for further assessment and care.

Participation and subject rights:

Participation in this study will equip doctors and nurses with better knowledge of the condition of acute heart failure. This knowledge will contribute to the improvement of care of patients all over the world but especially in Africa.

Participation in this study is entirely voluntary. If you decide not to participate, either now or at a later stage, you are free to do so and this will not in any way affect your current or future care or other benefits.

The Investigator retains the right to withdraw you from the study if it is considered to be important for your safety.

Information about you obtained because of your participation in this trial will be kept confidential and any reports from this study will be anonymous. Auditors will view the records to ensure that all ethical and protocol conditions have been applied. If you have any questions, please do not hesitate to ask your doctor or researcher.

Additional Information:

For the duration of the trial, you will be under the care of the hospital and your admitting doctor.
If at any time you have questions during your admission as part of the study, please do not hesitate to contact me.

The telephone number where you can reach me or another authorised person, is ?????

You may also contact the Trial co-ordinator: Prof BM Mayosi on 021 406 ???? if you have any additional questions.

If you have any additional questions regarding your rights as a research subject, you may discuss them with a member of the Ethics Committee at telephone number ????????

CONSENT STATEMENT

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions which have been answered to my satisfaction. I hereby consent to participate voluntarily in this study to assess the characteristics, causes, treatment and short term outcome of acute heart failure in Africa as outlined above.

Name:.....

Signature:..... Date:.....

Witness name: Signature

If illiterate: The content has been explained to me by the Investigator or dedicated research assistant, and additional explanation given to me in my own language by another person other than the researcher.

Signature/thumb print:..... Date:.....

Witness 1:..... Witness 2:.....

Signature of person who explained the content in participant's own language:..... Date:.....

Witness 1:..... Witness 2:.....

You can contact the investigator Dr .....at Tel number..... if you have queries.

THESUS-HF

Baseline

Patient Number:__ __ - __ __ __ __ Patient Initials:__ __ __

Demographics

1 Date of admission: __ __ / __ __ __ / 20__ __ (day / month / year) Time: __ __ : __ __ (00:00 to 23:59)

2 Date of birth: __ __ / __ __ __ / __ __ __ __ (day / month / year)

3 Sex: ☐ 1 Male ☐ 2 Female

4 Race: ☐ 1 Black ☐ 2 Asian ☐ 3 Caucasian

5 Height: __ __ __ cm

6 Weight: __ __ __ kg

Pre-Admission

1 Number of acute heart failure (AHF) admissions in the last 12 months: __ __

2 Date of last acute heart failure (AHF) admission: __ __ / __ __ __ / 20__ __ (day / month / year) **OR** ☐ 99 NA

3 NYHA (New York Heart Association) classification 1 month prior to admission: ☐ I ☐ II ☐ III ☐ IV

EGC (Electrocardiogram)

Please attach copy of admission ECG in the CRF divider pocket.

Baseline Labs First obtained at Admission

Lab	Value	Units
1 Creatinine	_____	☐ 1 mg/dL ☐ 2 µmol/L
2 BUN (blood urea nitrogen)/urea	_____	☐ 1 mg/dL ☐ 3 mmol/L
3 Sodium	_____	☐ 3 mmol/L ☐ 4 mEq/L
4 Glucose	_____	☐ 1 mg/dL ☐ 3 mmol/L
5 Hemoglobin	_____	☐ 5 g/L ☐ 3 mmol/L ☐ 6 g/dL
6 Total WBC (white blood count)	_____	☐ 7 x10^9/L or 10^3/mm^3 ☐ 8 /mm^3 or /cumm or /µL or /mcL
7 Lymphocytes %	_____	%
8 Cholesterol	_____	☐ 1 mg/dL ☐ 3 mmol/L
9 Triglycerides	_____	☐ 1 mg/dL ☐ 3 mmol/L
10 Peak CK (creatinine kinase)	_____	☐ 10 IU/L ☐ 11 µkat/L ☐ 12 nkat/L
11 Peak CK-MB (creatine kinase myocardial band)	_____	☐ 10 IU/L ☐ 13 µg/L ☐ 11 µkat/L ☐ 14 ng/mL ☐ 12 nkat/L ☐ 9 %
12 Peak Troponin	_____	ng/mL
13 NT Pro BNP (N Terminal Prohormone B-type natriuretic peptide)	_____	pg/mL OR BNP _____ pg/mL
14 Urine Protein (Dipstick)	☐ Negative	☐ Trace ☐ 1+ ☐ 2+ ☐ 3+ ☐ 4+

THESUS-HF

Baseline

Patient Number:__ __ -__ __ __ __ Patient Initials:__ __ __

Baseline Characteristics at Time of Admission

1 Diabetes ..... ☐ 0 No ☐ 1 Yes → **If Yes, controlled by (check all that apply):**
☐ 1 Diet ☐ 1 Oral ☐ 1 Insulin

2 Ischemic heart disease ... ☐ 0 No ☐ 1 Yes → **If Yes: Check all that apply:**
- ☐ History of MI (myocardial infarction)
- ☐ History of CABG (coronary artery bypass graft)
- ☐ History of PCI (percutaneous coronary intervention)
- ☐ Stable angina → **If Yes: Canadian Cardiovascular Society Class. Of angina:** ☐ I ☐ II ☐ III ☐ IV

3 Valvular disease ..... ☐ 0 No ☐ 1 Yes → **If Yes: Check all that apply:**
- ☐ Mitral stenosis
- ☐ Mitral regurgitation
- ☐ Aortic stenosis
- ☐ Aortic regurgitation
- ☐ Other (specify): _____

4 HIV test positive ☐ 96 Unknown ☐ 0 No ☐ 1 Yes → **If Yes: Antiretroviral therapy?** ☐ 0 No ☐ 1 Yes

5 Hypertension ..... ☐ 0 No ☐ 1 Yes

6 Hyperlipidemia ..... ☐ 0 No ☐ 1 Yes

7 Stroke ..... ☐ 0 No ☐ 1 Yes

8 PVD (Peripheral Vascular Disease) ..... ☐ 0 No ☐ 1 Yes

9 Smoking ..... ☐ 0 No ☐ 1 Yes

10 Malignancy ..... ☐ 0 No ☐ 1 Yes

11 Depression ..... ☐ 0 No ☐ 1 Yes

12 Dementia ..... ☐ 0 No ☐ 1 Yes

13 Atrial fibrillation ..... ☐ 0 No ☐ 1 Yes

14 Pacemaker ..... ☐ 0 No ☐ 1 Yes

15 Pericardial disease ..... ☐ 0 No ☐ 1 Yes

16 Cardiomyopathy ..... ☐ 0 No ☐ 1 Yes

17 Cor pulmonale ..... ☐ 0 No ☐ 1 Yes

18 Ejection fraction ..... _____%

THESUS-HF

Hospitalization

Patient Number: ___-_____ Patient Initials ____

Hospital Data (See opposite page for completion instructions)

Hospital Discharge Date: __/__/200__

Assessment Date →		__/__/200__	__/__/200__	__/__/200__	__/__/200__	__/__/200__
1 Symptom	**Scale**	**1 Month Pre**	**Admission**	**Day 1**	**Day 2**	**Discharge or Day 7**
Dyspnea	+3 to -3	NA	NA			
Well-being	+3 to -3	NA	NA			
Orthopnea	0 to 3					
Dyspnea on exertion	0 to 3 OR NA (not evaluable)	☐ NA	☐ NA	☐ NA	☐ NA	☐ NA
2 Signs	**Scale**	**1 Month Pre**	**Admission**	**Day 1**	**Day 2**	**Discharge or Day 7**
Blood pressure	systolic/diastolic mmHg	___/___	___/___	___/___	___/___	___/___
Heart rate	beats/minute	___	___	___	___	___
Respiration	breaths/minute	___	___	___	___	___
O2 saturation	%	___.___	___.___	___.___	___.___	___.___
Temperature	°C	___.___	___.___	___.___	___.___	___.___
Peripheral edema	0 to 3*					
Rales	0 to 3					
JVP (Jugular venous pressure)	0 to 3 OR NA (not evaluable)	☐ NA	☐ NA	☐ NA	☐ NA	☐ NA
Weight	kg	___	___	___	___	___
3 Labs	**Units**	**1 Month Pre**	**Admission**	**Day 1**	**Day 2**	**Discharge or Day 7**
Creatinine	☐ mg/dL ☐ µmol/L		NA*	NA	NA	
BUN/urea	☐ mg/dL ☐ mmol/L		NA*	NA	NA	
Sodium	☐ mmol/L ☐ mEq/L		NA*	NA	NA	
BNP	pg/mL		NA*	NA	NA	
NT Pro BNP	pg/mL		NA*	NA	NA	

*Record admission lab values on CRF page 1

Thesus-HF_V2.0_30 AUG 2006 Original – Momentum Research, Inc. Photocopy – retain at site CRF, page 3

THESUS-HF

Hospitalization

Patient Number:__ __ -__ __ __ __ Patient Initials:__ __ __

Medication and Therapies

4 IV Drugs/ Therapies	1 Month Pre	Admission	Day 1	Day 2	Discharge or Day 7
Nitrates	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Furosemide	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Dopamine	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Dobutamine	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Digoxin	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Mechanical ventilation	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
5 PO Drugs	**1 Month Pre**	**Admission**	**Day 1**	**Day 2**	**Discharge or Day 7**
ACE inhibitors/ angiotensin antagonists	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Loop diuretics	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Beta blockers	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Digoxin	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Hydralazine	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Nitrates	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Aldosterone inhibitor	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Statins	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Aspirin	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Anticoagulants	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes

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THESUS-HF

Echocardiographic Evaluation

Patient Number:__ __ -__ __ __ __ Patient Initials:__ __ __

Echocardiographic Evaluation

Date of echocardiogram: ___ ___ / ___ ___ ___ / 200___

1 Heart Rate _____ bpm

Dimensions and LV Function	Value
2 Left ventricular size systole	_____ mm
3 Left ventricular size diastole	_____ mm
4 Ejection fraction	_____ %
5 Intra ventricular septum *(diastole)*	_____ mm
6 Posterior wall *(diastole)*	_____ mm

Diastolic Function	Value
7 Left atrial size, antero-posterior	_____ mm
8 Left atrial size, planimetry	_____ mm^2
9 Mitral E-wave	_____ mm/sec
10 E-wave deceleration time	_____ msec
11 Mitral E-wave	_____ mm/sec
12 Mitral A-wave *(duration)*	_____ msec

Valvular	Severity	Rheumatic?
13 Aortic Stenosis	☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 No ☐ 1 Yes ☐ NA
14 Aortic regurgitation	☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 No ☐ 1 Yes ☐ NA
15 Mitral stenosis	☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 No ☐ 1 Yes ☐ NA
16 Mitral regurgitation	☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 No ☐ 1 Yes ☐ NA
17 Tricuspid regurgitation	☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 No ☐ 1 Yes ☐ NA
18 Other	☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 No ☐ 1 Yes ☐ NA
Pericardial Effusion	**Severity**	**Tuberculosis?**
19 Pericardial effusion	☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 No ☐ 1 Yes ☐ NA
20 Other conditions	☐ 0 No ☐ 1 Yes → **Specify:**	
21 Other conditions	☐ 0 No ☐ 1 Yes → **Specify:**	

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THESUS-HF

Diagnosis

Patient Number:__ __ -__ __ __ __ Patient Initials:__ __ __

Diagnosis		
Type of Heart Failure (HF) (please answer all questions):		
1 Diastolic dysfunction	☐ 0 No	☐ 1 Yes
2 Systolic dysfunction	☐ 0 No	☐ 1 Yes
3 Dilated-idiopathic cardiomyopathy (CM)	☐ 0 No	☐ 1 Yes
4 Peripartum cardiomyopathy	☐ 0 No	☐ 1 Yes
5 Ischemic heart disease	☐ 0 No	☐ 1 Yes
6 HIV cardiomyopathy	☐ 0 No	☐ 1 Yes
7 Rheumatic heart disease	☐ 0 No	☐ 1 Yes
8 Hypertensive cardiomyopathy (HTN CM)	☐ 0 No	☐ 1 Yes
9 Endomyocardial fibroelastosis	☐ 0 No	☐ 1 Yes
10 Pericardial effusion/tamponade	☐ 0 No	☐ 1 Yes
11 Other factors	☐ 0 No	☐ 1 Yes → **Specify:** _____
12 Other factors	☐ 0 No	☐ 1 Yes → **Specify:** _____

THESUS-HF

Follow-Up - 1 Month

Patient Number: __ __ - __ __ __ __ Patient Initials: __ __ __

Follow-Up Assessment (See opposite page for completion instructions)

Assessment Date ⟶		__/__ __/200__
1 Symptom	**Scale**	**Follow Up**
Dyspnea	+3 to -3	NA
Well-being	+3 to -3	NA
Orthopnea	0 to 3	_____
Dyspnea on exertion	0 to 3 OR NA (not evaluable)	NA
2 Signs	**Scale**	**Follow Up**
Blood pressure	systolic/diastolic mmHg	__ __ __/__ __ __
Heart rate	beats/minute	__ __ __
Respiration	breaths/minute	__ __ __
O2 saturation	%	__ __ . __
Temperature	°C	__ __ . __
Peripheral edema	0 to 3*	_____
Rales	0 to 3	_____
JVP (Jugular venous pressure)	0 to 3 OR NA (not evaluable)	☐ NA
Weight	kg	__ __ __
3 Labs		**Follow Up**
Creatinine		_____ ☐ mg/dL ☐ µmol/L
BUN/urea		_____ ☐ mg/dL ☐ mmol/L
Sodium		_____ ☐ mmol/L ☐ mEq/L
BNP		_____ pg/mL
NT Pro BNP		_____ pg/mL
4 PO Drugs		**Follow Up**
Ace inhibitors/ angiotensin antagonists		☐ 0 No ☐ 1 Yes
Loop diuretics		☐ 0 No ☐ 1 Yes
Beta blockers		☐ 0 No ☐ 1 Yes
Digoxin		☐ 0 No ☐ 1 Yes
Hydralazine		☐ 0 No ☐ 1 Yes
Nitrates		☐ 0 No ☐ 1 Yes
Aldosterone inhibitor		☐ 0 No ☐ 1 Yes
Statins		☐ 0 No ☐ 1 Yes
Aspirin		☐ 0 No ☐ 1 Yes
Anticoagulants		☐ 0 No ☐ 1 Yes

THESUS-HF

Follow-Up - 6 Months

Patient Number: __ __ - __ __ __ __ Patient Initials __ __ __

Follow-Up Assessment (See opposite page for completion instructions)

Assessment Date ⟶		__/__ __/200__
1 Symptom	**Scale**	**Follow Up**
Dyspnea	+3 to -3	NA
Well-being	+3 to -3	NA
Orthopnea	0 to 3	_____
Dyspnea on exertion	0 to 3 OR NA (not evaluable)	NA
2 Signs	**Scale**	**Follow Up**
Blood pressure	systolic/diastolic mmHg	__ __ __/__ __ __
Heart rate	beats/minute	__ __ __
Respiration	breaths/minute	__ __ __
O2 saturation	%	__ __ . __
Temperature	°C	__ __ . __
Peripheral edema	0 to 3*	_____
Rales	0 to 3	_____
JVP (Jugular venous pressure)	0 to 3 OR NA (not evaluable)	☐ NA
Weight	kg	__ __ __
3 Labs		**Follow Up**
Creatinine		_____ ☐ mg/dL ☐ µmol/L
BUN/urea		_____ ☐ mg/dL ☐ mmol/L
Sodium		_____ ☐ mmol/L ☐ mEq/L
BNP		_____ pg/mL
NT Pro BNP		_____ pg/mL

4 PO Drugs	Follow Up	
Ace inhibitors/ angiotensin antagonists	☐ 0 No	☐ 1 Yes
Loop diuretics	☐ 0 No	☐ 1 Yes
Beta blockers	☐ 0 No	☐ 1 Yes
Digoxin	☐ 0 No	☐ 1 Yes
Hydralazine	☐ 0 No	☐ 1 Yes
Nitrates	☐ 0 No	☐ 1 Yes
Aldosterone inhibitor	☐ 0 No	☐ 1 Yes
Statins	☐ 0 No	☐ 1 Yes
Aspirin	☐ 0 No	☐ 1 Yes
Anticoagulants	☐ 0 No	☐ 1 Yes

THESUS-HF

Outcomes

Patient Number:__ __ -__ __ __ __ Patient Initials:__ __ __

Rehospitalization Within 6 Months

1. Was the patient rehospitalized within 6 months? ☐ 0 No ☐ 1 Yes ☐ 96 UNK

If yes, provide details below:

Rehospitalization Data

Admission Date →	Rehospitalization #1 __ __ / __ __ __ / 200__	Rehospitalization #2 __ __ / __ __ __ / 200__	Rehospitalization #3 __ __ / __ __ __ / 200__
Reason for Rehospitalization			
Heart Failure	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Ischemia	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Arrhythmia	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes	☐ 0 No ☐ 1 Yes
Other cardiac	☐ 0 No ☐ 1 Yes → Specify _____	☐ 0 No ☐ 1 Yes → Specify _____	☐ 0 No ☐ 1 Yes → Specify _____
Non-cardiac	☐ 0 No ☐ 1 Yes → Specify _____	☐ 0 No ☐ 1 Yes → Specify _____	☐ 0 No ☐ 1 Yes → Specify _____

Death

1 Did the patient die within 6 months? ☐ 0 No ☐ 1 Yes ☐ 96 UNK

If yes, provide details below:

2 Date of death: __ __ / __ __ __ / 200__

3 In hospital at time of death? ☐ 0 No ☐ 1 Yes

4 Sudden death? ☐ 0 No ☐ 1 Yes

5 During acute heart failure? ☐ 0 No ☐ 1 Yes

6 During acute ischemia? ☐ 0 No ☐ 1 Yes

7 Associated with arrhythmia? ☐ 0 No ☐ 1 Yes

8 Other cardiac? ☐ 0 No ☐ 1 Yes → **Specify:** _____

9 Non-cardiac? ☐ 0 No ☐ 1 Yes → **Specify:** _____

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Adherence to Heart Failure Treatment Guidelines and Mortality of Patients with Acute Heart Failure: the Groote Schuur Hospital Experience

Dr Patryk Zygmunt Szymanski
Student number: SZYPAT001

Submitted to the University of Cape Town
In partial fulfilment of the requirements for the degree of

Master of Medicine (Medicine) (MMed (Med))

Faculty of Health Sciences
UNIVERSITY OF CAPE TOWN

Date of submission:
Supervisor: Prof Bongani Mayosi
Department of Medicine, Old Main Building, Groote Schuur Hospital, Observatory, Cape Town, South Africa

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11 August 2014

HREC REF: 579/2014

Prof B Mayosi
Medicine
J Floor
Old Main Building

Dear Prof Mayosi

PROJECT TITLE: EVALUATING THE ADHERENCE TO CURRENT HEART FAILURE TREATMENT GUIDELINES AND MORTALITY OF PATIENTS PRESENTING WITH ACUTE HEART FAILURE TO THE GROOTE SCHUUR HOSPITAL COMPLEX (Sub-study linked to 068/2008 The Sub-Saharan Africa Survey of heart failure - THESUS-HF) - MMED Candidate: Dr P Szymanski)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

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 30th August 2015

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.

Please explain to the HREC why participants will be telephoned as per the comment on the use of the Discovery Grant.

Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We also acknowledge that the MMed student, Dr P Szymanski is also involved in this study.

We congratulate Dr P Szymanski for receiving the Discovery Grant

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

Please quote the HREC REF in all your correspondence.

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