CHARACTERISTICS AND OUTCOMES OF ACUTE HEART FAILURE IN SUB SAHARAN AFRICA

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(SNXMAH001)

A thesis submitted in fulfilment of the requirements for the degree

Doctor of Philosophy

PhD

(Medicine)

Department of Medicine

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South Africa

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Declaration

I, Mahmoud Umar SANI hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicated otherwise). I declare 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. I empower the university to reproduce for the purpose of research either the whole or any portion.

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Table of contents

Abstract

Background:

Heart failure (HF) is one of the most important causes of morbidity and mortality both in the developed and the developing nations. Acute heart failure (AHF) is a syndrome characterized by hospital admission for heart failure as defined by the presence of acute dyspnea and the presence of heart failure signs by physical examination with at least 2 of the following: rales, edema, elevated JVP, hepatomegaly and ascites. AHF can occur de novo or as worsening of symptoms in patients with chronic systolic or diastolic HF. In most sub Saharan African (SSA) countries, AHF has not been well studied and the incidence, prevalence, treatment and outcome of AHF are not well defined. HF in Africa affects young people in their prime of life and as such pose a huge economic burden on the population. There is also limited information on the characteristics, outcome and predictors of HF in general and AHF in particular. Study of clinical characteristics of AHF patients including the role of conventional and novel biomarkers in prognostication is therefore a research priority in this region. The findings will guide appropriate clinical decisions on treatment and proper monitoring.

Methods:

This work involved two cohorts of acute heart failure patients. The first included patients enrolled into a multicenter prospective observational clinical registry for hospitalized patients with AHF while the second included patients recruited for a prospective, placebo controlled double blind randomized study to compare treatment with hydralazine – isosorbide dinitrate versus placebo on top of standard care in African patients admitted with AHF. Data from each subject were obtained using a uniform and standardized case report forms (CRF) for the particular study. In both cases we collected demographic data, date of diagnosis of HF and pre-admission history (previous heart failure related admissions). Others included New York Heart Association (NYHA) functional class, symptoms, signs, self reported cardiovascular

risk factors, aetiology of HF, precipitating factors, co-morbidities, blood investigations (including brain natriuretic peptide (BNP) and galectin-3 (Gal3) in the second cohort), Chest X-ray , 12-lead ECG, echocardiography and medications.

The main objective of this thesis was to study the clinical characteristics and short-term (6 months) outcome of acute heart failure as well as determine the role of conventional biomarker BNP and the novel biomarker Gal3 in the prognostication of acute heart failure patients. To achieve this, we investigated in the first cohort; 1) the demographic and clinical characteristic of patients with AHF, 2) their echocardiographic parameters and how they predict outcome, 3) the predictors of readmission and mortality, 4) the prevalence and impact of renal dysfunction on AHF and 5) the electrocardiographic pattern in AHF. The outcome measures were worsening renal function (WRF), length of hospital stay, HF readmissions and cardiovascular death within 60 days and all cause, cardiovascular or HF death through 180 days. In the second cohort, we investigated the demographics, clinical characteristics as well as the relationship between plasma levels of BNP and galectin 3 and outcomes (cardiovascular (CV) death or HF hospitalization through week 24) as well as the relationship between the plasma levels of BNP and Gal3 and both left ventricular (LV) and right ventricular (RV) remodeling in patients with AHF.

Results:

The first cohort enrolled 1006 patients with AHF. The mean age was 52.3 years, 50.8% were women, and the predominant race was black African (98.5%). HF was most commonly due to hypertension (45.4%), dilated cardiomyopathy (DCM) (18.8%) and rheumatic heart disease (RHD) (14.3%). Ischemic heart disease (IHD) was the cause of AHF in only 7.7%. The median hospital stay was 7 days, with an in-hospital mortality of 4.2% and estimated 180-day mortality was 17.8%

The main predictors of 60-day re-admission or death in a model excluding the geographic region were a history of malignancy, severe lung disease, admission systolic blood pressure, and signs of congestion (rales) and kidney function, i.e. abnormal blood urea nitrogen (BUN). In a model including region, the Southern

region had a higher risk. Predictors of 180-day mortality included malignancy, severe lung disease, smoking history, systolic blood pressure, heart rate, and symptoms and signs of congestion (orthopnoea, peripheral oedema and rales) at admission, kidney dysfunction (BUN), anaemia, and HIV positivity. The echocardiographic predictors of 60-day readmission or death were left atrial size and heart rate while heart rate, LV posterior wall thickness in diastole (PWTd), and presence of aortic stenosis (AS) were associated with the risk of death through 180 days. Renal dysfunction was found in 31 % of the AHF patients. WRF was seen in 9.8 % of those with follow up creatinine values available, and has different predictors compared with Western cohorts. It was nevertheless, associated with the severity of congestion and clinical outcome. Atrial Fibrillation (AF) is present in 20.8% of AHF patients, 44% of whom had valvular AF. Having valvular AF predicted death through day 180.

The second cohort randomized 133 patients; mean age was 53.2 years and 50.8 % were males. Eighty patients had data for biomarkers available for analysis. In this cohort, both BNP and galectin-3 predicted CV death or HF hospitalization through week 24. While BNP was not associated both with changes in markers of LV and RV remodeling, Gal3 at baseline predicted changes (week 24 to baseline) in left ventricular ejection fraction (LVEF), left ventricular end systolic and end diastolic diameters as well as tricuspid annular systolic excursion (TAPSE).

Conclusion:

AHF in Africa affects middle-aged men and women in their productive ages, has a predominantly non-ischaemic cause and is associated with high mortality. Except for HIV status association with mortality, the main predictors of outcome are largely similar in sub-Saharan Africa as in the rest of the world; both renal dysfunction and AF are prevalent in AHF patients as they are in western cohorts. Novel biomarker Gal3 is valuable in predicting changes (week 24 to baseline) in markers of LV and RV remodeling in African AHF patients.

Acknowledgements

First and foremost, I would like to express my deepest thanks to Almighty God, the Beneficent, the Merciful for giving the strength and patience to complete this program.

I am deeply indebted to my parents, Alhaji Umar Sani Babura and Hajiya Rabi Muhammad Umar for their love, unflinching support and prayers. May God reward your sacrifice and support.

To my supervisor, Prof Karen Sliwa, I would like to express my deepest gratitude for your kindness, generosity, constant source of encouragement and support over an extended period of time even before the program was started. You have gone beyond your role as supervisor; you have been diligent in steering me towards academic and professional excellence. Thank you very much for the mentorship and for all the sacrifices and the assistance.

To my co-supervisor, Associate Prof Gad Cotter, I thank you for your guidance, support and generosity in carrying out this work in particular as well as supporting the two projects upon which the thesis was based. I also want to thank Dr Beth Davison for her diligence in the data analysis and corrections of the thesis.

I would also like to extend my appreciation to Prof Bongani Mayosi for his support and encouragement over the years as well as his commitment towards research across the African continent.

My sincere appreciations also goes to Prof Abubakar A. Rasheed, my former Vice Chancellor and Prof Muhammad Y. Bello, the current Vice Chancellor of my University for their support and encouragement, without which the project would not have been possible. I also thank the management of Aminu Kano Teaching hospital for their support.

To my friends and colleagues in Cape Town, I am grateful for making my stay pleasant and worthwhile. They are Prof Mpiko Ntsekhe, Dr Friedrich Thienemann, Dr Liesl Zuhlkhe, Dr Frederic Nduhirabandi, Dr Ntobeko Ntusi, Dr Garba Yunusa, Dr Chima Ofoegbu and Dr Yaw Amoako. My special thanks go to Dr Feriel Azibani, who was very helpful in offering useful suggestions to make this work better.

I would also like to say a big thank you to all members of the Hatter Institute for Cardiovascular Research in Africa (HICRA), especially Tasneem Adam for her help in the conduct of experiments, and Olivia Briton, Sylvia Dennis and Maggie Grootboom for their friendship, support and helping with the logistics during my stay in Cape Town.

I also thank Christopher Edwards and other staff of Momentum Research for their help in analysing the data.

To my colleagues in the cardiology unit Bayero University Kano, I say thank you for sacrificing to do my part of the work while I was away in Cape Town. I also want to thank long term friends and associates; A. Garba Bello Kankarofi, Mustapha H. Falaki, Ibrahim Jibir Wudil, Prof Shehu Yusuf, Dr Tukur Jido, Malam Umar Indabawa, Idris S Gaya, Dr Magaji G Taura, Dr Muktar Aliyu, Dr Sani Aliyu and Muhammad Bala for their support and encouragement.

To all my friends for mutual inspiration and collaboration across the African continent, especially the investigators of the THESUS registry and BAHEF study, as well as members of the Mayosi research group, I say thank you.

This will not be complete without acknowledging the funders of the project. These include Bayero University Kano (BUK), HICRA, Maurice Hatter foundation, medical research council (MRC) of South Africa and Servier. I am very grateful for your support.

I would not forget all my teachers from primary school, right up to the medical school and the residency training programme. Your efforts and sacrifices are well appreciated.

Finally, I remain sincerely grateful to my dear wife Hauwa and our kids – Muhsin, Nana, Al-amin and Siddeeq for their sacrifice, unconditional support and encouragement, which were unlimited sources of energy and inspiration. Thank you very much. My brothers and sisters and my in-laws have shown continuous support and understanding over the years. May God reward all of you abundantly.

List of Tables

List of Figures

List of Abbreviations

6MWT	6 Minutes Walk Test
ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme
ACEI	Angiotensin Converting Enzyme Inhibitors
ACS	Acute Coronary Syndrome
ADA	Adenosine Deaminase
ADHF	Acute Decompensated Heart Failure
AF	Atrial Fibrillation
AGE	Advanced Glycation End Products
AHA	American Heart Association
AHF	Acute heart failure
AKI	Acute Kidney Injury
ALT	Alanine Transaminase
ANP	Atrial Natriuretic Peptide
AS	Aortic Stenosis
ASE	American Society of Echocardiography
AST	Aspartate Transaminase
AT_1	Angiotensin-1 Receptor
AT_2	Angiotensin-2 Receptor
BAHEF	Bi Treatment with Hydralazine/Nitrates versus Placebo in Africans
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAD	Coronary artery disease
CCF	Congestive Cardiac failure
CHF	Chronic Heart Failure
CKD	Chronic Kidney Disease
CNP	C type Natriuretic Peptide
CO	Cardiac Output

COPD	Chronic Obstructive Pulmonary Disease
Cr	Creatinine
CRD	Carbohydrate Recognition Domain
CRF	Case Report Form
CRP	C Reactive Protein
cTn	Cardiac Troponin
CV	Cardiovascular
CVD	Cardiovascular Disease
DALYs	Disability Adjusted Life Years
DBP	Diastolic Blood Pressure
DCM	Dilated Cardiomyopathy
DM	Diabetes Mellitus
ECG	Electrocardiogram
ED	Emergency Department
EF	Ejection fraction
EMF	Endomyocardial Fibrosis
ESC	European Society of Cardiology
Gal3	Galectin-3
GBD	Global Burden of Disease
GDF-15	Growth Differentiating Factor – 15
HAART	Highly Active Antiretroviral Therapy
HF	Heart Failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HHD	Hypertensive Heart Disease
HHF	Hypertensive Heart Failure
HICRA	Hatter Institute of Cardiovascular Disease in Africa
HICs	High Income Countries
HIVAC	HIV Associated Cardiomyopathy
HR	Hazard ratio
hsTnT	highly sensitive Troponin T

HYIS	Hydralazine and Isosorbide dinitrate combination
ICD(1)	Implantable Cardioverter Defibrillation
ICD(2)	International Classification of Disease
ICU	Intensive Care Unit
IHD	Ischaemic heart disease
IL-6	Interleukin – 6
IL1RL1	Interleukin-1-Receptor Like–1
IVCD	Intraventricular Conduction Defects
JVP	Jugular Venous Pressure
LA	Left Atrium
LAE	Left Atrial Enlargement
LBBB	Left Bundle Branch Block
LDH	Lactate Dehydrogenase
LDLc	Low density lipoprotein cholesterol
LFTs	Liver Function Tests
LMICs	Lower Middle Income Countries
LOS	Length of Stay in Hospital
LV	Left Ventricle
LVEDD	Left ventricular en diastolic diameter
LVEDP	Left Ventricular End Diastolic Pressure
LVEF	Left ventricular Ejection Fraction
LVESD	Left ventricular end systolic diameter
LVH	Left Ventricular Hypertrophy
LVM	Left Ventricular Mass
LVMI	Left Ventricular Mass Index
M-mode	Motion – mode
MAP	Mean Arterial Pressure
MCS	Mechanical Circulatory Support
MI	Myocardial Infarction
MMPs	Matrix Metalloproteinases
MRC	Medical Research Council

MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic Acid
NCDs	Non Communicable Diseases
NFkB	Nuclear Factor kappa Beta
NPR-C	Natriuretic Peptide Receptor type C
NPs	Natriuretic Peptides
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NSAIDs	Non Steroidal Anti Inflammatory Drugs
NT Pro-BNP	N-Terminal pro Brain Natriuretic Peptide
NYHA	New York Heart Association
OR	Odds ratio
PAP	Pulmonary artery pressure
PCI	Percutaneous Coronary Intervention
PCR	Polymerase Chain Reaction
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PPCM	Peripartum Cardiomyopathy
PRA	Plasma Renin Activity
PWTd	Posterior wall thickness at end-diastole
RAAS	Renin Angiotensin Aldosterone System
RCT	Randomized Clinical Trial
RHD	Rheumatic Heart Disease
RI	Renal impairment
ROS	Reactive Oxygen Species
RV	Right Ventricle
SBP	Systolic Blood Pressure
SNS	Sympathetic Nervous System
SSA	sub-Saharan Africa
ST2	Suppression Tumorigenicity - 2
STEMI	ST segment Elevation Myocardial Infarction
SVR	Systemic Vascular resistance

TAPSE	Tricuspid Annular Plane Systolic Excursion
TDF-B	Transforming Growth Factor Beta
TDI	Tissue Doppler Imaging
TEE	Trans Esophageal Echocardiography
THESUS-HF	The Survey of Heart Failure in Sub Saharan Africa
TIMPs	Tissue Inhibitors of Metalloproteinases
TNF	Tumour Necrosis Factor
TTE	Transthoracic Echocardiography
VAS	Visual Assessment Scale
WHO	World Health Organization
WRF	Worsening Renal Function

Summary of Chapters

Chapter 1 of this PhD thesis is an overview of the literature, reviewing the current knowledge and concepts on the definition, epidemiology, pathophysiology, diagnostic strategy and treatment of acute heart failure with particular emphasis on SSA. This chapter ends with a description of the gaps in the knowledge that subsequent chapters attempted to address.

Chapter 2 describes the hypothesis, aim and specific objectives of this doctoral research.

Chapter 3 is a description of the two studies upon which the thesis was based. These are the sub Saharan African survey of heart failure (THESUS-HF), a prospective multicentre registry of acute heart failure and a randomised clinical trial, the bi treatment with hydralazine/isosorbide dinitrate (HYIS) versus placebo in Africans admitted with AHF (BAHEF).

Chapters 4 to 10 present the results of this thesis including condensed publications, manuscripts that are still under review and those that were accepted (in press) by peer-reviewed journals.

- In Chapter 4 (2 published articles), we present the demography, aetiology and clinical characteristics of acute heart failure in SSA. We demonstrated that AHF in SSA affects young men and women, caused mainly by hypertension, DCM and RHD. HIV infection is as yet not a significant cause of AHF in SSA. Unlike the western population, IHD was responsible for only a small percentage of AHF. Most of the patients present late with severe disease had significant co-morbidities, high readmission rates and mortality.
- Chapter 5 (published article) described the predictors of readmission and death over 6 months in our AHF patients' cohort. These were a history of malignancy, severe lung disease, admission systolic blood pressure, and signs of congestion (rales) as well as kidney function.
- In chapter 6 (under review), we discussed symptoms and signs of HF at admission and discharge and outcomes in the SSA. Symptoms and signs of

HF were found to be valuable tools in predicting patients' outcomes. Simple assessments including edema, rales, oxygen saturation, respiratory rate and asking the patient about general well-being seem to add significant prognostic value to baseline characteristics and lab values.

- Chapter 7 (in press) focused on echocardiographic predictors. Left atrial (LA) size was associated with death or readmission within 60 days while left ventricular posterior wall thickness, and presence of aortic stenosis were associated with the risk of death through 180 days.
- Chapter 8 (published article) addressed prevalence and impact of renal dysfunction in our cohort; renal dysfunction was seen in a third of our patients. WRF was an independent predictor of death or readmission over 60 days and all-cause death over 180 days
- In Chapter 9 (under review), we investigated the prevalence, clinical characteristics and outcomes of valvular AF. We found valvular AF was associated with all-cause death through day 180 but was not a significant predictor of all cause death or readmission through day 60.
- Chapter 10 (ready to be submitted) investigated the prognostic value of NT-Pro BNP and Galectin-3 in a cohort of AHF patients enrolled in the BAHEF trial. We showed that both N terminal pro BNP (NT pro BNP) and Gal-3 at baseline predicted combined CV death or HF hospitalization. Gal-3 also predicted changes in markers of LV remodeling and RV remodeling.

Chapter 11 summarized the major findings of this thesis and recommended the potential areas of future research on AHF in SSA.

Appendix is a collection of documents that were mandatory for the conduct of this work including, ethical approvals, statements of originality, the list of contributors to the two multinational studies and the case report forms (CRFs) for the two studies.

Author's contribution

Two main studies contributed data to the analyses presented in this PhD thesis. They were both multicentre and multinational collaborative studies, and therefore involved many investigators (list provided in the Appendix).
My specific role in relation to each of these studies is outlined below:

The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF)

I was the principal investigator for Aminu Kano Teaching Hospital, Kano Nigeria. I participated in all phases from the conception of the protocol to recruitments of patients, interpretation of results and drafting of all related manuscripts. My centre had the highest number of patients enrolled in the THESUS-HF registry. For the majority of the manuscripts forming part of this thesis (chapters 6, 7, 8 and 9), I am the lead investigator and lead author, responsible for hypothesis generation, writing of the protocol, planning and guidance of the statistical analyses, interpretation of results, writing of the manuscript, submission to journals and coordinating the response to reviewer's comments.

The Bi treatment with hydralazine/nitrates vs. placebo in Africans admitted with acute Heart Failure (BAHEF)

After the success of THESUS-HF registry, we embarked on BAHEF, to answer a questioned that arose from THESUS. I was part of the steering committee for establishing the BAHEF study. I was part of the team that conceived the trial and generated the protocol. I was the principal investigator for my centre, the Aminu Kano teaching hospital, Kano, Nigeria and participated in the recruitments of patients, interpretation of results and drafting of all related manuscripts. Out of the 2 manuscripts included in this thesis, I am the lead author, responsible for hypothesis generation, writing of the protocol, planning and guidance of the statistical analyses, interpretation of results, writing of the manuscript, for the biomarker paper (chapter 10). The thesis did not include the details of the results of the BAHEF study, other than the baseline characteristics and the biomarker sections.

1. Chapter 1: Introduction/Background to the Thesis

1.1 Global Burden of Cardiovascular Disease

Cardiovascular disease (CVD) constitutes a major public health problem both in the developed and developing countries. By the turn of the 20th century CVD was responsible for fewer than 10% total global deaths. CVD is now leading cause of death worldwide accounting for over 30% of all deaths (Figure 1). [1,2] Of the 58 million deaths from all causes worldwide in 2005, an estimated 17.5 million were due to CVD, 3 times more deaths than are caused by infectious diseases including HIV/AIDS, tuberculosis, and malaria combined. [2] It is estimated that non-communicable diseases (NCDs) will account for more than three-fourths of all deaths in the year 2030, and deaths from CVD will rise to 23.4 million, an approximately 37% increase from 2004 rates. Furthermore, the leading causes of death in the world in 2030 are predicted to be ischemic heart disease (IHD) and cerebrovascular disease (stroke), both components of CVD.[3]

The World Health Organization (WHO) noted that CVD has no geographic, socioeconomic, or sex boundaries. It is the leading cause of death in both developed developing countries as well. Low- and middle-income countries (LMICs); defined as a gross national income per capita of less than $10,066 US dollars per annum in 2004, contribute to about 80% of CVD deaths.[3,4]

According to the Global Burden of Disease (GBD) study, a 55% rise would occur in disability adjusted life years (DALYs) loss attributable to CVD between 1990 and 2020 in the developing countries. [5] This would be in contrast to a 14.3% reduction in the proportion of DALY's loss attributable to CVD during the same period in the developed

countries (including both established market economies and former Socialist economies). The gap would widen further if the former Socialist economies, which are facing resurgence in CVD, were excluded.

A recent study of five countries emphasizes that a much higher proportion of deaths occur in the working age population in Brazil, India, and South Africa in contrast to the USA and Portugal.[6]

The potential results of the burden of CVD on the productive population of the community have far reaching implications. LMICs are confronted with a dual burden of communicable and degenerative diseases, which need tertiary care, and a subsequent diversion of inadequate resources. Apart from the loss of productive years of life, CVD leads to economic constraints with an impact on both the private and the public sectors.

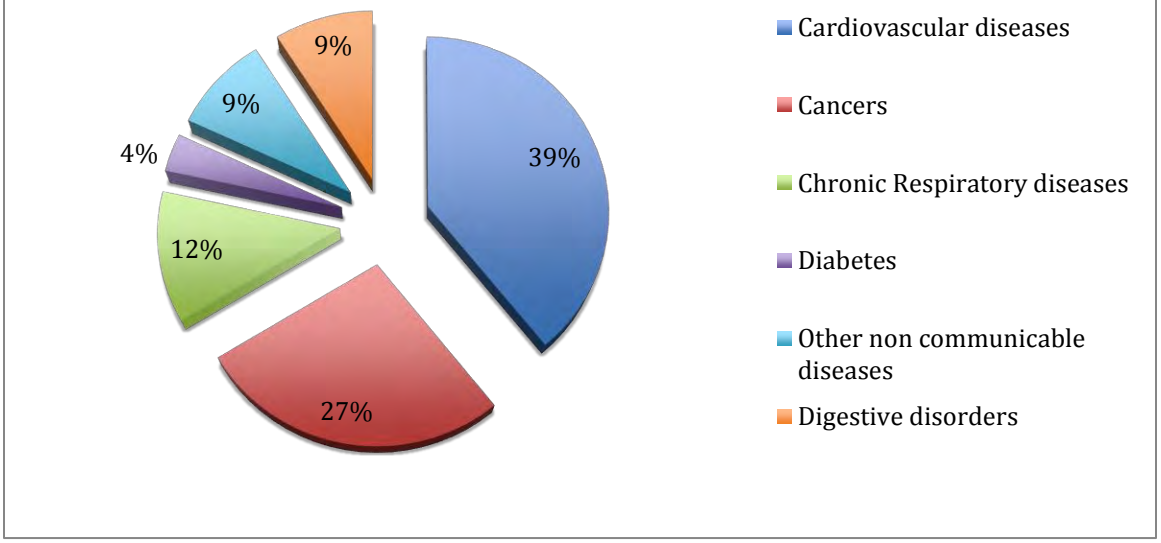

Figure 1.1 Proportion of global death caused by cardiovascular disease (adapted from World Health Organization

1.2 The Epidemiologic Transition

The epidemiological transition provides a useful framework for understanding changes in the patterns of disease as a result of socioeconomic and demographic developments. [7] It refers to the shift that occurs in developing countries as mortality rates from infectious diseases and nutritional deficiencies decrease and mortality from NCDs increases. Omran divided this epidemiological transition into 3 basic ages: pestilence and famine, receding pandemics, and degenerative and man-made diseases. [8] Olshansky and Ault added a fourth stage, delayed degenerative diseases. [9] A fifth regressive stage caused by social upheaval or war, with resurgence in infectious diseases, and high mortality from both CVD and non-CVD causes has been added recently (Table 1).[10]

Table 1.1 Modified Model of the Stages of Epidemiologic Transition as it pertains to cardiovascular diseases (adapted from Yusuf et al. 2001)

Stages of Development		Deaths from CVD (% of Total Deaths)	Prominent CVD and Risk Factors	Regional Examples
1	Age of pestilence and famine	5–10	Rheumatic heart disease, infections, and nutritional cardiomyopathies	Sub-Saharan Africa, rural India, South America
2	Age of receding pandemics	10–35	As above + hypertensive heart disease and hemorrhagic strokes	China
3	Age of degenerative and man-made diseases	35–65	All forms of strokes, ischemic heart disease at young ages, increasing obesity, and diabetes	Urban India, former socialist economies, aboriginal communities
4	Age of delayed degenerative Diseases	<50	Stroke and ischemic heart disease at old age	Western Europe, North America, Australia, New Zealand
5	Age of health regression and social upheaval	35–55	Re-emergence of deaths from rheumatic heart disease, infections, increased alcoholism, and violence; increase in ischemic and hypertensive diseases in the young	Russia
During Stages 1 to 4, life expectancy increases, whereas in Stage 5 life expectancy decreases compared with stages 4 and even 3.				

This shift or transition in disease and mortality rates reflects economic development, urbanization, industrialization, and changes in social organization within countries and regions with increased exposure to risk factors driven by changes in diet, physical activity, and environment. [8,11] The overall epidemiologic transition has been triggered by the "globalization" of dietary habits, characterized by increased consumption of fats and sugars, and urbanization. [12-15] Statistical projections suggest that by 2025, 43.5% of the population in the developing world will be living in urban centers, compared with 21.9%

in 1994. [7] Declining death rates from infectious diseases have also accompanied socioeconomic growth and improved vaccination and other primary health care services. Falling infant and child mortality has led to fast demographic changes leading to large increases in the number of individuals living until middle and older age, when chronic diseases become apparent—the so-called demographic transition. It is projected that by 2025, the number of Africans over 60 years old will increase from 39 million to 80 million.[16]

In addition, while European and North American populations underwent similar changes in demography, determinants, and disease rates over the course of a few centuries, African countries are passing through similar transitions in just a few decades. This forced pace of globalization has resulted in the "export of risk factors" from the West such as tobacco, refined foods, and lifestyles with high CVD risk. [17] At any given period, different countries in the world or even different regions within a country are at different stages of the epidemiologic transition. This transition can occur not only between different disease categories (e.g., deaths from childhood diarrhea and malnutrition giving way to adult chronic diseases), but also within a particular disease category e.g., rheumatic heart disease (RHD) of the young giving way to chronic coronary artery diseases of middle age or valve calcification, degeneration, and HF of the elderly.[10]

Even though countries tend to enter these stages at different times, the progression from one stage to the next tends to proceed in a predictable manner, with both the rate and the nature of CVD changing over the course of the transition.[18]

1.3 Emerging Epidemic of Cardiovascular Disease in sub Saharan Africa

Sub-Saharan Africa (SSA), consisting of those countries that are fully or partially located south of the Sahara Desert, are currently experiencing one of the most rapid epidemiological transitions characterized by increasing urbanization and changing lifestyle factors, [19] which in turn have raised the incidence of NCDs, especially CVD. [20] Studies indicate that urbanization and economic development have also led to the appearance of a nutritional transition characterized by a shift to a higher caloric content diet and/or reduction of physical activity. [21] Together, these transitions create enormous public health challenges, and failure to address the problem may impose significant burden for the health sector and the economy of sub-Saharan African countries.[22]

The increasing epidemic in of CVD in developing countries is not only driven by the emergence of established risk factors, but also by other contributors to a hostile cardiovascular (CV) environment, which have perhaps been less emphasized (Figure 1.2).[23]

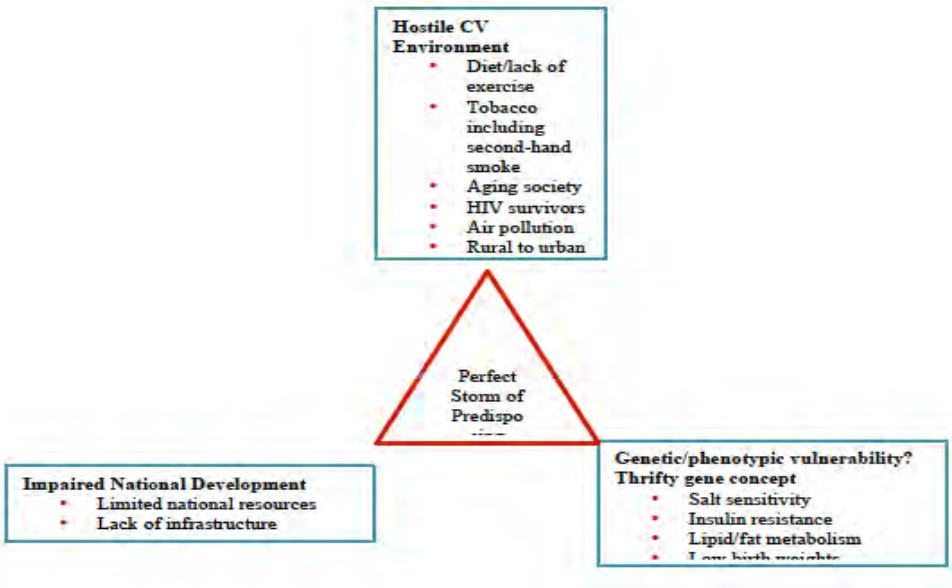

Figure 1.2 The potential epidemic of cardiovascular disease in Africa (modified from Gersh et al. 2010)

Based on the global burden of disease estimates in 2001, CVD and IHD were the eighth and ninth leading causes of death in SSA, and contributed 3.3 and 3.2%, respectively, of total deaths recorded in that year.[24] Overall, in 2001, 10% of all deaths in SSA occurred as a result of CVD, and 4% of (DALYs) were related to a CVD. CVDs and chronic diseases are compounding an under-resourced and understaffed public health care system in SSA, and there is a huge financial burden as well.[25] It has been projected that by 2030, IHD and cerebrovascular diseases will overtake HIV/AIDS as the leading causes of death in this region, contributing over 20% of total deaths and 7% of DALYs in SSA.[26]

This representation is however incomplete because CVD epidemiology studies have been limited in the region, and complete vital registration of deaths by cause and burden of disease assessments have been done by only a handful of SSA countries.[27]

The GBD study of 2010 estimated CVD mortality and burden of disease in SSA in 1990

and 2010, based on the available data. [28] They showed that compared with all other world regions, the SSA region had the smallest proportion of disease burden attributed to CVD in 2010: 8.8% of total deaths, 3.9%of years of life lost, and 3.5% of DALYs. [28] The corresponding CVD proportions for combined high-income regions were 35.7%, 27.2%, and 16.4%. Within SSA, the Southern region had the highest proportional CVD burden and the Western region the lowest.

At present, there are glaring economic forces propelling previously isolated rural groups into the peri-urban and urban areas. As they migrate, a pattern of increasing risk factors with higher rates of urbanization is observed. In South Africa, the increasing migration of blacks to urban centers has led to increased poverty, obesity, hypertension, and elevated cholesterol, and this is likely to similar in most of SSA countries. [7] As "civilization" spreads, so does CVD become an increasing health burden that requires skillful and cost-effective management.[18] The effect of potentially modifiable risk factors associated with myocardial infarction (MI) in 52 countries (INTERHEART) study has shown that hypertension is a strong contributor to the hazards of CVD in black Africans, with an OR of 7.0 versus 2.3 to 3.9 in other ethnic groups. [29] Both poverty and affluence may bring disease. According to the "fetal" origins of adult disease, as put forward by Barker, environmental factors and particularly poor maternal nutrition during pregnancy may program risks for adverse health that appear only later in adult life. [30] Specifically, there is an inverse relation between birth weight and CVD in later life, as shown in a longitudinal study from Scotland. [31] Fetal and infant under nutrition have recently been shown to be associated with significantly increased risk of hypertension and impaired glucose tolerance in 40-year-old Nigerians. [32]

Other major CVD in Africa include the consequences of HIV/ AIDS (often manifesting as tuberculous pericarditis), RHD, and cardiomyopathy (DCM), each of which has at least some environmental component.[33-35]

With increasing CV risk factors comes increase in CVD. Many of CV risk factors when not effectively managed will lead to HF. HF is an important cause of death and disability in SSA, and unlike in the high-income countries (HICs) of North America and Europe, it is most often caused by hypertensive heart disease (HHD), RHD, or DCM and rarely by IHD. [35-37] HF is however conspicuously absent among the major CVDs in SSA on the GBD report. [28] This is because the GBD cause list was based on international classification of disease (ICD), and in the ICD, HF is not classified as an underlying cause of death and disability, it is assigned to its root CVD causes. [28] The limitation of this emphasis on primary HF prevention is that the likely benefits of treating HF cases and improving prevalent HF disability burden are not explicitly estimated, to some degree taking HF off the public health agenda for SSA. It is likely that if HF underlying causes were reclassified into HF burden, HF would rise to be among the major CVDs in SSA. [28] GBD HF burden estimates are therefore required urgently in SSA.

1.4 Definition & Classifications of HF/AHF

Many definitions of HF have been put forward over the last 50 years. [38] In recent years, most definitions have emphasized the need for both the presence of symptoms of HF and physical signs of fluid retention. [39-42] HF can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate

commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or at the expense of increased filling pressures).[43] Table 1.2 gives a historical perspective on HF definitions.[44] The diagnosis of HF can be difficult and many of the symptoms of HF are non-discriminating and, therefore, of limited diagnostic value.[45-47]

Table 1.2 A historical perspective of heart failure definitions (adapted from Sliwa & Stewart 2016)

Wood, 1968	'A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory venous filling pressure.'
Braunwald & Grossman, 1992	'A state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues or, to do so only from an elevated filling pressure.'
Packer, 1988	'A complex clinical syndrome characterised by abnormalities of left ventricular function and neurohormonal regulation which are accompanied by effort intolerance, fluid retention and reduced longevity.'
Poole-Wilson, 1987	'A clinical syndrome caused by an abnormality of the heart and recognised by a characteristic pattern of haemodynamic, renal, neural and hormonal responses.'
ACC/AHA Heart Failure Guidelines, 2005[40]	'Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.'
ESC Heart Failure Guidelines, 2005[39]	'A syndrome in which the patients should have the following features: symptoms of heart failure, typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling and objective evidence of cardiac dysfunction at rest.'
ACC/AHA Heart Failure Guidelines, 2009 (Update)[41]	Definition essentially unchanged, with reinforcement of the stages of heart failure (see legend below – note that the first two stages are not heart failure) and the central importance of the following statement: "The single most useful diagnostic test in the evaluation of patients with HF is the comprehensive 2-dimensional echocardiogram coupled with Doppler flow studies to determine whether abnormalities of myocardium, heart valves, or pericardium are present and which chambers are involved. Three fundamental questions must be addressed: 1) Is the LV ejection fraction (EF) preserved or reduced? 2) Is the structure of the LV normal or abnormal? 3) Are there other structural abnormalities such as valvular, pericardial, or right ventricular abnormalities that could account for the

	clinical presentation?"
ESC Heart Failure Guidelines, 2012 (Update) [42]	'A syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles and displaced apex beat) resulting from an abnormality of cardiac structure or function.

1.4.1 Mild, Moderate or Severe HF

Mild, moderate, or severe HF is employed as a clinical symptomatic narrative, where mild is used for patients who can move around with no important restrictions from dyspnoea or fatigue, severe for patients who are markedly symptomatic and demand frequent medical attention, and moderate for those in between. Two classifications of the severity of HF are commonly employed. Table 1.3 shows the comparison between these two classifications. [48] The New York heart association (NYHA) functional classification is based on symptoms and exercise capacity. [49] It is clinically important and is employed routinely to select patients in almost all randomized treatment trials in HF and, to describe which patients benefit from effective therapies. Patients in NYHA class I have no symptoms; those in NYHA classes II, III or IV are sometimes said to have mild, moderate or severe symptoms, respectively. It is important to note, however, that symptom severity correlates poorly with ventricular function, and that although there is a clear relationship between severity of symptoms and survival, patients with mild symptoms may still have a relatively high absolute risk of hospitalization and death.[50,51] The other classification is the American College of Cardiology (ACC) and American Heart Association (AHA), which designates HF in stages based on structural changes and symptoms. All patients with overt HF are in stages C and D. [52]

Table 1.3 Comparison of the classification of heart failure by structural abnormality (ACC/AHA), or by symptoms relation to functional capacity (NYHA) (adapted from Yancy et al. 2013)

ACC/AHA stages of heart failure [49,52]		**NYHA functional classification[63]**	
Stage of heart failure based on structure and damage to heart muscle		**Severity based on symptoms and physical activity**	
Stage A	At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms	**None**	
Stage B	Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms	**Class I**	
Stage C	Symptomatic heart failure associated with underlying structural heart disease.	**Class I**	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
		Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
		Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea.
	.	**Class IV**	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.
Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy	**Class IV**	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Regrettably, despite a lot of progress made in the treatment of HF, a significant minority of patients continues to do poorly with conventional therapy. These patients are classified to have advanced HF. Clearly, patients who are in need of inotropic therapy or left ventricular assist devices to sustain life are believed to be in this group. However, they also include a larger group of patients who may not be as critically ill but still at substantial risk of hospitalization and death. Therefore, the current literature suggests that the working definition of advanced HF should include persistence of severe clinical symptoms and signs despite treatment, presence of marked left ventricular (LV) systolic dysfunction, and poor exercise capacity. [53] Prognostic studies support the following specific criteria: NYHA functional class III or IV for 3 months despite attempts at standard therapy combined with a left ventricular ejection fraction (LVEF) <30% and a peak oxygen consumption during symptom-limited exercise testing of <14 ml/kg/min (Table 1.4). [53] Other supplementary clinical findings give additional support for the diagnosis of advanced HF.

Table 1.4 Diagnostic Criteria for advance heart failure (adapted from Adams & Zannad 1998)

A	**A Major criteria (all required)**
	1 - Resting left ventricular ejection fraction <30%
	2 - Presence of NYHA functional class III or IV or, if available, peak oxygen consumption <14 ml/kg/min on symptom-limited exercise testing
B	Additional criteria that contribute to the diagnosis
	1 - Trial of standard therapy (ACE inhibitors, digoxin, diuretics) for at least 3 months
	2 - Plasma norepinephrine >900 pg/ml
	3 - Noninvasive evidence of pulmonary hypertension indicated by high velocity of tricuspid regurgitation (>2.5 m/sec)
	4 - Hyponatremia with serum sodium <130 mmol/L in patients not treated with ACE inhibitors

1.4.2 Systolic vs. Diastolic HF

Systolic dysfunction is characterized by decreased contraction and emptying of the LV so that stroke volume is preserved by an increase in end-diastolic volume. This results in dilatation of the LV and the heart ejects a smaller fraction of a larger volume. The more advanced the systolic dysfunction, the more the ejection fraction (EF) is reduced from normal and, usually, the greater the end-diastolic and end-systolic volumes. An EF below or above 40%, distinguishes between large or normal left end-diastolic ventricular volumes. [42] It is considered important in HF, not only because of its prognostic importance (the lower the EF the poorer the survival) but also because most clinical trials selected patients based upon EF (usually measured using a radionuclide technique or echocardiography). EF values are dependent on the imaging technique used, method of analysis, and operator. Because other techniques may indicate abnormalities in systolic function among patients with a preserved EF, it is preferable to use the terms preserved or reduced EF over preserved or reduced systolic function. Patients with diastolic HF have

symptoms and/or signs of HF and a preserved LVEF >40–50%.[54] There is no consensus concerning the cut-off for preserved EF. Other phrases have been used to describe diastolic HF, such as HF with preserved ejection fraction (HFpEF) or HF with normal ejection fraction (HFNEF). [43]

1.4.3 HF with reduced EF (HFrEF)

About half of patients with HFrEF present with variable degrees of LV enlargement may accompany HFrEF.[55,56] The definition of HFrEF has varied, with guidelines of left ventricular ejection fraction (LVEF) ≤35%, < 40%, and ≤40%.[41,42,57] The major trials in patients with HF and a reduced EF (HFrEF), or 'systolic HF', mainly enrolled patients with an EF ≤35%, and it is only in these patients that effective therapies have been demonstrated to date. Most patients with HFrEF commonly have evidence of diastolic dysfunction at rest or on exercise. [58] Although coronary artery disease (CAD) with antecedent MI is a major cause of HFrEF, many other risk factors may lead to LV enlargement and HFrEF.

1.4.4 HF with preserved EF (HFpEF)

In patients with clinical HF, studies estimate that the prevalence of HFpEF is approximately 50% (range 40% to 71%).[59] These estimates vary largely because of the differing EF cut-off criteria and challenges in diagnostic criteria for HFpEF. HFpEF has been variably classified as EF >40%, >45%, >50%, and ≥55%.[48] Some of these patients clearly did not have an entirely normal EF (generally considered to be >50%) neither do they have a major reduction in systolic function either. Because of this, the term HF with 'preserved' EF (HFpEF) was created to describe these patients. Patients with an EF in the range of 40% to 50% represent an intermediate group. These patients are often treated for

underlying risk factors and comorbidities. Several criteria have been proposed to define the syndrome of HFpEF. These include a) clinical signs or symptoms of HF; b) evidence of preserved or normal LVEF; and c) evidence of abnormal LV diastolic dysfunction that can be determined by Doppler echocardiography or cardiac catheterization. [60] Studies have suggested that the incidence of HFpEF is increasing and that a greater portion of patients hospitalized with HF have HFpEF. [61] In the general population, patients with HFpEF are usually older women with a history of hypertension. Obesity, CAD, diabetes mellitus (DM), AF, and hyperlipidemia are also highly prevalent in HFpEF in population-based studies and registries.[59,62] It has been recognized that a subset of patients with HFpEF previously had HFrEF. [63] These patients with recovery in EF may be clinically different from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients. The diagnosis of HFpEF is more difficult than the diagnosis of HFrEF because it also involves exclusion of potential non-cardiac causes of the patient's symptoms (such as anaemia or chronic lung disease must first be discounted.[64,65] Usually these patients do not have a dilated heart and many have an increase in LV wall thickness and increased LA size. Most have evidence of diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients (hence the term 'diastolic HF').[64,65] There are few reports on HF with preserved systolic function from SSA. This is commonly seen due to HHD either alone or in addition to systolic HF.[66]

1.4.5 Acute versus chronic HF

The word 'acute' in the context of acute HF (AHF) has become confusing because some clinicians use the word to indicate severity (life-threatening pulmonary oedema) and

others use the word to indicate decompensated, recent-onset, or even new-onset HF. [67] The word is then an indicator of time rather than severity. The words acute, advanced, and decompensated should not be used as synonyms when applied to HF. AHF diagnosis is made when a sudden onset of symptoms or signs of HF is found in a patient with no history of HF and previously normal cardiac function or when a patient wit established diagnosis of HF develops increasing signs or symptoms of the disease after a period of relative stability. The former syndrome is also called new-onset ('de novo') HF and is usually caused by an acute change in LV performance or in structural cardiac integrity.[68] Common examples new-onset HF would be HF associated with acute MI, mechanical complications such as papillary muscle rupture, or fulminant myocarditis. Therapy in such cases must be directed both at the underlying condition (such as MI) and at the HF itself. However, the majority of patients with AHF are those who present with acute decompensation or exacerbation of chronic heart failure (CHF) and they represent the majority of hospitalizations for HF. [68] After initial management and stabilization of patients with decompensated HF, they should no longer be considered acute but chronic HF. [69] Patients who have had HF for some time are often said to have CHF. A treated patient with symptoms and signs, which have remained generally unchanged for at least a month, is said to be 'stable'. If a stable CHF patient deteriorates, it usually leads to hospital admission, an event of considerable prognostic importance. Although symptoms and signs may resolve in these patients, their underlying cardiac dysfunction may not, and they remain at risk of recurrent 'decompensation'. Some other patients, particularly those with 'idiopathic' DCM, may also show substantial or even complete recovery of LV systolic function with modern evidenced based HF therapy [including an angiotensin

converting enzyme inhibitor (ACE-I), beta-blocker, and mineralocorticoid receptor antagonist (MRA)].[42]

AHF therefore encompasses 3 different patient groups: (1) patients with worsening chronic systolic or diastolic HF that appears to respond to therapy; (2) patients with de novo HF secondary to a precipitant factor, such as a large MI or a sudden increase in blood pressure (BP) superimposed on a noncompliant LV; and (3) patients with worsening of end-stage/advanced HF (ie, HF that is refractory to therapy), with predominantly LV systolic dysfunction associated with a low-output state.[70] Irrespective of the underlying cause (e.g., ischemic event) or precipitant (e.g., severe hypertension), pulmonary and systemic congestion due to elevated ventricular filling pressures with or without a decrease in cardiac output (CO) is a nearly universal finding in AHF.[71]

'Congestive HF' is a term that is sometimes still used, and may describe acute or chronic HF with evidence of congestion (i.e. sodium and water retention). Congestion, though not other symptoms of HF (e.g. fatigue), may resolve with diuretic treatment. Many or all of these terms may be accurately applied to the same patient at different times, depending upon their stage of illness.[42] In practice, the Framingham HF criteria can apply to both chronic HF and acute HF.[72]

The difference between new-onset AHF and acute HF on a background of chronic HF (including advanced HF) is in the degree of physiologic response, which is more pronounced in the acute de novo cases and is more subtle in the chronic cases because of adaptive pathophysiology.[67] Patients with new-onset AHF have strong sympathetic activation. The microvascular permeability can be enhanced, and therefore the clinical signs are acute and manifest. The clinical presentation of AHF reflects a spectrum of

conditions, and any classification will have its limitations. The patient with AHF will usually present in one of six clinical categories. Pulmonary oedema may or may not complicate the clinical presentation. Cardiogenic pulmonary oedema is accumulation of fluid in the lung interstitium and alveoli due to increase in hydrostatic pressure secondary to elevated pulmonary venous pressure. It can result from many causes including excessive intravascular volume administration, pulmonary venous outflow obstruction (e.g. mitral stenosis and left atrial myxoma) and LV failure secondary to systolic or diastolic dysfunction of the LV. In contrast, acute circulatory failure or shock refers to a situation where there is inadequate or inappropriately distributed tissue perfusion resulting in generalized cellular hypoxia with associated hemodynamic disturbances, end-organ dysfunction and elevated biochemical markers of impaired tissue perfusion. Figure 1.3 demonstrates the potential overlap between these conditions.[69]

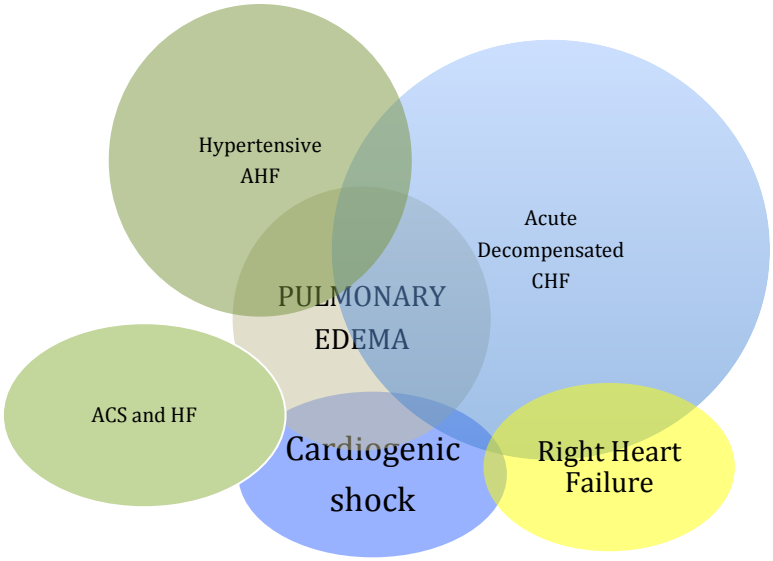

Figure 1.3 Clinical classification of Acute Heart Failure

1.5 Epidemiology of HF/AHF

HF is the end stage of all diseases of the heart and is growing at alarming proportions especially in the elderly. It is one of the most important causes of morbidity and mortality both in the developed and the developing nations. While HF was not listed as a primary cause of death in the GBD studies, [28] it was included as one of the non-fatal health outcomes and as a significant parameter in the monitoring of population health. The GBD studies have been the only studies to quantify non-fatal health outcomes across an exhaustive set of disorders at global and regional level. Left-sided and right-sided symptomatic HF was one of the 289 impairments included in the GBD cause-sequelae list in many locations. [73] It was estimated that there were 37.7 million cases of prevalent HF recorded globally in 2010, leading to 4.2 years lived with disability (YDLs). More than two-thirds (68.7%) of HF globally was attributable to four underlying causes: IHD, chronic obstructive pulmonary disease (COPD), HHD and RHD. Importantly, there were marked regional differences, with HHD, RHD, DCM and myocarditis making a larger contribution in developing countries (Table 1.5). [44]

Table 1.5 Global years lived with disability (DALYs) for heart failure from a comprehensive list of 289 causes and selected sequelae in 1990 and 2010for all ages, both sexes combined and per 100,000 (adapted fro Vos et al. 2012)

	ALL ages YDLs (thousands)			YLDs (per 100 000)		
Cause of heart failure	**1990**	**2010**	**% Δ**	**1990**	**2010**	**% Δ**
Cardiovascular and circulatory diseases	14 373 (11 094–18 134)	21 985 (16 947–27 516)	53.0%	53.0% 271 (209–342)	319 (246–399)	17.7%
Rheumatic HD	290 (191–412)	420 (278–592)	45.1%	5 (4–8)	6 (4–9)	11.6%
Ischaemic HD	894 (609–1236)	1518 (1038–2128)	69.9%	17 (11–23)	22 (15–31)	30.8%
Hypertensive HD	292 (202–412)	460 (315–639)	57.4%	6 (4–8)	7 (5–9)	21.1%
HF due to Cardiomyopathy and Myocarditis	272 (183–378)	394 (269–551)	44.8%	5 (3–7)	6 (4–8)	11.4%
HF due to endocarditis	42 (28–59)	61 (42–87)	45.8%	1 (1–1)	1 (1–1)	12.2%
HF from other circulatory diseases	183 (123–259)	268 (180–372)	46.3%	3 (2–5)	4 (3–5)	12.6%

According to the ESC, there are at least 15 million patients with HF in Europe. [42] The prevalence of HF is between 2 and 3% and rises sharply at about 75 years of age, so the prevalence in 70- to 80-year-old people is between 10 and 20%.

In the United States of America (USA), approximately 5.1 million persons have clinically manifest HF. The lifetime risk of developing HF is 20% for Americans who are ≥40 years of age. [74] HF incidence also increases with age, rising from approximately 20 per 1,000 individuals 65 to 69 years of age to >80 per 1,000 individuals among those ≥85 years of age. Persons younger than 50 years are hardly ever found to have HF in the west. In a recent US population-based study, the prevalence rate of HF was 2.2%, increasing with age: 0.7% in persons aged 45–54 years, 1.3% in persons aged 55–64 years, 1.5% in persons aged 65–74 years, and 8.4% for those aged 75 years or older. [75]

The rise in the incidence and prevalence of HF globally is the result of improved care of acute MI combined with the ageing of the population as well as the emerging pandemic of CVD in the developing countries. [76]

HF has been shown to have a significant impact on health-related quality of life, [77] and appears to impose a huge economic burden to all nations. [78] It is associated with shorter life expectancy, greater morbidity and impaired quality of life than most common diseases. About 30% of people die within 3 months of HF diagnosis, and annual mortality is 10% thereafter. Those with severe HF have an annual mortality of >50%.[79,80]

AHF is the most common reason for hospital admission in patients over the age of 65 years and is also associated with increased cost of care. Furthermore, the prognosis of patients admitted with AHF remains dismal, with over 20% of the patients being readmitted with HF and over 20% dying during the first year after initial admission. [81]

In SSA, acute decompensated heart failure (ADHF) has been found to be the most common primary diagnosis for patients admitted to hospital with heart disease.[36,82] Even though AHF is common, there is limited data on their clinical presentation, characteristics, and outcome. This is partly because AHF has not been sufficiently described because various definitions have been used. In addition, previous studies were generally focused on a one aspect of the syndrome, such as decompensated chronic heart failure, heart failure following MI, acute pulmonary edema, or cardiogenic shock.

Registries that consider AHF as a distinct clinical entity have been published. The most important are: (1) the Acute Decompensated Heart failure National registry (ADHERE) from the US, (2) the European Heart Failure Surveys (EHFS I and II), (3) national surveys in France, Finland, and Italy, (4) the Japan AHF registry and more recently (5) the Survey of Heart Failure in sun Saharan Africa (THESUS - HF). ADHERE included more than 100,000 patients from 282 American. [83] EHFS I provides a description of clinical characteristics and management of 11, 327 patients with HF hospitalized in 115 hospitals across 24 European Countries, 40% of whom had AHF as the primary cause of hospitalization. [84,85] EHFS II addressed AHF and recruited 3,580 patients from 30 countries in Europe. [86] The Etude francaise de l'insuffisance cardiaque aigue (EFICA) translated as French Study of AHF included randomly selected 581 patients admitted to 60 intensive care units (ICU) or coronary care units (CCU) in France. [87] Also from Europe two additional national surveys on AHF from Italy and Finland (Finnish Acute Heart Failure Study, FINNAKVA) have been recently published [88,89] The Italian registry recruited 2,807 patients from 206 cardiology centers while the Finnish study had 620 consecutive AHF patients recruited from fourteen University, central and regional

hospitals. [88,89] In Japan, the ATTEND registry recruited a total of 4,842 patients from 52 academic and non-academic hospitals. [90] Finally the THESUS - HF registry recruited 1006 patients from 12 centres in 9 sub- Saharan African countries. [36]

Although there were differences in disease definitions, methods used and, recruiting conditions, these studies present a coherent epidemiological picture of patients hospitalized with AHFS. [91] It is apparent from the THESUS-HF that there are major differences between the epidemiology of acute decompensated heart failure in sub-Saharan Africa, compared to North America, Europe and Asia. Table 1.6 compares the characteristic from patients with AHFS from the US, Europe, Asia and sub Saharan Africa. [92]

Table 1.6 Features of patients with acute decompensated heart failure in the ADHERE (USA), EHFS II (Europe), ATTENT (Asia) and THESUS -HF (sub-Sharan Africa) registries (modified from Sliwa K. 2013)

Registry / Features	*ADHERE Registry (n = 105,388)	#ADHERE - AP (n = 10,171)	ǂEHFS II Registry (n= 3,580)	$ATTEND Registry (n= 4842)	¶THESUS-HF Registry (n = 1,006)
Male, %	48	57	61	58	49
Mean age, years	72	66	70	73	52
Hypertension	73	64	63	69	45
Coronary artery disease, %	57	50	54	31	7
Diabetes, %	44	45	33	34	11
Atrial fibrillation, %	31	24	39	36	18
Anaemia, %	NA	NA	15	NA	15
Renal insufficiency, %	30	NA	17	69	8
Length of Hospital Stay (Median) days	4.3	6	9	21	7
In Hospital Mortality (%)	3.8	4.8	6.7	7.7	4.2

*ADHERE = Acute Decompensated Heart Failure National Registry;

#ADHERE-AP = ADHERE Asia Pacific; ǂEHFS II, EuroHeart Failure Survey II;

¶THESUS-HF = The Sub-Saharan Africa Survey of Heart Failure.

$ATTEND = The acute decompensated heart failure syndromes (ATTEND) registry

1.6 Heart Failure in sub-Saharan Africa

Earlier reports on HF in SSA were mainly from clinical and necropsy studies. The Heart of Soweto study is the largest clinical and echocardiographic study from SSA in recent times. [82] It included 1,593 patients and confirmed that 44% of patients with newly diagnosed CVD had heart failure, whereas only 10% had CAD. Data from selected urban echocardiographic centers reveals the common etiologies of HF include non ischemic cardiomyopathies, RHD, congenital heart disease (CHD), HHD, and endomyocardial fibrosis (EMF); IHD remains relatively uncommon. [93-97] Additionally, there may be significant variation within the continent as EMF, in particular, appears to be more predominant in pockets of East and Central Africa.[98,99] These studies have revealed peculiarities of HF on the continent.

First, heart failure cases in SSA are largely due to the major non-ischemic causes, with HHD, RHD and DCM accounting for over 75% of cases in most series. Second, IHD remains an uncommon cause of HF with no apparent increase in its contribution to the cases of HF. Thirdly, many of the causes of HF such as RHD, DCM and EMF present in the young and middle-aged, contrary to what happens in the developed countries where HF is a disease of the elderly. Finally, the contribution of cor pulmonale and pericarditis to about 20% of cases of HF reflects the continuing impact of tuberculosis on heart disease on the continent.[100]

SSA is home to 70% of adults and 90% of children living with human immunodeficiency virus (HIV) and 75% of the 30 million who have died of acquired immunodeficiency syndrome (AIDS)-related illnesses. [101] As a consequence, HIV related heart diseases mainly HIV associated cardiomyopathy (HIVAC), pericardial disease and HIV related pulmonary hypertension (PH) have become important causes

of heart failure in many African countries.[33]

Peripartum cardiomyopathy (PPCM) is a disorder associated with symptoms of HF and occurs between the last month of pregnancy and the first five months postpartum, [102] has its highest incidence in northern Nigeria where it has been reported to be at a frequency of 1 in 100 births. [103]

Before the THESUS- HF, little is known about AHF in Africa. [37] This registry has shown that, in addition to the high prevalence of endemic causes of HF, Africa is clearly facing an additional burden of emerging causes, such as IHD and HHD, particularly in some countries. [36]

1.7 Risk Stratification Models and Predictors of Mortality in AHF

Despite relatively modest in-hospital mortality, the event rate of patients with AHF after hospitalization is unacceptably high, higher than that of outpatients with advanced HF. Accurate risk stratification is required for clinical care, distribution of health care resources, and research. Patient management requires an appreciation of the risk of future events to make suitable decisions about acuteness of care (e.g, admission to an intensive care unit versus a less monitored setting), triaging patients among the available therapies, and to plan hospital discharge and intensity of follow up.[104] This is particularly important in HF, given the need to allocate health care resources in the face of a rapidly increasing population of patients with high health care utilization. The need for accurate risk stratification for HF patients will increase as expensive emerging technologies, such as biventricular pacing, implantable defibrillators, and ventricular assist devices, become increasingly used in this patient population.[104] There are many studies that address the long term prognostic factors in CHF, [105,106] little has been done in the risk stratification of patients presenting with

acute decompensated HF.[107,108]

Additionally, as new therapies for the management of AHF continue to evolve, there is need for accurate estimation of risk through prognostic modelling to appropriately design and power clinical trials. The identification of high-risk subgroups allows trials to be designed that focus on patients with high event rates, potentially speeding the development of new therapies and limiting the exposure of patients to potentially risky experimental therapies. Lastly, risk factors that may be amenable to modification (such as low serum sodium or hemoglobin) may be potential targets for the development of new treatment strategies.[104]

In a Canadian study that evaluated 153 patients who arrived at the emergency department with AHF, the authors identified prior admission for AHF, intraventricular conduction delay (IVCD), the cumulative dose of intravenous furosemide, and serum sodium as being associated with increased rates of mortality.[107] An analysis of data from the Flolan International Randomized Survival Trial (FIRST) trial identified male sex, randomization to epoprostenol, presentation with NYHA class IV HF, and treatment with continuous dobutamine infusion as independent risk factors for mortality in a population with advanced HF. [109]

Table 1.7 [110] shows emerging prognostic factors in patients admitted with AHF from recent clinical trials and observational studies. [104,111-119] These include SBP on admission and early post-discharge, [120] CAD, both related to the extent and severity of CAD and the presence of other comorbidities, [121] ventricular dyssynchrony, [122] sustained ventricular or atrial arrhythmias[123] and renal impairment (RI). [124,125] Markers of RI, either BUN, Cr, BUN /Cr ratio, estimated glomerular filtration rate (GFR), and/or cystatin C all have important prognostic significance. [124-127] Other prognostic factors are hyponatraemia, [128,129] cardiac troponin (cTn) release elevated

natriuretic peptide (NP) levels, elevated PCWP, liver disease, anemia, severe symptoms, older age, and increased heart rate appear to be markers of increased post-discharge mortality risk. [104,130-133]

Some of these prognostic indicators can be treated (eg, elevated wedge pressure and hyponatremia), whereas others are not readily modifiable. The use of biochemical markers as prognostic indicators for HF outcomes has expanded in the last decade. Increases in BNP may be predictive of early readmission and mortality rates in patients hospitalized with AHF. [134] The combination of elevated BNP and cTn was associated with a 12-fold increased risk of mortality in another study. [115]

Similar clinical and biological characteristics, clinical scores as well as a large and ever increasing number of biomarkers have been associated with outcome and a few have also been developed as 'predictors' of outcome in HF. A non-exhaustive list of factors includes age, gender, ethnicity, aetiology, co-morbidity, NYHA class, exercise capacity, peak VO2, poor quality of life, low body weight, left bundle branch block (LBBB), AF, non-sustained, sustained, and inducible ventricular tachycardia (VT), increased PR and QRS duration, T-wave alternans, QT dispersion, low heart rate variability, depressed baroreflex sensitivity, history of HF hospitalization, resuscitated death, hyponatraemia, hypokalaemia, raised serum Cr and BUN. Others include transaminases, bilirubin and urates, anaemia, neuroendocrine activation, high serum BNP, low LVEF, abnormal diastolic function parameters, raised serum levels of markers of extracellular matrix metabolism, viable myocardium, and central haemodynamics. [135-139] Prognostic analyses have been predominantly carried out on populations with LV systolic dysfunction. Much less data are available for HF with preserved systolic function. [136] Specific predictors of sudden death have also been developed. Beyond low LVEF, none has a strong enough predicting value to be the

basis for indicating an implantable cardioverter defibrillator (ICD). Similarly, beyond low LVEF and wide QRS complex, none has a strong enough predicting value for indicating cardiac resynchronization therapy (CRT).[76]

Table 1.7 Potential Indicators and Potential Targets of therapy in Acute Heart failure (adapted from Gheorghiade et al. 2009)

SBP	Admission and early post-discharge SBP inversely correlates with post-discharge mortality. The higher the BP, the lower both in-hospital and post discharge mortality. However, the readmission rate of approximately 30% is independent of the SBP at time of admission
CAD	Extent and severity of CAD appears to be a predictor of poor prognosis. Associated with 2-fold increase in postdischarge mortality compared with patients with primary cardiomyopathy
Troponin release	30–70% of patients hospitalized with AHFS have detectable plasma levels of cardiac troponin. Results in a 3-fold increase in in-hospital mortality, a 2-fold increase in post-discharge mortality, and a 3-fold increase in the re-hospitalization rate
Ventricular dyssynchrony	Increase in QRS duration occurs in approximately 40% of patients with reduced systolic function and is a strong predictor of early and late post-discharge mortality and re-hospitalization.
Renal impairment	BUN and BUN/creatinine ratio appear to be better prognostic indicators than creatinine. Associated with a 2- to 3-fold increase in post discharge mortality. Worsening renal function during hospitalization or soon after discharge is also associated with an increase in in-hospital and post-discharge mortality.
Hyponatremia	Defined as serum sodium _135 mmol/l, occurs in approximately 25% of patients, and is associated with a 2- to 3-fold increase in post-discharge mortality.
Clinical congestion at time of discharge	An important predictor of post-discharge mortality and morbidity.
LVEF	Similar early post-discharge event rates and mortality between reduced and preserved EF.
BNP/NT-proBNP	Elevated natriuretic peptides associated with increased resource utilization and mortality.
PCWP	Reduction in PCWP during hospitalization, but not an increase in the cardiac output, has been associated with improved postdischarge survival Reduction in PCWP with agents such as milrinone and dobutamine is associated with worse outcomes
Functional capacity at time of discharge	Pre-discharge functional capacity, defined by the 6- min walk test, is emerging as an important predictor of post-discharge outcomes.
Other Predictors	Anemia, diabetes mellitus, new sustained arrhythmias, and nonuse of neurohormonal antagonists
***This is not an all-inclusive list. SBP = systolic blood pressure; CAD =coronary artery disease; LVEF = left ventricular ejection fraction; BNP = brain natriuretic peptide**	

In a recent systematic review and analysis of risk prediction in patients with HF, Rahimi and colleagues identified 48 studies that reported 64 main multivariable models (43 for prediction of risk of death, 10 for hospitalization, and 11 for death or hospitalization). [140] Their results showed that despite the multiple differences in clinical settings, population characteristics, and use of candidate variables, a few variables emerged as consistent and strong predictors of risk across different studies. For prediction of death, these variables comprised age, renal function, blood pressure, sodium level, EF, sex, BNP (or NT-pro BNP) level, NYHA functional class, DM, weight/body mass index, and exercise capacity. [140] Apart from the type of outcome to be predicted and the duration of follow up, none of the other study markers investigated were found to be significantly associated with the ability of the prognostic models to discriminate between those who are likely to experience an event and those who are not. [140]

The efficacy of the a new scoring system the Acute Physiology and Chronic Health Evaluation - HF (APHACHE II - HF) in comparison with second version of the APHACHE II scoring system for predicting outcomes has recently been evaluated in AHF. [141] The APHACHE II consists of three parts including the acute physiology score, chronic health points and age points. The total number of points for the three parts is calculated as APHACHE II score, which has been reported predict adverse outcomes in patients requiring intensive care. [142] Okazaki and colleagues constructed a new predictive scoring system based on eight significant APACHE II factors that were significantly different between the alive group and the dead group. [141] These are mean arterial pressure (MAP), pulse, sodium, potassium, hematocrit, Cr, age, and Glasgow Coma Scale (GCS); giving each one point, defined as the APACHE-HF score. The patients were then assigned to five groups by the APACHE-HF score.

They observed poorer prognosis, including all-cause death and HF events (death, re-admission-HF), in Group 5 and Group 4 than in the other groups with lower APHACHE II – HF Scores. The conventional APACHE II scoring system was not useful in adequately predicting the prognosis of patients with AHF. However the new scoring system named APACHE-HF, which comprised a combination of parameters mentioned above, exhibited significantly higher sensitivity and specificity with an adequate area under the curve (AUC) and could be used to predict adverse mid-term outcomes in patients with AHF.[141]

Finally the long-term survival of a cohort of patients discharged following hospitalization for AHF has recently been investigated in the Acute Heart Failure Database (AHEAD) registry. [143] In this study however, the authors assessed a population of 3438 patients, all of whom survived at least 31 days after admission. They showed that the highest mortality rate of discharged patients was during the first year following discharge. The 3-year survival rate of patients after day 30 post-admission was 64.5% and there was no significant difference among the groups in terms of varying AHF syndromes. High levels of NPs were the most powerful predictors of high mortality risk in long-term follow-ups; other negative factors included older age and comorbidities, such as mild RI, anemia, DM, COPD or previous stroke.[143]

1.8 Aetiology/Peculiarities of AHF in sub Saharan Africa

The scourge of HF has been recognized in SSA for the past 60 years. [144] As previously mentioned, recent studies from SSA have shown that HF is mainly due to non-ischaemic causes, like HHD, RHD and heart muscle disease caused by infectious or unknown agents. This includes region-specific cardiomyopathies such as EMF; peripartum cardiomyopathy (PPCM) and cardiac manifestations of HIV include forms

of HIVAC. [82,98,145] Additionally, the contribution of cor pulmonale and pericarditis to about 20% of cases of HF reflects the continuing impact of tuberculosis on heart disease on the continent.

Table 1.8[146] shows a comparison of causes of HF from various studies in sub Saharan Africa. Details of each of the causes will be discussed in the section on various causes of HF in the region.

Table 1.8 Comparison of the causes of heart failure from studies in sub-Saharan Africa (modified from Ogah et al. 2014)

Study/Authors/Reference	Country	N	Women (%)	Mean Age	HHF (%)	DCM (%)	VHD (%)	RHF (%)	IHD (%)	LOS (days)	Mortality (%)
THESUS HF[36]	Sub Saharan Africa	1006	50.7	52.0	45.4	18.8	14.3	NR	7.7	7.0	4.2
Stewart et al[147]	South Africa	844	57	55.0	33.3	35.3	7.9	14.3	7.9	NR	NR
Ogah et al[146]	Nigeria	452	45	56.6	78.5	7.5	2.4	4.4	0.4	11.0	3.8
Laabes et al[148]	Nigeria	102	68.6	44.8	44.1	21.6	22.5	NR	1.0	NR	NR
Ojji et al[149]	Nigeria	315	49.1	50.6	62.6	13.8	7.4	1.8	NR	NR	NR
Oyoo & Ogola[150]	Kenya	91	51.6	NR	13.2	25.2	32.0	NR	2.2	NR	NR
Kingue et al[95]	Cameroun	167	40.7	57	54.5	26.3	24.6	NR	2.4	NR	NR
Soliman & Juma[151]	Malawi	3980	39.9	58.9	24.0	19.0	34.0	NR	0.08	NR	NR
Habte et al[152]	Ethiopia	781	47.6	43.5	24.2	20.2	32.8	3.8	12.0	NR	NR
Amoah & Kallen[93]	Ghana	572	NR	42.0	21.3	16.6	20.1	NR	10.0	NR	NR
Onwuchekwa & Asekomeh [153]	Nigeria	423	42.8	54.0	56.3	12.3	4.3	2.1	0.2	NR	NR
Kuule et al[154]	Uganda	157	66.2	45.0	25.1	27.3	28.2	NR	1.9	NR	NR
Ogah et al[155]	Nigeria	1441	48.4	54.0	56.7	3.0	3.7	1.6	0.6	NR	NR
Tantchou et al[156]	Cameroun	462	42.9	42.5	15.0	32.0	35.0	8.0	NR	13.0	9.2
Karaye & Sani[157]	Nigeria	79	44.3	46.9	57.0	24.0	12.7	2.5	7.6	NR	NR

DCM = dilated cardiomyopathy; HHF = hypertensive heart failure; IHD = ischemic heart disease; LOS = length of stay in hospital; NR = not reported; RHF = right heart failure; THESUS-HF = The Sub-Saharan Africa Survey of Heart Failure; VHDX = valvular heart disease.

1.8.1 Hypertensive Heart Disease (HHD)

The diagnosis of hypertension is based on an arbitrary cut off point for a measure that has a continuous and graded relation across its whole range with the risk of various CV diseases.[158] In addition, 50% of the disease burden attributable to high BP relates to values below this arbitrary cut off point.[159] Hypertension was therefore defined as the level of BP for which investigation and management do more good than harm. In most national and international guidelines the threshold for the diagnosis of hypertension is a SBP measured in a clinic or office of at least 140 mm Hg, a diastolic blood pressure (DBP) of at least 90 mm Hg, or both. [160,161] The latest data from the GBD project showed that raised BP continues to be the biggest single contributor to the GBD and to global mortality, leading to 9.4 million deaths each year.[162]

Hypertension in SSA however has some important peculiarities. Many of studies done, looked at the general prevalence, not providing information on age specific prevalences. This is very important because African patients are younger and have very severe BP. Secondly, more studies are done in urban centres or tertiary hospital in big cities than in rural communities. The high general prevalence, the rising incidence of hypertension as well the premature mortality calls for more research into the details of hypertension on the continent.

A recent review by Ogah et al revealed the prevalence of hypertension in the two national studies from SSA, was about 31% (35.7% and 37% in men and 37% and 29% in women in Mozambique and Malawi, respectively). They also found that, in rural areas, the prevalence ranged from 16% in rural Rwanda to as high as 46.4% in a rural community in Eastern Nigeria. The values for urban studies ranged from 15.2% in the Democratic

Republic of Congo to as high as 47.5% in Cameroon.[163]

In their review, Twagirumukiza et al[164] published the estimates of the current and projected prevalence of hypertension in SSA from population based studies in the region. The overall prevalence of hypertension in SSA for 2008 was estimated at 16.2% (95% CI 14.2% to 20.3%). The estimated number of hypertensive individuals in the region was put at 74.7 million (95% CI 65.2 to 93.4 million). Furthermore, the overall prevalence of hypertension in SSA when adjusted to the WHO standard population was 23.3%. They predicted a 68% increase in numbers affected between 2008 and 2015. [199]

In SSA, hypertension commonly manifests in Africa with HF, stroke and chronic kidney disease (CKD). [165] Africans also tend to present late, develop more severe hypertension compared to other ethnic groups and more resistant to treatment, [166,167] often leading to HHD and HF.

HHD is the cardiac damage related to chronic systemic arterial hypertension. It has been documented that some genes are implicated in the development of cardiomyocyte hypertrophy in patients with hypertension which affect intracellular signaling, degradation of normal extracellular collagens and contractile dysfunction among other functions ultimately leading to left ventricular hypertrophy (LVH) and HF. [168] There is also the possibility that these genes interact with environment as seen in black Americans whereby weight gain, high salt intake and psychosocial factors may facilitate the rapid development of hypertension and HHD in susceptible individuals. [169] The presence of LVH adversely affects the prognosis of patients with arterial hypertension. In the Framingham Study, CV mortality among patients with arterial hypertension and increased LV mass measured by echocardiography was double in comparison with patients with normal mass.[170] LVH can be characterized by geometric subtypes, based on

LV mass indexed to body size (LVMI) and relative wall thickness (RWT), which further refines CV risk assessment.

HHF consistently ranks in the top three causes of HF from all regions of the continent (Table 1.9). It is diagnosed in the presence of symptoms of HF, past or presently documented high BP and evidence of LVH (by electrocardiogram (ECG) or echocardiogram).

Ojji and colleagues[171] compared 1515 consecutive HF patients with 4626 patients from the Heart of Soweto project. [82] They showed that hypertension contributed 60% of all cases presented with HF in Abuja versus 33% in Soweto. On an age- and sex-adjusted basis, compared with the Soweto cohort, the Abuja cohort were more likely to present with a primary diagnosis of hypertension (adjusted OR 2.10, 95% CI 1.85–2.42) or HHD/HHF (OR 2.48, 95% CI 2.18–2.83); $P < 0.001$ for both. In the Heart of SOWETO study, HHF (682/1196 – 57%, mean age 60 ± 14 years) was the most common manifestation of HHD among African women with diagnosis of hypertension. [172] Table 1.9 above showed the contribution of HHD to HF from 16 HF studies in SSA.

1.8.2 Dilated Cardiomyopathy (DCM)

DCM competes with HHD and RHD as leading causes of heart failure in SSA. [173] Across the region, DCM accounts for 3 – 35 % of causes of HF (Table 1.9). [146] DCM occurs commonly in the third and fourth decades of life, with men affected twice as commonly as women. Two-thirds of African patients with DCM, especially those who are more than 55 years of age, have persistently low arterial blood pressure, ventricular arrhythmias and/or atrioventricular valve incompetence and die within five years of their first symptom. [174,175] While there are no population-based studies on the epidemiology of

DCM in SSA, hospital series reveal that DCM accounts for 20% of admissions to African hospitals for heart failure. [176] DCM has a 4-year mortality of 34% after onset of symptoms. [177]

Studies from Europe and North America have long suggested that 20–50% of patients with DCM may have familial disease. [178] More than 40 genes have been identified with the most common mode of inheritance being autosomal dominant. [179] Khogali and colleagues from South Africa have shown an association with HLA-DR1 and DRw10 antigens as well as a common mitochondrial polymorphism with idiopathic DCM. [180] Also from South Africa, Ntusi et al[181] were the first to determine the frequency and probable mode of inheritance of familial DCM in patients referred for investigation of the cause of DCM at a tertiary centre in Cape Town. They found that familial DCM affected at least a quarter of African patients with DCM, presented at a young age compared with idiopathic DCM (mean age of presentation 28 vs 39 years), was associated with PPCM in 7% of cases, and followed an autosomal dominant pattern of inheritance in the majority of families. These findings extend the recommendation for family screening for familial DCM in all cases of unexplained DCM, including patients with PPCM, to African patients with the disease. [182]

A genetic association of the β1- and α2c-adrenoreceptor variants and G308A polymorphism of the tumour necrosis factor (TNF) α gene with idiopathic DCM and the mitochondrial DNA T16189C polymorphism has been show to occur in African populations. [183] These associations were noted with regard to the aldosterone synthase gene and improvement in LVEF in DCM and the mitochondrial DNA T16189C polymorphism in addition to the HLA variants in increasing the risk of DCM. [35] There has been no clinical or histological criteria, other than family history and careful

examination of relatives, to distinguish familial from non-familial DCM on the basis of phenotype. [184] Myocarditis is an etiologic factor for DCM in up to 24% of cases and is associated with autoimmune disorder. [185] Auto-immune mediated myocarditis due to inappropriate immunologic responses has been identified as a possible precursor of DCM in SSA. [184] Commonly reported infective agents include toxoplasmosis and coxsackie viruses though this is not a consistent finding in studies where serology is used to diagnose the infections.[185,186]

Echocardiography allows the evaluation of cardiac chamber sizes and wall thickness as well as systolic and diastolic function. It is one of the most important tools to rule out other causes of HF such as valvular heart disease, pericardial effusion or other cardiomyopathies. With DCM being a heterogeneous group of heart muscle diseases of diverse etiologies, idiopathic DCM is diagnosed after investigating and ruling out possible causes. HIV testing is usually indicated in any patient presenting with DCM owing to its high prevalence. Serum viral antibody testing is occasionally done but the yield is low. [187] Based the clinical profile of the patient, investigations for connective tissue diseases may need to be carried out. Similarly, endomyocardial biopsy should be considered when a specific diagnosis is suspected that would influence therapy.[52]

Ntusi et al[188] have followed-up 120 patients with familial and idiopathic DCM over 14 years at a tertiary centre in Cape Town. A mortality of 10% per year occurred in both familial and idiopathic DCM. The presence of NYHA functional class III and IV symptoms was an independent predictor of mortality, while heart transplantation was an independent predictor of survival. Digoxin use was a significant predictor of mortality in idiopathic DCM, which has reopened the controversy on the value of digoxin for HF. [189] A recent meta-analysis of the contemporary literature indicates that digoxin therapy

particularly without proper serum level control is associated with an increased mortality risk in patients with AF and with CHF. The sensitivity analysis of the authors, however, suggests negative effects of digoxin particularly in the AF population but somewhat less unfavourable effects in the CHF population. [190] This calls for randomized trials of dose-adjusted digoxin therapy at least in CHF patients. Until such proper randomized controlled trials are being completed, digoxin should be used with great caution (including monitoring plasma levels), particularly when administered for rate control in AF.[190]

1.8.3 Peripartum Cardiomyopathy (PPCM)

PPCM was thought to be a variant of idiopathic DCM that was unmasked by the haemodynamic stress of pregnancy, [191] but it now considered an independent disease, whose diagnosis relies on its relation to pregnancy and the exclusion of other cardiomyopathies. [192,193] The disease is heterogeneous and seems to have important phenotypic variations in different geographical regions; and is associated with high morbidity and mortality. [194] Recent observations from Haiti suggest that a latent form of PPCM without clinical symptoms might exist with asymptomatic systolic dysfunction on echocardiography, which subsequently either develop clinically detectable DCM, or improve and completely recover heart function. [195]

It seems likely that women of reproductive age all over the world have some risk of developing PPCM. The regions with potential hotspots are Africa (1:100 to 1: 1000) and Haiti (1:299). [35,194,196-198] PPCM shares many common features with other forms of non-ischaemic cardiomyopathy. [176] The important distinction is that women with PPCM are younger, have a higher rate of spontaneous recovery of left ventricular function, and have a better survival than patients with idiopathic cardiomyopathy. [199,200]

Although the patho-mechanisms that lead to PPCM are still evolving, a number of contributing factors have received attention. These include general risk factors for CVD such as hypertension, diabetes, smoking as well as maternal age, gravidity and parity, African decent toxemia, malnutrition, and tocolytics (Figure 1.4). [201] A role for infectious agents, in particular cardiotropic enteroviruses, has been implicated in PPCM because selected studies have found the presence of viral transcripts in cardiac tissues of patients with PPCM. [202,203] In contrast, the presence of HIV infection seemed not to have an additional adverse effect on patients with PPCM. [185]

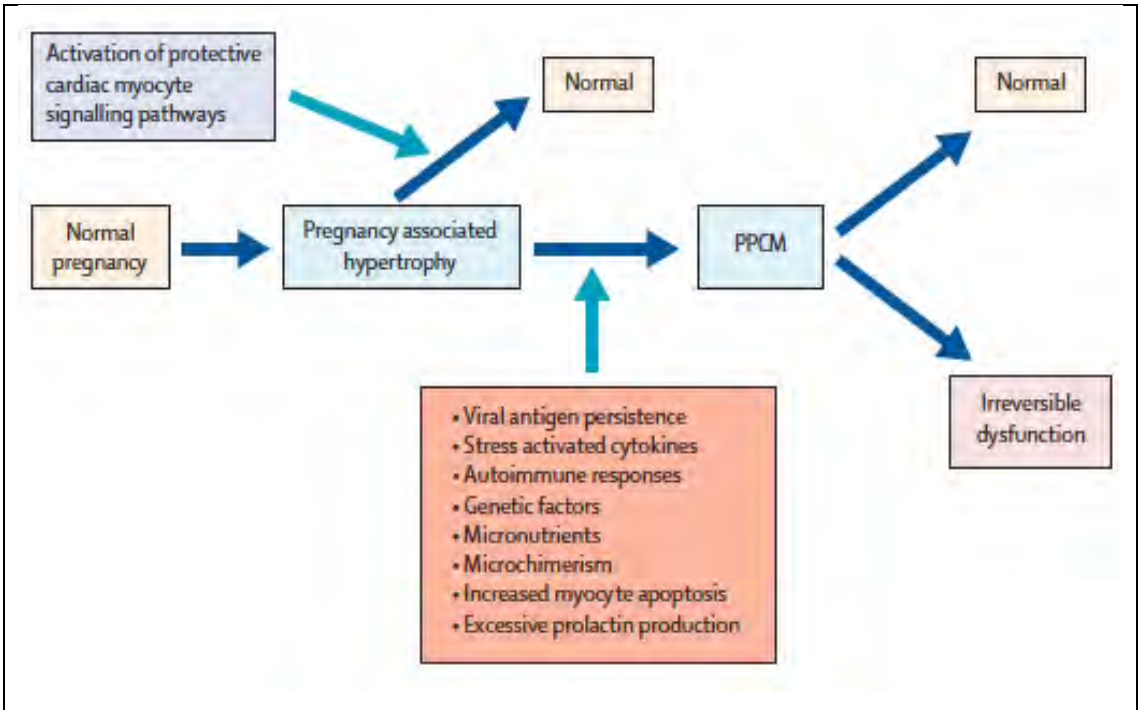

Figure 1.4 Some of the factors contributing to the pathogenesis of PPCM (adapted from Sliwa et al. 2006)

The higher incidence of PPCM in certain geographic areas, that is, sub- Saharan region of Africa, South Africa, and Haiti, emphasize the involvement of genetic factors and/or cultural habits. Genetic components gain importance after reports of PPCM in a mother

and her daughter in Haiti[204] and observations of PPCM in sisters in South Africa and in Germany. [205] Indeed, subsets of PPCM patients are carriers of mutations associated with familial DCM forms. [206-208] While PPCM has been described as a non-familial and non-genetic form of HF, the reality shows that it is not easy to distinguish non-genetic PPCM from genetic forms of peripartum HF and therefore careful familial history should be taken in all PPCM patients.

Cultural habits may be associated with increased risk for PPCM, for example, in northern Nigeria with 1 PPCM in every 100 women. [209] This observation of increased frequency in Nigeria was believed to be as a result of volume overload due to ingestion of "kanwa", a high sodium containing dried lake salt and lying on heated mud beds twice daily for 40 days postpartum.[209]

Several other factors have recently been found to play key roles in the pathophysiology of PPCM. Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and a biological system's capacity to detoxify ROS or repair the resulting damage. The level of oxidative stress rises during pregnancy, and late pregnancy is associated with the formation of particles that are susceptible to oxidation (high LDL-cholesterol level) and an increase in oxidative damage. [210] However, in normal pregnancy, increased ROS production is paralleled by an increase in antioxidant capacity, with an early postpartum peak in healthy women. [210] A compromised antioxidant defense system results in a shift towards increased oxidative stress, which predisposes to PPCM.[211,212]

PPCM, being a disease of late pregnancy and early postpartum, might be triggered by factors specifically present in the late-gestational period like the nursing hormone pro-lactin which is secreted in large quantities in this period. [213] Prolactin can exert opposing

effects on angiogenesis depending on proteolytic processing of the potentially proangiogenic, full-length, 23 kDa form of the hormone into an antiangiogenic, 16 kDa derivative.[213] This prolactin variant is generated from full-length prolactin by cathepsin D[214] or other proteolytic enzymes, such as matrix metalloproteinases (MMPs). Studies have shown that the serum level of MMP-2 is significantly higher in women with PPCM than in matched pregnant controls and the MMP-3 level was substantially increased in the hearts of mice with PPCM as a result of cardiomyocyte-specific knockout of *Stat3* (*Stat3*–/–).[211,215] Interestingly, lowering of oxidative stress in mice provided only partial rescue from PPCM, whereas blocking prolactin with bromocriptine completely prevented the onset of PPCM.[211] It is known that 16 kDa prolactin enhances endothelial inflammation by promoting leukocyte adhesion to endothelial cells.[216] It is also known to activate nuclear factor kappa beta (NF-κB) signalling in endothelial cells and thereby up regulates microRNA-146a (miR-146a), which mediates most of the adverse effects of 16 kDa prolactin in endothelial cells.[217]

The role of inflammation in PPCM has also been investigated. It has been observed in a cohort of African women with PPCM that increased levels of prolactin and IFN-γ correlated with both a sustained inflammatory state and poor prognosis.[215] In addition, both prolactin and IFN-γ might contribute to the pathology of PPCM, because they up-regulate the proinflammatory C–C motif chemokine 2 (CCL2) also induced CCL2 expression in cardiomyocytes, which was mediated via activation of Akt signalling.[218] Akt activation might be protective for the maternal heart during pregnancy, but needs to be down-regulated in the peripartum phase.

AHF due to PPCM provides a challenge for treating physicians. Moreover, in patients still pregnant, therapeutic interventions need always to consider the health of both the

mother and the foetus. Especially challenging are severe forms of PPCM, as the mortality of these women is quite high. The use of inotropic drugs and mechanical circulatory support devices may be necessary in the initial phase of severe forms of acute PPCM. Many patients, after initial stabilization, recover LV function.[219]

PPCM is sometimes difficult to be distinguished from peripartum discomfort in healthy women. [192,201,220] Therefore, the choice and value of diagnostic tools is critical. In addition to conventional ECG, Echocardiography and Chest X ray, cardiac magnetic resonance imaging (CMR) in the assessment of patients with PPCM has been found to provide valuable information about myocardial structure and right-ventricular function and should be considered in more severe forms of PPCM. [221]

The management of PPCM patients is multi-disciplinary and timely diagnosis and treatment is crucial. Figure 1.5 [219] is a pre-specified protocols of interdisciplinary work-up of AHF during pregnancy.

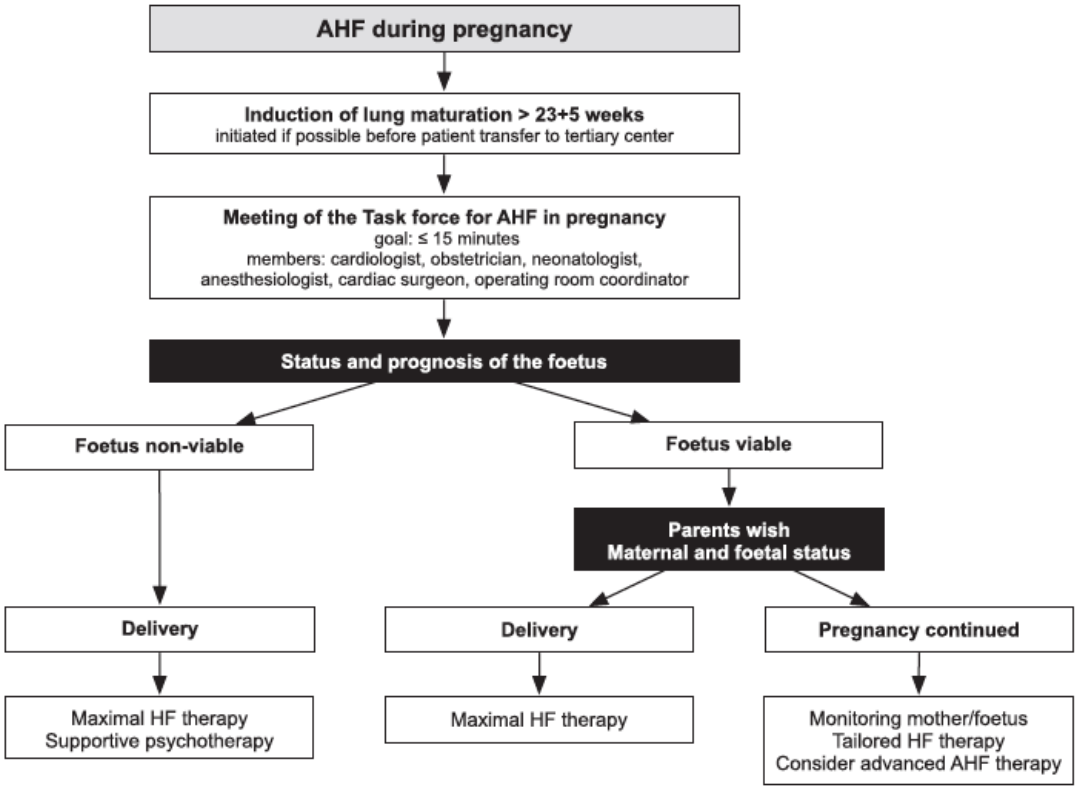

Figure 1.5 A pre-specified protocol of interdisciplinary work up for acute heart failure during pregnancy (adapted from Bauersachs et al. 2016)

Although patients with PPCM have a higher rate of spontaneous recovery of LV function than patients with other forms of non-ischaemic cardiomyopathy, [222] normalisation of LV function at 6 months has been reported to occur in 23–54% of patients. [199,223] Factors predicting poor outcome in African patients with PPCM are increased LV systolic dimension, lower body mass index (BMI) and low serum cholesterol at presentation, while older age and smaller left ventricular end systolic diameter (LVESD) appear to be independently associated with a higher chance of LV recovery. [224]

There are novel therapeutic concepts that have evolved in PPCM over the last decade. A pilot study in South Africa reported highly beneficial effect of the prolactin-blocker bromocriptine on top of HF medication in patients with acute onset PPCM. [201,225] There is a need for a full-scale trial that is adequately powered to study the effect on maternal

mortality and childhood outcomes in the resource-poor environment of Africa.

PPCM patients have an increased risk for sudden death and seem to benefit from ICD and CRT. [215,223,226]

1.8.4 Rheumatic Heart Disease

In the developed world, valvular heart disease is usually degenerative, afflicts the elderly, is insidious in onset and is frequently associated with other comorbidities; whereas, in SSA, valvular heart disease is encountered in the young, not infrequently in children of school-going age or in young females of child-bearing potential and with a course that is more rapid. [227] Recurrent pharyngeal infections with group A beta- hemolytic streptococci and subsequent acute rheumatic carditis predispose to the development of RHD. RHD remains the leading cause of acquired heart disease among the young worldwide.[34,228]

It has been projected that more than 15 million people suffer from RHD worldwide, [34,229] which is likely a significant underestimation according to the increasing data on subclinical RHD. [230] Historically, SSA has had the greatest prevalence of clinically detected RHD, ranging from less than 1 to 14 per 1000. [228,231-233] Since the first report of echocardiography as a potential screening tool, [234] surveys were carried out in Mozambique, and subsequently in Uganda and Senegal. [231,233,235,236] All these studies demonstrated that echocardiography detects a significant additional number of children with clinically silent RHD, estimated to 7.5–51.6 per 1000 children.[34]

Whereas Africa has 10% of the world's population, as many as half of the 2.4 million children affected by RHD globally live on the continent. RHD accounts for a major proportion of all CVD in children and young adults in African countries and for 17-43%

of all cardiovascular disease in SSA. [237] The disease causes 400,000 deaths annually, mainly among children and young adults living in developing countries[238] At least 2 million patients with RHD require repeated hospitalizations and 1 million needing often unaffordable, heart surgery in the next 5-20 years. [239]

A large multinational African study demonstrated that RHD prevails as the most frequent cause of HF among children and young adults, and importantly that the 180-day mortality is as high as 17.8%.[36] The GBD Study reports that the number of years lived with disability due to RHD was estimated in 2010 at 1430 (944–2067) worldwide, a figure that represents up to a fourth that from all neoplasms. [73] Hospital-based studies reported that RHD accounts for 6.6–34.0% of CVD-related hospital admissions or echocardiographic examinations performed in several institutions across the continent.[37,97,151,156,240,241] Further data are needed to assess the social and economic impact of RHD in sub-Saharan countries.

RHD has been documented to be relatively frequent among pregnant women (up to 2.3%), although symptomatic forms remains more rarely encountered. [242] Furthermore, recent data emphasise that pregnancy in patients with RHD remains a challenge bearing high morbidity and mortality, requiring multidisciplinary antenatal and postnatal care. [243]

The recently published Global Rheumatic Heart Disease Registry (REMEDY) enrolled 3343 patients (median age 28 years, 66.2% female) presenting with RHD at 25 hospitals in 12 African countries, India, and Yemen between January 2010 and November 2012. The majority (63.9%) had moderate-to-severe multivalvular disease complicated by congestive cardiac failure (CCF) (33.4%), PH (28.8%), AF (21.8%), stroke (7.1%), infective endocarditis (4%), and major bleeding (2.7%). One-quarter of adults and 5.3% of children had decreased LV systolic function; 23% of adults and 14.1% of children had

dilated LVs. Among 1825 women of childbearing age (12–51 years), only 3.6% (n. 65) were on contraception.[244]

Rapid progression and symptomatic presentation of RHD is the rule more than the exception in SSA. [231,233] Even with severe mitral regurgitation, many patients will remain asymptomatic at rest until there is LV failure, PH or the onset of AF. The most recent guidelines for diagnosing RHD recommend using echocardiography and incorporating morphologic criteria as well as Doppler-based assessment of regurgitant flow. Presumably, these expanded criteria offer the possibility of correctly identifying more subclinical disease in time to prevent progression to clinical RHD but there is no empiric evidence to support this assumption. The World Heart Federation (WHF) guidelines categorize findings into three categories - definite RHD, borderline RHD and normal – with different criteria for those above and below 20 years of age.[230]

Medical therapy for RHD is largely preventive or prophylactic for complications. South African guidelines suggest that in communities where rheumatic fever is endemic, all cases of sore throat among children between 3 and 15 years of age should be regarded and treated as streptococcal infection unless there are signs suggesting otherwise (i.e., oral ulceration, hoarseness, watery nasal discharge and/or conjunctivitis). [245]

Although research in vaccines using highly conserved antigens and 30-valent N-terminal region remains active, [246-248] no vaccine is scheduled for phase 2 clinical trials in the foreseeable future. The high heritability and ongoing research on genetic susceptibility may be particularly helpful for a better understanding of the pathogenesis of acute rheumatic fever (ARF) and may guide vaccine development.[249]

Sadly, RHD diagnosis in SSA is usually made at an advanced stage of the disease, when severe valve lesions become symptomatic, and significant intervention is indicated. [250]

However, percutaneous mitral dilatation, closed heart mitral commissurotomy and open heart surgery are limited to a few centres in Africa. [34] Valve replacement presents a dilemma due to the generalised lack of adequate facilities for anticoagulation. Recent experience from Senegal evaluated the mid-term outcome of mitral valve repair in children, demonstrating encouraging results, dependent on careful patient selection and evaluation of lesions. [251] Findings from South Africa confirm superior long-term outcome in patients who underwent mitral valve repair while also demonstrating reasonable long-term results for mitral valve replacement in an indigent population.[252]

1.8.5 HIV Associated Cardiomyopathy

HIV associated cardiomyopathy (HIVAC) is a significant contributor to morbidity and mortality in SSA and portends a particularly poor prognosis. [253] The reported prevalence of cardiomyopathy in HIV infection from post-mortem studies in the pre-HAART era varied from 2% to over 40%.[254] In developed countries, highly active anti-retroviral therapy (HAART) has been associated with ~50% reduction in HIVAC, [255] possibly related to a reduction in opportunistic infections and myocarditis. By contrast, in developing countries, where the availability of HAART is limited and the potential pathogenic impact of nutritional factors is significant, there is ~32% increase in the prevalence of HIVAC and a related high mortality from CCF. [256] Nevertheless, studies from Africa have reported low rates of HIVAC in series with high uptake of HAART, such as a recent study suggesting that, with appropriate implementation of antiretroviral therapy, this rising trend can be challenged. Although the true prevalence in Africa is not known, echocardiographic studies of HIV-infected patients found varying prevalence in different countries, ranging from 5% in Nigeria to as high as 57% in Burkina Faso. [257-259]

In the Heart of Soweto Study, which defined cardiomyopathy as LVEF ≤45% in the absence of CAD, it was the most common cause of de novo CVD in patients with HIV (38%) presenting to Chris Hani Baragwanath Hospital in South Africa. [260]

There is a wide range of hypotheses regarding the pathogenesis of HIV-associated cardiomyopathy. [145,261-263] These include the direct results of myocardial invasion with HIV itself, post-viral autoimmunity and immune system dysregulation, adverse effects of viral proteins (including apoptosis), interference with β-adrenergic stimulation, endothelial dysfunction, and transcriptional activation of cellular genes. In addition to these effects of HIV and related immunosuppression, there is evidence that certain antiretroviral therapies may be responsible. Nucleoside reverse transcriptase inhibitors (NRTIs) are known to cause mitochondrial DNA damage through inhibition of mitochondrial DNA polymerase, with zalcitabine (ddC) exhibiting the greatest toxicity and associated with an 80% higher incidence of cardiomyopathy. [255] In a recent review, HAART has been shown to be widely available in SSA and the cardiac effects of HAART could lead to HF. [264]

Malnutrition has been postulated to be a contributory factor of HIVAC in Africa. In a recent study, patients with HIVAC had evidence of under-nutrition compared with HIV-infected people without cardiomyopathy (body mass index 20.9 vs 27.0 kg/m2, p=0.02), and a lower BMI was the only independent anthropometric risk factor for cardiomyopathy (OR 0.76, 95% CI 0.64 to 0.97, p=0.02).[265]

The role of genetic factors in HIVAC is largely not known. The mitochondrial DNA T16189C polymorphism, with a homopolymeric C-tract of 10–12 cytosines— a putative genetic risk factor for idiopathic DCM in the African and British populations—was not associated with HIVAC in a South African case– control study. [266]

The role of HIV infection as a risk factor for PPCM is not known. In a study of pregnant Ugandan women in their third trimester and without signs of HF, HIV infection was not associated with any of the seven pre-specified echocardiographic signs of cardiomyopathy. [267] However, in recent publication, Sliwa et al[223] demonstrated that HIV-infected women, despite having mild to moderate immunosuppression, have a similar 2-year prognosis to uninfected women with PPCM in South Africa.

The link between HIV and HF in the HAART era has been described in high-income countries (HICs) in the last decade. [268,269] A meta-analysis of 11 studies of HF in HIV-positive patients showed a prevalence of 8.3% for systolic dysfunction and 43.4% for diastolic dysfunction. [270] HIV causes damaged myocardium directly and also indirectly through inflammation and increased susceptibility to infections, toxins, and, eventually, ischemia. The endothelium serves as a reservoir of HIV and also acts to elaborate cytokines, such as TNF and interleukin-6 (IL-6), and free radicals in response to increased inflammation (Figure 1.6). [271]

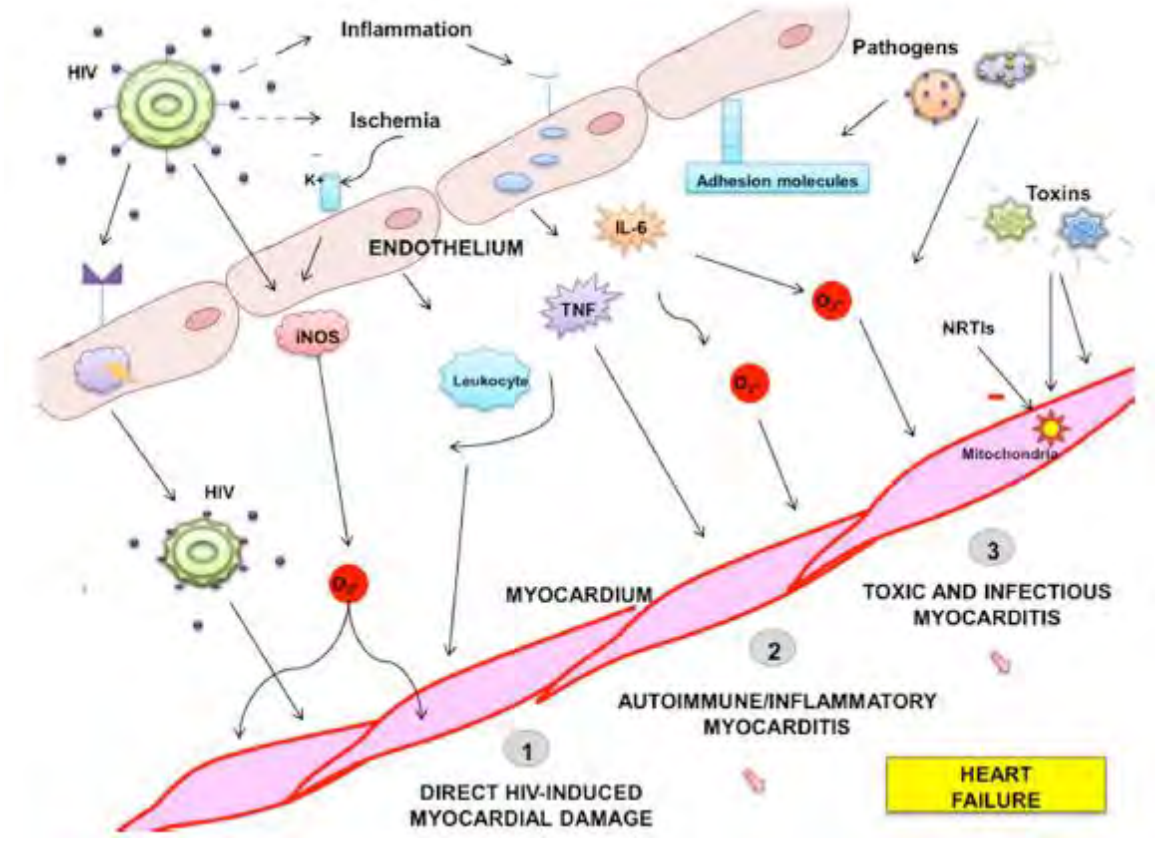

Figure 1.6 Pathophysiology of HIV associated heart failure (adapted from Remick 2014)

Data from most of the LMICs implicating HIV as a cause of HF were generated before the widespread availability of HAART in LMICs. During this era, systolic HF was commonly reported in association with HIV; however, diastolic dysfunction was also documented in a large proportion (86%) of asymptomatic HIV-positive patients. [272]

Studies in the HAART era demonstrate that cardiomyopathy is still a relevant form of HIV-associated CVD. [33] Systolic dysfunction remains the most commonly investigated form; however, diastolic dysfunction is concurrent in 21%–46% of HIV-positive patients with cardiomyopathy depending on the clinical presentation.[260]

The clinical presentation, chest X-ray, ECG and echocardiography of HIVAC in symptomatic patients are generally similar to cardiomyopathy due to other causes. The

use of dobutamine stress echocardiography was found to be of incremental value to NYHA class in risk-stratifying risk of cardiac death in patients with HIVAC. [273] With less contractile reserve, there was a sevenfold increase in risk as well as less improvement in LVEF with standard cardiac medication and HAART. BNP may be a useful screening tool for underlying structural heart disease. A study of HIV-infected patients demonstrated higher levels of BNP with HF, cardiomyopathy and CAD. [274]

In addition to the conventional therapy of HF, other therapies such as immune suppressants and selenium supplementation have been suggested. ACEI may be poorly tolerated because of low systemic vascular resistance from diarrhoeal disease, infection or dehydration. Patients with myocarditis have enhanced sensitivity to digoxin, and anticoagulation presents risks to patients with cerebral vasculopathy and possible aneurysm formation. [261] Although HAART has not been shown to conclusively reverse or improve cardiac function once cardiomyopathy is established, there is prevention of deterioration, [145] although data from small series suggest that some patients may experience improvement on echocardiography. [275] While heart transplantation has been successfully performed in an HIV-infected patient with advanced cardiomyopathy, [276] this treatment is not readily available in a resource-poor setting such as SSA.

1.8.6 Ischaemic Heart Disease (IHD)

SSA, similar to many parts of rural India and South America, is mostly in the earliest stage of the epidemiological transition. Data for the existence of an orderly shift from one stage of the transition to the next are incomplete; however, evidence of a changing disease profile with coexistence of infectious diseases, nutritional deficiencies and NCDs is becoming more common. In addition, studies from many urban areas in SSA suggest a

pattern of adverse lifestyle choices and health behaviours that are now leading to a rising prevalence of the major coronary risk factors. [277] This increase in urbanization leads to concomitant rise in the prevalence of hypertension and diabetes. [278]

An important development has been the publication of the first longitudinal study, with the aim of examining the changing pattern of disease at the primary health level, conducted over a 13 year period in Agincourt, a small rural district in South Africa. [279] This study is the first to demonstrate, longitudinally, the changing pattern of disease in an African setting, and shows how a rural area in SSA now has to contend with the twin scourges of communicable disease (mainly HIV and TB) and NCDs (hypertension, stroke, IHD and HHD). Despite the high morbidity and mortality from HIV and TB coinfection, stroke, CAD and HHD increased by 65% in those over 30 years of age, during the study period.

Many previous reviews and reports have highlighted the rarity of CAD in SSA. In a study conducted in 1960, CAD was shown to be 'extremely rare' in Africans, [280] and, in fact, in a later study, Africans were declared to be 'virtually free' from CAD. [281] Between 1992 and 1994, the Chris Hani Baragwanath hospital reported an average of 35 cases of CAD in African patients (prevalence of 0.2%), hence emphasizing the rarity of CAD in urban Africans. [282]

In Nigeria, the spectrum of cardiac disease in patients admitted to public teaching hospitals and the proportion with ischemic heart disease has been recently described by a number of authors. [155,283] Of the 5124 admissions to Aminu Kano Teaching hospital in the 5 years prior to 2005, 1347 had cardiac disease and only 46 (0.9%) had a diagnosis of IHD. [283] Elsewhere in the same country, in a retrospective analysis of the spectrum of heart disease evaluated at a tertiary centre over a 24-month period between 2005 and

2007, IHD was detected in less than 1% of the 992 patients.[155]

At a private hospital with modern cardiac care facilities in Nairobi, Kenya, 5.1% of the admissions to the ICU between 2008 and 2010 had acute coronary syndrome.[284]

Reports from SSA hospitals also indicate that African patients with CAD tend to be younger, with males outnumbering females, and that the clinical and laboratory features and complications of CAD are similar to those in the white population.[285,286]

In the INTERHEART Africa study, hypertension and DM were common risk factors among Black Africans while abdominal obesity, tobacco smoking and dyslipidemia were more common among European Africans. [29] Black Africans in the highest tertile of income had a higher risk of MI than those in the lowest tertile of income. The relationship was reversed among European Africans and did not exist among colored Africans demonstrating important differences with regard to the epidemiologic transition of CVD risk. The authors concluded that known CVD risk factors account for approximately 90% of the CAD observed in the African population, which is consistent with results of the overall INTERHEART study.[11,29]

The reported rarity of IHD in SSA must however be accepted cautiously, as the evidence was not strong enough to confirm that IHD was rare, without accounting for misdiagnoses, limited access to and lack of facilities for making the appropriate diagnosis. [37]

A recently published systematic review on worldwide risk factors for HF by Khatibzadeh and colleagues demonstrated that IHD was a risk factor for HF in more than 50% of patients in Western high income regions, as well as Eastern and Central European

regions. In Sub-Saharan Africa IHD contributed less than 10% to heart failure. [287]

More recently, the aetiological spectrum of 1006 patients with acute heart failure recruited from 12 cardiology centres in nine countries has been published. Ischemic heart disease was found to be the cause in 7.7% of cases [36] A potential limitation of the study was that coronary angiography was not used, but the results were consistent with the paucity of cases of acute coronary syndromes (ACS) reported in the same regions. [29] The Heart of Soweto Study was designed to determine the aetiological spectrum of clinically apparent heart disease among a predominantly black African population in one of South Africa's largest urban communities. [82] Interestingly, in this contemporary cohort, despite high prevalence of modifiable risk factors for atherosclerosis, of 1593 consecutive patients with cardiac symptoms, presenting for evaluation, only 6% among those identified as black African had a diagnosis of CAD. [82]

The age-adjusted mortality rate provides an alternative measure of the myocardial infarction and stroke-related outcomes in a population. Only South Africa and the Seychelles, two middle-income countries thought to have a comparatively high burden of coronary artery and cerebrovascular disease have provided recent data on this measure of outcome for these diseases. [288] In the Seychelles, the age-adjusted mortality rates for myocardial infarction and stroke have declined substantially over the last two decades. [289] In South Africa, estimates are that the age-standardised IHD-related mortality for the ethnic black majority ranges from 5.3 to 70 per 100 000, 55.1 to 171 per 100 000 in people of mixed ancestry and 165.3 to 230 per 100 000 in the white minority. [16,29] These findings have important implications for projections of the CVD epidemic elsewhere in Africa and the rest of the world.

Although insightful and important, the degree to which the outcome data from these two countries with unique ethnic and racial mixes and relatively high per capita income levels are generalisable to the rest of the continent is questionable.[288]

Recommendations for the treatment of ischemic cardiomyopathy apply worldwide. For the SSA region where access to revascularization is limited, the focus should be on improving the quality of medical therapy in ischaemic Cardiomyopathy. [66]

1.8.7 Pericardial Disease

Acquired heart diseases of the pericardium manifest clinically as acute pericarditis, pericardial effusion or constrictive pericarditis. The latter two cause cardiac compression leading to HF from impaired diastolic filling. Constrictive pericarditis has traditionally been considered as end stage manifestation of persistent pericardial inflammation in which the pericardium looses elasticity through fibrosis and at times with dystrophic calcification.[290]

In Africa, heart disease is still dominated by nonischemic causes such as RHD, HHD, DCM, cor pulmonale, and tuberculous pericarditis. [291,292]

Tuberculous pericarditis, which accounts for a 10th of all patients that are hospitalized for HF in Africa and over two thirds of patients with large pericardial effusion in developing countries, [293] is important to recognize because it is a potentially curable cause of heart disease. [294] Tuberculosis (TB) is said to be the most frequent cause of constrictive pericarditis in Africa and Asia. [294,295] By contrast, tuberculosis is no longer a significant cause of either large pericardial effusion or constrictive pericarditis in industrialized countries. [296,297] Pericardial tuberculosis is a serious form of extrapulmonary tuberculosis that is associated with substantial morbidity and death during treatment of tuberculosis.[298]

The incidence of tuberculous pericarditis in SSA has increased as a result of the HIV epidemic, and this trend is likely to occur in other parts of the world where the spread of HIV is leading to a resurgence of tuberculosis. [299] Pericardial disease was the second most common manifestation of HIV-associated CVD in the Heart of Soweto Study (12.5%),[82] although in other series, it is the most common, such as in a study of 102 patients in Tanzania recruited between 2009 and 2010, in whom 42% had pericardial effusion.[300]

A multicenter prospective study that recruited patients from centers in Cameroon, Nigeria, and South Africa showed marked regional variation in the prevalence of HIV-associated tuberculous pericarditis, with an average of about 50% of patients with tuberculous pericarditis infected with HIV. [301] This is in stark contrast to developed countries, where TB is a cause of only 4% of pericardial effusions.[302]

Hospital-based studies demonstrate that tuberculous pericarditis is a common cause of HF in SSA, being less common than RHD, but more common than HHD and cardiomyopathy in the Eastern Cape Province of South Africa and in Zimbabwe. [303,304] Echocardiography studies of the relative importance of the causes of HF in African hospitalized patients indicate that tuberculous pericarditis accounts for 8-13% of cases in South Africa and Kenya and 3% overall in the SSA region. [150,176,293] In patients with Tuberculous pericarditis, HIV co-infection worsens the prognosis (mortality rates 7% in HIV seronegative patients compared to 40% in HIV seropositive patients).[305]

There are four recognized stages of TB pericarditis and two general modes of clinical presentation (Table 1.9). [306] In the first mode of presentation, pericardial involvement is asymptomatic and is an incidental finding in patients who have evidence of active tuberculosis elsewhere in the body. [307] Evidence for this stems from autopsy findings, which suggest that the pericardium is involved in 1–2 % of HIV uninfected patients

known to have pulmonary TB. [308] Among HIV-infected patients, the proportion of asymptomatic involvement of the pericardium may be much higher. Both autopsy and observational studies show that HIV is associated with a higher prevalence of widespread, multi-site, extra-pulmonary TB. [309-311]

Table 1.9 The Four Stages of Tuberculous Pericarditis (adapted from Reuter et al 2006)

Stage	Pathological manifestation	Clinical manifestation
One	Dry stage (least common)	Acute pericarditis (chest pain, pericardial friction rub and widespread ST elevation without effusion
Two	Effusive stage (most common)	(1) Moderate to large pericardial effusion with symptoms and signs of heart failure and/or cardiac tamponade (2) Effusive constrictive pericarditis with evidence of simultaneous compressive pericardial fluid and visceral constrictive pericarditis
Three	Adsorptive stage	Symptoms and signs compatible with constrictive pericarditis but radiological and echocardiographic evidence of thick fibrinous fluid around the heart
Four	Constrictive stage	Symptoms, signs and echocardiography compatible with constrictive pericarditis with no residual fluid in the Pericardium

The definitive diagnosis of a tuberculous etiology in patients with pericarditis rests on demonstrating the presence of tubercle bacilli in stained smear or culture of pericardial fluid or caseating granulomata on pericardial histology. [312] These include looking for microbiological evidence of TB elsewhere in the body and the use biomarkers like adenosine deaminase (ADA) in patients with an inflammatory pericardial exudate. [312,313] DNA-based techniques such as polymerase chain reaction (PCR) have proved to be very disappointing. The sensitivity is well below 30 % and is particularly poor where pericardial tissue is not available, as is most often the case.[298,314]

Where resources are limited, a chest X-ray may often be the only imaging modality available to the clinician (Figure 1.7). It has been shown that chest X-ray positively identified 53% of patients with pericardial effusion. [315] The amount of fluid drained

correlated with the radiographic finding of cardiac enlargement in this study. The ECG shows ST-segment elevation (in acute pericarditis) that is diffuse, involving both limb and precordial leads. Other ECG findings include PR segment depression and electrical alternans. Echocardiography remains the most sensitive tool for the diagnosis of pericardial effusion by showing an echo-free space around the heart and variable amounts of fibrous strands (Figure 1.8). [316] In addition to measuring the size of the effusion, echocardiography allows for an assessment of any hemodynamic consequences.

Overall, the etiology is determined in only about a quarter of patients. [316] A scoring system, the Tygerberg score, has been validated for tuberculous pericarditis and is currently being utilized in research settings. [317] One point each is allotted for the presence of weight loss, night sweats or fever. Two points are given for fever and three points for either serum globulin >40g/L or blood leukocyte count <10 x 10^9. A score of 6 or greater is highly suggestive of tuberculous pericarditis.

Treatment regimens recommended for pericardial TB are the same as for pulmonary tuberculosis, consisting of 6 months of anti-tuberculous antibiotics. Corticosteroids are frequently prescribed. The effectiveness of systemic steroids in the treatment of TB pericarditis was evaluated in a large multi-centre trial (IMPI Trial) that involved several African countries. [318] There was no significant difference in the primary outcome (composite of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis) between patients who received prednisolone and those who received placebo. Prednisolone therapy, as compared with placebo, was associated with significant reductions in the incidence of constrictive pericarditis and hospitalization, but was associated with a significant increase in the incidence of HIV associated cancer. [318] Non-steroid anti-inflammatory drugs (NSAIDs) remain the cornerstone of treatment of other

forms of pericarditis and colchicine reduces the recurrence rate. [319] Therapeutic pericardiocentesis is usually a life-saving intervention and is essential in patients with cardiac tamponade. Surgery is needed for resection of the pericardium in patients with calcific constrictive pericarditis and after a 6– 8 week trial of anti-tuberculosis treatment in patients with persistent signs of constriction.[320,321]

Figure 1.7 Chest X ray showing a globular heart from pericardial effusion

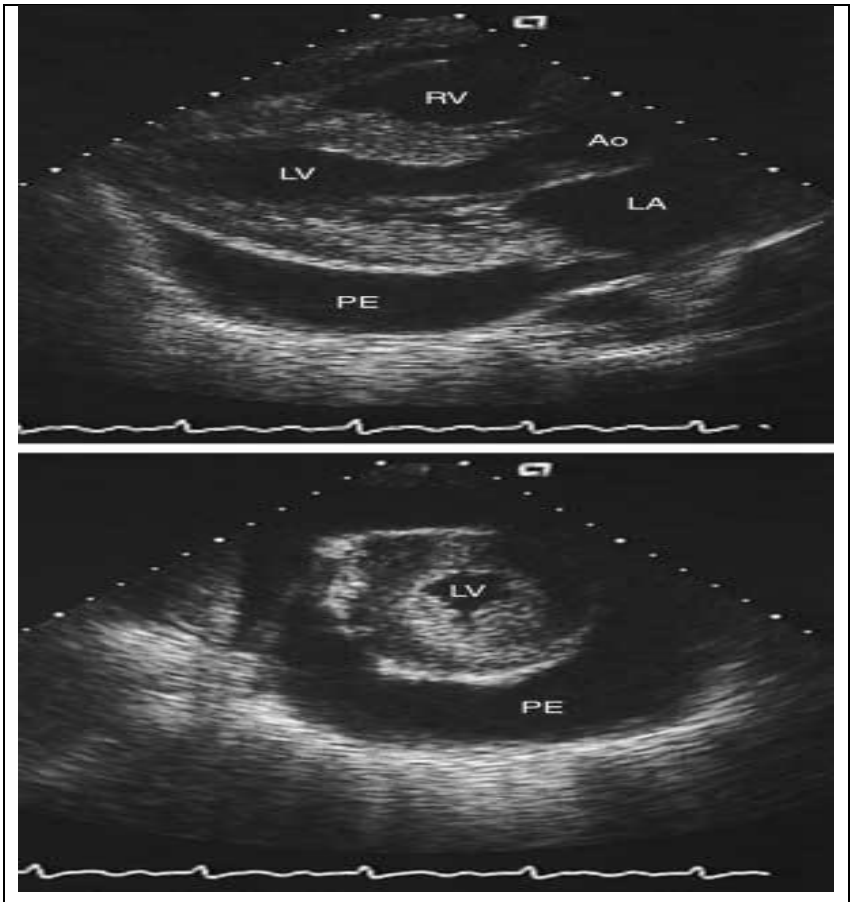

Figure 1.8 Echocardiographic pictures - parasternal long axis view (above) and parasternal short axis view (below) showing pericardial effusion

1.9 Pathophysiology of Acute HF

AHF is characterized by an acute decrease in cardiovascular function associated with pulmonary congestion, injury or end-organ dysfunction, including myocardial damage, worsening renal function, and hepatic impairment (Figure 1.9). [322,323] This multi organ dysfunction has been shown to be an independent predictor of increased mortality in patients with AHF. [110] Signs of unresolved congestion and its most severe manifestation, episodes of worsening HF, are also strong predictors of poor outcomes.[324]

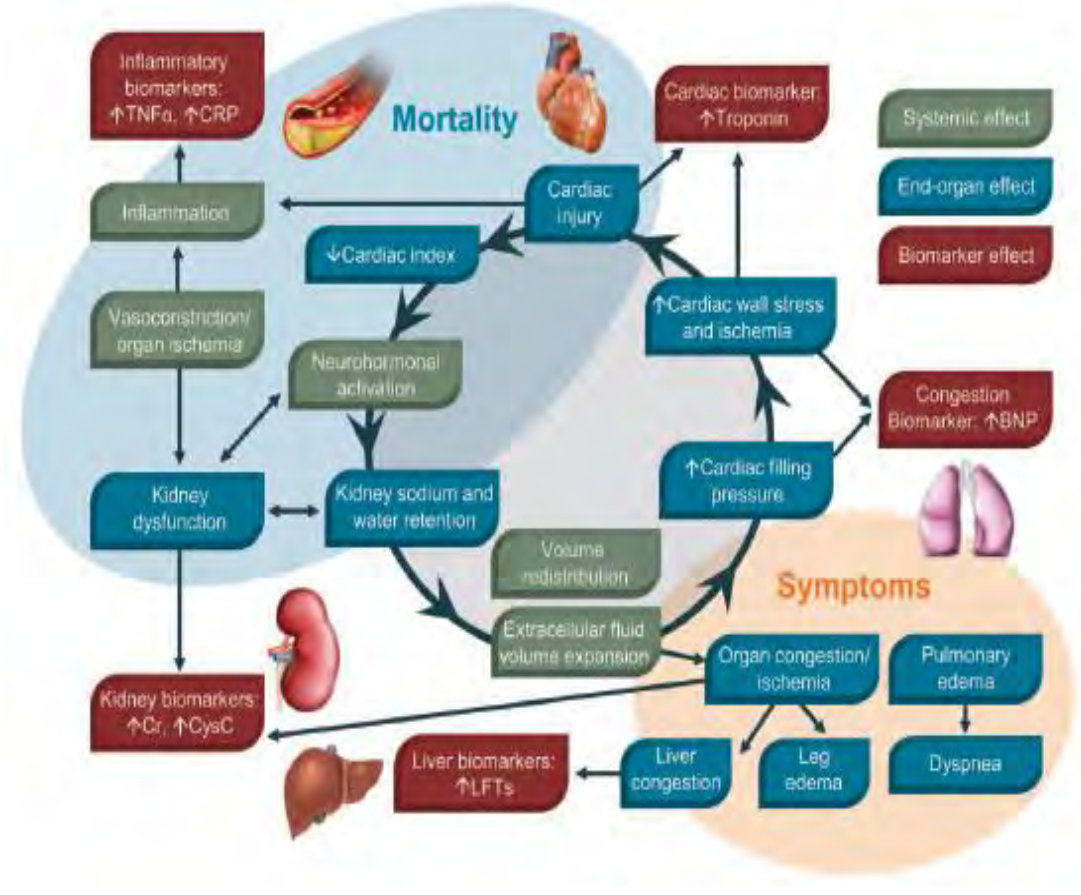

Figure 1.9 Multi-organ system involvement in acute heart failure (adapte from Teichman et al. 2014). BNP, brain natriuretic peptide; Cr, creatinine; CRP, C-reactive protein; CysC, cystatin C; LFTs, liver function tests; TNF, tumour necrosis factor

AHF is a heterogeneous clinical syndrome with complex and variable pathophysiology. It has many overlapping pathophysiologic mechanisms that may be operative in a given clinical scenario to a greater or lesser degree. The pathophysiology of AHF is said to result from the interaction of underlying substrate with initiating mechanisms or triggers, and amplifying mechanisms, all of which contribute to a common set of clinical signs and symptoms (primarily related to congestion or end-organ dysfunction, or both) that define AHF (Fig.1.10).[325] Here, the substrate refers to underlying cardiac

structure and function. The underlying substrate may be one of normal ventricular function, as in patients without a previous history of heart failure in whom AHF develops because of sudden changes in ventricular function from an acute insult such as MI, acute myocarditis or sudden rise in blood pressure. Alternatively, some patients may have no previous history of HF but exhibit an abnormal substrate (e.g., those with stage B heart failure associated with asymptomatic LV dysfunction) with a first presentation of HF (de novo HF). Finally, in most patients with AHF, the original substrate is one of compensated CHF, followed by decompensation with development of AHF.

Regardless of the substrate or initiating factors, a number of "amplifying mechanisms" perpetuate and contribute to the episode of decompensation. These include neurohormonal and inflammatory activation, oxidative stress, ongoing myocardial injury with progressive myocardial dysfunction, WRF, interactions with the peripheral vasculature, as well as factors triggering AHF may include ischemia, hypertension, arrhythmias, non-cardiac comorbidities, and administered drugs. [326] All these contribute to the propagation and worsening of the AHF episode.

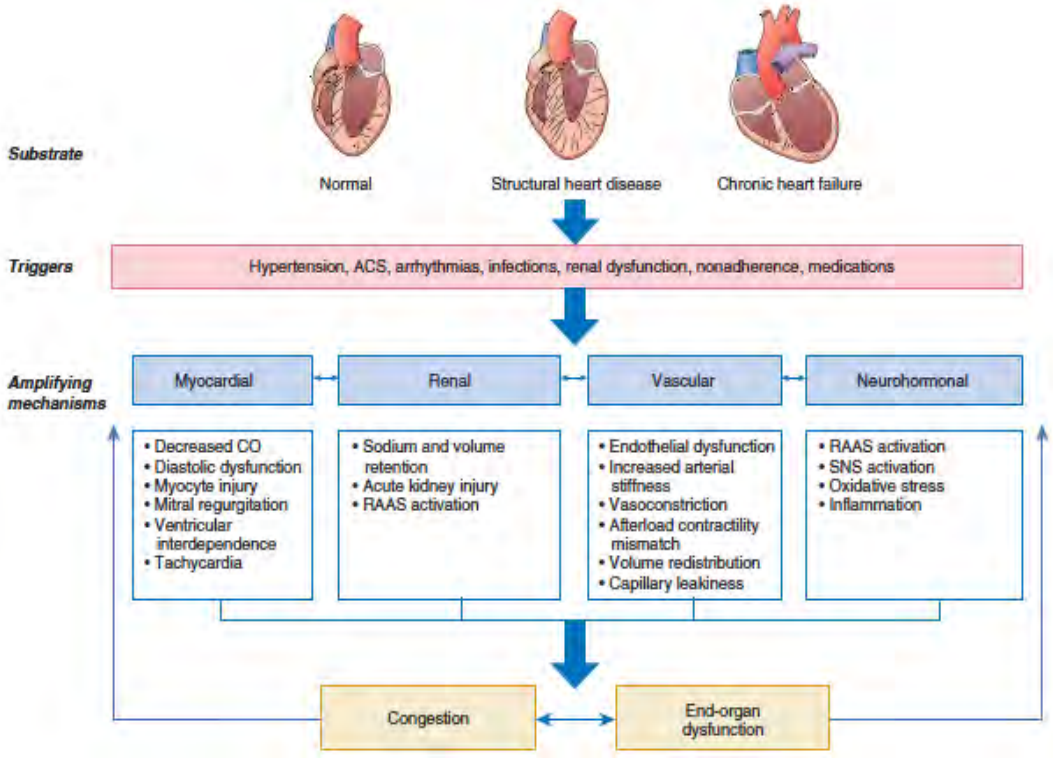

Figure 1.10 Schematic representation of the pathophysiology of acute heart failure (adapted from Felker & Teerlink 2015). ACS, acute coronary syndrome; CO, cardiac output; RAAS, renin angiotensin aldosterone system; SNS, sympathetic nervous system

Injury to cardiac myocytes and the extracellular matrix after myocardial injury results in pathological remodeling of the left ventricle with dilatation, impaired contractility, perfusion, fibrosis and electrical instability. [327]

1.9.1 Neurohormonal Activation, Inflammatory Mediators and Oxidative Stress

Circulatory decompensation is characterized by neurohormonal activation, inflammatory activation and oxidative stress. [326] These are distinct but closely related mechanisms, which are initially compensatory as they improve myocardial performance but only for a limited time. They then become maladaptive and

detrimental, augmenting the circulatory insufficiency and impairing generalized homeostasis. These mechanisms are involved in the progression of heart dysfunction, both during the acute phase of circulatory decompensation, and also afterwards, as their influence far exceeds beyond the episode of AHF and contributes to a steady progression of CHF. [328] Finally, they are considered as strong predictors of poor outcome, being predictors of increased short and long-term mortality as well as of an increased risk of recurrent hospitalizations due to subsequent episodes of AHF. [326]

Neurohormonal activation includes but not limited to, the activation of the renin-angiotensin-aldosterone system (RAAS) , the sympathetic nervous system (SNS), arginine vasopressin (AVP) and the system of NPs. [329] Inflammatory activation leads stimulation of innate immune response with increased expression of pro-inflammatory mediators. [330]

These cascades lead to progressive myocardial dysfunction and associated structural abnormalities, including cardiomyocyte hypertrophy, cardiomyocyte apoptosis, depressed myocardial contractility, inhibited cardiomyocyte responsiveness to b-adrenergic stimulation, fibroblast growth, fibrosis, and remodeling.

On the other hand, myocardial ischemia and necrosis may occur during an episode of AHF as a consequence of a transient reduction in coronary perfusion due to increased left ventricular filling pressure, reduced systemic arterial BP, tachycardia, coronary vasoconstriction and endothelial dysfunction mediated by neurohormonal activation (Figure 1.11). [331]

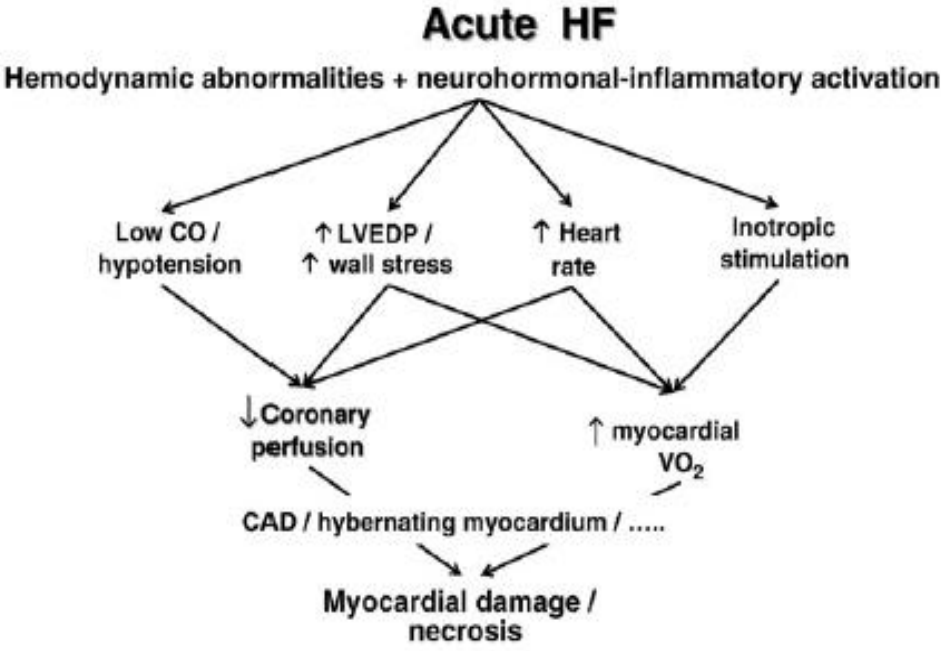

Figure 1.11. Mechanisms of myocardial damage in patients with acute heart failure (adapted from Metra et al. 2010). CO, cardiac output; LVEDP, left ventricular end diastolic pressure; CAD, coronary artery disease; VO2, oxygen consumption.

1.9.2 Renin Angiotensin Aldosterone System (RAAS)

Renin is synthesized by granular cells of the juxtaglomerular apparatus and released by the afferent arteriole in response to decreased mean arterial pressure (MAP), sensed by baroreceptor cells in the arteriolar vessel wall, decreased intracellular chloride levels inside macula densa cells lining the renal tubules at the end of Henle's loop. This is potentiated by potassium depletion; and sympathetic activation. Renin breaks down angiotensinogen secreted by the liver, to form angiotensin I, which is subsequently converted into angiotensin II by the angiotensin-converting

enzyme (ACE), mainly from the pulmonary vasculature (Figure 1.12). Angiotensin II is a strong vasoconstrictor and the most potent stimulator of aldosterone release by the adrenal glands. This system plays a vital role in the pathophysiology of heart failure. [332] Indeed, persistent and excessive RAAS activation causes adverse cardiac remodeling and contributes to fluid retention with signs and symptoms of congestion. For this reason, plasma renin activity (PRA) and plasma aldosterone levels are of potential interest not only as markers of disease severity but also as mediators of heart failure progression. Although their level notoriously variable, they can be accurately measured and reflect the degree of activation of the RAAS.[333]

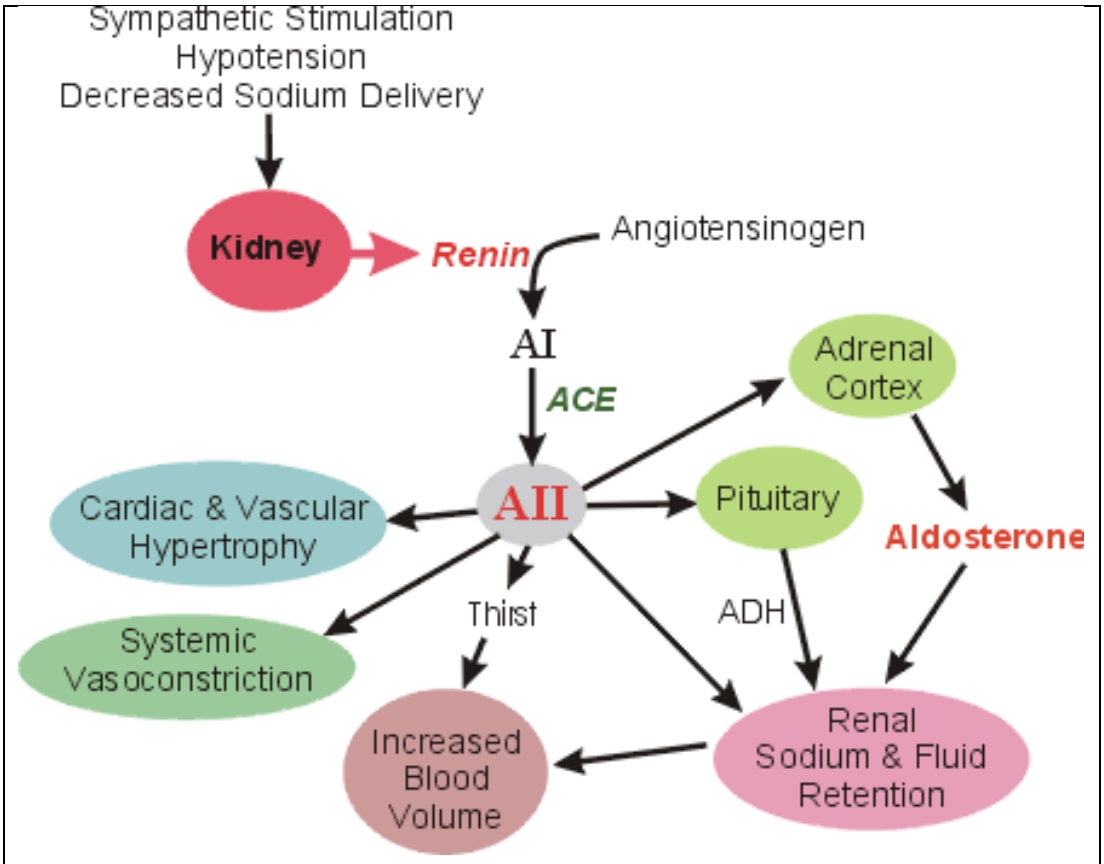

Figure 1.12 Activation of the renin angiotensin aldosterone system (RAAS)

1.9.3 Inflammatory Activation

Evolving evidence suggests that the RAAS and the immune system interact and significantly influence each other in HF in general and AHF in particular. It has been shown that angiotensin II activates NF-κB, the transcription factor responsible for up-regulating numerous inflammatory mediators. [334] In the isolated perfused heart and isolated cardiomyocyte studies, angiotensin II stimulation results in increased TNF-α messenger RNA (mRNA). [335] This effect appears mediated through the AT-1 receptor as evidenced by lack of a similar effect under blockade by the angiotensin II receptor blocker losartan. [336] In a separate study, pretreatment with quinapril attenuated the increase in mRNA of multiple pro-inflammatory cytokines. [337] TNF-α has been shown to increase AT-1 receptor expression as well as cardiac angiotensin II concentrations in cardiac fibroblasts and in a murine model.[338]

Apart from TNF-α, a variety of cytokines have been reported to be elevated in patients with HF, both systemically and within the failing myocardium. They include interleukins 1α, 6, and 8, interferon α, growth stimulation-expressed gene 2 (ST-2, also known as interleukin 1 receptor-like 1 or IL1RL1), advanced glycation end-product (AGE), Gal-3, and C-reactive protein (CRP). These cytokines cause a decrease in cardiac contractility and are associated with poorer clinical outcomes. [339] Some of these markers – specifically IL-6, CRP, and TNF-α- – were elevated in patients with AHF, especially in those with non-ischemic etiology. [329] It was also shown that the degree of activation of these inflammatory markers was correlated with disease severity. [340] Growth differentiation factor 15 (GDF-15) is another potential prognostic biomarker in CVD. GDF- 15 is a member of the transforming

growth factor-β (TGF-β) family, [341] and elevated levels have been associated with acute injury, inflammation, cancer, and cardiac stretch. IL-1, TNF-α, and TGF-β in macrophages are known to stimulate release of GDF-15, inactivating macrophage inflammation and apoptosis.

Elevated GDF-15 levels have been shown to be present in patients with end stage non-ischemic dilated cardiomyopathy, and levels decrease markedly one month following LVAD placement, in strong correlation with markers of end-organ (renal, hepatic) dysfunction improvement, suggesting that GDF −15 may be an important marker of organ perfusion. [342]

Recent studies have also suggested that relative lymphocyte count may be a strong marker in identifying increased risk of mortality risk in CVD. [343] Specifically, low (below 13 %) relative lymphocyte counts were associated with less improvement of dyspnea, greater worsening of HF, longer length of initial hospital stay, and fewer days alive and out of hospital. [344] The exact reason for these associations is not clear, although some studies have suggested an association between activation of a specific population of monocyte and liver congestion with reduced relative lymphocyte counts. [345] There are however no prospective studies to assess the association between inflammatory markers and outcomes in AHF.[339]

1.9.4 Oxidative Stress

Oxidative stress is associated with an excess of ROS, which reacts with nitric oxide, disrupt physiologic signaling, and lead to the production of toxic and reactive molecules and increased purine catabolism, which in turn increases xanthine oxidase

activity and subsequently serum uric acid levels and also induces an augmented release of myeloperoxidase by activated neutrophils and monocytes.[346,347]

Hyperuricaemia is a quite reliable marker of inflammatory cytokine activation, of endothelial dysfunction, and of oxidative stress; in fact, uric acid synthesis also generates superoxide radicals, hydroxyl, and hydrogen peroxide.[348]

In addition to the oxidative potential, uric acid could also induce several direct harmful effects, such as the stimulation of smooth muscle proliferation, renin synthesis, reduction of intra-myocardial NO synthesis, and reduction of calcium release by the sarcoplasmic reticulum in cardiomyocytes. [349] In a study of 294 hospitalized decompensated HF patients, Anker et al, observed that uric acid levels above 9.5 mg/dl at 12 and 18 months of follow-up were related to a survival of 52% and 36% at 12 and 18 months, respectively.[349]

1.9.5 Sympathetic Nervous System (SNS)

The SNS activation is mediated through three receptors β 1, β 2, and α 1. In HF patients, both β 1 and β 2 receptors are activated and, along with the α 1 receptors, eventually lead to myocardial toxicity, which results in decreased EF, arrhythmias, and tachycardia due to overstimulation by the SNS (Figure 1.13). [350] In the peripheral vasculature, activation of the β-1 and α-1 receptors leads to activation of the RAAS, which causes vasoconstriction, sodium and water retention.[350]

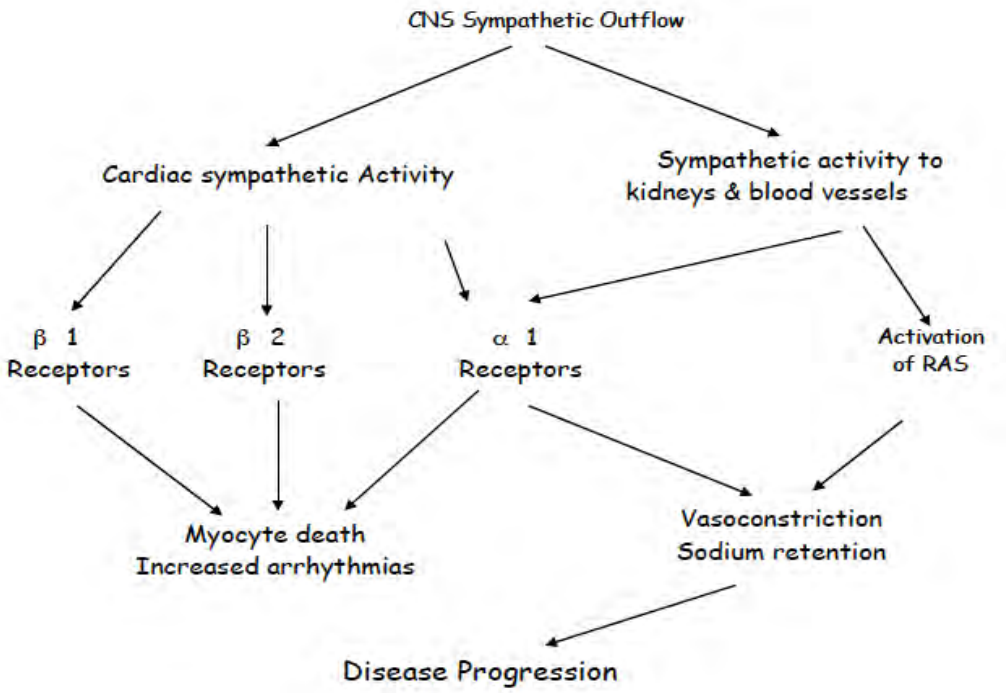

Figure 1.13 Activation of the sympathetic nervous system in heart failure

1.9.6 Arginine Vasopressin

Vasopressin is produced in the hypothalamus and secreted by the posterior pituitary gland. Its release is facilitated by angiotensin II formation and is also controlled via a negative feedback loop. When the MAP falls in HF, this is detected by central baroreceptors, which decrease their inhibitory impulses to the hypothalamus, thereby lifting the negative regulation and leading to an increase in vasopressin release. Increased vasopressin causes vasoconstriction as well as increased water retention, both of which augment the decrease in MAP in HF.[351]

1.9.7 Natriuretic Peptides (NPs)

These are atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and c-type natriuretic peptide (CNP), which serve to counteract the effects of

vasoconstriction of the other neurohormonal systems. [352] ANP and BNP are found in the atria and ventricles, respectively, and are released following atrial or ventricular stretch. CNP is found predominantly in the central nervous system and the vascular endothelium. These hormones act directly on blood vessels to cause vasodilation; cause salt and water excretion; and inhibit secretion of renin, aldosterone, and vasopressin. Elevated BNP in particular is thought to be one of the first signs of AHF and is used to follow the progression of disease.[353]

1.9.8 Endothelial dysfunction

Endothelial dysfunction may be due to an imbalance within neurohormonal, inflammatory and oxidative milieu in the circulation and endothelial cells, as well as due to other unidentified factors. This leads to myocardial hypoperfusion, increased vascular stiffness and further aggravating myocardial damage, vasoconstriction, endothelin- related secondary SNS activation and catecholamine release, as well as renal dysfunction. [354]

1.9.9 Renal Dysfunction or the Cardiorenal Syndrome

Renal dysfunction plays an important role in the complex pathophysiology of AHF, but its mechanism is not completely understood.[355] It is believed that renal dysfunction can trigger or aggravate AHF episodes as well as contribute to further progression of HF and poor outcomes. [355] It is hypothesized that impaired intra-renal haemodynamics (from impaired haemodynamics regulatory mechanisms), intrinsic renal disease (like DM and hypertension) and drugs may contribute to the development of renal dysfunction in AHF. [356] It is known that decrease cardiac

output, high venous pressure or vasodilatation directly influence renal function. It is likely that in HF, activation of various neurohormones, even in patients with normal cardiac output, can cause renal dysfunction. The renal dysfunction related to cardiac function and/or activation of neurohormones results in sodium and water retention and further activation of the RAAS. [357] Sodium and water retention by the kidneys causes hypervolemia and hyponatremia. The increase in sodium reabsorption produces a parallel increase in urea reabsorption that increases BUN levels. Thus, a vicious cycle occurs that promotes progression of HF (i.e., the Cardiorenal syndrome).

Majority patients with AHF and renal abnormalities have a component called vasomotor nephropathy (abnormal hemodynamics and/or activation of neurohormones resulting in a vasoconstriction of the afferent arteriole) that is partially or completely reversible. These patients are characterized by marked BUN elevation and modest elevations of Cr, despite having signs and symptoms of congestion. [357] It is becoming apparent that in addition to improving hemodynamics and neurohormonal profile, improving renal function is also an important target for therapy and for research in AHF.

Renal dysfunction carries a poor prognosis in patients with AHF and is as powerful an adverse prognostic factor as are most clinical variables, including LVEF and NYHA class. Renal function that worsens during hospitalization is a more important predictor of adverse outcomes than is baseline renal function. [358,359] Recent data from the ADHERE registry [112] have demonstrated the important role of renal dysfunction in the pathophysiology of and adverse outcomes associated with hospitalization for

worsening CHF.

1.9.10 Liver Dysfunction in AHF

In AHF, there is an increased filling pressure, progressive volume overload that eventually leads to increased intra-abdominal pressure causing interstitial edema and ascites. This results in both hepatic and splenic congestion. It is likely that changes in distribution of WBC, with reduced lymphocyte count, are as a result of sequestration of lymphocytes in the spleen. Abnormalities in liver function test (LFT) are prevalent in patients with chronic and acute HF, with limited data for the AHF. In a recent analysis of the PROTECT study, abnormal LFTs are frequent in AHF at baseline and during hospital stay and predict worse outcomes.[360]

Similarly, analysis of the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study, showed that abnormal LFTs in form of elevations in aspartate and alanine aminotransferases (AST & ALT) and lactate dehydrogenase (LDH) are present in 46 % of patients with AHF. [361] Other laboratory abnormalities include elevated bilirubin as well as prolongation of prothrombin time. [362] Over time, these levels gradually returned to normal in the majority of patients, persisting only in patients with unresolved congestion and signs of hypoperfusion and were associated with increased 180-day mortality. [363] In the RELAX-AHF study, although LFT values at baseline were not significantly prognostic of 180-day mortality, multivariable adjustment revealed that increases in AST and ALT of $\geq$ 20 % at day 2 were observed in almost 10 % of patients and were associated with an increased 180-day mortality risk.[339]

1.9.11 Congestion

It has been shown from large trials and registries that most hospitalizations for AHF occur because of congestion (rales, jugular venous distension, edema) rather than a low cardiac output. [83,84] Although it is thought that congestion starts as a compensatory mechanism in response to reduced cardiac performance, clinical and experimental data suggest that congestion actually contributes to the progression of AHF (Table 1.10). [364] Increased left ventricular filling pressures augment left ventricular wall stress; change the shape of the ventricle (making it more spherical), resulting in repositioning of papillary muscles and secondary mitral regurgitation. [365]

Table 1.10 Potential deleterious effects of high left ventricular filling pressure (adapted from Filippatos et al. 1999)

● Subendocardial ischemia/cell death by necrosis/apoptosis
● Changes in extracellular matrix
● Changes in left ventricular shape (spherical) resulting in: —Increased afterload —Mitral regurgitation
● Impaired cardiac venous drainage from coronary veins (may result in diastolic dysfunction)
● Lower threshold for arrhythmias

It is very essential to distinguish between clinical congestion and hemodynamic congestion. Although patients present with signs and symptoms of systemic congestion such as dyspnea, rales, elevated jugular venous pressure, and edema, this state often is preceded by hemodynamic congestion, defined as high LV diastolic

pressures without overt clinical signs. Similarly, clinical congestion may resolve with treatment but hemodynamic congestion may persist, leading to a high risk of re-hospitalization. It has been postulated that hemodynamic congestion may contribute to the progression of heart failure because it may result in wall stress, as well as in RAAS and SNS activation. These effects may trigger a variety of molecular responses in the myocardium, including myocyte loss and increased fibrosis. Concomitant abnormal processing of the natriuretic peptides, which are the intrinsic counter regulatory hormones in heart failure, leads to decrease in their biologic activity in patients with advanced disease. [366] These mechanisms also play an important role in pathologic remodeling of the ventricle, a chronic process that may be accelerated by each episode of decompensation. This is evident by the fact that each hospitalization for AHF leads to worsening of the long-term prognosis, an effect that appears additive with recurrent hospitalizations. [367] Data from studies with implantable hemodynamic monitors have confirmed that chronically elevated filling pressures (i.e. hemodynamic congestion) are associated with increased risk of future events.[368]

1.9.12 AHF and Cardiac Remodeling

As outlined above AHF can occur in the presence of strictly normal heart. In this case, heart failure is the result of the failure of the cardiac pump while myocardial structure and function are normal. Examples of situations of AHF and with no previous cardiac remodeling have already been alluded to in the section on definition.

More commonly however, often the heart and its structures may have been subjected previously to a longstanding remodeling process due to very diverse chronic pathophysiologic mechanisms. This is a more or less sudden decompensation of a thus far well-compensated chronically failing heart usually triggered by a precipitating event. In this situation the heart, ventricles, myocardium, and myocytes have been more or less severely remodeled by long period of a more or less severe biomechanical stress resulting from the originating disease. [369] Table 1.11 shows the common precipitating factors to consider in acute decompensated heart failure. [327]

Table 1.11 Precipitating factors to consider in acute decompensated heart failure (modified from Kraus et al. 2016)

- Anaemia
- Onset of a new arrhythmia (e.g. atrialfibrillation/flutter, supraventricular tachycardia, ventricular tachycardia)
- Hyperthyroidism
- Infection
- Pregnancy
- Infective endocarditis
- Recurrence of rheumatic fever
- Renal failure
- Malignant hypertension
- Myocardial infarction
- Pulmonary embolism
- Excessive alcohol intake
- Non-compliance on maintenance therapy
- Drugs – NSAIDS, negative inotropes

Cardiac remodeling is the alterations in the size, shape, structure, and function of the ventricle as a result of haemodynamic or neurohormonal stresses. [370] There are two types of anatomic remodeling of the LV; the concentric LV remodeling seen in hypertrophic cardiomyopathies and untreated chronic hypertension in which the

remodeling process concerns more the ventricle itself (its shape and thickness and stiffness of its wall) than the myocardium and myocytes. This type of remodeling is essentially responsible for acute diastolic HF due to alterations in the so-called passive properties of the LV, with little remodeling of cardiac myocytes. The other type is eccentric remodeling seen in dilated cardiomyopathies of any etiology in which the LV dilation is associated with an insufficiently thickened and hypocontractile myocardium. Identification and understanding of the triggers and signaling mechanisms of cardiac remodeling in general is important since it will largely guide the therapeutic approach and determine the short and long-term prognosis.

These signals activate a host of complex intracellular signal transduction pathways (also called cascades), often interconnected as a web, which finally activate or block a number of transcription factors, thus modulating gene expression, while other factors modulate messenger RNA (mRNA) translation into protein. These processes, which also take place in other cells, are responsible for myocyte/myocardial hypertrophy and remodeling of the extracellular matrix. In cardiac myocytes, they lead a specific alteration in protein phenotype known as "re-expression of the fetal program" (also called the hypertrophic phenotype). [371] One typical example of this process is the production of natriuretic peptides (ANP and BNP) by ventricular myocytes, a production that occurred in the fetal ventricle and ceased shortly after birth. This remodeling process, although possibly beneficial in the short term, is detrimental in the long term, being responsible for the progression to heart failure. [371] As the ventricle continue to enlarge and the myocardium hypertrophies, this leads to

increased wall tension and fibrosis, which eventually impair contractility. The long-term process of remodeling also leads to an increase in myocardial apoptosis. There is also significant contractile dyssynchrony in the dilated and remodeled ventricle leading to less effective pumping.

The results of myocyte and myocardial remodeling for LV function differ according to the type of remodeling considered. Concentric LV hypertrophy often associated with increased myocardial stiffness usually characterizes diastolic HF. In the case of LV dilatation and remodeling, the situation depends very much on the causal disease. Valvular regurgitations cause chronic volume overload and is different from LV dilatation and remodeling seen during sustained physical training during which no detrimental myocardial/myocyte remodeling is seen for a long period of time.

1.9.13 LV Systolic dysfunction

Left ventricular systole is defined by preload, afterload, and contractility. Impaired myocardial contractility occurs due to a loss of functional myocytes or a decrease in function of viable myocytes. These processes may be due to primary myocardial dysfunction, in which permanent damage to the myocytes has generally occurred, or other conditions that adversely affect myocardial function and are generally reversible if the condition can be remedied. Loss of myocytes results from either necrosis (ischemia, toxic damage, or myocarditis) or from the process of apoptosis.

It is thought that the decrease in cardiac contractility that occurs in HF is an important compensatory mechanism that decreases energy use by the failing myocardium and thereby improves long-term survival of cardiac myocytes. [372] In

contrast to CHF, during AHF there is further worsening of hemodynamic function (particularly with very high end-diastolic pressures) and further activation of neurohormones. In addition, the medications used to treat AHF often result in increased contractility and/or decreased BP. These changes (high LV diastolic pressure, decreased BP, and increased contractility) may result in myocardial injury in patients with primary cardiomyopathy with viable but non-contractile myocardium, further worsening the HF.[357]

Regardless of the underlying molecular mechanisms and triggering factors, episodes of AHF are postulated to be associated with marked cardiomyocyte loss (necrosis) and dynamic changes in the architecture of the myocardial extracellular matrix (remodeling). Cardiomyocyte damage can be reflected by confirmation of high levels of circulating cardiac troponins. [115] Cardiac troponins (cTn) in AHF are discussed in section on diagnosis.

The acceleration of myocardial remodeling during AHF may be reflected by an increased expression of 2 groups of molecules involved in the regulation of the dynamically changing status of extracellular matrix, i.e. MMPs degrading fibrillar collagens and tissue inhibitors of metalloproteinases (TIMPs), [373] as well as Gal3, a b-galactoside–binding lectin produced mainly by macrophages, involved in the fibroblast activation and tissue fibrosis.[374]

The leading causes of LV systolic dysfunction in SSA uncontrolled hypertension, non-ischaemic cardiomyopathy and volume overload due to valvular regurgitations.

The consequence of LV dysfunction is decreased CO which in turn leads to global hypoperfusion. In addition, LV dysfunction causes an increase in the amount of

blood in the ventricle and therefore an increase in both end-systolic and end-diastolic volumes. This in turn leads to an increase in LV end-diastolic pressure (LVEDP) which causes elevations in left atrial pressures which in turn lead to increases in the pressure of the capillaries in the lungs. This elevated pressure in the lungs forces fluid out of the pulmonary capillaries and leads to pulmonary congestion and the major clinical symptom of dyspnea. These signs and symptoms of LV dysfunction are all the result of increased left atrial pressure and pulmonary congestion.[353]

In addition to the changes described above there is also a rise in the systemic vascular resistance (SVR) and this is deleterious to a failing heart. This is more profound in hypertensives where the heart is pumping against a high resistance. This is the basis for the importance of reduction of afterload (or SVR) in such patients.

1.9.14 LV Diastolic Dysfunction

Diastolic dysfunction refers to abnormal mechanical properties of the myocardium and includes abnormal LV diastolic distensibility, impaired filling, and slow or delayed relaxation. In diastolic dysfunction, the ventricle cannot accept blood at low pressures and ventricular filling is slow or incomplete unless atrial pressure rises. [375] Therefore, there is an increased dependence on filling through atrial contraction and there are higher atrial pressures to maintain filling or cardiac output. [376] With regards to relaxation, any mechanism that interferes with actin myosin cross-bridge detachment or with removing calcium from the cytosol can delay this process.[377]

Diastolic dysfunction during the late filling phase of diastole can be a result of increased LV operating stiffness (diastolic stiffness) which is determined mainly by

myocardial mass and myocardial composition. In fact, numerous factors can influence LV stiffness including age, increased LV wall thickness relative to cavity size (such as in hypertension or aortic stenosis (AS)), intracellular changes in titin or microtubules, extracellular changes in collagen, and infiltration. [377-379] In addition, neurohormonal and cardiac endothelial activities also modulate ventricular stiffness and relaxation.[380]

Diastolic heart failure can be defined as a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction, and diastolic dysfunction. The presence of a preserved ejection fraction indicates that systolic hemodynamic pump performance (sometimes called "global pump" performance) is preserved, whereas contractile function of the myocardium may already be compromised. From a conceptual perspective, diastolic heart failure occurs when the ventricular chamber is unable to accept an adequate volume of blood during diastole, at normal diastolic pressures, and at volumes sufficient to maintain an appropriate stroke volume. These abnormalities are caused by impaired ventricular relaxation or by an increase in ventricular stiffness, both resulting in higher filling pressures at rest; more frequently, these impairments may produce elevated filling pressures during exercise and result in exercise dyspnea or exercise intolerance. [381] Elements and processes intrinsic to the cardiomyocyte contributing to diastolic dysfunction are summarized in Table 1.12. [382] In general, these relate to processes responsible for calcium removal from the myocyte cytosol (calcium homeostasis), to processes involved in cross bridge detachment, and to cytoskeletal functional elements. Changes in any of the processes and elements can lead to abnormalities in both

active relaxation and passive stiffness. [377]

Recent works in animal and human models have implicated titin isoform shifts, oxidative stress, nitric oxide synthase dysfunction, and myosin binding protein C in diastolic dysfunction. Titin isoform shift, or the overexpression of the stiff isoform of titin, has been found in endomyocardial biopsy samples of those with HFpEF. [383] Nitric oxide is a known mediator of cardiac relaxation, and cardiac oxidation leading to uncoupling of cardiac nitric oxide synthase results in diastolic dysfunction. [384] Lastly, myosin binding protein C, a protein located in cross bridge zones of muscle sarcomeres, is important in regulating muscle contraction. Phosphorylation of this important protein leads to deregulations of cardiac muscle contraction and subsequent dysfunction of the ventricles. [385] Indeed, Paulus describes a paradigm shift in thinking of HFpEF as a process of comorbid conditions leading to a systemic inflammatory state and microvascular inflammation, rather than focusing on myocardial structure and function.[386]

Table 1.12 Causes leading to diastolic dysfunction (modified from Zile & Brutsaert 2002)

Inappropriate tachycardia	Impaired systolic relaxation	Decreased compliance
Intermittent atrial fibrillation;	Load-induced Pressure-volume overload	Extracellular matrix Fibrillar collagen Basement membrane proteins Proteoglycans MMP/TIMP
atrial tachyarrhythmlas	Impaired inactivation processes ✓Calcium homeostasis ✓ calcium overload ✓calcium transport (sarcolemma, SR) ✓modifying proteins (phospholamban, calmodulin)	Abnormal activity of cardiac endothelial system (especially NO)
	✓Myofilaments ✓ Tn-C calcium binding ✓ Tn-l phosphorylation ✓myofilament calcium sensitivity	Cytoskeletal abnormalities ✓Microtubules ✓Intermediates filaments (desmin) ✓Titin ✓Nebulin
	✓Energetics ✓ ADP/ATP ratio ✓ ADP and Pi concentration	
	Nonuniformity of load or inactivation processes in space or time. e.g. “asynchrony” by conduction disturbances	
	Abnormal activity of RAAS, OS, ANP/BNP, cardiac endothelial system	

ADP, adenosine diphosphate; ANP, atrial natriuretic protein; ATP, adenosine triphosphate; BNP, B-type natriuretic protein; MMP, matrix metaloproteinase; NO, nitric oxide; OS, orthosympathic nerve system ; RAAS, renin-angiotensin-aldosterone system; Tn-C, troponin-C ; Tn-I, troponin-I.

Modern imaging technology like tissue Doppler imaging (TDI), radionuclide imaging and magnetic resonance imaging (MRI) are able to detect significant systolic abnormalities of the ventricular muscular pump in patients with diastolic

dysfunction and failure.[381] Importantly, these systolic abnormalities occur at normal ventricular ejection fractions, indicating that ejection fraction and parameters directly or indirectly related to it are indices of the ventricular hemodynamic pump, insensitive for measuring the performance of ventricular muscular pump. A preserved ejection fraction merely indicates that the radial (or circumferential) fibers of the ventricle compensate for longitudinal LV dysfunction to preserve overall hemodynamic pump performance, but does not imply that the systolic function of the muscular pump is normal.[387]

The observations of evidence of systolic dysfunction in patients with heart failure with preserved ejection fractions have further reinforced the conjecture that systolic and diastolic heart failure are more closely related than previously anticipated. In fact, HF should be thought as a continuous spectrum of phenotypes in which the two extremes, i.e. (pure) diastolic and (pure) systolic heart failure, do probably not exist. Often patients at risk of heart failure have an uneven distribution of disease modifiers like hypertension, diabetes and female gender, with each of these modifiers affecting ventricular remodeling and symptom progression during the progression of heart failure, paradoxically often in an opposite direction.[388-390]

1.9.15 Right Ventricular (RV) Dysfunction

The RV provides low-pressure perfusion of the pulmonary circulation, but is sensitive to changes in loading conditions and intrinsic contractility. Factors that affect RV preload, RV afterload, or LV function can adversely influence the functioning of the RV and induce or worsen right ventricular failure (RVF).

Pathophysiologic changes in RHF vary according to the underlying cause, and are shown in Figure 1.14. [391] Often, patients experience RVF secondary to a combination of decreased right ventricular contractility, increased RV pressure, and increased RV volume.

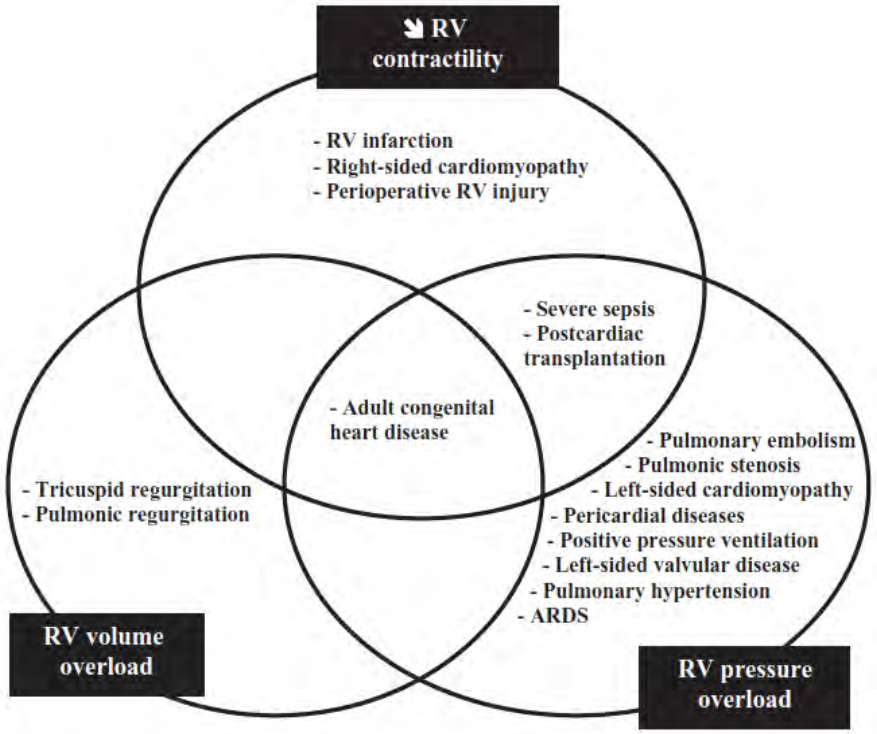

Figure 1.14 Conditions associated with right ventricular (RV) failure categorised by initial pathophysiology (adapted from Piazza & Goldhaber 2005). ARDS, acute respiratory distress syndrome

There is also a high degree of ventricular interdependence due to the role of the interventricular septum in the contraction of both ventricles, which is pronounced due the existence of pericardium. [392] Indeed, increases in the end-diastolic volume of the LV are transmitted to the RV by movement of the interventricular septum toward

the RV, increasing the end-diastolic pressure of the RV. [393] Similarly, when RV end-diastolic volume is increased, the interventricular septum shifts toward the left cavity during diastole due to restrictions imposed by the pericardium on the RV as the cavity volume increases. This leftward shift impairs the function of the LV due to the reduction in LV volume, decreasing both left ventricular filling and compliance, manifested as increased LV muscle stiffness. In fact, the most common cause of RV failure is LV failure. As the RV fails, there is a similar increase in the amount of blood in the ventricle, which in turn leads to elevated right atrial pressure (RAP) and increased pressure in the vena caval system which impairs venous drainage from the body. This leads to increased pressure in the liver, the gastrointestinal tract, and the lower extremities and to the clinical signs and symptoms of abdominal pain, hepatomegaly, and peripheral edema.[394]

Compared to the LV, RVF progresses quickly from compensated to end-stage heart failure because of a vicious cycle of auto-aggravation as shown in Figure 1.15. [394] This is unique to the RV and is rarely seen in isolated left ventricular failure. A sudden increase, although modest, in RV afterload on an ischemic RV immediately dilates the RV, induces a tricuspid regurgitation, and decreases cardiac output. This cascade of events must be prevented as soon as possible and implies that any sign of RVF should result in an immediate treatment in order to avoid this vicious cycle.[394]

The RV plays a pivotal role in hemodynamic homeostasis, and changes in its function can have profound effects on the pulmonary and systemic circulation. The principal therapeutic goals of the early management of RVF depend on its underlying etiology, but primarily involve breaking the vicious circle of reduced

cardiac output. This will allow restoring adequate oxygen delivery to the myocardium and reducing right ventricular overload. Treatment of RVF, therefore, should focus on alleviating congestion (limit volume loading), increasing right coronary artery flow, improving RV contractility, and reducing RV afterload.

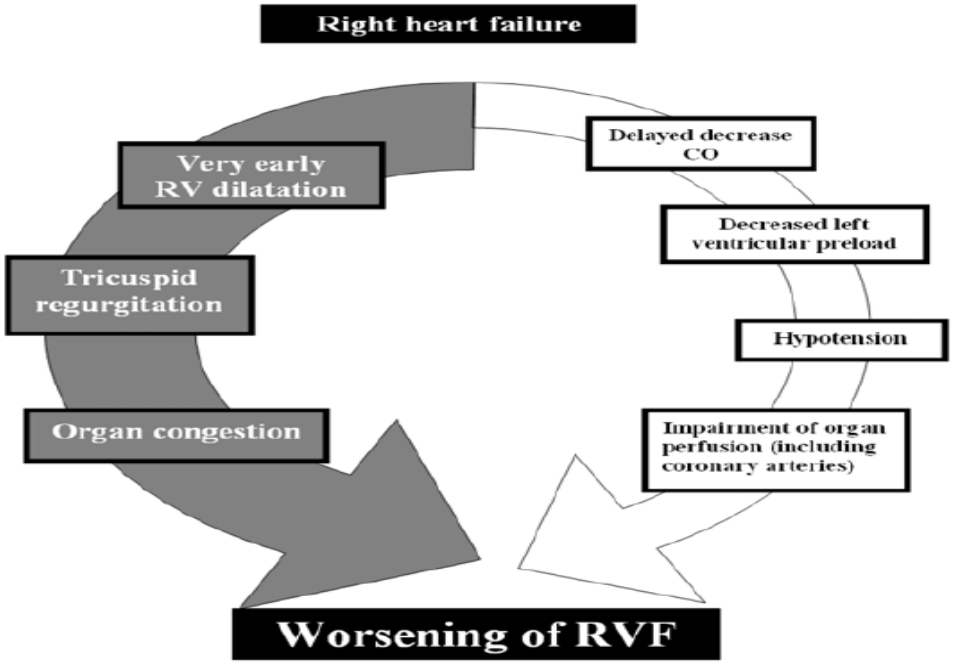

Figure 1.15 Vicious cycle of auto-aggravation (adapted from Gayat & Mebazaa 2008)

1.10 Diagnosis of AHF

1.10.1 Clinical Evaluation

A careful history and physical examination remain the cornerstones in the assessment of patients with HF. The history provides information to the cause of the HF, the possible trigger, the severity of the disease and the patient's prognosis and

identifies opportunities for therapeutic interventions. The physical examination provides information about the severity of illness and allows assessment of volume status and adequacy of perfusion. Table 1.13 summarizes the symptoms and signs of acute decompensated HF. [325] Sometimes atypical symptoms can predominate, especially in elderly patients, in whom fatigue, depression, altered mental status, or sleep disruptions may be the primary complaint.

HF remains a clinical diagnosis, and the physical examination continues to play a fundamental role in its detection. BP measurement is a critical part in the evaluation of patients with AHF; hypotension is one of the strongest predictors of poor outcomes and helps to define the clinical profile of the patient and appropriate therapeutic interventions. Majority of the patients with AHF present with either normal BP or high BP. [83] The pulse pressure is also a useful measure that is an indirect marker of cardiac output. A low pulse pressure correlates with low cardiac output and confers an increased risk in patients admitted with AHF. A high pulse pressure may alert the physician to a high-output state, including the possibility of unrecognized thyrotoxicosis, aortic regurgitation, or anemia.[325]

The jugular venous pressure (JVP) is literally a barometer of systemic venous congestion and is the single most useful physical examination finding in the assessment of patients with AHF. It reflects the RAP, which is an indirect measure of LV filling pressures in the absence of isolated RVF. Rales or inspiratory crackles are the most common physical examination finding and have been noted in 66% to 87% of patients admitted for AHF. However, rales are often not heard in patients with a background of CHF and pulmonary venous hypertension, because of

increased lymphatic drainage, reinforcing the important clinical pearl that the absence of rales does not necessarily imply normal LV filling pressures.

Peripheral edema is present in up to 65% of patients hospitalized with AHF and is less common in patients presenting with predominantly low-output HF or cardiogenic shock. As with rales, the presence of edema has a reasonable positive predictive value for ADHF but a low sensitivity, so its absence does not exclude that diagnosis. Hepatomegaly and splenomegaly can occur acutely in patients with AHF as a consequence of increased central venous pressure and in such cases often result in significant tenderness. Ascites occurs in response to elevated central venous pressures by retarding emptying of the peritoneal veins and the hepatic veins. Of note, visceral congestion may occur independently of ascites or palpable organomegaly. [325]

Table 1.13 Common presenting symptoms and signs of decompensated heart failure (adapted from Felker & Teerlink 2015)

SYMPTOMS	SIGNS
Predominantly Related to Volume Overload	
Dyspnea (exertional, paroxysmal nocturnal dyspnea, orthopnea, or at rest); cough; wheezing	Rales, pleural effusion
Foot and leg discomfort	Peripheral edema (legs, sacral
Abdominal discomfort/ bloating; early satiety or anorexia	Ascites/increased abdominal girth; right upper quadrant pain or discomfort; hepatomegaly/splenomegaly; scleral icterus Increased weight Elevated jugular venous pressure, abdominojugular reflux Increasing S3, accentuated P2 heart Sounds
Predominantly Related to Hypoperfusion	
Fatigue	Cool extremities
Altered mental status, daytime drowsiness, confusion, or difficulty concentrating	Altered mental status, daytime drowsiness, confusion, or difficulty concentrating
Dizziness, presyncope, or syncope	Pulse pressure (narrow)/proportional pulse pressure (low) Pulsus alternans
Other Signs and Symptoms of AHF	
Depression Sleep disturbances Palpitations	Orthostatic hypotension (hypovolemia S4 Systolic and diastolic cardiac murmurs

1.10.2 Laboratory Investigations

The main objectives of initial evaluation of the patient with AHF are: (1) to establish a definitive diagnosis of AHF as quickly and efficiently as possible; (2) to provide emergency treatment for potentially life-threatening conditions (e.g., shock,

respiratory failure), (3) to identify and address any relevant clinical triggers, (4) to risk stratify for triage of the patient to an appropriate level of care (e.g., ICU, telemetry unit, observation unit); and (5) to define the clinical profile of the patient (based on BP, volume status, and renal function) to allow rapid implementation of the most appropriate therapy. Based the pathophysiology (described above), a range of investigations is done in AHF to supplement the symptoms and signs in achieving the above objectives. These include serum NPs, cTn, electrolytes, liver enzymes and haemoglobin. An assessment of renal function is a critical component in the management of patients with AHF. BUN is more directly related to the severity of AHF than Cr and typically is elevated on admission in a large proportion of patients with AHF. In addition to reflecting intrinsic renal function, the BUN level is roughly proportional to neurohormonal activation in AHF.

The ECG and echocardiogram are the most useful investigations, as they confirm the presence of underlying structural heart disease. The likelihood of a normal ECG in a patient presenting with HF is low, making it an extremely helpful screening tool. [327] Echocardiography is recommended for all patients with a diagnosis of HF as it confirms the type of structural heart disease present and provides information on cardiac function. [395] A summary of the applications and limitations of cardiac imaging techniques in the diagnosis and management of AHF is given below (Table 1.14) [395].

Table 1.14 Main applications and limitations of cardiac imaging techniques in the diagnosis and management of acute heart failure (modified from del Villar et al. 2015)

	Main Applications	**Limitations**
Chest X-ray	Diagnosis of HF Diagnosis of concurrent extra cardiac disease(pneumothorax, pleural effusion, consolidation, etc.)	Low specificity Limited correlation with hemodynamic parameters
Focused TTE	Global assessment of cardiac structure and function in acute situations Qualitative assessment of: • Pericardial effusion • Intravascular volume • Ventricular size and function Pulmonary ultrasound	Equipment technically inferior Specific training Stressful situations Risk of missing important abnormalities Window
Comprehensive TTE	Syndromic diagnosis (preserved vs reduced LVEF) Etiological diagnosis (ischemia, valvular heart disease, cardiomyopathies, etc.) Noninvasive hemodynamic Assessment	Specific training Window
TEE	As with TTE Endocarditis, intracardiac thrombus, aortic dissection Valvular heart disease (severity and mechanism) Monitoring of therapeutic procedures Possibility of continuous monitoring (miniaturized probes)	Adequate training Esophageal probing
CT	Triple rule out: noninvasive coronary angiography, pulmonary thromboembolism, acute aortic syndrome Diagnosis of concurrent pulmonary and chest disease	Radiation Iodinated contrast (hypersensitivity, nephrotoxicity)
MRI	Characterization of myocardium Quantification of severity of valvular heart disease Aortography	Hemodynamic instability Metallic implants, devices, etc. Availability Gadolinium contrast

CT, computed tomography; HF, heart failure; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

1.10.3 Chest X-ray in AHF

In acute left heart failure, there is a progressive increase in pulmonary venous pressure. At a PCWP of 10 - 15 mm Hg, blood flow is uniform from bases to apices of the lungs due to capillary distention and recruitment. When the PCWP increases to between 15 and 25 mm Hg, a vascular redistribution of blood flow to the apices is observed and vessels appear larger than basal vessels (upper lobe diversion on the chest X-ray). [396] These modest elevations in pulmonary venous pressure are accommodated without the development of pulmonary edema. However, at higher filling pressures, fluid begins to cross the microvascular barrier, and pulmonary edema then develops. This first involves the interstitial compartment followed by the interlobular septa and the peri-bronchovascular spaces, and reaches the hila. This gives Kerley A lines situated at the apices and Kerley B lines located at the bases on the chest X-ray. If the pressure raises a value above 35 mm Hg, alveolar pulmonary edema occurs and produces a bilateral alveolar syndrome in a medullary distribution, with sparing of the periphery of the lung fields known as “bat’s wing” or “butterfly” pattern.[396]

Chest X-ray may be limited in the diagnosis of pulmonary edema when presentation is atypical. [397] Alveolar edema is not always uniformly distributed owing to gravity. Lower lobe predominance can be observed when the patient is upright, and posterior distribution if the patient is supine. Coexisting lung disease may obscure pulmonary edema. Pulmonary edema may also present differently depending on the course of the disease. Patients with long-standing elevations in pulmonary wedge pressure like severe mitral stenosis undergo remodeling of their alveolo-capillary membranes,

which protects the lung from pulmonary edema. On the other hand, a previously healthy patient with AHF from acute MI or massive volume overload may show dense alveolar peri-hilar infiltrates. Cardiomegaly may be absent especially in diastolic heart failure or in iatrogenic pulmonary edema due to fluid overload. Acute MI and acute cardiac arrhythmias can also result in pulmonary edema of cardiac origin with a normal sized heart.

1.10.4 Echocardiography in AHF

Echocardiography remains a very important tool is assessing patients with AHF. The diagnosis of cardiogenic pulmonary edema relies on the documentation of elevated LV filling pressure in a suggestive clinical setting. This finding is typically associated with LV systolic dysfunction. In this case, echocardiography quantifies LV pump function and identifies the underlying cardiac disease responsible for the congestive heart failure. Importantly, the echocardiographic abnormalities should be addressed in the context of the clinical setting.

In the presence of a preserved LV systolic function but still elevated LV filling pressure, the presence of a high output AHF should be ruled out. The absence of dilatation of left cardiac cavities is usually consistent with an acute volume overload (e.g., valvular regurgitation, iatrogenic volume overload). However, markedly dilated left cardiac chambers reflect a progressive adaptation of the heart to a chronic volume overload. Associated LV hypertrophy is usually interpreted as a marker of associated LV pressure overload (e.g., aortic regurgitation).[398]

The level of PH may also help in distinguishing recent from rather chronic LV volume overload. Since a normal RV may barely generate a systolic pressure >60

mm Hg, [399] higher values usually denote the presence of a sub-acute or chronic PH rather than an acute increase of RV output impedance. Finally, echocardiography may clearly identify the cause of acute LV volume overload (e.g., endocarditis, ruptured papillary muscle, or mitral chordae) and confirms its severity.

The diagnosis of pure LV diastolic dysfunction can be considered after ruling out a congestive and a high output AHF by echocardiography. This clinical scenario typically corresponds to hypertensive AHF and frequently involves elderly patients with a history of hypertension. [39] Standardized diagnostic criteria of LV diastolic dysfunction have been proposed. [60] In the setting of AHF patients presenting with pulmonary edema and preserved LV systolic function, echocardiography represents a valuable diagnostic method for assessment of LV diastolic function, measurement of increased LV filling pressures, and identifying cardiac abnormalities known to be associated with impaired LV filling e.g. LVH. In practice, the prevalence of primary LV diastolic dysfunction in AHF patients identified by echocardiography may reach 38%.[400]

Importantly, echocardiography should be performed as close as possible to the AHF event (i.e., when symptoms are still present), since LV filling pressure may rapidly change in response to treatment-induced variations of loading conditions (e.g., diuretics, nitrates, mechanical ventilation, sedation).

Patients with right heart failure typically present with acute-onset dyspnea at rest, physical signs of peripheral congestion, and clear lung fields. In a patient presenting with systemic venous congestion but no RV dilatation, a tamponade physiology should be sought for. Echocardiographic diagnosis of cardiac tamponade is

straightforward in the presence of a pericardial effusion with diastolic compression of right cardiac cavities.

Regardless of the origin of right heart failure, echocardiography enables a comprehensive evaluation of both global and regional RV systolic function.[401]

AHF can complicate acute aortic syndrome (AAS) especially when it involves the aortic root rather than the descending aorta. Accordingly, trans-thoracic echocardiography (TTE) plays a key role in the evaluation of these patients since it is accurate for the diagnosis of acute condition of the ascending aorta and better tolerated than trans-esophageal echocardiography (TEE) in this specific clinical setting. [398] Although there may be no evidence for an intimal flap or an intramural hematoma based on TTE examination, the presence of a dilated ascending aorta and findings consistent with blood extravasation (i.e. haemo-pericardium) or aortic regurgitation is highly suggestive of AAS. In this situation, TEE should be done and may be safely performed in the operating room, under general anesthesia, followed by pericardial decompression if needed.[398]

In the absence of acute disease of the ascending aorta, echocardiographic documentation of a new regional wall motion abnormality (RWMA) is indicative of acute MI.

Cardiogenic shock is the most severe clinical presentation of peripheral hypoperfusion related to AHF syndrome. [39] It is attributable to a failing cardiac pump, regardless of the nature of the insult. Echocardiography in cardiogenic shock has the unparalleled advantage of documenting and assessing the severity of cardiac pump failure, excluding any preload-dependency of the heart, differentiating

between a low cardiac output due to a failing LV and a RHF and determining if LV stroke volume is mostly generated by myocardial contractility rather than LV cavity dilatation.[402]

1.10.5 Coronary angiography in AHF

The decision to perform a coronary angiography in acute heart failure must be well balanced between the need to diagnose acute coronary occlusion and revascularization on the one hand and the procedure's need for recumbency and contrast, which increases the loading conditions and can impair renal function on the other hand.[403]

There are several causes of CAD related cardiogenic shock that can be diagnosed without coronary angiography, mainly using echocardiography; these causes include acute mitral regurgitation, and septal or free wall rupture. AHF and particularly cardiogenic shock occur in 5% to 10% of patients who suffer acute MI. [404] Despite therapeutic advances in the management of acute MI, prior reports, including those from large thrombolytic trials, suggest no change in the incidence or overall mortality (55% to 80%) of cardiogenic shock in this setting. [405]

Two randomized clinical trials by them have examined the role of emergency revascularization in STEMI complicated by cardiogenic shock. Both trials showed a clinically important (even if statistically insignificant) absolute 9% reduction in 30-day mortality. [406-408]

The ACC/AHA recommended (class IA) primary PCI for patients younger than 75 years old with ST segment elevation MI (STEMI) or new LBBB who develop shock within 36 hours of MI and are suitable for revascularization that can be performed

within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care.[409]

Coronary angiography is available only in a few centres in Africa and may not be available for evaluation of AHF patients in the region.

1.10.6 Biomarkers in Heart Failure

Biomarkers have become increasingly important in diagnoses, prognostication, risk stratification and achieving guideline directed medical therapy in heart failure. These are enzymes, hormones, biologic substances, and other markers of cardiac stress and malfunction, or myocyte injury. [410] Although they include serum levels of hemoglobin, electrolytes, liver enzymes, BUN, creatinine, thyroid hormones and ferritin, often biomarkers refer to conventional or novel markers derived from blood or urine other than those mentioned above. Figure 1.16 showed clinically available biomarkers and their mechanistic implications in hearts failure.[411]

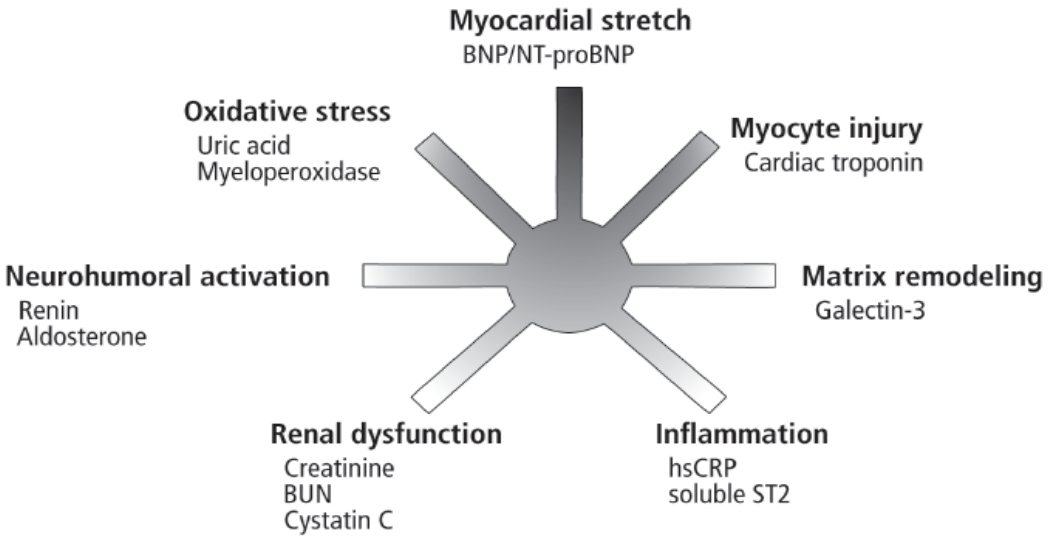

Figure 1.16 Clinically available circulating biomarkers and their mechanistic implications in heart failure (adapted from BranwauldE. 2013). BNP, B-type natriuretic peptide; NT-pro BNP, N-terminal pro BNP; BUN, blood urea nitrogen; ST2, suppression tumorigenicity-2

It has been proposed that a biomarker should fulfill three criteria to be useful clinically. [412] First, accurate, repeated measurements must be available to the clinician at a reasonable cost and with short turnaround times; second, the biomarker must provide information that is not already available from a careful clinical assessment; and finally, knowing the measured level should aid in medical decision making. Although relatively few of the biomarkers satisfy all three criteria, many appear to provide important information regarding the pathogenesis of heart failure or the identification of subjects at risk for heart failure or appear to be useful in risk stratification, in the diagnosis of heart failure, or in monitoring therapy. This section will discuss cTn, GDF-15, BNP/NT Pro BNP and Gal3. The last two are part of the specific objectives of this thesis.

1.10.6.1 Brain Natriuretic Peptide (BNP) and NT Pro BNP

BNP belongs to the NPs family together with other structurally similar peptides, namely ANP, CNP and urodilatin. The NPs have in common a characteristic biochemical structure, which consists of a 17 amino-acid ring and a disulfide bridge between two cysteine molecules.[413] Figure 1.17 shows the structure of Pro BNP and NT-pro BNP.

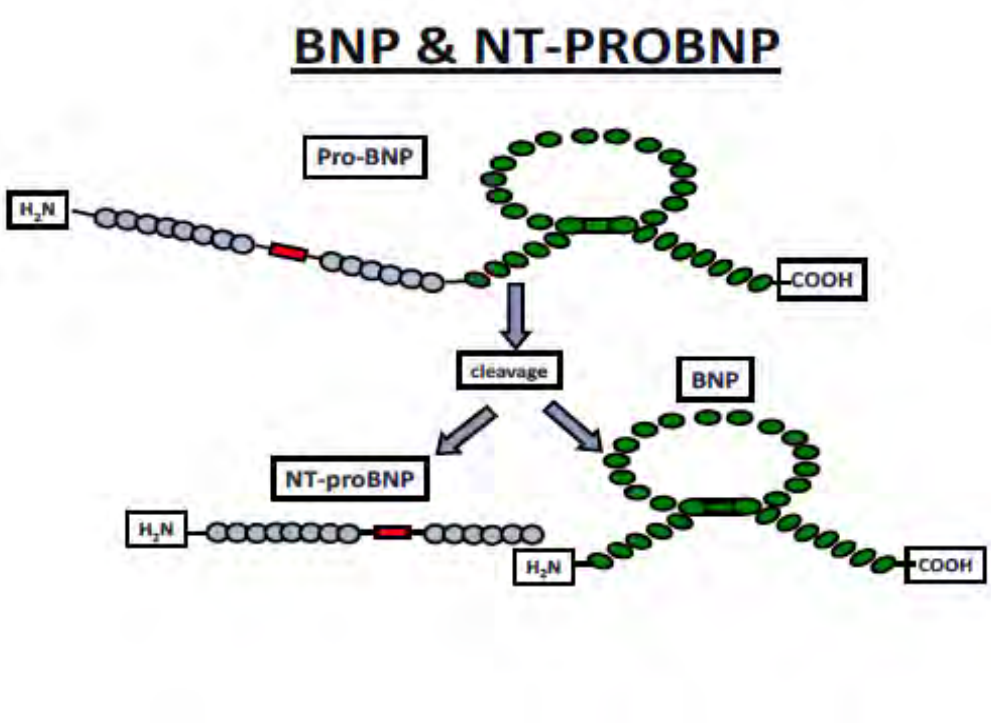

Figure 1.17 Structure Pro BNP and NT-proBNP

BNP is a hormone that is secreted by atrial and ventricular myocardial cells but predominantly by the ventricular cells, and reaches very high plasma concentrations in subjects with congestive HF or AHF. BNP's gene is located on the short arm of chromosome 1, close to the ANP loci. Its mRNA is translated to a chain of 108

amino acids called pro BNP that co-exist with ANP in some secretory vesicles of the atrial and ventricular myocardial cells. BNP is synthesized in the heart as a reaction to cardiac wall distension and stretching, and neurohormonal activation. The cardiomyocytes synthesize a pre-propeptide (prepro BNP 134 amino acids), which is split into a signal peptide and a propeptide (pro BNP 108 amino acids). During secretion from the cardiomyocytes, proBNP is split at a ratio of 1:1 into the physiologically active BNP (32 amino acids), which corresponds to the C-terminal fragment, and the biologically inactive N-terminal fragment (NT-pro BNP, 76 amino acids). [414]

The physiological effects of BNP are manifold and comprise natriuresis/diuresis, peripheral vasodilatation, and inhibition of the RAAS and the SNS. BNP is cleared from plasma by binding to the NP receptor type C (NPR-C) and through proteolysis by neutral endopeptidases. In contrast, NT-pro BNP is mainly cleared by renal excretion; however, recent studies suggest that there might also be other important clearing mechanisms for NT-pro BNP.

1.10.6.2 Brain Natriuretic Peptide (BNP) and NT Pro BNP in AHF

B-type Natriuretic Peptide (BNP) and its precursor N-terminal pro-BNP are very useful in AHF diagnosis. They add value in the setting of undifferentiated dyspnea by improving diagnostic discrimination, [415] and they correlate with cardiac filling pressures and ventricular stretch. [416] Testing for NPs is a class 1 recommendation by the ACC/AHA, [48] and may be particularly useful when the etiology of dyspnea is unclear and has been shown to have greater utility than chest X-ray for diagnosing

AHF. [415] Patients with HFpEF have a smaller LV radius and thicker walls than HFrEF, resulting in proportionally lower NPs levels for similar degrees of AHF, suggesting that different diagnostic thresholds are needed depending on whether LVEF is preserved or reduced. [417] At the moment, natriuretic peptide testing cannot reliably distinguish HFpEF from HFrEF in an individual patient. [325]

Secreted NPs levels are elevated in acute MI, LV systolic dysfunction, LV diastolic dysfunction and RHF. [418] Elevated peptide levels are directly correlated with prognosis, NYHA score, intra-ventricular pressure, pulmonary pressure, and inversely proportional to CO. [419] It has been proposed that patients with BNP concentrations of less than 20 pmol/L have less chances of suffering from HF, while patients with higher concentrations should have further CV investigations. [420] In general, changes of > 50% from baseline represent worsening HF; however, significant variation in NP levels can occur within the same patient, and intra-individual differences between measurements do not necessarily represent an acute clinical event. [421] Recent studies in patients with normal systolic function verified by echocardiography have shown that BNP levels correlate well with Doppler measurements showing diastolic dysfunction of the LV.[422]

In the Breathing Not Properly study, a BNP threshold of 100 pg/mL maximized sensitivity and specificity to differentiate dyspnea that was ultimately confirmed to be due to AHF (based on a review of clinical data by a blinded panel of cardiologists) from dyspnea from other causes. [325] Importantly, the negative predictive value of a BNP level less than 100 pg/mL was particularly high (89%), whereas the positive predictive value of this decision threshold was more modest

(79%). Subsequent studies using NT-pro BNP, such as the Pro BNP Investigation of Dyspnoea in the Emergency department (PRIDE) study, have shown that NT-pro BNP has similar diagnostic value, although the appropriate cut points are higher overall and vary with age.[423]

Assessing BNP levels and adjusting the dosage of therapy according to its level can lead to achieving the best possible treatment of HF. [424] These workers suggested that using BNP concentrations to monitor patients with HF and managing their medical therapy accordingly might improve overall morbidity and mortality.

High levels of natriuretic peptides are associated with recurrent hospitalization and risk of sudden death, [425] and pre discharge BNP level appears to be a strong predictor for identifying subsequent death or hospital admission at 6 months. [426,427] Although "hard targets" for pro BNP values are not entirely defined, morbidity and mortality in CHF appear to increase markedly with a pro BNP concentration >500 pg/ml.

In the Australia–New Zealand HF Group study, [428] levels of pro BNP above the median were associated with increased risks for new decompensated HF events and all-cause mortality during 18 months of follow-up, independently of age, NYHA functional class, LVEF, previous MI, or previous HF admission.

In the Valsartan Heart failure (Val-Heft) trial, pro BNP ranked as the first prognostic factor on multivariate analysis independent of and more powerful than traditional risk factors, such as NYHA class, age, LV dilation, or renal dysfunction. [429] The Val-Heft study also showed NPs to be superior to several other recognized neurohormonal markers of risk in HF, including norepinephrine, renin activity, aldosterone, and endothelin in predicting outcome. [429]

1.10.6.3 BNP Versus NT Pro BNP

In practice, measuring NT-pro BNP has advantages over routine BNP. NT-pro BNP is more stable than BNP with a half-life of 60-120 minutes, as against a half-life of 18-22 minutes for BNP. This explains why NT-pro BNP serum values are approximately six times higher than BNP values, even though both molecules are released in equimolar proportions. [430] Once blood is collected BNP levels are not stable in vitro for long periods, dropping significantly over the first 24 hours, while there is very little variation in the level of NT-pro BNP for at least 72 hours or even longer. Therefore, NT-pro BNP can be assayed from stored or delayed specimens with confidence that the levels have not degraded with storage. In addition, assaying NT-pro BNP has been found to be easier than assaying BNP and this is because of higher plasma concentration. NT-pro BNP has also been found to be better in identifying patients with HF. [431,432]

1.10.7 Galectin 3 (Gal3)

Gal3 is a soluble **β**-galactoside-binding lectin secreted by immune cells that regulate fibrogenesis, inflammation, cell proliferation and tissue repair. [433] Gal3 is encoded by a single gene, LGALS3, which is located on chromosome 14. [434] It is a chimera-type galectin composed of a non-lectin domain connected to a carbohydrate-recognition domain (CRD). Galectins share remarkable sequence similarities in the CRD, and many family members preferentially recognize galactose-containing saccharide ligands. The carbohydrate recognition domain has about 130 amino acid residues (attached to Gal3 binding partner), the collagen-like domain is proline-, glycine-, and tyrosine-rich repeating domain (about 100 residues) and the N-terminal

domain has about 30 residues. (Figure 1.18). [374] Gal3 is ubiquitously expressed and it is present both in the cytoplasm, nucleus and outside cells.

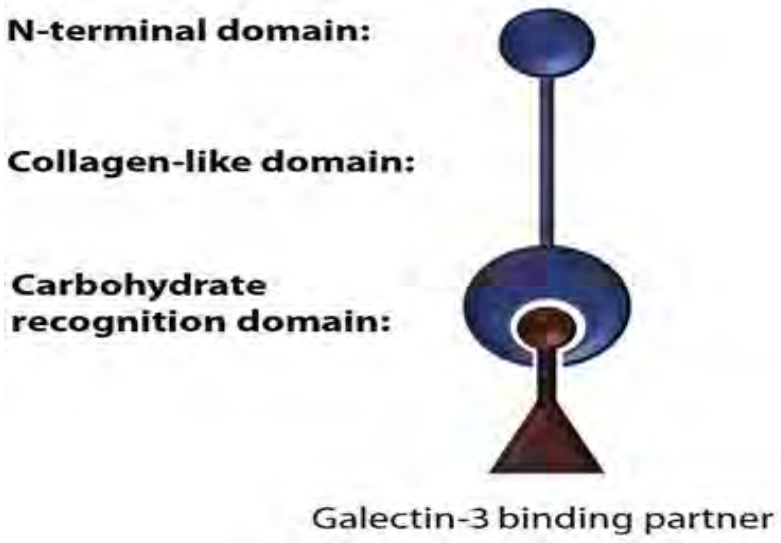

Figure 1.18 Schematic drawing of the structure of galectin-3 (adapted from Filipe MD et al. 2015)

Gal3 is recently discovered to be involved in the pathophysiology of HF through mediation of myocardial fibrosis and inflammation, contributing to myocardial remodeling. [435] The evidence for the role of Gal3 in the pathogenesis of cardiac fibrosis has been described in detail by McCullough and coworkers. [436] Production of Gal3 from local pericytes, mast cells, and macrophages, induces resident fibroblasts and myofibroblasts to produce procollagen which is irreversibly cross-linked to collagen generating cardiac fibrosis. [437] Gal3 as a paracrine protein also directs cell adhesion, activation, chemoattraction, growth and differentiation, up-regulation of the cell cycle, and apoptosis. [438] In the myocardium, Gal3 assists transforming

growth factor β (TGFβ) to increase cell cycle (cyclin D1) of myofibroblasts, which results in their proliferation and synthesis of procollagen 1. [439] In total, the available data strongly suggest that Gal3 is a critical participant in the pathogenesis and progression of HF, [440] and a biomarker reflecting tissue damage, independent of cardiac loading conditions. [441]

1.10.7.1 Galectin-3 in AHF

Due to its physiopathology, there is no clear proof of the effectiveness of Gal3 for the diagnosis of HF; however, the prognostic power of galectin-3 has undergone more assessment. Plasma Gal3 seems to be a prognostic marker of HF outcomes such as death and readmissions for HF[442,443] and is associated with increased risk for incident HF. [444] Van Kimmenade and colleagues have also shown that serum Gal3 levels are elevated in subjects with AHF and it was able to identify those HF patients at risk of short-term death or the combination of death or readmission within 60 days better than NT-proBNP. [442] However, the combination of both markers seemed to further refine predictive utility. In this study, compared with NT-pro BNP and all clinical data available, the elevated concentration of Gal3 was the best independent predictor of 60-day mortality (OR10.3; $P < 0.01$) and 60-day death/recurrent HF (OR 14.3;$P < 0.001$).

In addition, Femann and colleagues found a subset of patients of AHF patients, whose Gal3 levels were elevated beyond what would be predicted by their BNP elevations, and these patients were more likely to have acute kidney injury (AKI), with a tendency towards an increased 30-day event rate. They hypothesized that Gal3 could be useful for identifying the subset of AHF patients with cardiorenal

syndrome that is not identified as high-risk when natriuretic peptides are used in isolation.[445]

In a meta-analysis of three studies and 893 patients, that included 582 patients from Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) study, 181 patients from the PRIDE study and 129 patient University of Maryland Pro-BNP for Diagnosis and Prognosis in Patients Presenting with Dyspnea, DeBoer[446] reported that patients with elevated Gal3 above 17.8 ng/ml were nearly three times as likely to suffer short-term re-hospitalization (OR 2.80, 95% CI 1.41–5.57, and 3.01, 95% CI 1.79–5.05, for 30- and 90-day readmissions, respectively). Also, baseline Gal3 was a predictor of re-hospitalization even after adjustment for age, gender, estimated GFR, NYHA functional class, LVEF and NT-pro BNP levels. The authors of this meta-analysis concluded that in acute HF, an elevated Gal3 during an emergency department (ED) visit, hospital admission, or at hospital discharge is independently associated with early HF readmission. These findings are of clinical significance because the results of these studies suggest that Gal3 may identify AHF patients with elevated risk for death and re-hospitalization independent of the severity of signs and symptoms at presentation. Identification of those AHF patients at highest risk by combined assessment of serum markers may help to tailor the most appropriate treatment strategy on a more individualized basis.

The direct inhibition of Gal3 is possible by N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP). This is a naturally occurring tetra-peptide that has been shown to prevents and reverses inflammation and collagen deposition in the heart in hypertension and HF after MI. [439] It is possible that Ac-SDKP prevents Gal3-induced

cardiac inflammation, remodeling and dysfunction and that these effects are mediated by the transforming growth factor signaling pathway.[447]

1.10.8 Growth Differentiating Factor (GDF) – 15 in AHF

Growth Differentiaing factor 15 (GDF-15) is a member of the TGF-β cytokine superfamily. [448] Like TGF-β, GDF-15 is synthesized as a precursor protein that undergoes disulfide- linked dimerization. Proteolytic cleavage of the correctly folded GDF-15 precursor releases the N-terminal propeptide from the mature GDF-15 peptide, which is then secreted as a disulfide-linked dimer with a molecular mass of ~28 kDa. [449]

Cardiac myocytes produce and secrete large amounts of GDF-15 in response to oxidative stress, stimulation with angiotensin II or pro-inflammatory cytokines, ischemia, and mechanical stretch. [450]

The prominent anti-apoptotic, anti-hypertrophic, and anti-inflammatory actions of GDF-15 in CVD models indicate that GDF-15 plays an important counter-regulatory role in the context of acute CV injury, such as MI or acute pressure overload.[451]

Patients presenting with signs and symptoms of HF, have higher GDF-15 levels than do patients who are haemodynamically stable. [452] GDF-15 levels are elevated in HF, independent to disease severity (NYHA class, BNP, peripheral edema), CV risk factors (age, DM), renal dysfunction, inflammation and neurohormonal activation (CRP, uric acid, norepinephrine), and high-sensitivity troponin T (hs-TnT). [342] GDF-15 levels are elevated in HF with preserved ejection fraction to a similar degree as in HF with reduced ejection fraction.[453]

In a recent study by Cotter and colleagues, [454] they found that in AHF patients

enrolled in the RELAX-AHF study, baseline GDF-15 was not associated with the composite endpoint of heart failure or renal failure (HF/RF) readmission at 60 days /CV death or CV death at 180 days. In contrast, larger increases in GDF-15 levels at days 2 and 14 were associated with a greater risk of 60-day HF/RF re-hospitalizations/CV death and CV death at 180 days .

Data also show a tight relation between GDF-15 level and other biomarkers such as NT-pro BNP in heart failure patients. Furthermore, the combined use of GDF-15 and NT-pro BNP to predict prognosis significantly improves the accuracy.[341]

1.10.9 Cardiac Troponin (cTn) in AHF

Cardiac troponin (cTn) is released by cardiac myocytes when they are injured. It is classically considered as marker of acute myocardial infarction but now considered as a marker of myocardial ischaemia regardless of the cause. Studies have now shown that cTn is in fact increased in AHF and even minor increase in concentrations have been shown to independently predict disease severity as well as short term and long term prognosis.[455]

The prognostic utility of cTn in patients presenting with ADHF was explored in the ADHERE trial. [456] 4240 out of approximately 85,000 patients with ADHF had abnormal cTn. The incidence of in-hospital mortality was higher in patients with elevated cTn compared to patients without elevated cTn (adjusted odds ratio 2.55; 2.24–2.98, 95% CI, p b 0.001), and among patients with detectable cTn, mortality increased in a stepwise fashion with cTn.

In another study of ADHF patients, cardiac troponin T (cTnT) and NT-proBNP were tested at both admission and discharge to determine which set of combined

measurements was better at stratifying long term morbidity and mortality. [457] Patients who at admission had elevations of neither biomarker, one biomarker, or both biomarkers had 85%, 60%, and 34% ADHF-free re-hospitalization survival rates (a composite of mortality and rehospitalization for HF), respectively. Patients who at discharge had elevations of neither biomarker, one biomarker, or both biomarkers had 63%, 71%, and 26% ADHF-free re-hospitalization survival rates, respectively. Thus, in this study, a predictive model using admission values for both cTnT and NT-pro BNP appears to have the greatest prognostic value for long-term adverse outcomes.

Xue et al. [458] performed serial high sensitive cardiac troponin I (hs cTnI) and BNP measurements in 144 patients with ADHF. Biomarkers were quantified on admission, during hospitalization, and at discharge and the patients were then followed for mortality and rehospitalization for HF for ninety days after discharge. cTnI was detectable in over 99% of the samples. Elevated cTnI was strongly associated with greater ninety-day mortality and an increased rate of rehospitalization and the risk of these adverse outcomes tended to increase with higher cTnI. Moreover, patients with increasing cTnI, defined as a peak cTnI greater than admission cTnI, were at higher risk of dying by the time of follow-up than those with stable or decreasing cTnI (hazard ratio 4.52, $p = 0.047$). The presence of both elevated cTnI and BNP was associated with the worst prognosis.

The fore going has made the ACC/AHA Task Force on Practice Guidelines to recommend measurement of cTn to be routine in this ADHF patients.[48]

Compared with conventional troponin assays, hsTn methods detect substantially more myocardial necrosis in patients with HF and are incrementally prognostic, typically providing information that is additive to the natriuretic peptides and other biomarkers such as soluble ST2. [459] In the context of AHF therefore, elevated hsTn should not be assumed to be from acute coronary syndrome (ACS) but should be interpreted in the overall clinical picture especially because such increase during hospitalization or at discharge is predictive of a worse prognosis. [460] In summary, troponins identify both death and recurrent AHF episodes requiring readmissions and the hsTn has a graded association with mortality and is of independent prognostic importance.[455]

1.11 Differential Diagnoses of Acute Heart Failure Syndrome

Acute dyspnea is mostly due to potentially life-threatening cardiac or respiratory conditions, and treating it promptly requires understanding of the underlying mechanisms. Other than AHFS, a number of disorders can present with acute dyspnea, including COPD, asthma, pulmonary embolism, pneumonia, metabolic acidosis, neuromuscular weakness, and others. Depending on the hospital setting, AHFS accounts for 30% to 70% of acute dyspnea in the emergency unit. [461] Rapid identification of AHFS remains crucial and lifesaving, and may lead to prompt admission of the patient into the intensive care. Early diagnosis of AHFS was shown to be cost-effective and to reduce the hospital length of stay. [462] Thus, a simple and quick way of differentiating cardiac and pulmonary causes of dyspnea is essential in patients admitted to the emergency unit.

In practice, medical history, symptoms, physical examination, chest X-ray, ECG, and, more recently, use of biomarkers like BNP are sufficient to recognize AHFS in most patients presenting with acute dyspnea. Other investigations like echocardiography or cardiac catheterization (discussed above) require time and expertise and thus cannot be used as a screening procedure. Table 1.15 identifies some of the common differential diagnosis of AHFS and their characteristics.

Table 1.15 Differential diagnoses of acute heart failure syndrome

Differential	Features
COPD	Smoking Chronic bronchitis Low PEF Hypercapnia
Asthma	Young patient Atopy Previous exacerbation Low PEF β2-agonists effective
Pulmonary Embolism	Probability clinical score D-dimer ELISA test for patients with low probability clinical score
Respiratory Infection	Rare cause of acute dyspnoea Fever, Purulent sputum
Interstitial and other lung diseases	Exacerbation of other chronic respiratory conditions (tuberculosis sequelae, interstitial lung diseases, cystic fi brosis, and others) Less frequent cause of acute dyspnea in the ED. BNP BNP level <100 pg/mL
ARDS	Presence ARDS risk factor Normal cardiac silhouette Peripheral topography of infiltrates and absence of Kerley's B lines on CXR, BNP level <100 pg/mL
Spontaneous Pneumothorax	Young smokers CXR is diagnostic
Pericardial/pleural effusion	Echo/CXR diagnostic

ARDS, acute respiratory distress syndrome; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; CT, CXR, chest x-ray; ECG, electrocardiogram; ELISA, enzyme-linked immunosorbent assay; PEF, peak expiratory flow.

1.12 Treatment of Acute Heart Failure

The available treatment options for AHF have been largely empirical and limited by an incomplete understanding of the epidemiology and pathophysiology of the condition. The current general approach focuses on the successful treatment of clinical and hemodynamic congestion, while limiting untoward effects on myocardial or end-organ function, identifying addressable triggers, and optimizing proven long-term therapies.[325]

The use of invasive hemodynamic management with pulmonary artery cath-eterization may be a useful strategy in the management of some patients with AHF. This is an invasive procedure that provides detailed hemodynamic data, including direct assessment of filling pressures and cardiac output, and calculation of pulmonary and systemic vascular resistance. It has the potential risks of bleeding, infection, arrhythmias, and rare catastrophic events, such as pulmonary artery rupture or infarction.

As mentioned earlier there is a complex interaction of structural, functional, cellular, genetic, neurohormonal, and inflammatory factors in AHF. This makes its pharmacological treatment challenging especially as regards to short- and long-term benefits. Currently pharmacological treatment for AHF is still based on the use of intravenous diuretics in a combination of series drugs such as vasodilators, (nitrates , levosimendan), ACE inhibitors, oxygen, digoxin and morphine. Dopamine should be used in patients with AHF complicated by cardiogenic shock. [463] There is a growing evidence for and interest in the use of novel drugs that are potent vasodilators with diuretic and natriuretic properties such as ularitide and relaxin. Other molecules

acting at various levels of cardiac smooth muscle cells, arterioles or renal blood flow are currently being investigated. [463] Table 1.16 Summarizes the emerging medical therapies in AHF.[325,463]

Table 1.16 Emerging medical therapies in acute heart failure

Drug	Mechanism of Action	Trail/Study	Results
Ularitide	Natriuretic peptide	TRUE-AHF	Improves haemodynamics, symptoms and signs, no WRF
Relaxin	Peptide, a recombinant analog of the endogenous human hormone, relaxin Releases nitric oxide, inhibits endothelin and angiotensin II	RELAX-AHF	Relief of dyspnea and with a decrease in the combined endpoint of cardiovascular death and readmission at 60 days
Omecamtiv Mecarbil	Cardiac myosin activator that increases the transition of the actin-myosin complex and inhibits the nonproductive hydrolysis of (ATP).	ATOMIC AHF	dose-dependent increases in systolic ejection time, fractional shortening, stroke volume, and ejection fraction and was well tolerated over a broad range of plasma concentrations.
Cledivipine	Short-acting calcium channel blocker Selectively dilates arterioles and has no effect on myocardial contractility	open-label study performed in AHF patients with systolic blood pressure over 160 mmHg in the emergency.	significant dyspnea improvement for up to 3 hours, and a blood pressure improvement
Istaroxime	Inotropic, Lusitropic peptide. Stimulates membrane-bound Na-K/ATPase and enhances the activity of SR Ca/ ATPase type 2a	HORIZON –HF	reduced pulmonary wedge pressure, improved diastolic function and cardiac index, and increased systolic blood pressure in AHF patients compared with placebo
Cinaciguat	Activates soluble guanylate cyclase, thus increasing cGMP production in smooth muscle cells	COMPOSE	Improve haemodynamics; decrease of systolic blood pressure and improvement of cardiac output but causes hypotension
Stresscopin,	Urocortin, a peptide	Studies in HF	dose-related increases in

	hormone that bind with strong affinity to the corticotropin-releasing hormone receptor type 2 (CRH-R2), which is highly expressed in the myocardium Inotropic and Lusitropic	patients	cardiac output, heart rate, and LV ejection fraction while decreasing systemic vascular resistance.
Aliskiren	Direct renin inhibitor	ASTRONAUT	No reduction in CV death or HF rehospitalization at 6 months or 12 months after discharge.
Rolofylline	Reno protective agent - Adenosine A1 receptor antagonists have been developed to increase renal blood flow and enhance diuresis	PROTECT	No clinical benefit, including renal protection, associated with more seizure and stroke events when compared with placebo

TRUE-AHF, Trial of Ulatiride's efficacy and safety in patients with AHF; RELAX-AHF, Relaxin in AHF; ATOMIC-AHF, Acute Treament with Omecamtiv Mecarbil to Increase Contractility in AHF; HORIZON HF, Haemodynamic Effects of Istaroxime in patients with worsening HF and reduced LV systolic function; COMPOSE, Efficacy and Tolerability of Cinaciguat given intravenously in patients with ADHF; ASTRONAUT, Aliskiren Trial on AHF; PROTECT, Placebo Controlled Randomized Study of the Selective A1 Adenosine receptor antagonist Rolofylline for patients hospitalized with ADHF.

Despite recent advances in pharmacological management, the prognosis of patients with ADHF remains poor. Consequently, non-pharmacological approaches are being developed and increasingly used. Such techniques may include several modalities of positive airway pressure therapy, ultrafiltration, mechanical circulatory support (MCS), myocardial revascularization, and surgical treatment, among others. Cardiac transplantation can also be considered as an option in severe AHF known to have poor outcome. However, transplantation cannot be done until patient is stable enough to undergo such major operation, until such MCS is what is required. [464]

1.12.1 Treatment of Acute Heart Failure in sub Saharan Africa

The treatment of AHF in sub Saharan Africa is not different from the rest of the world. However, the THESUS-HF[36] data provided some important observations about medical therapy for AHF (Figure 1.19).[36] First, there was a high incidence of the use of aspirin in patients with non-ischemic HF in the sub-Saharan African region. Secondly, the rate of beta-blocker use, even at follow-up, is relatively low. Although many patients in THESUS -HF have HF with preserved systolic function for which the use of beta blockers is less clearly indicated, the rate of beta blocker use in THESUS–HF is lower than that described in other regions.[83,465] Thirdly, despite the encouraging results of A-HeFT,[52,465] the THESUS-HF data show that patients in sub Saharan Africa are rarely treated with a combination of hydralazine and nitrates, or the fixed-dose combination BiDil that was used in A-HeFT, since this preparation is unavailable in Africa.[36] These observations provided an opportunity to improve the quality of the care of patients with HF in the region. This led to a randomized study (BAHEF)[466] investigating the combination treatment with hydralazine and nitrates (HYIS) versus placebo in Africans admitted with AHF. This study was planned and carried out in nine centres in 6 sub-Saharan African counties to examine the short-term (6 months) effects of HYIS in patients admitted for AHF.

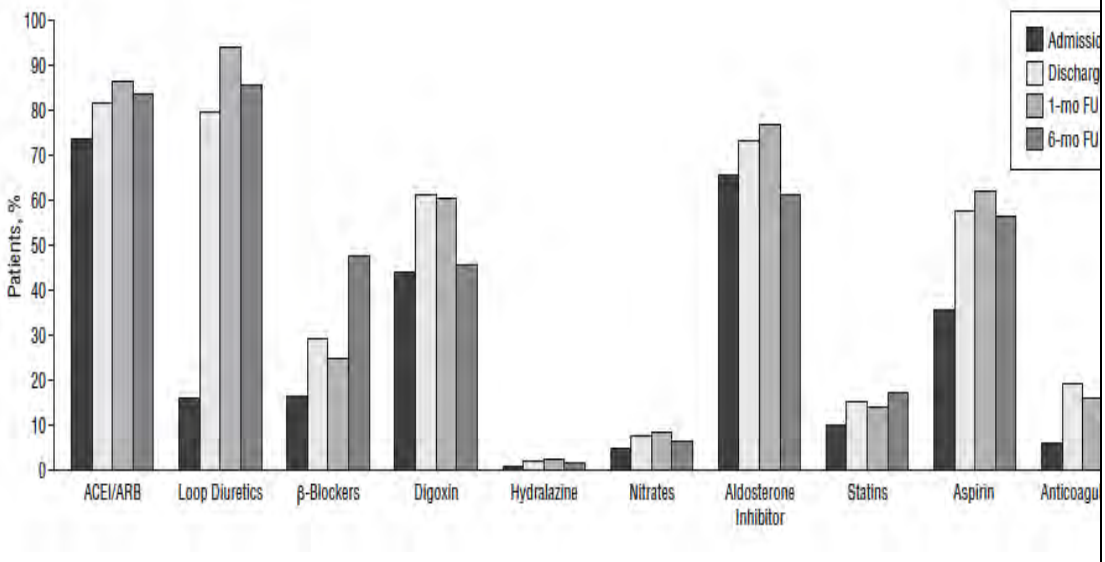

Figure 1.19 Prescribed oral medication in sub Saharan Africa (adapted from Damasceno et al 2012)

Although the primary endpoint in BAHEF was not met due to poor recruitment, however, the results from the limited data set for several secondary outcomes were consistent with expected effects of HYIS, including a lower rate of cardiovascular mortality through 24 weeks, a non-statistically significantly lower number of HF and all-cause admissions per patient, and fewer days dead or in hospital in the active arm. Other findings consistent with a benefit include that in the HYIS group compared with the placebo group, by 24 weeks systolic BP dropped more, weight decreased more, 6MWT improved more, and there was a larger drop in BUN. On echocardiographic evaluation, parameters such as improvement in the LVEF, and a decrease in LV end-systolic diameter and LV end-diastolic diameter all favoured the active group, although again in a statistically non-significant manner. [466]

1.13 Knowledge gaps and implications for Sub Saharan Africa

This chapter has presented a review of contemporary literature on AHF with emphasis on sub Saharan Africa.

Despite advancement in medical therapeutics, AHF has remained the most common reason for hospital admission in patients over the age of 65 years and its prognosis still dismal, with over 20% of the patients being readmitted with HF and over 20% dying during the first year after initial admission[81].

Acute heart failure is a major health issue, accounting for a large proportion of patients admitted to hospitals. Patients with recent hospitalizations for AHF are at high risk for future cardiovascular events and death. [467] In contrast to treatments for chronic heart failure, advances in the management of AHF have been limited while its incidence has been increasing in developed countries.

The reviewed literature showed that current knowledge on epidemiology of HF in general and AHF in particular is based on studies in Europe and America with very few studies from Africa. Africa is witnessing a population explosion, increased life expectancy in many countries resulting in increasing HF prevalence. The continent also has both endemic and emerging causes of HF. In addition, the data on HF obtainable from studies in SSA are limited with most of them based on clinical diagnosis alone with few having echocardiography or biomarkers.

In most SSA countries, AHF has not been well studied and the incidence, prevalence, treatment and outcomes of AHF are not well defined. There is also limited information on the characteristics, outcome and its predictors of heart failure in general and AHF in particular. Study of clinical characteristics of AHF patients

including the role of the conventional and novel biomarkers in diagnosis and outcome will guide appropriate clinical decisions on treatment and proper monitoring. This can also allow designing specific strategies tailored to particular communities or countries based on their needs, for example control of hypertension and adequate treatment for pharyngitis to prevent Rheumatic fever. Because HF is both a preventable and treatable disease, early diagnosis and treatment of heart failure can lead to dramatic decreases in the morbidity and mortality.

The findings obtained will also serve as baseline data on which larger initiatives exploring both pathophysiology and treatment of AHF would be built upon in the future. They can also be the bases for adequate planning for reduction of morbidity and mortality from AHF.

In the next chapter, we present the hypothesis, aims and specific questions investigated in this doctoral research.

2 CHAPTER 2: HYPOTHESIS, AIMS AND SPECIFIC OBJECTIVES

2.1 Hypothesis

We hypothesized AHF in SSA to have significant morbidity and mortality, affecting young patients in their prime of life. We also hypothesize that NT-pro BNP and the novel biomarkers GDF-15 and Gal3 will have a role in predicting outcome in this setting.

2.2 General Aim

The primary aim of this doctoral research project is to investigate the clinical characteristics and short-term (6 months) outcome of acute heart failure as well as determine the role of conventional biomarker NT-pro BNP and the novel biomarkers GDF -15 and Galactin 3 in the prognostication of acute heart failure patients in sub Saharan Africa.

2.3 Specific objectives

To fulfill the aim of this project the following specific objectives were pursued as shown on Figure 2.1

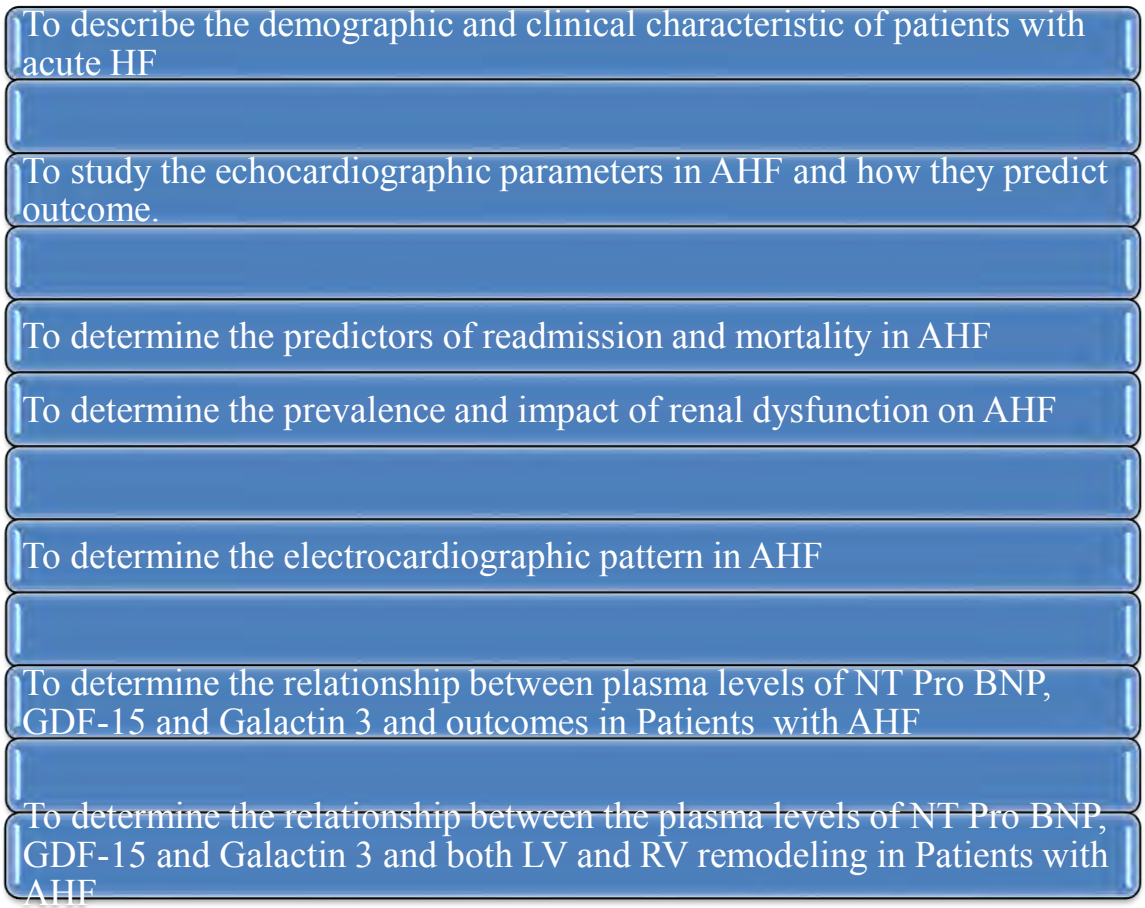

Figure 2.1 Specific objectives of the thesis

2.4 Outcome Measures

The outcome measures that were examined in the study are shown below in Figure 2.2

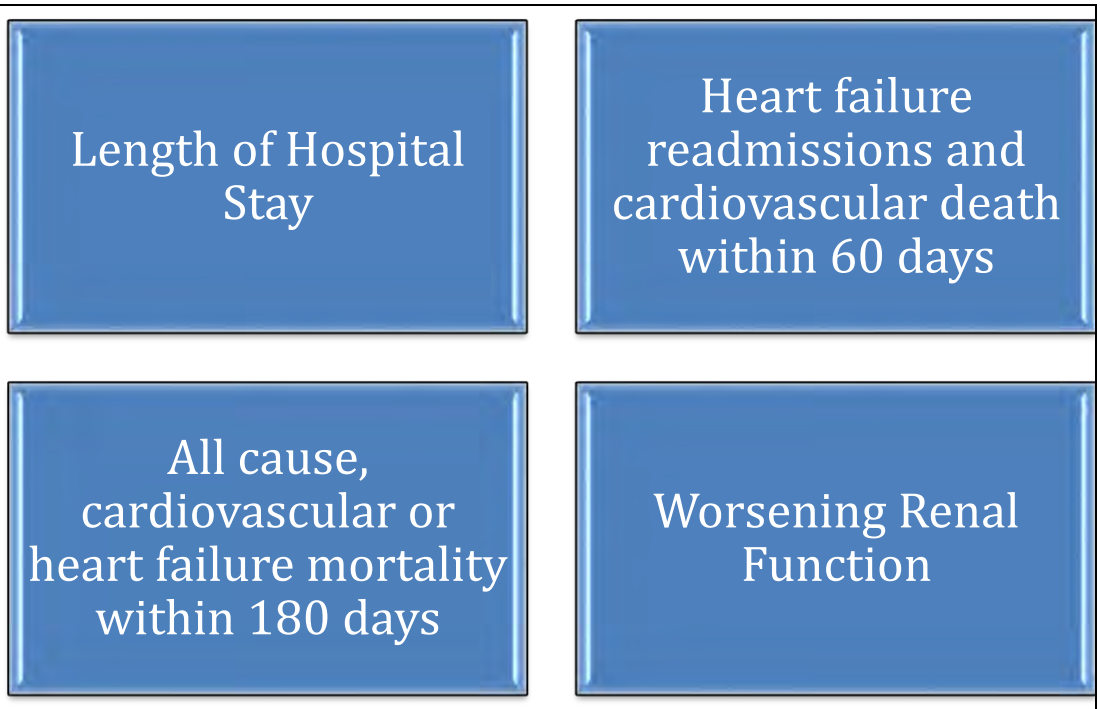

Figure 2.2 Outcome measures of the study

2.5 Protocol Modification

In the course of this study, there was a slight modification in the submitted protocol as regards the biomarker assessment. Because of limitations to obtain the funding for specific assays due to the weakening Rand and therefore doubling of the costs one of the assays, GDF – 15 assay was not carried out. This neither affected the overall aim of the study nor the outcomes.

3 CHAPTER 3: OVERVIEW OF STUDY METHODS

3.1 Introduction

This thesis involved cohorts of AHF patients from two prospective studies. Both the studies were conducted in centres in SSA. They both adhere to the Declaration of Helsinki. Ethical clearance for all studies was granted by the Human Research Ethics Committee of the University of the Cape Town as well as the ethical committees of the various centres involved.

3.2 Study Populations

The first cohort include patients recruited for the sub Saharan African Survey on Heart Failure (THESUS-HF), which is a multicenter prospective observational clinical registry for hospitalized patients with AHF. The second cohort include patients recruited for the Bi treatment with hydralazine/nitrates versus placebo in Africans admitted with acute heart Failure in (BAHEF) which is a prospective, placebo controlled double blind randomized study to compare treatment with hydralazine – isorsobide dinitrate versus placebo on top of standard care in African patients admitted with AHF. Patients were considered to have AHF if they were admitted with acute dyspnea and the presence of heart failure signs by physical examination with at least 2 of the following: rales, edema, elevated JVP, hepatomegaly and ascites. Stable outpatient chronic heart failure cases were excluded. Details of inclusion and exclusion criteria for THESUS-HF and BAHEF studies are shown in Table 3.1 and 3.3 respectively.

Data collected from AHF patients enrolled in both studies were analyzed. These include demographic information (age gender, ethnicity), clinical and laboratory data

collected at the time of enrollment. They included extensive documentation of their HF state, CV history, general medical history, and management, including careful recording of medication usage.

3.3 Study Design

3.3.1 The sub Saharan African Survey on Heart Failure (THESUS-HF)

The study was a multicenter prospective observational clinical registry. Patients hospitalized with AHF were screened and enrolled if they met entry criteria as early as possible following admission.

Patients had their baseline clinical and laboratory data collected at the time of enrollment. In addition, daily follow-up medical data were collected concerning the patient's course in the hospital with particular attention to the HF symptoms and signs, recurrent or persistent HF events, medications administered including intravenous diuretics, vasodilators and inotropes.

Patients were followed-up through telephone call 30-180 days after enrollment to collect data on vital status, hospital re-admissions, clinical status and outcome.

Table 3.1 Inclusion and Exclusion criteria of the THESUS-HF registry

Inclusion criteria

1. Age $\geq$ 12 years
2. Hospital admission for acute heart failure as defined by the presence of acute dyspnea and the presence of heart failure signs by physical examination
3. Physical findings of congestive heart failure (pedal oedema, raised jugular venous pressure, pulmonary congestion, and tender hepatomegaly)
4. NT-proBNP >900 pg/ml, > 1800 pg/ml if the patient has Atrial fibrillation at screening or > 450 pg/ml if BMI > 35 kg/m^2.
5. Subjects with primary diagnosis of acute HF regardless of the cause.
6. Availability of regular follow up

Exclusion criteria

1. Severe known renal failure (patient on dialysis or creatinine > 4 mg/ml), nephrotic syndrome, hepatic failure or other cause of hypoalbuminaemia.
2. Reversible etiology of acute heart failure such as myocarditis, acute myocardial infarction, arrhythmia
3. Recent Acute coronary syndromes within 2 weeks from screening
4. Non-cardiac pulmonary edema
5. Patients' refusal or inability to sign informed consent or patient refusal to participate in the study.

Table 3.2 Details of patients' evaluation in the THESUS-HF registry

First Assessment	Hospitalization, discharge and follow up
1. Inclusion and exclusion criteria 2. Demographics 3. Heart failure history (if any) and its etiology 3. Comorbidities 4. Medications prior to admission 5. Total IV diuretics and other vasoactive drugs administered during first hours of admission 6. O_2 saturation and vital signs (systolic and diastolic BP and pulse). 7. Fever and weight. 8. Symptoms and signs of heart failure (orthopnea, dyspnea at rest, dyspnea during exercise, fatigue, paroxysmal nocturnal dyspnea, NYHA class, rales on lung bases, JVP and peripheral edema).- These will be recorded based on file information and the first measurement of study coordinator after consent. 9. NT pro BNP, troponin, renal function and electrolytes (sCr, Bun, K+, Mg+, Na+).	1. O_2 saturation and vital signs (BP and pulse) at 3,6 and 24 hours, discharge or 7 days, 30 days and 6 months follow up 2. Fever, blood pressure and weight at 1,2 and 7 days or discharge, 30 days and 6 months follow up. 3. Symptoms and signs of heart failure (orthopnea, dyspnea at rest, dyspnea during exercise, fatigue, paroxysmal nocturnal dyspnea, NYHA class, rales on lung bases, JVP and peripheral edema) at 6, 24 and 48 hours, 7 days or discharge and 30 days and 6 months follow up. 4. NT pro BNP and troponin, renal function and electrolytes daily (sCr, Bun, K+, Mg+, Na+). 5. Echo including LVEF, RVEF, wall motion, cavity size, pressures, valvular function, diastolic function 6. Medical Rx at 1, 2 and 7 days (or discharge) as well as follow up. 7. Worsening heart failure events or death either during the initial admission or leading to repeated admissions.

3.3.2 Bi treatment with hydralazine/nitrates versus placebo in Africans admitted with acute heart Failure in (BAHEF)

This was a prospective, randomized, double-blind, placebo controlled trial comparing the combination of isosorbide dinitrate and hydralazine (HYIS) with placebo. Patients were screened within 96 hours from admission for AHF. Patients were evaluated for inclusion and exclusion criteria and underwent echocardiographic examination, serum chemistry (Cr and BUN), NT-pro-BNP. Patients willing to participate in the study and who signed an informed consent were randomized to receive either HYIS or placebo. Randomized patients underwent full clinical evaluation including physical examination, collection of patient's self-report of dyspnea severity by a visual assessment scale (VAS), and physician's assessment of heart failure signs and symptoms. At selected centers, blood was drawn for central assessment of inflammatory, neurohormonal and novel biomarkers. Patients were started at the study drug low dose, and up-titrated to the higher dose at 2 weeks depending on tolerability. Patients were followed up from randomization to discharge; pre-discharge evaluations were conducted at the earlier of day 7 or discharge and included dyspnea assessment, physical examination and measurement of NT-pro-BNP. Post-admission follow-up included clinic visits every 4 weeks through 24 weeks follow up. Evaluations at 8 weeks and 24 weeks included dyspnea assessment, physical examination, and laboratory assessments. Patients who discontinued the study drug prior to 24 weeks were still followed up through 24 weeks.

After the initial 24 weeks double-blind phase of the study, patients were given the option of continuing in the open-label extension of the study. In this phase, patients

were treated with active HYIS for up to an additional 24 weeks. They were followed up every 4 weeks through 24 weeks.

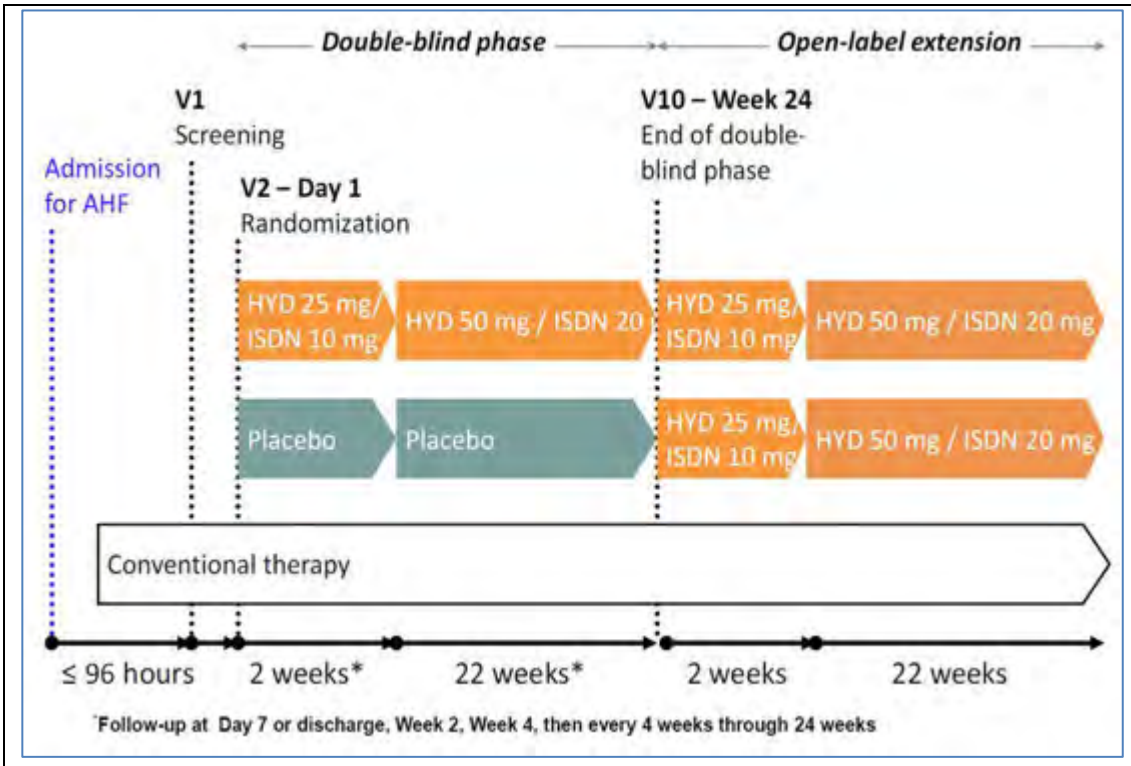

Figure 3.1 Schema of the BAHEF study

Table 3.3 Inclusion and Exclusion criteria of the BAHEF study

Inclusion criteria

≥18 years of age

Hospital admission for acute heart failure as defined by the presence of acute dyspnea and the presence of heart failure signs by physical examination with at least 2 of the following: rales, edema, elevated JVP, hepatomegaly, ascites

NT-proBNP >900 pg/ml, > 1800 pg/ml if the patient has Atrial fibrillation at screening or > 450 pg/ml if BMI > 35 kg/m^2.

LVEF <45% assessed by echocardiography or other method within the previous 12 months

Background therapy with at least ACE-inhibitor or ARB and beta-blocker (unless beta-blocker is contraindicated due to severe volume overload, low output heart failure, or cardiogenic shock)

Available for regular follow up

Exclusion Criteria

Any intravenous treatment for heart failure, except IV furosemide (e.g. IV inotropes, pressors, nitrates, or nesiritide) at the time of screening

Systolic blood pressure <100 mmHg

Greater than 96 hours after admission

Reversible etiology of acute heart failure such as myocarditis, acute myocardial infarction, arrhythmia

Hypertrophic obstructive cardiomyopathy, restrictive or constrictive cardiomyopathy, endomyocardial fibroelastosis

Known severe congenital heart disease (such as uncorrected tetralogy of fallot or transposition of the aorta)

Significant stenotic valvular disease

Renal impairment (defined by creatinine > 3 mg/dL) at screening or on any type of dialysis

Women who are pregnant or lactating

History or presence of any other disease including AIDS and malignancy with life expectancy of < 12 months

3.4 Consent

In both the two studies, subjects were required to provide written informed consent to participate in the study in question.

3.5 Enrolment and data collection

All hospital admissions for which dyspnea was the main complaint were screened. Patient adjudicated to have AHF that satisfies the inclusion criteria were enrolled in the studies.

Data from each subject were obtained using a uniform and standardized CRF. The data obtained included: study identification number, demographic data, date of diagnosis of HF and pre-admission history (previous HF related admissions). Others include NYHA functional class, symptoms, signs, self-reported CV risk factors, aetiology of HF, precipitating factor, co-morbidities, blood investigations, Chest X-ray , 12-lead ECG, echocardiography and medications.

3.5.1 Anthropometric Measurements

The height and weight of the subjects were measured. Height and weight were measured with the participants standing, wearing indoor clothes with no shoes. Body mass index was calculated as weight in kilograms divided by the square of height in meters.

3.5.2 Blood Measurements

Blood samples were drawn for fasting blood sugar, fasting lipid profile, electrolyte, urea and creatinine and full blood count.

In addition to the above blood tests, another 20mls were collected from each patient for assays of NT-pro BNP of Gal3, for patients from the second cohort of the study (BAHEF). The blood was transfused into EDTA tubes and samples were immediately centrifuged, plasma was separated and then stored at -80 degrees Celsius until assayed. Samples were transported from the various centres in dry ice and shipped to the Hatter Institute for Cardiovascular research in Africa (HICRA). Plasma NT-Pro BNP was measured by a standard electrochemiluminescence immunoassay. NT-Pro BNP levels were measured from a banked aliquot from stored blood samples using BNP EIA fragment kit from Biomedica Gruppe. A sensitive and specific non-radioactive immunoluminometric (ILMA) assay based on competitive ligand binding was used. Plasma Gal3 was assayed using human Gal3 enzyme linked immunosorbent (ELISA) assay for in vitro diagnostic use (Human Galectin-3 Platinum Elisa, eBiosciences). Both assays were performed at the HICRA.

3.5.3 Plasma NT-pro BNP Assay

We used BNP Fragment ELISA Assay kit (Cat no: BI-20852W, Standard range: 0 to 6400 pmol/L, Detection limit: 171 pmol/L) manufactured by Biomedica Gruppe.

This kit quantitatively determines the human BNP Fragment (NT-pro BNP 8-29) in serum, citrate plasma, EDTA plasma or heparin plasma.

Plasma NT-pro BNP was measured by a standard electrochemiluminescence immunoassay. NT-pro BNP levels were measured from a banked aliquot from stored blood samples. A sensitive and specific non-radioactive immunoluminometric (ILMA) assay based on competitive ligand binding was used. Stored samples were acidified with 1% trifluoroacetic acid (TFA) and loaded unto cartridges and eluted

with 1% TFA containing 60% acetonitrile. The samples were lyophilised in a centrifugal evaporator and re-dissolved in assay buffer consisting of 0.1mol/L sodium phosphate (pH 7.4), 0.1% Triton X-100 for the measurement. NT- pro BNP concentrations were determined blind to the clinical details of a subject.

The principle of the test: In a first step, sample and conjugate (sheep anti human NT-pro BNP-HRPO) are pipetted into the wells of the microtiter strips, which are pre-coated with polyclonal sheep anti NT-proBNP antibody. NT-proBNP present in the sample binds to the pre-coated antibody in the well and forms a sandwich with the detection antibody. In the washing step all non-specific unbound material is removed. In a second step, the substrate (TMB Tetramethylbenzidine) is pipetted into the wells. The enzyme catalysed colour change of the substrate is directly proportional to the amount of NT-proBNP present in the sample. This colour change is detectable with a standard microtiter plate ELISA reader (Figure 3.2).

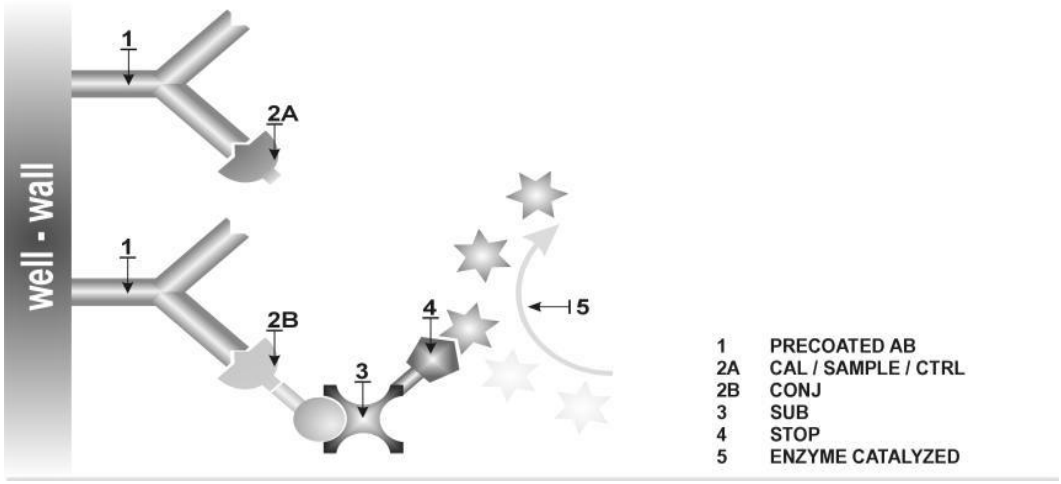

Figure 3.2 Principle of assay of BNP Fragment (NT-pro BNP 8-29) in human serum. AB, antibody; CTRL, control, CONJ, conjugate; SUB, substrate

The reagents are reconstituted as follows: The wash buffer (WASHBUF) was reconstituted by diluting the concentrate in a ratio of 1:20 (e.g. 50 ml of WASHBUF concentrate to 950 ml of distilled water. This is stable at 2-8 ^{o}C until its labeled expiry date. Only the diluted WASHBUF was used for the assay. The standard (STD) was reconstituted by pipetting 200 µl of distilled water into each vial. It was left for 20 min at room temperature (18 – 26 ^{o}C) and swirled gently. This is stable at - 25^{o}C or lower until its labeled expiry date. The control (CTRL) was reconstituted by pipetting 200 µl of distilled water into the vial. It was left for 20 min at room temperature (18 – 26 ^{o}C) and swirled gently. This is also stable at - 25^{o}C or lowers until its labeled expiry date. For the STD and the CTRL, care was taken to avoid freeze – thaw cycles. Figure 3.3 showed the NT-pro BNP assay kit used for the study.

Figure 3.3 Picture of the NT Pro BNP used for the study

The protocol of assay used is as follows (according to manufacturer's intructions): The reagents and samples were at room temperature (18-26°C) before use in the assay. The positions for BLANK/STD/SAMPLE/CTRL (Blank/Standard/Sample/Control) were marked on the protocol sheet. The microtiter strips were taken out of the aluminum bag, and a blank well was chosen. The unused strips were stored with desiccant at 4°C (2-8°C) in the aluminum bag. The following steps were then followed one after another:

1. 150 µ l of assay buffer (ASYBUF) was added to all wells except the blank
2. 30 µl of STD/SAMPLE/CTRL (Standards/Sample/Control) in duplicate was added into respective well, except blank.
3. 50 µl CONJ (Conjugate) was then added into each well, except blank and swirled gently.
4. Microtiter strips were covered tightly and incubated overnight (16 -25 hours) at 4°C (2-8 °C) in the dark.
5. The wells were aspirated and washed 5x with 300 µl diluted WASHBUF (Wash buffer), the remaining wash buffer was removed by hitting plate against paper towel after the last wash.
6. 200 µl SUB (Substrate) was then added into each well and incubated for 20 min at room temperature (18-26°C) in the dark.
7. 50 µl of STOP (Stop solution) was added into each well and shook well.
8. Absorbance was immediately measured at 450 nm with reference 630 nm.
9. The optical density (OD) of all wells was read on a plate reader using 450 nm wavelength (correction wavelength 630 nm).

10. The blank optical density (OD) was subtracted from the values of STD, CTRL and sample. A standard curve was constructed from the OD values of the STD. The sample concentration was obtained from a standard curve. Dilution factors were taken into consideration for calculation of the samples.
11. Using a graph paper, the sample concentration was obtained from this standard curve. The assay was evaluated with a 4PL algorithm.

3.5.4 Plasma Galectin - 3 Assay

Plasma galectin-3 was assayed using human Galectin-3 enzyme linked immunosorbent (ELISA) assay (eBioscience BMS279/4TEN, Plasma (EDTA) samples, Sensitivity: 0.29 ng/ml Range: 0.47-30 ng/ml) for in vitro diagnostic use.

The Gal3 levels were measured from a banked aliquot from stored blood samples in triplicate. Prior to assay, the frozen samples were brought to room temperature slowly and mixed gently. Gal3 concentrations were determined blind to the clinical details of a subject.

Principle of the test: An anti-human Galectin-3 coating antibody is adsorbed onto micro-wells. Human Gal3 present in the sample or standard binds to antibodies adsorbed to the micro-wells. A biotin-conjugated anti-human Galectin-3 antibody is added and binds to human Gal3 captured by the first antibody. Following incubation unbound biotin conjugated anti-human Galectin-3 antibody is removed during a wash step. Streptavidin- HRP is added and binds to the biotin conjugated anti-human Gal3 antibody. Following incubation unbound Streptavidin- HRP is removed during a wash step, and substrate solution reactive with HRP is added to the wells. A

coloured product is formed in proportion to the amount of human Galectin-3 present in the sample or standard. The reaction is terminated by addition of acid and absorbance is measured at 450 nm. A standard curve is prepared from 7 human Gal3 standard dilutions and human Gal3 sample concentration determined.

The kit reagents were stored between 2° and 8°C. Immediately after use remaining reagents were returned to cold storage (2° to 8°C).

The Buffer Concentrates were brought to room temperature and diluted according to the manufacturer's recommendation before starting the test procedure. If crystals have formed in the Buffer Concentrates, they were gently warmed until they have completely dissolved. The dilution of the Buffer Concentrates was as follows: Wash Buffer Concentrate (20x ie 50 ml:950 ml of distilled water), Assay Buffer Concentrate (20x – 5ml : 95 ml of distilled water), Biotin conjugate (1:100 dilution of the concentrated Biotin-Conjugate solution with Assay Buffer (1x)) and Streptavidin-HRP (1:400 dilution of the concentrated Streptavidin-HRP solution with Assay Buffer (1x)). The Wash Buffer (1x) and the Assay Buffer (1x) are stable for 30 days. The Biotin-Conjugate and the Streptavidin-HRP were used within 30 minutes of dilution, in keeping with manufacturer's recommendation.

The human Gal3 standard was reconstituted by addition of distilled water to give a concentration of 50 ng/ml. The standard was allowed to reconstitute for 10-30 minutes before dilutions were made. The remaining standard was discarded after use.

For eternal standard dilution, 7 tubes were labeled S1, S2, S3, S4, S5, S6, S7 one for each standard point. We then prepared 1:2 serial dilutions for the standard curve as

follows: 225 µl of Sample Diluent was pipetted into each tube. Then 225 µl of reconstituted standard (concentration = 50 ng/ml) was pipetted into the first tube, labelled S1, and mix (concentration of standard 1 = 25ng/ml). Thereafter 225 µl of this dilution was pipetted into the second tube, labelled S2, and mix thoroughly before the next transfer. These serial dilutions were repeated 5 more times thus creating the points of the standard curve.

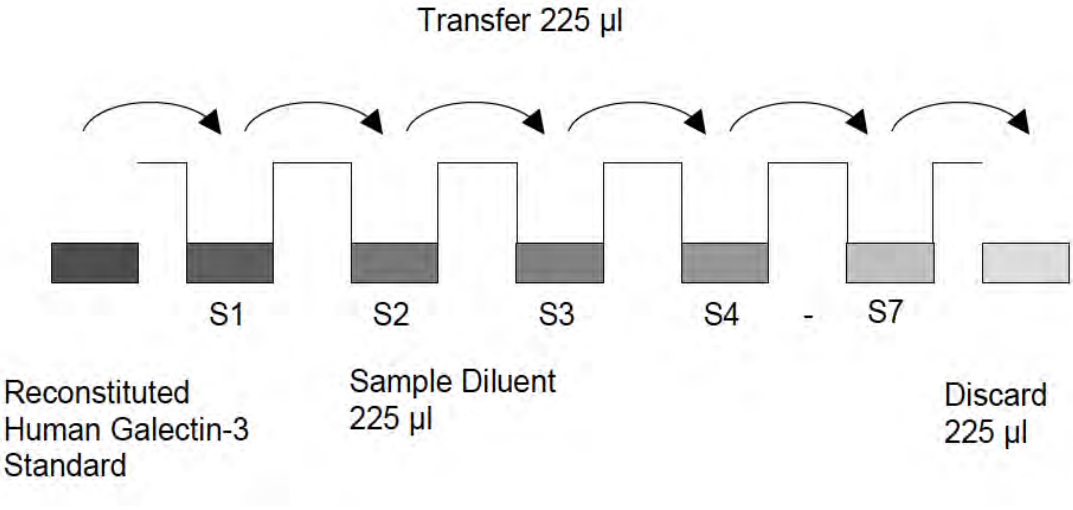

Figure 3.4 Serial dilutions of human galectin-3 standard

The protocol of the assay is as follows (according to manufacturer's intructions): We determined the number of microwell strips required to test the desired number of samples plus appropriate number of wells needed for running blanks and standards. Each sample, standard, blank and optional control sample was assayed in duplicate.

Table 3.4 Micro wells strips for galectin-3 assay - 7 Standard concentrations: 25, 12.5, 6.25, 3.13, 1.56, 0.78, 0.39 ng/ml

	1	2	3	4	5	6
A	Blank	STD4	Sample 1	Sample 1	Sample 5	Sample 9
B						
C	STD1	STD5	Sample 1	Sample 2	Sample 6	Sample 10
D						
E	STD2	STD6	Sample 1	Sample 3	Sample 7	Sample 11
F						
G	STD3	STD7	Sample 1	Sample 4	Sample 8	Sample 12
H						

The following steps were then followed:

a. We washed the micro-well strips twice with approximately 400 µl Wash Buffer per well with thorough aspiration of micro-well contents between washes. The Wash Buffer was allowed to sit in the wells for about 10 – 15 seconds before aspiration.

b. After the last wash step, the wells were emptied and micro-wells strips tapped on absorbent pad or paper towel to remove excess Wash Buffer. Care was taken not to allow the wells to dry.

c. 100 µl of Sample Diluent was added in duplicate to all standard wells. 100 µl of prepared standard was then pipetted in duplicate into the first 2 well in the first row (wells A1, A2). The contents were mixed well (concentration of standard 1, S1 = 25 ng/ml), and 100 µl from these well was transferred to the first 2 well in the second row (wells B1, B2), respectively. This procedure was continued 5 times, creating

two rows of human Galectin-3 standard dilutions ranging from 25.00 to 0.39 ng/ml. 100 µl of the contents from the last microwells (G1, G2) used was discarded.

d. 100 µl of Sample Diluent was added in duplicate to the blank wells.

e. 50 µl of Sample Diluent was added to the sample wells.

f. 50 µl of each sample was added in duplicate to the sample wells.

g. 50 µl of Biotin-Conjugate was added to all wells. Biotin –Conjugate had to be used within 30 minutes of preparation

h. The microwell strips were covered with an adhesive film and incubated at room temperature for 2 hours, on a microplate shaker set at 400 rpm.

i. The adhesive film was removed the wells were emptied wells. The microwell strips were washed 3 times in accordance with the test protocol.

j. 100 µl of diluted Streptavidin-HRP was added to all wells, including the blank wells. Streptavidin – HRP had to be used within 30 minutes of preparation

k. The micro-well strips were covered with an adhesive film and incubated at room temperature for 1 hour, on a micro-plate shaker set at 400 rpm.

l. The adhesive film was removed the wells were emptied wells. The microwell strips were washed 3 times in accordance with the test protocol.

m. 100 µl of TMB Substrate Solution was pipetted to all wells.

n. The micro-well strips were incubated at room temperature for about 10 min, avoiding direct exposure to intense light.

o. The colour development on the plate was monitored and the substrate reaction stopped. The stop solution was added when the highest standard has developed a dark blue colour or when Standard 1 has reached an optical density (OD) of 0.9 –

0.95, monitored by the ELISA reader at 620 nm (Figure 3.5).

q. The enzyme reaction by quickly stopped by pipetting 100 µl of Stop Solution into each well. It was spread quickly and uniformly throughout the micro-wells to completely inactivate the enzyme.

Figure 3.5 Colour change in after adding the Stop solution to the Standard

r. Results were read immediately after the Stop Solution is added. The absorbance of each microwell was read on a spectro-photometer using 450 nm as the primary wave length. (optionally 620 nm as the reference wave length; 610 nm to 650 nm is acceptable). The absorbance of both the samples and the standards were determined. If incubation was done without micro-plate shaker, the obtained O.D. values may be lower, but the results are still valid (Figure 3.6).

Figure 3.6 Measurement of optical densities using spectrophotometer (left side of the picture). The values are read on the computer screen (right side)

s. The average absorbance values were calculated for each set of duplicate standards and samples. Duplicates should be within 20 per cent of the mean value. A standard curve was created by plotting the mean absorbance for each standard concentration on the ordinate against the human Galectin-3 concentration on the abscissa. The best fit curve was drawn through the points of the graph (a 5-parameter curve fit is recommended).

t. The concentration of circulating human Gal3 for each sample was determined, first by finding the mean absorbance value on the ordinate and extending a horizontal line to the standard curve. At the point of intersection, a vertical line was extended to the abscissa and the corresponding human Gal3 concentration was read

u. The concentration read from the standard curve was multiplied by the dilution factor (x 2 - 50 µl sample + 50 µl Sample Diluent).

v. Samples with a concentration exceeding standard 1 were repeated with further

external pre-dilution according to expected human Gal3 values with Sample Diluent in order to precisely quantitate the actual human Gal3 level. If this is not done, the values will be incorrectly low human Gal3 levels (Hook Effect).

w. To validate the results, the laboratory control sample of known human Galectin-3 concentration was run with each assay.

Figure 3.7 below shows the picture of human Gal3 kits used for the project

Figure 3.7 Galectin-3 assay kits used for the study

3.6 Transthoracic Echocardiography

Subjects were examined in the left lateral decubitus position using standard parasternal, short-axis and apical views. Studies were performed according to the recommendations of the American Society of Echocardiography (ASE). [468] M-mode echocardiograms were derived from 2D images. The M-mode cursor on the 2D scan was moved to specific areas of the heart to obtain measurements, according to the recommendation of the committee on M-mode standardization of the ASE. Measurements were averaged over 3 cardiac cycles. The LV measurements taken include inter-ventricular septal thickness at end diastole (IVSd), the posterior wall thickness at end diastole (PWD), LV end diastolic diameter (LVEDD) and LV end systolic diameter (LVESD) (Figure 3.8). LV systolic function was calculated by Teichholz's formula. [469] LV mass (LVM) was calculated using the formula of Teichholz: LVM = 0.8 [1.04 37 (IVSTd + LVIDd + PWT d) 3 + 0.6g].

This has been shown to yield values closely related to necropsy left ventricular weight and that has good inter study reproducibility (r=0.90). The left and right atria areas were measured at end-ventricular systole when the atria chambers were at their greatest dimension, and with the bases of both atria at their greatest dimensions.

LV inflow velocities were measured using pulsed-wave Doppler from the apical 4-chamber view, with the sample volume located between the tips of the mitral valve leaflet during ventricular diastole. Peak velocity of early rapid filling (E), peak velocity of late filling caused by atrial contraction (A) and the interval from peak of E wave to its extrapolation to the baseline or deceleration time (DT) were measured. The ratio of peak E-wave to A- wave was calculated. Diastolic function was categorized using mitral inflow and Doppler Tissue Imaging parameters. Grade 3 diastolic dysfunction or restrictive filling pattern was defined as E/A ratio greater than 2, with deceleration less than 130 milliseconds. Grade 1 diastolic dysfunction was defined as E/A ratio less than 1 and a deceleration time of 220 milliseconds, while grade 2 diastolic dysfunction or pseudo-normal filling was diagnosed when deceleration time was greater than 220 milliseconds and the E/A ratio was between 1 and 2.

RV remodeling was assessed using the RV size and wall thickness as well as the RV systolic function. RV systolic function was assessed on echocardiography using M-mode recordings through the lateral tricuspid valve annulus for the purpose of measuring the tricuspid annular plane systolic excursion (TAPSE). TAPSE is a method used to measure the distance of systolic excursion of the RV annular segment along its longitudinal plane, from a standard apical 4-chamber window.

TAPSE represents longitudinal function of the right ventricle. It is inferred that the greater the descent of the base in systole, the better the RV systolic function. TAPSE is usually acquired by placing an M-mode cursor through the tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole (Figure 3.9). [470] A TAPSE value less than 16 mm denotes right ventricular systolic dysfunction. [471]

Echocardiography examinations also included assessment of valvular architecture; a semi-quantitative estimate of the severity of valvular regurgitation; and presence of pericardial effusion. Other abnormalities like evidence of pulmonary arterial hypertension were also noted. The pulmonary artery systolic pressure (PASP) was estimated by measuring the maximum velocity of the tricuspid regurgitant velocity (TRV), the trans-tricuspid pressure gradient was then calculated using the modified Bernoulli equation $4(TRV)^2$ (Figure 3.10). [472] The right ventricular systolic pressure (RVSP) was calculated using the formula: RVSP = 4(TRV)2 + Right Atrial Pressure(RAP). The TRV was measured from the continuous wave Doppler of tricuspid regurgitant jet from apical four-chamber or from the parasternal right ventricular inflow view if the regurgitant jet was eccentric. The PASP is equivalent to RVSP in the absence of pulmonary outflow obstruction. The RAP is estimated by the respiratory variation size of the vena cava inferior in M-mode. [473]

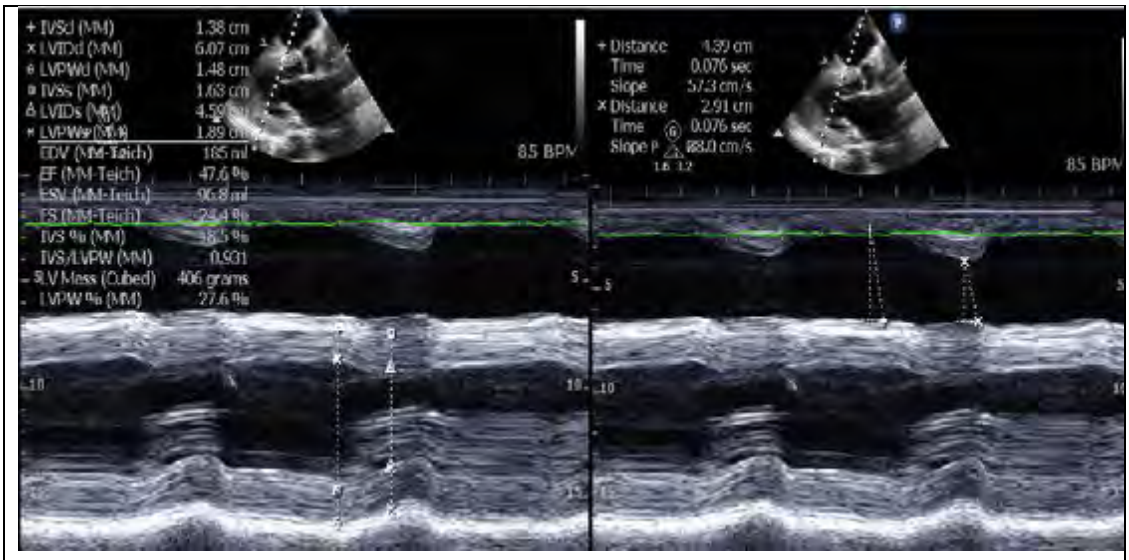

Figure 3.8 Parasternal Long Axis view with the M-mode cursor at the TV and the LV. Left image: M-mode image showing how LV measurement is done. Right image: M-mode showing RV measurement

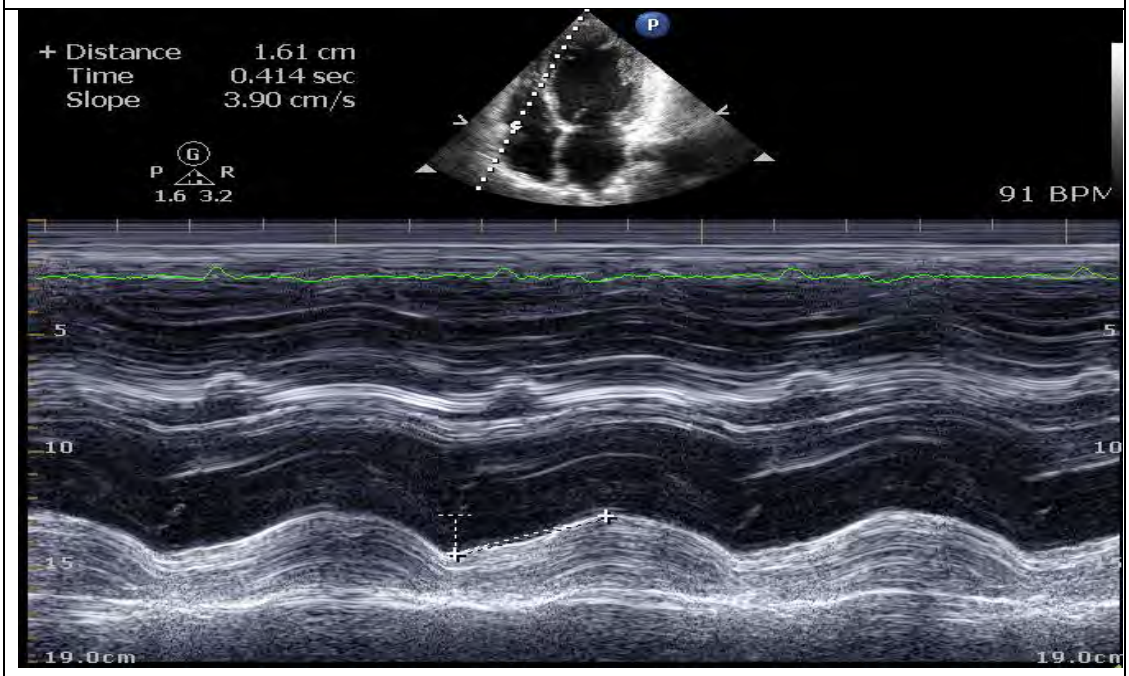

Figure 3.9 Apical four-chamber view with M-mode cursor at the tricuspid annulus. Bottom Image: M-mode image showing measurement of the tricuspid annular plane systolic excursion (TAPSE)

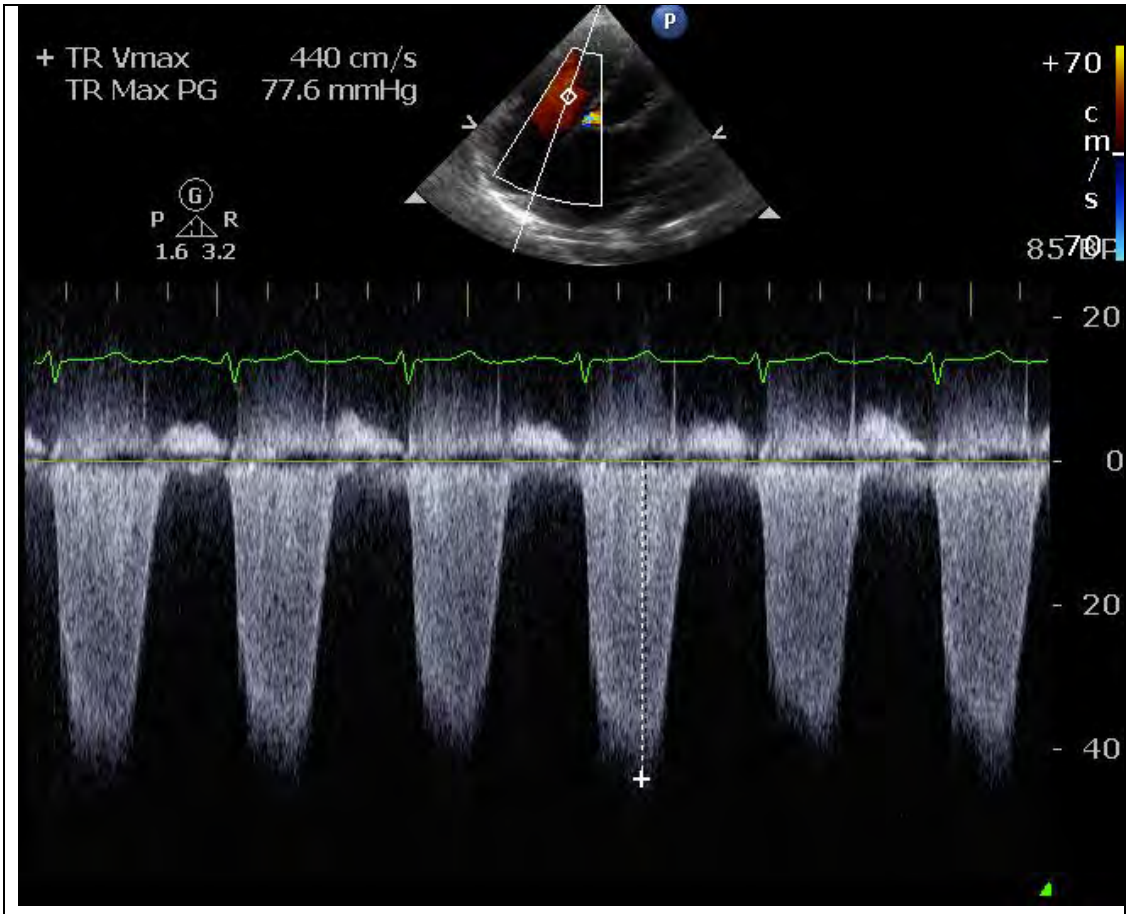

Figure 3.10 Continuous -wave across the TV in the four chamber view showing severe TR, despite the less impressive colour-flow jet seen across the valve

3.7 Data analysis

Data for both studies were processed at Momentum Research, Inc. Data were verified and analyzed using commercially available software (SAS, version 9.2; SAS Institute, Inc). Continuous data were presented as mean (SD) or median (interquartile range, i.e., 25th and 75th percentiles). Continuous variables were compared using 2-tailed, 2-sample t tests and categorical variables using Chi-square tests. Sex-adjusted differences between patients with the various causes were estimated using weighted least squares regression for dichotomous characteristics

and ordinary linear regression for continuous characteristics. The cumulative survival probabilities were estimated using the method of Kaplan –Meier for all-cause mortality, and readmission for worsening HF.

The time to the first event was considered; times for patients without the event of interest were censored at the earlier of the last date the patient was known to be alive or the period of interest.

The univariate proportional hazard regression was used to evaluate the relation of baseline measurements (age, gender, NYHA functional class, aetiology of HF, systolic blood pressure, LVEF, LVEDD, LVESD, serum Cr , serum biomarkers to 6-month mortality. Prevalence of renal dysfunction at baseline and its association with outcome was determined.

Univariable models of the association of each of the biomarkers (NT-pro BNP, Gal3) with the outcomes were carried out. A multivariable model with all biomarkers, adjusted for covariates associated with the outcome were done using those found to be significant in THESUS prognostic models.

Correlation coefficients were calculated by linear regression analysis with NT-pro BNP and Gal3 log-transformed to establish normality, and correlations between NT-pro BNP and Gal3 and continuous demographic, clinical, laboratory and echocardiographic values evaluated. Multivariate linear regression analyses were performed with log transformed NT-pro BNP and Gal3 concentrations as dependent variables, with inclusion of demographic, clinical, laboratory and echocardiographic parameters and biomarkers.

Variable selection in multivariate modeling was based on clinical and statistical significance ($p<0.05$)

Details of statistical analysis and modeling are described in the relevant chapters of this thesis answering specific objectives.

4 Chapter 4: The demographic and clinical characteristic of patients with acute heart failure patients in sub Saharan Africa

4.1 Introduction

The problem of heart failure has been recognized in sub-Saharan Africa for over 60 years. [144] Heart failure is an important cause of morbidity and mortality in Africa. The majority of the clinical studies of heart failure in sub-Saharan Africa were conducted in the pre-echocardiographic era or without the application of echocardiography in the majority of cases. [100,150] These clinical studies as well as necropsy studies that examined the etiology of heart failure of hospitalized Africans showed the vast majority of heart failure cases in sub-Saharan Africa are due to the major nonischemic causes, with rheumatic heart disease, hypertensive heart disease, and cardiomyopathy accounting for over 75% of cases in most series.[100]

There was also a lack of data on the incidence, prevalence, etiology, treatment, and outcome of the disease in general and its geographical variation by region and country in Africa. We planned and conducted the THESUS-HF registry of patients admitted to hospital with heart failure in 9 sub Saharan African countries to address the gaps in knowledge mentioned above. This registry included information on the patients' course before the admission, the in-hospital phase, echocardiographic evaluation and a short follow-up (6 to 12 months).

THESUS-HF was followed by an RCT (BAHEF) investigating the combination treatment with hydralazine and nitrates (HYIS) compared to placebo in Africans

admitted with AHF carried out in 6 sub-Saharan African countries.

In this chapter, we describe the demographic and clinical characteristics of patients admitted with AHF in SSA, based on the THESUS-HF registry and the BAHEF clinical trial.

Our results have demonstrated that AHF in SSA affects young men and women in their early fifties, predominantly of black race. The aetiologies are mainly hypertension, idiopathic dilated cardiomyopathy and rheumatic valvular heart disease. HIV infection is as yet not a significant cause of AHF in SSA, despite high prevalence of the disease in the continent. Unlike the western population, ischemic heart disease was responsible for only a small percentage of AHF. Most of the patients present late in NYHA functional class III and IV had significant co-morbidities, high readmission rates and mortality. In addition the data from THESUS –HF showed a high incidence of the use of aspirin in patients with non-ischemic HF, low rates of use of beta-blockers and combination of hydralazine and nitrates This chapter is presented in form of two published research papers below, in the Archives of Internal Medicine and the European Journal of Heart Failure.

1. Damasceno A, Mayosi BM, **Sani M**, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam CK, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Davison BA, Cotter G, Sliwa K. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. Arch Intern Med. 2012 Oct 8;172(18):1386-94.
2. Sliwa K, Damasceno A, Davison BA, Mayosi BM, **Sani MU**, Ogah O, Mondo C, Ojji D, Dzudie A, Kouam CK, Yonga G, Ba SA, Ogola E, Edwards C, Cotter G. Bi treatment with hydralazine/nitrates vs. placebo in Africans admitted with acute HEart Failure (BA-HEF). Eur J Heart Fail. 2016 May 20. doi: 10.1002/ejhf.581.

Statement of originality document: Please see Appendix

The Causes, Treatment, and Outcome of Acute Heart Failure in 1006 Africans From 9 Countries

Results of the Sub-Saharan Africa Survey of Heart Failure

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Background: Acute heart failure (AHF) in sub-Saharan Africa has not been well characterized. Therefore, we sought to describe the characteristics, treatment, and outcomes of patients admitted with AHF in sub-Saharan Africa.

Methods: The Sub-Saharan Africa Survey of Heart Failure (THESUS–HF) was a prospective, multicenter, observational survey of patients with AHF admitted to 12 university hospitals in 9 countries. Among patients presenting with AHF, we determined the causes, treatment, and outcomes during 6 months of follow-up.

Results: From July 1, 2007, to June 30, 2010, we enrolled 1006 patients presenting with AHF. Mean (SD) age was 52.3 (18.3) years, 511 (50.8%) were women, and the predominant race was black African (984 of 999 [98.5%]). Mean (SD) left ventricular ejection fraction was 39.5% (16.5%). Heart failure was most commonly due to hypertension (n=453 [45.4%]) and rheumatic heart disease (n=143 [14.3%]). Ischemic heart disease (n=77 [7.7%]) was not a common cause of AHF. Concurrent renal dysfunction (estimated glomerular filtration rate, <30 mL/min/173 m^2), diabetes mellitus, anemia (hemoglobin level, <10 g/dL), and atrial fibrillation were found in 73 (7.7%), 114 (11.4%), 147 (15.2%), and 184 cases (18.3%), respectively; 65 of 500 patients undergoing testing (13.0%) were seropositive for the human immunodeficiency virus. The median hospital stay was 7 days (interquartile range, 5-10), with an in-hospital mortality of 4.2%. Estimated 180-day mortality was 17.8% (95% CI, 15.4%-20.6%). Most patients were treated with renin-angiotensin system blockers but not β-blockers at discharge. Hydralazine hydrochloride and nitrates were rarely used.

Conclusions: In African patients, AHF has a predominantly nonischemic cause, most commonly hypertension. The condition occurs in middle-aged adults, equally in men and women, and is associated with high mortality. The outcome is similar to that observed in non-African AHF registries, suggesting that AHF has a dire prognosis globally, regardless of the cause.

Arch Intern Med. 2012;172(18):1386-1394.
Published online September 3, 2012.
doi:10.1001/archinternmed.2012.3310

HEART FAILURE (HF) AND especially acute HF (AHF) are important causes of morbidity and mortality in the developed world. The high rate of rehospitalization, the unproductive years of life, and the price of treatment constitute an important economic burden. Little is known about acute and chronic HF in sub-Saharan Africa.[1] Recent studies[2-5] suggested that the main underlying causes of HF are different in Africa, including some conditions that are almost unique, such as endomyocardial fibrosis and tuberculous pericarditis,[6,7] as well as a high prevalence of peripartum cardiomyopathy and idiopathic dilated cardiomyopathy.[8] At the same time, with a nonuniform epidemiologic transition to a more Western way of living, prevalences of hypertension, obesity, and diabetes are increasing, particularly in urban centers, with a possible effect on the etiology of HF.[9]

See Invited Commentary at end of article

The Sub-Saharan Africa Survey of Heart Failure (THESUS–HF) was initiated to determine the causes and treat-

Author Affiliations are listed at the end of this article.

ment of AHF and morbidity and mortality among those with the disease in the African subcontinent.

METHODS

STUDY DESIGN AND CLINICAL SETTING

We conducted THESUS–HF as a prospective, multicenter, international observational survey in 12 cardiology centers from 9 countries in the southern, eastern, central, and western regions of sub-Saharan Africa. The countries and centers were selected on the basis of availability of a physician trained in clinical cardiology and echocardiography who had previously participated in research projects. Ethiopia, Kenya, and Senegal joined the study late, resulting in a shorter enrollment period.

INCLUSION AND EXCLUSION CRITERIA

Patients older than 12 years admitted with dyspnea as the main complaint and diagnosed with AHF based on symptoms and signs that were confirmed by echocardiography (de novo or decompensation of previously diagnosed HF) were enrolled in the present study. Exclusion criteria were acute ST-elevation myocardial infarction, severe known renal failure (patients undergoing dialysis or with a creatinine level of >4 mg/dL) (to convert to micromoles per liter, multiply by 88.4), nephrotic syndrome, hepatic failure, or another cause of hypoalbuminemia. Written informed consent was obtained from each subject who was enrolled into the study. Ethical approval was obtained from the ethical review board of the participating institutions, and the study conformed to the principles outlined in the Declaration of Helsinki.

DATA COLLECTION AND CASE DEFINITION

A comprehensive range of clinical data was collected on a standardized case report form. A detailed echocardiographic assessment of ventricular function, valvular structure and function, and regional wall abnormalities was performed. All echocardiographic procedures were undertaken by trained physicians, and measurements were made according to the American Society of Echocardiography Guidelines.[10] Electrocardiograms were read centrally by a cardiologist at Momentum Research, Inc, using standard reference ranges.[11] Laboratory evaluations provided by the local institution and intravenous and oral medications were recorded at admission and on days 1, 2, and 7 (or at discharge if earlier). Symptoms and signs of HF, vital signs, and laboratory test data (when indicated) were collected at baseline and through day 7 (or at discharge if earlier). The probable primary cause of HF was based on the European Society of Cardiology guidelines[12] and as recently applied in the chronic HF cohort of the Heart of Soweto Study.[13] Ischemic causes were determined on the basis of accepted criteria, such as history, or results of noninvasive (eg, electrocardiography, stress test) or invasive tests when available. Testing for human immunodeficiency virus infection was only performed when clinical findings raised suspicion and after patient consent was obtained.

Subjects underwent evaluation for symptoms and signs of HF and laboratory testing (when indicated) at the 1- and 6-month follow-ups. Information on readmissions and death, with respective reasons and cause, was collected through the 6-month follow-up. We initiated telephone contact with patients who could not attend additional clinic visits because they moved to a different location or to another province. Patients who could not be contacted were censored at the last available contact.

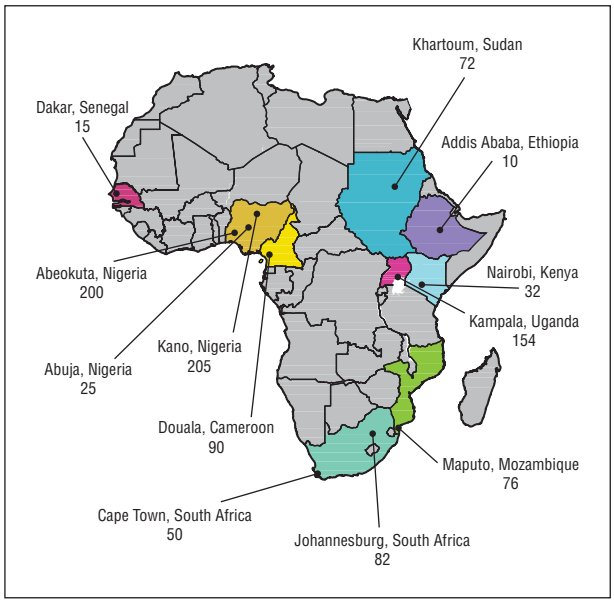

Figure 1. Patients included in the Sub-Saharan Africa Survey of Heart Failure per country. Case report forms were available for 1006 of 1011 patients.

To better understand the changes in the pattern of AHF in Africa, the present cohort was classified as having endemic causes (group 1; ie, rheumatic heart disease, the cardiomyopathies, and infective causes, such as pericarditis and human immunodeficiency virus–associated cardiomyopathy), and emerging causes (group 2; ie, hypertension and ischemic heart disease).[14-17]

STATISTICAL ANALYSES

All data were processed at Momentum Research, Inc. Data were verified and analyzed using commercially available software (SAS, version 9.2; SAS Institute, Inc). Continuous data were presented as mean (SD) or median (interquartile range, ie, 25th and 75th percentiles). Continuous variables were compared using 2-tailed, 2-sample *t* tests and categorical variables using χ^2 tests. Sex-adjusted differences between patients with emerging and endemic causes were estimated using weighted least squares regression for dichotomous characteristics and ordinary linear regression for continuous characteristics. Kaplan-Meier estimates of mortality and readmission rates were provided. The time to the first event was considered; times for patients without the event of interest were censored at the earlier of the last date the patient was known to be alive or the period of interest.

RESULTS

BASELINE PATIENT CHARACTERISTICS ON ADMISSION

From July 1, 2007, to June 30, 2010, 1011 patients were enrolled in the study, for whom 1006 case report forms were received (**Figure 1**).

Table 1 shows the demographic and clinical presentation on admission for the entire cohort and compares men with women (50.8% of the cohort). Electrocardiographic strips were available for 814 patients. The most frequent arrhythmia was atrial fibrillation, which was found in 147 of 806 patients (18.2%). The most frequent

Table 1. Demographic and Clinical Presentation[a]

Characteristic	All (N=1006)	Men (n=494)	Women (n=511)	*P* Value
Age, y				
Mean (SD)	52.3 (18.3)	54.0 (16.9)	50.7 (19.5)	.005
Median (IQR)	55.0 (39.0-67.0)	55.0 (43.0-67.0)	53.0 (33.0-67.0)	
Black African, No. (%)	984 (98.5)	486 (98.8)	497 (98.2)	.47
Atrial fibrillation, No. (%)	184 (18.3)	77 (15.7)	107 (21.1)	.03
No. of AHF admissions in last 12 mo				
Mean (SD)	0.37 (0.78)	0.41 (0.77)	0.34 (0.78)	.15
Median (IQR)	0 (0-0)	0 (0-1)	0 (0-0)	
Hyperlipidemia, No. (%)[b]	90 (9.2)	52 (10.8)	38 (7.6)	.09
History of smoking, No. (%)	98 (9.8)	85 (17.3)	13 (2.6)	<.001
History of hypertension, No. (%)	556 (55.5)	296 (60.0)	259 (51.0)	.004
History of diabetes mellitus, No. (%)	114 (11.4)	58 (11.8)	56 (11.0)	.68
Body mass index[c]				
Mean (SD)	25.2 (9.0)	24.7 (4.9)	25.7 (11.6)	.08
Median (IQR)	24.0 (20.9-28.1)	24.0 (21.2-27.6)	23.9 (20.5-28.6)	
Systolic blood pressure, mm Hg				
Mean (SD)	130.4 (33.5)	132.4 (33.7)	128.4 (33.3)	.06
Median (IQR)	126.5 (106.0-150.0)	130.0 (110.0-151.0)	120.0 (102.0-150.0)	
Diastolic blood pressure, mm Hg				
Mean (SD)	84.3 (20.9)	85.5 (21.2)	83.2 (20.7)	.08
Median (IQR)	80.0 (70.0-100.0)	82.0 (70.0-100.0)	80.0 (70.0-96.0)	
Heart rate, bpm				
Mean (SD)	103.7 (21.6)	101.6 (21.4)	105.7 (21.6)	.003
Median (IQR)	104.0 (90.0-116.0)	100.0 (88.0-112.0)	108.0 (90.0-120.0)	
LVEF, %				
Mean (SD)	39.5 (16.5)	37.8 (16.2)	41.1 (16.6)	.002
Median (IQR)	38.0 (27.0-50.0)	37.0 (25.0-112.0)	40.0 (28.4-53.0)	
Creatinine level, mg/dL				
Mean (SD)	1.44 (1.19)	1.57 (1.21)	1.30 (1.16)	<.001
Median (IQR)	1.12 (0.89-1.50)	1.23 (0.96-1.65)	1.01 (0.80-1.33)	
SUN level, mg/dL				
Mean (SD)	35.6 (34.1)	41.1 (38.9)	30.2 (27.7)	<.001
Median (IQR)	26.6 (16.5-42.0)	30.5 (20.0-49.0)	23.2 (14.3-34.5)	
Sodium level, mEq/L				
Mean (SD)	135.1 (6.6)	134.9 (6.5)	135.3 (6.8)	.33
Median (IQR)	135.8 (131.0-139.1)	135.0 (131.0-139.0)	146.0 (131.4-140.0)	
Glucose level, mg/dL				
Mean (SD)	109.7 (49.7)	109.7 (44.0)	109.5 (54.9)	.94
Median (IQR)	93.7 (84.0-117.0)	97.2 (84.6-122.0)	93.0 (82.8-111.6)	
eGFR, mL/min/1.73 m^2				
Mean (SD)	83.3 (48.0)	85.3 (51.4)	81.4 (44.4)	.20
Median (IQR)	76.7 (54.0-103.5)	79.6 (55.5-106.2)	74.7 (52.6-101.3)	
Renal dysfunction, No. (%)[d]	73 (7.7)	35 (7.5)	38 (7.8)	.83
Hemoglobin level, g/dL				
Mean (SD)	12.2 (2.6)	12.6 (2.6)	11.8 (2.5)	<.001
Median (IQR)	12.3 (10.7-13.7)	13.0 (11.0-14.5)	11.8 (10.5-13.1)	
Anemia, No. (%)[e]	147 (15.2)	68 (14.3)	79 (16.1)	.43
Total WBC count, No./μL				
Mean (SD)	7699 (4092)	7484 (3505)	7914 (4581)	.10
Median (IQR)	6800 (5200-8980)	6700 (5200-8900)	6900 (5200-9000)	
Lymphocyte count, %				
Mean (SD)	30.3 (13.4)	29.8 (12.9)	30.9 (13.8)	.25
Median (IQR)	30.0 (20.0-39.6)	30.0 (20.0-39.0)	30.5 (20.3-40.0)	

(continued)

conduction abnormality was left anterior hemiblock, present in 143 of 804 patients (17.8%). Complete left and right bundle branch blocks were seen in 62 of 803 (7.7%) and 39 of 803 patients (4.9%), respectively.

CAUSES OF HF

Figure 2 shows the causes of HF in the entire study cohort. In some patients, more than 1 cause was identified. **Table 2** shows the characteristics by endemic vs emerging HF causes and interaction of those causes with sex. **Figure 3** shows the different causes of AHF by country.

THERAPIES FOR HF

The most commonly administered intravenous medication at admission was furosemide in 927 of 998 patients (92.9%), with use decreasing to only 215 of 938 patients (22.9%) at day 7 or discharge. The next commonly administered parenteral drugs on admission were digoxin in 13.7% and nitrates in 7.9%. Parenteral inotropes (ie, dopamine hydrochloride and dobutamine hydrochloride) were used in 5.0% and 5.1%, respectively, on admission. Mechanical ventilation was rarely used (0.6%). **Figure 4** shows

Table 1. Demographic and Clinical Presentation[a] (continued)

Characteristic	All (N=1006)	Men (n=494)	Women (n=511)	*P* Value
Cholesterol level, mg/dL				
Mean (SD)	157.6 (54.2)	160.0 (59.0)	155.2 (49.1)	.26
Median (IQR)	152.1 (124.0-187.0)	156.0 (124.8-187.2)	152.1 (120.9-183.3)	
Triglyceride level, mg/dL				
Mean (SD)	106.2 (53.9)	109.8 (56.7)	102.7 (50.9)	.09
Median (IQR)	97.9 (71.2-124.6)	97.9 (73.5-125.0)	95.5 (71.2-124.6)	
CK level, U/L				
Mean (SD)	232.2 (447.7)	259.4 (412.6)	210.8 (473.9)	.40
Median (IQR)	88.0 (55.0-171.0)	110.0 (62.5-251.6)	83.0 (48.9-139.0)	
CK-MB fraction, U/L				
Mean (SD)	37.4 (76.0)	39.1 (83.9)	35.9 (68.6)	.78
Median (IQR)	19.0 (13.0-32.0)	19.0 (14.0-31.0)	20.0 (12.0-32.5)	
Seropositive for HIV, No./No. undergoing testing (%)	65/500 (13.0)	30/240 (12.5)	35/260 (13.5)	.75[f]

Abbreviations: AHF, acute heart failure; CK, creatine kinase; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IQR, interquartile range; LVEF, left ventricular ejection fraction; SUN, serum urea nitrogen; WBC, white blood cell.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; CK to microkatals per liter, multiply by 0.0167; creatinine to micromoles per liter, multiply by 88.4; glucose to millimoles per liter, multiply by 0.0555; hemoglobin to grams per liter, multiply by 10.0; lymphocyte fraction to a proportion of 1, multiply by 0.01; sodium to millimoles per liter, multiply by 1; SUN to millimoles per liter, multiply by 0.357; triglycerides to millimoles per liter, multiply by 0.0113; WBC count to cells $\times 10^9$ per liter, multiply by 0.001.

[a] Data are computed from nonmissing values, the number of which may vary from variable to variable. The sex of 1 patient was not reported.

[b] Indicates cholesterol level of more than 200 mg/dL, low-density lipoprotein level of at least 130 mg/dL, or high-density lipoprotein level of less than 30 mg/dL.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Indicates eGFR of less than 30 mL/min/1.73 m^2.

[e] Indicates hemoglobin level of less than 10 g/dL.

[f] Calculated as comparison of seropositivity for HIV test with negative/unknown results.

prescribed oral medications on admission and follow-up.

PATIENTS' FOLLOW-UP AND OUTCOMES

Of 1006 patients, 1-month follow-up assessments were completed for 578 (57.5%) and 6-month assessments for 461 (45.8%). A total of 159 of 1006 patients (15.8%) died without completing a 6-month assessment; an additional 316 (31.4%) had a last date known alive provided and were included in the analysis. The remaining 70 patients (7.0%) were lost to follow-up. Reasons for loss to follow-up were provided for 35 of these patients and included lack of telephone contact (2.3%), financial constraints (0.3%), unwillingness to come for follow-up (0.3%), lack of transportation to the site (<0.1%), and others, for example, transfer of care to other facilities (0.5%). **Table 3** reports the main clinical outcomes observed in the study. The rate of death or readmission at 60 days was 15.4% (**Figure 5**A), and the estimated 6-month mortality rate was 17.8% (Figure 5B). Mortality rates were similar among countries, except that a somewhat lower rate was reported in the Ugandan center (6.3%).

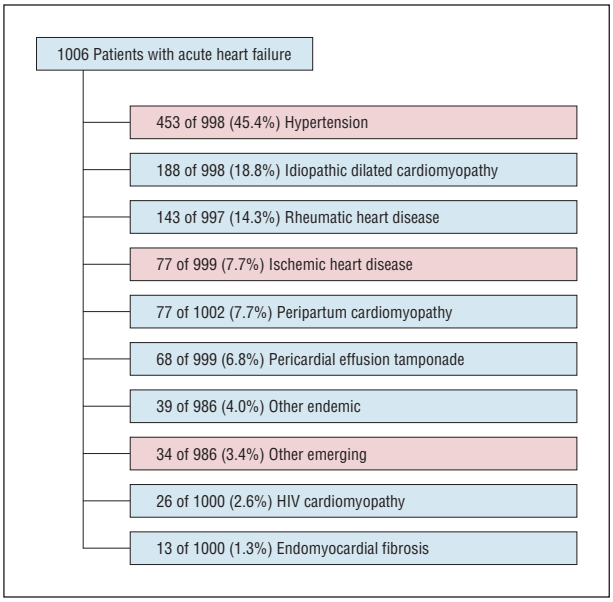

Figure 2. Causes of acute heart failure in the study cohort. Blue indicates earlier stages of epidemiologic transition (endemic causes); pink, later stages of epidemiologic transition (emerging causes); and HIV, human immunodeficiency virus.

COMMENT

To our knowledge, our data represent Africa's first and largest multinational prospective registry of AHF. This registry reveals a few unique characteristics of AHF in sub-Saharan Africa.

One of the most striking features of this cohort of African patients with AHF is the relative youth of the patients affected (median age, 55 years). In industrialized countries, AHF is a disease of the elderly, with a mean age of 72 years (median age, 66-70 years)[18]; hence, the condition presents 2 decades earlier in sub-Saharan Africa. Acute HF therefore strikes patients in the prime of their lives in sub-Saharan Africa, with major economic implications because it affects the generation of breadwinners and caregivers. With respect to sex, despite the relative youth of the patients, the disease affects men and women equally, although the characteristics and causes

Table 2. Sociodemographic and Risk Factor Profile of HF Patients According to Endemic vs Emerging Causes

Characteristic[a]	All Patients (N=1006)	Endemic Causes (n=473)		Emerging Causes (n=506)		Sex-Adjusted Difference[b]	
		Men (n=197)	Women (n=276)	Men (n=287)	Women (n=219)	Difference (95% CI)	*P* Value
Sociodemographic Profile							
Age, y							
Mean (SD)	52.3 (18.3)	46.8 (18.2)	41.0 (18.3)	59.0 (13.7)	62.6 (13.6)	17.0 (15.0 to 19.1)	<.001
Median (IQR)	55.0 (39.0-67.0)	46.0 (34.0-59.0)	36.0 (25.0-54.0)	60.0 (50.0-69.0)	64.0 (55.0-73.0)		
Risk factor profile, No./ No. not missing (%)							
Total cholesterol level >193 mg/dL	112/649 (17.3)	16/129 (12.4)	21/190 (11.1)	44/185 (23.8)	30/128 (23.4)	11.9 (5.9 to 17.9)	<.001
History of smoking	98/1001 (9.8)	34/197 (17.3)	6/276 (2.2)	50/285 (17.5)	7/218 (3.2)	0.9 (–1.8 to 3.6)	.50
Hypertension	555/1001 (55.4)	43/197 (21.8)	60/274 (21.9)	247/286 (86.4)	189/219 (86.3)	64.5 (59.6 to 69.3)	<.001
Type 2 diabetes mellitus	114/1003 (11.4)	14/197 (7.1)	17/276 (6.2)	43/285 (15.1)	37/219 (16.9)	9.3 (5.3 to 13.3)	<.001
BMI >30	158/969 (16.3)	14/188 (7.4)	41/269 (15.2)	43/278 (15.5)	52/210 (24.8)	8.6 (4.1 to 13.1)	<.001
Clinical Presentation							
NYHA, No./No. not missing (%)							
II	303/706 (42.9)	60/141 (42.6)	97/200 (48.5)	72/200 (36.0)	67/147 (45.6)		
III	216/706 (30.6)	46/141 (32.6)	49/200 (24.5)	69/200 (34.5)	47/147 (32.0)		
IV	28/706 (4.0)	4/141 (2.8)	8/200 (4.0)	13/200 (6.5)	2/147 (1.4)		
Systolic blood pressure, mm Hg							
Mean (SD)	130.4 (33.5)	116.1 (28.5)	115.7 (24.3)	143.8 (32.3)	143.8 (36.4)	27.9 (24.0 to 31.8)	<.001
Median (IQR)	127 (106 to 150)	110.0 (100.0 to 130.0)	110.0 (100.0 to 130.0)	140.0 (120.0 to 160.0)	140.0 (120.0 to 160.0)		
Diastolic blood pressure, mm Hg							
Mean (SD)	84.3 (20.9)	76.5 (19.5)	77.1 (17.0)	92.0 (19.8)	90.9 (22.4)	14.6 (12.1 to 17.1)	<.001
Median (IQR)	80 (70 to 100)	73.0 (65.0 to 89.0)	75.0 (67.0 to 90.0)	90.0 (80.0 to 100.0)	90.0 (79.0 to 100.0)		
Heart rate, bpm							
Mean (SD)	103.7 (21.6)	103.8 (24.3)	109.1 (22.4)	100.2 (19.3)	101.7 (20.0)	–5.5 (–8.3 to –2.8)	<.001
Median (IQR)	104 (90 to 116)	102.0 (89.0 to 116.0)	111.0 (93.0 to 122.0)	100.0 (88.0 to 112.0)	103.0 (89.0 to 112.0)		
Peripheral edema score[c]							
Mean (SD)	1.8 (1.0)	1.9 (1.0)	1.7 (1.0)	1.9 (1.1)	1.8 (1.1)	0.1 (–0.1 to 0.2)	.35
Median (IQR)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)		
Echocardiographic Evaluation							
Heart rate, bpm							
Mean (SD)	94.6 (17.9)	97.3 (18.4)	98.1 (18.9)	91.1 (17.5)	9.19 (15.9)	–6.2 (–8.7 to –3.6)	<.001
Median (IQR)	94.0 (84.0 to 104.0)	96.5 (87.5 to 105.0)	98.0 (88.0 to 110.0)	90.9 (80.0 to 102.0)	92.0 (81.0 to 101.0)		
Dimensions and LV Function							
LV systole size, mm							
Mean (SD)	46.0 (13.1)	49.3 (13.4)	45.7 (13.5)	47.3 (12.6)	42.8 (12.3)	–2.4 (–4.1 to –0.8)	.004
Median (IQR)	47.0 (37.0 to 55.0)	51.0 (39.0 to 58.8)	46.7 (36.0 to 55.0)	48.0 (39.5 to 55.0)	43.4 (33.0 to 53.0)		
LV diastole size, mm							
Mean (SD)	57.7 (11.6)	60.9 (11.5)	57.9 (11.9)	58.6 (11.3)	54.0 (10.7)	–3.1 (–4.5 to –1.6)	<.001
Median (IQR)	58.0 (50.0 to 65.0)	62.0 (54.0 to 68.0)	58.0 (50.0 to 65.0)	58.7 (53.0 to 65.0)	54.0 (46.0 to 63.0)		
Ejection fraction, %							
Mean (SD)	39.1 (16.3)	36.9 (16.4)	40.2 (17.1)	37.3 (15.4)	40.8 (15.5)	0.6 (–1.5 to 2.7)	.59
Median (IQR)	37.2 (26.0 to 50.0)	35.0 (24.0 to 49.0)	38.0 (27.0 to 53.0)	37.0 (25.0 to 47.0)	39.5 (29.4 to 50.0)		
Intraventricular septum (diastole), mm							
Mean (SD)	11.2 (3.3)	10.7 (3.1)	9.8 (3.1)	12.3 (3.1)	11.8 (3.0)	1.8 (1.4 to 2.2)	<.001
Median (IQR)	11.0 (9.0 to 13.0)	10.0 (9.0 to 12.1)	9.6 (8.0 to 11.0)	12.0 (10.0 to 14.0)	11.3 (10.0 to 13.4)		

(continued)

Table 2. Sociodemographic and Risk Factor Profile of HF Patients According to Endemic vs Emerging Causes (continued)

Characteristic[a]	All Patients (N=1006)	Endemic Causes (n=473)		Emerging Causes (n=506)		Sex-Adjusted Difference[b]	
		Men (n=197)	Women (n=276)	Men (n=287)	Women (n=219)	Difference (95% CI)	*P* Value
Dimensions and LV Function							
Posterior wall (diastole), mm							
Mean (SD)	10.7 (2.9)	10.2 (2.9)	9.5 (2.7)	11.7 (2.7)	11.2 (2.7)	1.6 (1.2 to 2.0)	<.001
Median (IQR)	10.2 (9.0 to 12.9)	10.0 (8.0 to 12.0)	9.2 (8.0 to 11.0)	12.0 (9.9 to 13.6)	11.0 (9.4 to 13.0)		
Diastolic Function							
Left atrial anteroposterior size, mm							
Mean (SD)	47.1 (9.2)	49.1 (9.7)	47.4 (10.5)	46.9 (8.1)	45.7 (7.8)	−1.9 (−3.1 to −0.8)	.001
Median (IQR)	47.0 (41.0 to 53.0)	48.6 (43.0 to 55.0)	47.0 (41.0 to 53.0)	47.0 (42.0 to 52.0)	45.0 (40.0 to 50.9)		
Left atrial planimetry size, mm^2							
Mean (SD)	2782 (924)	3039 (1001)	2882 (1110)	2782 (770)	2532 (7808)	−306 (−465 to −147)	<.001
Median (IQR)	2635 (2200 to 3285)	2930 (2250 to 3540)	2770 (2130 to 3400)	2728 (2295 to 3200)	2478 (2100 to 2900)		
Mitral E wave, cm/s							
Mean (SD)	544.2 (500.6)	537.1 (587.0)	571.3 (585.6)	529.6 (404.7)	529.4 (449.7)	−25.8 (−97.0 to 45.4)	.48
Median (IQR)	480.0 (96.0 to 880.0)	243.0 (87.2 to 810.0)	332.0 (88.0 to 920.0)	526.0 (101.7 to 880.0)	460.0 (102.2 to 880.0)		
E-wave deceleration time, ms							
Mean (SD)	150.0 (92.1)	151.3 (146.2)	145.3 (102.9)	143.2 (54.6)	159.0 (64.4)	3.6 (−9.8 to 17.0)	.60
Median (IQR)	130.0 (100.0 to 171.0)	120.0 (92.0 to 158.0)	122.0 (100.0 to 165.0)	134.0 (106.0 to 171.0)	140.6 (120.0 to 189.0)		
Mitral A wave, m/s							
Mean (SD)	324.4 (330.2)	302.0 (289.3)	334.9 (396.1)	295.5 (274.9)	365.5 (344.9)	13.3 (−38.5 to 65.0)	.61
Median (IQR)	215.0 (53.0 to 513.0)	206.0 (52.6 to 500.0)	149.5 (44.2 to 498.0)	220.0 (59.6 to 498.0)	270.0 (69.0 to 580.0)		
Mitral A-wave duration, ms							
Mean (SD)	126.4 (45.1)	114.3 (38.1)	126.7 (57.5)	130.7 (44.1)	128.4 (34.2)	8.5 (0.6 to 16.4)	.03
Median (IQR)	123.0 (100.0 to 150.0)	20.0 (90.0 to 140.0)	118.0 (100.0 to 150.0)	130.0 (100.0 to 160.0)	128.0 (101.0 to 150.0)		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HF, heart failure; IQR, interquartile range; LV, left ventricular; NYHA, New York Heart Association class.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

[a] Statistics are computed from nonmissing values, the number of which may vary from variable to variable. The HF causes were reported for 980 patients; sex was not reported for one of these.

[b] Calculated as the sex-adjusted difference in proportions or means between endemic and emerging causes of HF.

[c] Examined in a dependent area, including the lower extremities and sacral area, and scored as 0 (a complete absence of skin indentation with mild digital pressure in all dependent areas), 1+ (indentation of the skin that resolves in 10-15 seconds), 2+ (indentation of the skin that is easily created with limited pressure and disappears slowly [15-30 seconds or longer]), or 3+ (large areas of indentation are easily produced and slow [>30 seconds] to resolve).

differ by sex (Tables 1 and 2), probably contributing to slight differences in outcomes (Table 3).

Three important observations are worth noting about medical therapy for AHF (Figure 3). First, we have observed a high incidence of the use of aspirin in patients with nonischemic HF in the sub-Saharan African region. In addition, the combination of hydralazine hydrochloride and nitrates, which has been shown to be effective in patients of African descent,[19,20] is hardly ever used in the sub-Saharan region. Third, the rate of β-blocker use, even at follow-up, is relatively low. Although many patients in the present study have HF with preserved systolic function for which the use of β-blockers is less clearly indicated, the rate of β-blocker use in THESUS–HF is lower than that described in other regions.[18,21,22] These observations provide an opportunity to improve the quality of the care of patients with HF in the region. A larger randomized study investigating the combination treatment with hydralazine and nitrates vs placebo in Africans admitted with AHF will commence soon in the centers that participated in the THESUS–HF registry.

The cause of AHF remains predominantly nonischemic, with hypertension, rheumatic heart disease, and the endemic cardiomyopathies (ie, idiopathic dilated cardiomyopathy, peripartum cardiomyopathy, and endomyocardial fibrosis) accounting for 75.5% of the cases (Figure 2 and Table 2). Although the rate of ischemic heart disease may have been underestimated owing to limited diagnostic tools, this finding is in striking contrast to registries in Europe or the United States,[18,21,22] where ischemic heart disease (a rarity in Africa) accounts for most of the cases. However, Africa is clearly facing an additional burden because, in addition to the high prevalence of endemic diseases, we are observing a high (and probably increasing) burden of emerging diseases, such as ischemic heart disease and hypertension, in particular in some countries (Figure 3). As socioeconomic changes continue to progress across the continent, the

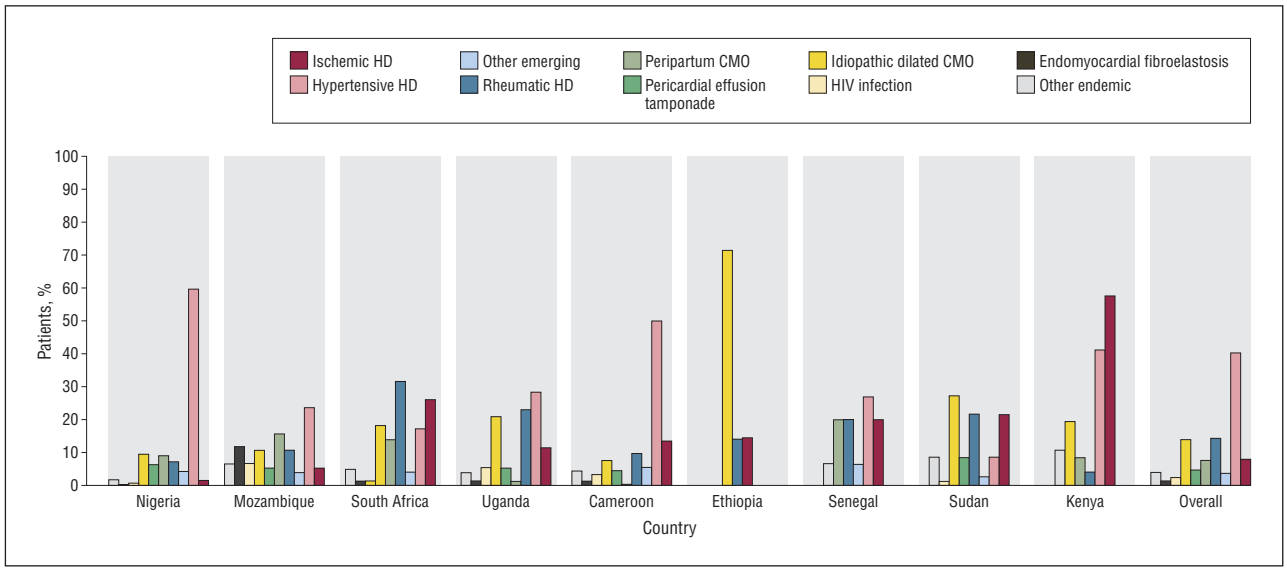

Figure 3. Primary causes of heart failure by country. CMO indicates cardiomyopathy; HD, heart disease; and HIV, human immunodeficiency virus.

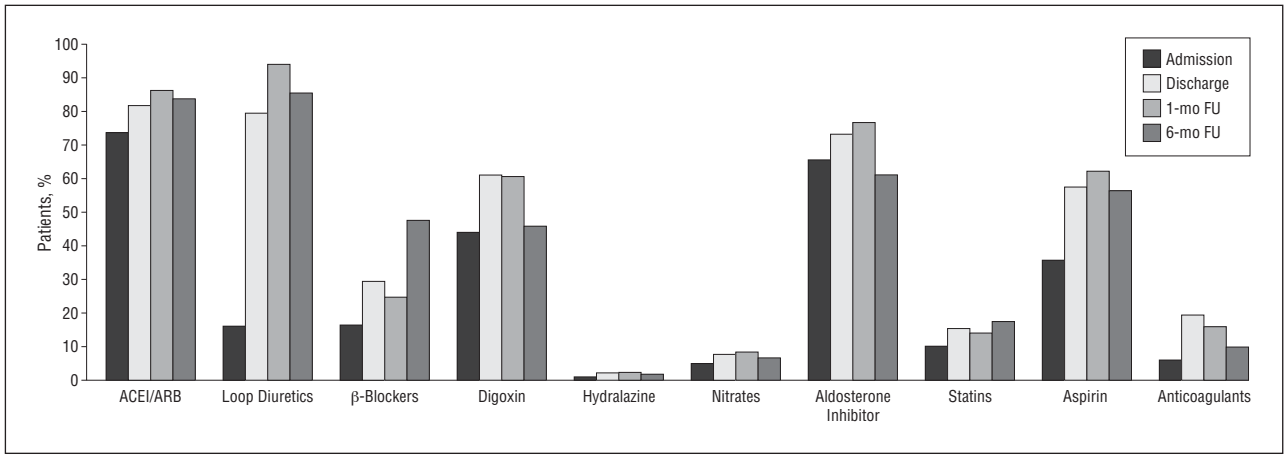

Figure 4. Prescribed oral medication. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; FU, follow-up.

Table 3. Clinical Outcomes[a]

Outcome	Patient Groups			Causes of HF	
	All (N=1006)	Men (n=494)	Women (n=511)	Endemic (n=473)	Emerging (n=506)
Length of initial hospital stay, d					
Mean (SD)	9.2 (9.3)	9.4 (10.4)	9.1 (8.1)	9.8 (11.5)	8.7 (6.6)
Median (IQR)	7 (5-10)	7 (5-10)	8 (5-10)	8 (5-11)	7 (5-10)
Initial hospitalization mortality, No. (%)	42 (4.2)	24 (4.9)	18 (3.5)	28 (5.9)	14 (2.8)
Readmission to day 60	9.1 (7.3-11.3)	9.7 (7.2-13.1)	8.5 (6.2-11.6)	9.4 (6.8-12.8)	9.0 (6.6-12.2)
Death to day 60	10.6 (8.7-12.8)	11.0 (8.4-14.3)	10.2 (7.7-13.4)	12.5 (9.7-16.0)	9.0 (6.7-12.1)
Death or readmission to day 60	15.6 (13.3-18.1)	16.6 (13.5-20.5)	14.5 (11.6-18.2)	17.3 (14.0-21.2)	14.1 (11.2-17.8)
Death to day 180	17.8 (15.4-20.6)	18.3 (14.9-22.4)	17.4 (14.1-21.4)	20.5 (16.9-24.8)	15.5 (12.4-19.4)

Abbreviations: HF, heart failure; IQR, interquartile range.
[a] Unless otherwise indicated, data are expressed as Kaplan-Meier estimate (95% CI).

number of AHF cases (particularly in women) caused by noncommunicable forms of heart disease may further increase. Finally, human immunodeficiency virus infection, which can affect the myocardium in various ways,[23] is a common condition among patients with HF in Africa. Whether the early introduction of antiretroviral therapy in human immunodeficiency virus–seropositive patients with HF and otherwise no indication for antiretroviral therapy will change their outcome remains to be established in future studies.

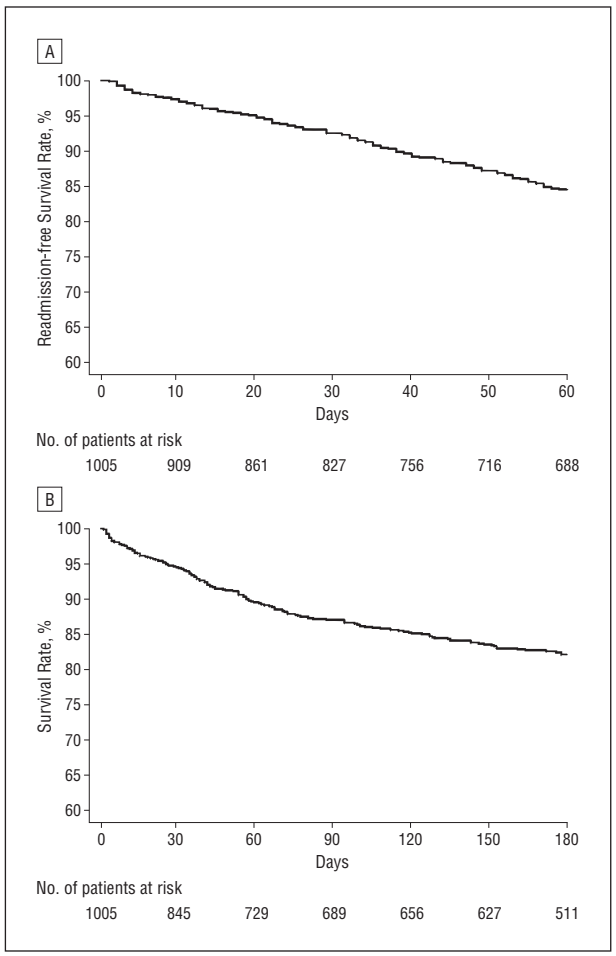

Figure 5. Kaplan-Meier estimates of study outcomes. A, Kaplan-Meier estimates of the cumulative risk for all-cause death or readmission to 60 days. B, Kaplan-Meier estimates of the cumulative risk for all-cause death to day 180.

Few studies of the outcome of HF in sub-Saharan Africa exist.[24] The outcome of AHF in this study, including high in-hospital and 6-month mortality rates (the latter a possible underestimation owing to higher rates of loss to follow-up) are remarkably similar to those observed in registries in Europe and the United States.[18,21,22] This finding is remarkable because this almost identical outcome was registered despite large differences in patient characteristics (eg, a 20-year difference in age) and causes of HF, suggesting that once AHF occurs, it may have a distinct course independent of patient characteristics. When we compared endemic and emerging causes, AHF due to emerging causes had a slightly better outcome, probably secondary to the better outcome of hypertensive AHF. However, these data should be confirmed in other studies.

Our study's limitations deserve mention. Loss to follow-up was higher in THESUS–HF than in studies conducted in other regions. This finding is common in the population studied owing to such factors as the opportunity to work if the patient is still healthy (in the case of migrant workers) or the need to obtain care if unhealthy. Some inhabitants of those regions have no telephone contact.

This registry has been compiled in selected centers and may represent only AHF patients seen in specialized centers. This limitation has to be seen in the context that many African countries do not train cardiologists and that access to cardiac ultrasonography is limited.

Unfortunately, there are no criterion standards for definitively categorizing HF. We applied a clinically oriented approach based on published criteria. As a clinical registry, we did not systematically validate diagnostic criteria. Owing to no access to cardiac catheterization in a number of centers, we might have missed HF due to ischemic origin.

CONCLUSIONS

Acute HF affects patients in sub-Saharan Africa at an extremely early age and is caused mostly by hypertension and primary cardiomyopathies. The disease leads to a high burden of readmission and death, similar to that observed in other countries, affecting younger patients in the prime of their life. These data challenge us to recognize and respond to HF in Africa by responding to common precursors, such as hypertension and the urgent need for culturally sensitive interventions. Dedicated awareness programs that strive to improve the pharmacological and nonpharmacological management of AHF (including better follow-up) need to be developed.

Accepted for Publication: May 19, 2012.
Published Online: September 3, 2012. doi:10.1001/archinternmed.2012.3310
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Financial Disclosure: None reported.

Funding/Support: This study was supported by Momentum Research, Inc.

Additional Contributions: The authors thank all the physicians, nurses, and patients who participated in the registry. Siem Abebe, BS, and Leslie Quinn, BS, coordinated the trial; Olga Milo, MD, provided ECG interpretation; and Sylvia Dennis assisted with manuscript preparation.

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European Journal of Heart Failure (2016)
doi:10.1002/ejhf.581

Bi treatment with hydralazine/nitrates vs. placebo in Africans admitted with acute HEart Failure (BA-HEF)

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Received 23 April 2016; revised 4 May 2016; accepted 5 May 2016

Aims Patients with acute heart failure in Africa are rarely being treated with a hydralazine/nitrates combination. Therefore the effect of this treatment was studied here

Methods and results The study was planned to enrol 500 patients during an acute heart failure (HF) admission, from nine sub-Saharan African countries. Patients were randomized in a double-blind manner to receive 50 mg hydralazine/20 mg isosorbide dinitrate (HYIS) t.i.d. or matching placebo for 24 weeks followed by open label HYIS for all patients. The study was terminated after 147 patients were enrolled due mostly to issues with recruitment into a prospective, placebo-controlled study. Most patients were recruited from Mozambique, South Africa, Kenya, and Uganda. The primary endpoint of death or HF readmission through 24 weeks was neutral [hazard ratio (HR) 1.05, 95% confidence interval (CI) 0.48–2.27, $P = 0.90$] in the 133 randomized patients included in the analyses. There were non-signficant effects in favour of HYIS in secondary endpoints including change in dyspnoea severity at day 7 or discharge, decrease in systolic blood pressure, greater decrease in weight, and increase in 6-min walk test distance at week 24. There were also small changes in echocardiographic indices of cardiac size and function in favour or HYIS, but none was significant.

Conclusion The BA-HEF trial demonstrated challenges in recruiting the expected number of patients with acute HF in a number of African countries, which highlights the need for strategic logistic support.
Trial registration: NCT01822808.

Keywords Treatment • Acute heart failure • Hydralazine • Nitrates • Africa

Introduction

Acute heart failure (AHF) is one of the most common reasons for admission to hospital and a major driver for health-related costs worldwide. A number of recent studies from Soweto, South Africa;[1] Abeokuta, Nigeria;[2] Abuja, Nigeria;[3] and Dar-es-Salaam, Tanzania[4] have shown the prevalence to be high, with a 6-month mortality >15%, despite the population being two decades younger than those in studies of higher income regions.[5,6]

Acute heart failure exacts a heavy social and economic burden on families and society in Africa.[2] In contrast to high-income countries where AHF affects patients with an average age of >70 years,

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the THESUS-HF registry[7] has shown that in sub-Saharan Africa AHF affects men and women in the most productive years of life, at an average age of 52.3 years, and is mostly caused by hypertension and not ischaemic heart disease (IHD). The THESUS-HF registry has also observed the use of a hydralazine/isosorbide dinitrate (HYIS) combination in <5% of patients, despite it being a Class IIb B indication for Black African patients with chronic HF,[8] and shown in previous studies to be especially effective in African Americans with chronic HF and reduced EF.[9–11]

The BA-HEF study was planned based on the limited evidence-based therapy for AHF altogether and because HYIS is available as a relatively affordable generic in most sub-Saharan countries. The purpose of the study was to examine the short-term (6 months) effects of HYIS in patients admitted for AHF in sub-Saharan Africa and treated with HYIS during the last days of admission through 6 months. The doses of HYIS used in the BA-HEF study were slightly lower than those used in the AHeFT study, and were introduced slowly through careful up-titration (see below) in order to avoid hypotension.

Methods

Patients and data collected

The BA-HEF study was a prospective, multicentre, randomized double-blind study which aimed to recruit a total of 500 patients during an admission for AHF from countries in the southern, eastern, central, and western regions of sub-Saharan Africa. AHF was diagnosed based on symptoms and signs, supported by echocardiographic findings, and was confirmed by a cardiologist. Inclusion criteria were presenting at ≥18 years of age, hospital admission for AHF, as defined by the presence of acute dyspnoea, and the presence of HF signs by physical examination with at least two of the following: rales, oedema, elevated jugular venous pressure (JVP), hepatomegaly, and ascites; LVEF <45% assessed by echocardiography or another method within the previous 12 months; background therapy with at least an ACE inhibitor or ARB and beta-blocker (unless a beta-blocker is contraindicated due to severe volume overload, low output HF, or cardiogenic shock); and availability for regular follow-up. Exclusion criteria were any intravenous treatment for HF, except i.v. furosemide (e.g. i.v. inotropes, vasopressors, nitrates, or nesiritide) at the time of screening; systolic blood pressure (BP) <100 mmHg; plan for revascularization; presentation >96 h after admission; reversible aetiology of AHF such as myocarditis, acute myocardial infarction, arrhythmia; hypertrophic obstructive cardiomyopathy, restrictive or constrictive cardiomyopathy, severe congenital heart disease, or significant stenotic valvular disease; marked renal impairment (defined by creatinine >3 mg/dL) at screening or on any type of dialysis; known cholestasis (total bilirubin >3 mg/dL) or increased ammonia levels at screening; known sensitivity or intolerance to ACE inhibitors or allergy to organic nitrates; severe cerebrovascular disease, including acute stroke or cerebral ischaemia; women who were pregnant or lactating; or history or presence of any other diseases (i.e. including malignancies or AIDS) with a life expectancy of <12 months.

Primary and secondary endpoints

The study was designed to investigate the effect of the combination of hydralazine/isosorbide dinitrate (HYIS) on the rate of the primary endpoint: all-cause death or re-admission for HF during 24 weeks of therapy. The intended sample size was estimated to provide 80% power to detect a hazard ratio (HR) of 0.61 assuming a 35% event rate in the placebo group.

The HYIS combination was also compared with placebo with respect to the following pre-specified secondary endpoints: (i) change in symptoms of HF from baseline to 7 days post-randomization or discharge, as assessed by dyspnoea severity and global well-being on a visual analogue scale (VAS); (ii) change in systolic BP from baseline to 7 days post-randomization or discharge, and at 8 weeks and 24 weeks post-randomization; (iii) functional status assessed by the 6-min walk test (6MWT) at 7 days post-randomization or discharge, and at 8 weeks and 24 weeks post-randomization; (iv) changes in markers of renal function [serum creatinine, urea, and estimated glomerular filtration rate (eGFR)] from baseline to 7 days post-randomization or discharge, and at 24 weeks post-randomization; and (v) change in LV dimensions and LVEF from baseline to 24 weeks post-randomization.

Approval was obtained from the ethics committee of each participating institution, and the study conformed to the principles of the Declaration of Helsinki. All patients gave written, informed consent prior to participation. The study was governed by a Steering Committee and monitored by an independent Data and Safety Monitoring Committee. The membership of both committees is detailed in Appendix 1. Investigators were trained through investigator meetings, and study personnel monitored study conduct through remote monitoring, telephone contacts, and site visits. The study is registered at Clinicaltrials.gov as NCT01822808.

Study visits

Within 96 h of admission for AHF, and during the admission, patients were screened and randomized into the study if the inclusion criteria were met. Patients' self-report of dyspnoea severity by VAS was measured and a 6MWT was performed. Patients were randomized to receive increasing doses of HYIS, starting with 25 mg hydralazine/10 mg isosorbide dinitrate and up-titrating to 50 mg hydralazine/20 mg isosorbide dinitrate t.i.d. or placebo (*Figure 1*). The study drug was provided by Sandoz SA. The dose selection and careful up-titration were done in order to avoid hypotension in these patients during and immediately after an AHF admission. Patients received standard HF therapy at the discretion of their treating physician and according to evidence-based guideline recommendations (ACE inhibitors, ARBs, beta-blockers, aldosterone antagonists, and diuretics). Patients were followed by clinic visit through 6 months for the occurrence of readmissions and death. Patients who completed the 24-week double-blind phase were given the option of continuing open-label treatment with active medication for up to 24 weeks.

Statistical methods

Events reported by investigators were reviewed in a blinded manner by two independent cardiologists. Time-to-event endpoints, including the primary outcome, were compared between treatment groups on an intention-to-treat basis using a log-rank test. Kaplan–Meier estimates of event rates and associated 95% confidence intervals (CIs) are presented along with HRs and associated 95% CIs from Cox regression models that included only the treatment effect. The proportional hazards assumption was tested post-hoc through inclusion of a treatment × time interaction effect in the model. Patients were censored at the earlier of the last contact date or the time period of interest.

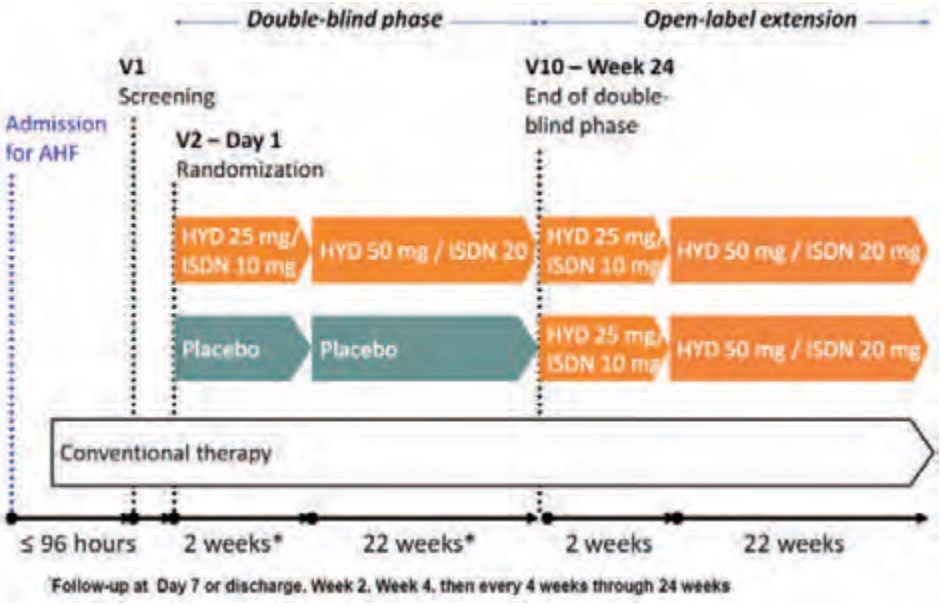

Figure 1 Schematic of the study design. AHF, acute heart failure.

For continuous outcomes, mean and standard deviation (SD) and/or median and first and third quartiles, and absolute and relative frequencies for categorical variables, are presented. The geometric mean and corresponding 95% CIs are also included for secondary laboratory endpoints that were log-transformed. Missing values were imputed using linear interpolation between nearest flanking non-missing values or through last observation carried forward (LOCF) where no following non-missing value was available. Values following a death were imputed as the worst reported score for dyspnoea and general well-being VAS, as zero for the 6MWT distance, as the LOCF for vital signs and laboratory values, and as the baseline plus or minus the worst reported change across all subjects for echocardiographic measures. Changes from baseline were compared between treatment groups using analysis of covariance with adjustment for the baseline value; least square mean differences and associated 95% CIs are presented, or the ratio of the geometric means with adjustment for the log-baseline result. Post-hoc analyses exploring effects on rehospitalizations included a comparison of the number of HF hospitalizations, where death was included as an event, using negative binomial regression. Additionally, days in hospital or dead from randomization through the earlier of 168 days or end of follow-up was compared between treatment groups using a *t*-test; length of hospital stay was imputed with the overall median (5.5 and 7 days, respectively) for three initial hospitalizations and one rehospitalization missing the discharge date. Data from one site in Senegal were excluded from the analyses due to major protocol non-compliance. SAS® 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for analyses.

Results

Twelve centres from nine African countries were invited to paticipate, of which nine centres from six African countries (Mozambique, South Africa, Nigeria, Kenya, Uganda, and Senegal) participated. Data for 14 randomized patients from one centre in Senegal were excluded due to non-compliance with the protocol. This issue was reported to the site's local ethics committee after being discovered during routine monitoring. From March 2012 to March 2015, a total of 619 patients were screened and subsequently 133 patients were randomized (*Figure 2*) at the remaining eight centres. The primary reasons for exclusion from the study were (i) lack of test results, e.g. echo or laboratory, available within 96 h of admission; (ii) kidney function too poor; (iii) lack of background treatment with an ACE inhibitor and/or beta-blocker; (iv) liver function too poor; and (v) not eligible due to low BP. The study had to be terminated prematurely due to low recruitment and expiry of the study medication. Although as described below some patients screened failed to meet eligibility criteria, as seen in *Figure 2*, most of the lag in enrolment was related to lower than expected screening rates, in this double-blind, prospective, randomized study. Efforts were made to overcome these enrolment challenges including repeat investigators' meetings, frequent calls to the sites, and site visits by study personnel and the study Principal Investigator.

Demographic characteristics of the patients were rather similar across participating countries, except with a higher proportion of patients of race other than Black African enrolled in South Africa (Supplementary material online, *Table S1*). The randomization was blocked by study centre, however, so randomization to the two study arms was balanced within each country.

Baseline characteristics of the study population by treatment group are outlined in *Table 1*. For convenience of comparison, the last two columns of *Table 1* contain the baseline characteristics from the A-HeFT study.[11] The mean age of the entire group was 53.2 ± 14.8 years, with 49.2% being female. The majority (66.7%) of patients had hypertension, while few (5.3%) had a history of IHD.

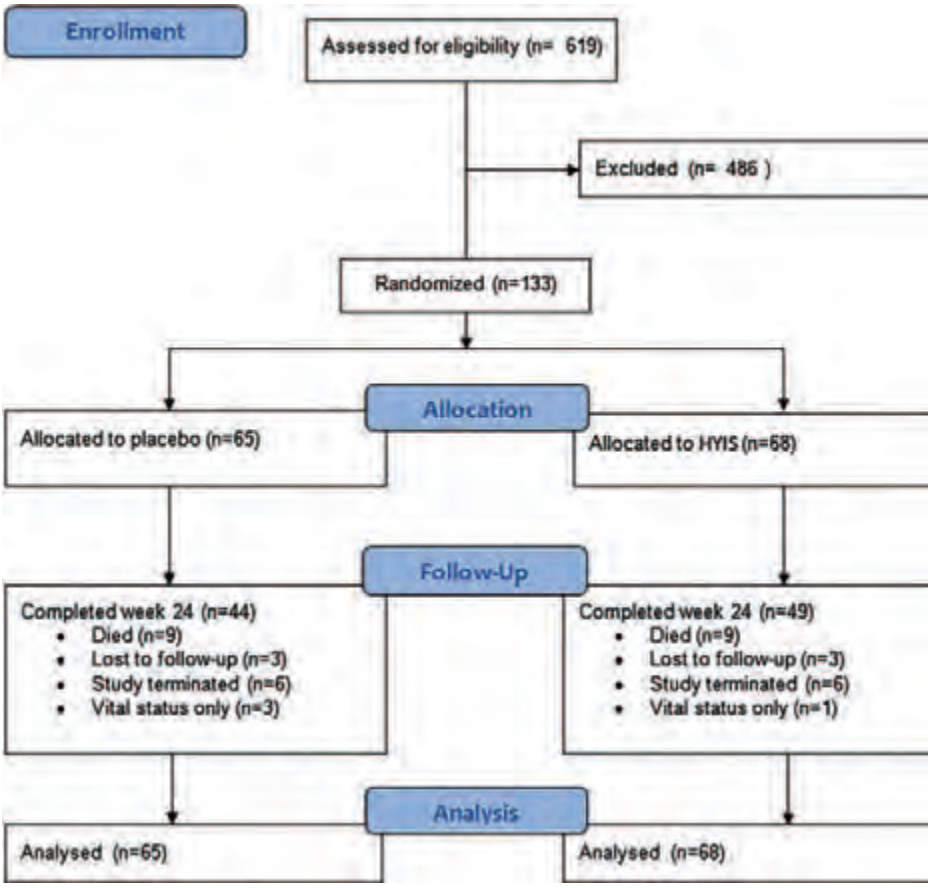

Figure 2 Study flow diagram. Excludes patients (25 screened, 14 randomized, 6 to placebo and 8 to hydralazine/isosorbide dinitrate) in one site in Senegal due to major protocol non-compliance.

Baseline characteristics were similar in the active and the placebo groups. Twenty-nine (22%) of the 133 patients were >65 years old, 26 (92.9%) of whom did not have a history of IHD. Of the 103 patients ≤65 years old, 98 (95.1%) had no history of IHD.

A total of 111 (83.5%) of the randomized patients either died or completed the study through week 24 (*Figure 2*). Twelve (9.0%) patients were discontinued prematurely when the study was terminated; 6 patients were lost to follow-up, and for 4 patients who had stopped attending visits, only the vital status at week 24 was obtained. The mean follow-up was 145.0 days. Over 60% of patients (63.5% and 67.6% in the placebo and HYIS groups, respectively) had a final dose of 50 mg hydralazine/20 mg isosorbide dinitrate t.i.d., while ~75% (73.8% and 77.9% in the placebo and HYIS groups, respectively) were on this dose at any point in the study.

The primary endpoint was not met, with a HR for death or HF readmission at 24 weeks of 1.05 (95% CI 0.48–2.27, $P = 0.90$). Fourteen patients in the HYIS arm died or had a HF readmission by week 24 as compared with 12 in the placebo arm. However, this was driven by an early potential benefit [at 60 days the HR was 0.49 (95% CI 0.18–1.32)] that decreased with time (*Figure 3A*). By day 60, 6 patients in the HYIS group and 11 patients in the placebo group had died or been hospitalized for HF, which was reflected by a statistically significant treatment × time interaction ($P = 0.0268$). Nine patients in each treatment group died by week 24: five in the HYIS group and nine in the placebo group from cardiovascular causes. One patient in the HYIS group and five patients in the placebo group died from a cardiovascular cause by day 60. There was a trend to benefit on cardiovascular mortality at 24 weeks where the HR was 0.51 (95% CI 0.17–1.52, $P = 0.22$) (*Figure 3B*).

In a post-hoc analysis we observed that patients in the placebo arm had more HF rehospitalizations per patient. The total number of events—deaths or HF readmissions—through week 24 was 18 in the HYIS arm vs. 26 in the placebo group, giving a rate ratio of 0.54 (95% CI 0.16–1.82, $P = 0.32$). Fifteen patients in the HYIS arm died or had a readmission for any cause by week 24 as compared with 17 in the placebo arm; however, patients in the placebo arm had more readmissions per patient. The total number of deaths or all-cause readmissions was 21 in the HYIS arm vs. 33 in the placebo arm ($P = 0.25$). The mean number of days dead or in hospital through 24 weeks was 18.3 ± 36.4 days [median 6.0, interquartile range (IQR) 3.0–8.5 days] in the HYIS group compared with 26.4 ± 45.9 days (median 7.0, IQR 5.0–15.0 days) in the placebo group ($P = 0.26$).

Table 1 Baseline characteristics of the study population

Characteristic	BA-HEF	AHeFT	
	Overall ($n = 133$)	Isosorbide dinitrate plus hydralazine ($n = 518$)	Placebo ($n = 532$)
Age, years, mean (SD)	53.2 (14.76)	56.7 (12.7)	56.9 (13.3)
Male sex, %	50.8	55.8	63.9
Weight, kg, mean (SD)	74.1 (19.1)	92.5 (21.4)	94.1 (25.5)
Primary cause of heart failure, %[a]			
Ischaemic heart disease	5.3	23.4	22.7
Hypertension	66.7	40.0	37.4
Idiopathic	13.7	24.5	27.6
Valvular cause	11.3	2.5	3.2
Other	–	9.7	9.0
NYHA class at screening, %			
I	1.1	0	0
II	22.2	0.2	0
III	55.6	96.7	94.7
IV	21.1	3.1	5.3
Diabetes, %	12.9	44.8	37.0
Atrial fibrillation, %	7.6	15.0	18.0
Cardiac resynchronization therapy, %	0.8	2.0	2.1
Implantable cardiac defibrillator, %	0	16.6	17.3
Ejection fraction at screening, %, mean (SD)	24.6 (10.2)	23.9 (7.3)	24.2 (7.5)
LVIDD, cm, at screening	6.3 (1.1)	6.5 (0.9)	6.5 (1.0)
Blood pressure, mmHg, mean (SD)			
Systolic	130.9 (19.6)	127.2 (17.4)	125.3 (18.1)
Diastolic	85.8 (14.8)	77.6 (10.3)	75.6 (10.5)
Medication for heart failure, %			
Diuretic	66.2	88.0	91.5
ACE inhibitor	85.7	69.4	69.5
ARB	9.8	17.2	16.5
Beta-blocker	43.6	74.1	73.5
Carvedilol	33.0	55.2	55.8
Digoxin	22.6	58.5	60.7
Spironolactone	27.8	40.2	37.6
Race, %			
African or Black	81.5	–	–
Coloured or mixed race	16.9	–	–
Caucasian or White	1.6	–	–
Time from presentation to randomization, hours, mean (SD)	73.1 (80.5)	–	–

LVIDD, left ventricular end-diastolic internal diameter.
[a]History of condition for BA-HEF.

The secondary endpoints showed non-significant trends in most outcomes in favour of HYIS vs. placebo. Dyspnoea improved by 1.6 mm more on a 100-mm VAS in the active group from an overall mean baseline of 57.7 mm, i.e. 3%, at day 7 or discharge ($P = 0.58$) (*Table 2*). General well-being improved to day 7 or discharge by 2.5 mm more in the active group ($P = 0.31$) from an overall mean baseline of 59.7 mm. The 6MWT distance improved at 24 weeks by 17.2 m more in the active group ($P = 0.48$) (*Table 2*). The overall mean baseline systolic BP was 126.7 mmHg, and decreased by 3.8 mmHg (95% CI −11.0 to 3.5) more in the active group ($P = 0.31$) at week 24 (*Figure 4*). The overall mean baseline weight was 73.7 kg and decreased by 2.7 kg (95% CI −5.52 to 0.13) more in the active group ($P = 0.06$) at 24 weeks (*Figure 5*). There was a similar drop in creatinine, a 13% larger drop in blood urea nitrogen (BUN; $P = 0.11$), and a 3.7 mL/min/1.73 m^2 greater improvement in eGFR ($P = 0.49$) at 24 weeks in the active group (*Table 3*). On echocardiographic evaluation, LVEF increased by 0.3% ($P = 0.92$), LV end-systolic diameter decreased by 2.0 mm ($P = 0.22$), and LV end-diastolic diameter decreased by 1.1 mm ($P = 0.55$) more in the active group (*Table 4*).

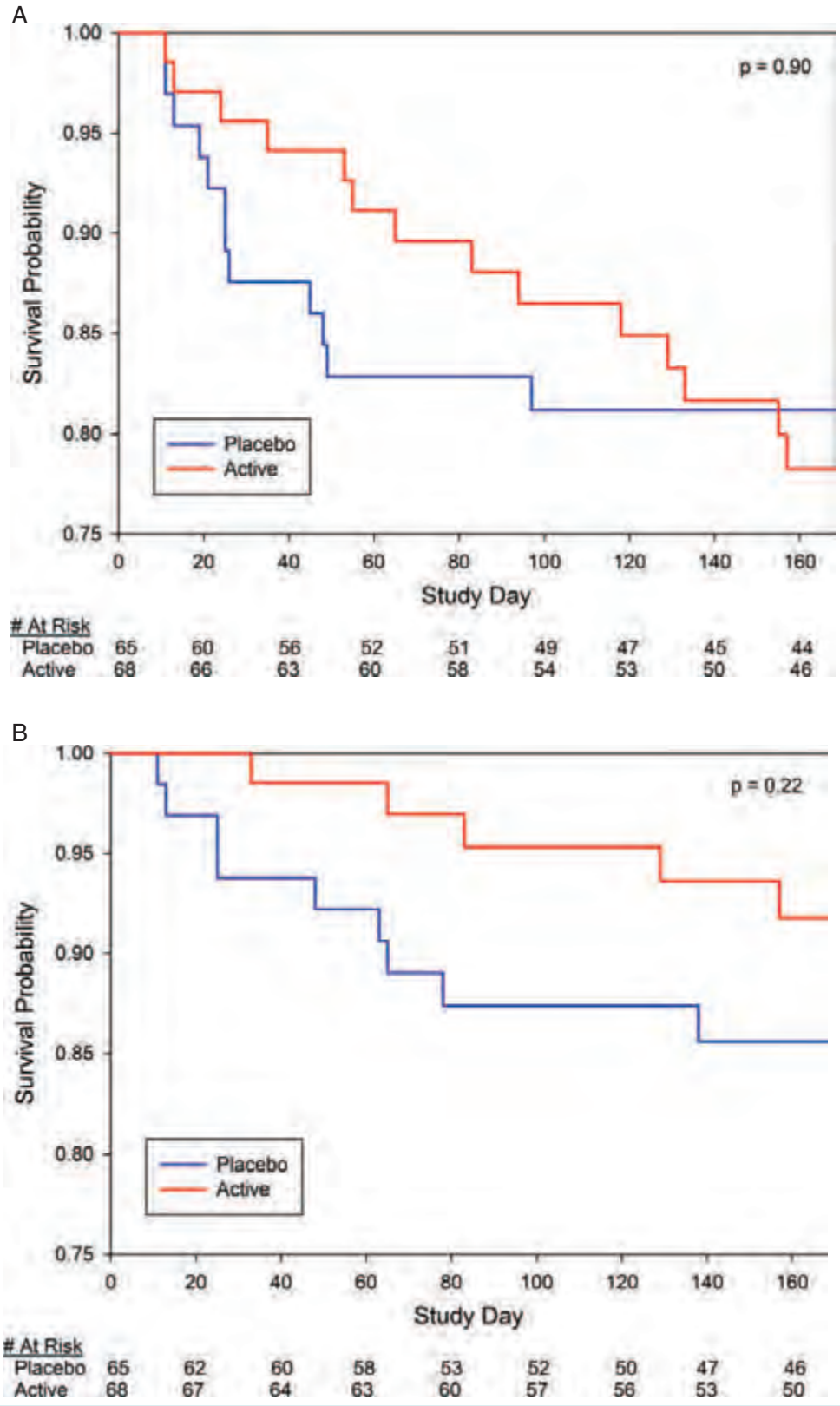

Figure 3 Kaplan–Meier curves for (*A*) all-cause death or heart failure rehospitalization through 24 weeks and (*B*) cardiovascular death trought week 24.

Table 2 Changes in dyspnoea, general well-being, and 6-min walk test distance

Measure	Statistic	Placebo ($n = 65$)	HYIS ($n = 68$)	LS mean difference (95% CI)	*P*-value
Dyspnoea VAS, mm					
Baseline	Mean (SD)	56.2 (18.24)	59.1 (21.58)		
	Median (Q1, Q3)	60.0 (50.0, 68.0)	60.0 (42.0, 73.0)		
Change to Day 7 or discharge	Mean (SD)	12.3 (18.57)	12.7 (19.91)	1.6 (−4.3, 7.5)	0.5842
	Median (Q1, Q3)	8.0 (0.0, 24.0)	7.0 (0.0, 20.5)		
Change to week 8	Mean (SD)	13.2 (25.41)	14.8 (27.29)	3.0 (−5.4, 11.5)	0.4804
	Median (Q1, Q3)	10.0 (0.0, 30.0)	12.5 (0.0, 30.0)		
Change to week 24	Mean (SD)	14.2 (31.79)	10.0 (32.81)	−2.9 (−13.6, 7.8)	0.5932
	Median (Q1, Q3)	20.0 (0.0, 36.0)	10.0 (0.0, 30.0)		
General well-being VAS, mm					
Baseline	Mean (SD)	59.2 (17.72)	60.3 (19.67)		
	Median (Q1, Q3)	60.0 (47.0, 72.0)	60.0 (50.0, 77.5)		
Change to Day 7 or discharge	Mean (SD)	9.0 (14.79)	11.2 (15.78)	2.5 (−2.4, 7.4)	0.3066
	Median (Q1, Q3)	5.0 (0.0, 19.0)	8.0 (0.0, 20.0)		
Change to week 8	Mean (SD)	12.4 (22.96)	14.6 (23.76)	2.9 (−4.1, 9.9)	0.4134
	Median (Q1, Q3)	15.0 (0.0, 24.0)	14.5 (0.0, 30.0)		
Change to week 24	Mean (SD)	12.3 (24.66)	10.6 (29.89)	−0.7 (−9.3, 7.8)	0.8661
	Median (Q1, Q3)	12.0 (0.0, 30.0)	13.0 (0.0, 30.0)		
6-min walk test distance, m					
Baseline	Mean (SD)	253.8 (115.60)	244.3 (123.37)		
	Median (Q1, Q3)	252.0 (170.0, 318.0)	229.0 (150.0, 333.0)		
Change to Day 7 or discharge	Mean (SD)	41.0 (52.93)	35.3 (101.42)	−6.7 (−35.0, 21.7)	0.6412
	Median (Q1, Q3)	28.0 (0.0, 74.0)	17.0 (0.0, 60.0)		
Change to week 8	Mean (SD)	42.3 (104.40)	66.7 (128.48)	23.0 (−18.1, 64.0)	0.2704
	Median (Q1, Q3)	45.0 (0.0, 114.0)	49.0 (8.0, 98.0)		
Change to week 24	Mean (SD)	48.1 (119.76)	65.7 (149.0)	17.2 (−30.5, 65.0)	0.4764
	Median (Q1, Q3)	37.0 (0.0, 129.0)	48.0 (0.0, 145.0)		

CI, confidence interval; HYIS, hydralazine/isosorbide dinitrate; LS, least squares; VAS, visual analogue scale.

Rates of reported serious adverse events were similar in the two treatment groups: 18 (27.7%) placebo and 19 (27.9%) HYIS patients. Adverse events leading to discontinuation of study drug were also similar and were reported for 4 (6.2%) placebo and 6 (8.8%) HYIS patients.

Discussion

The BA-HEF study was initiated on the heels of the THESUS-AF registry where we observed low use of a HYIS combination therapy in patients with HF in Africa.[7] Based on the screening and enrolment rates in the THESUS-AF registry, it was planned to enrol 500 patients during an AHF admission over a period of 12 months and test whether administration of HYIS would reduce the risk of death or HF readmission over 6 months. Regretfully, despite our best efforts, after 4 years we managed to enrol fewer than 150 patients and the study drug had expired and could not be renewed further. Hence, the study was terminated, all patients in the active part of the study crossed to active open-label HYIS, and the database was locked.

The primary endpoint was not met. However, in this limited data set, results for several secondary outcomes were consistent with expected effects of HYIS, including a lower rate of cardiovascular mortality through 24 weeks, a non-statistically significantly lower number of HF and all-cause admissions per patient, and fewer days dead or in hospital in the active arm. Other findings consistent with a benefit include that in the HYIS group compared with the placebo group, by 24 weeks systolic BP dropped more, weight decreased more, 6MWT improved more, and there was a larger drop in BUN. On echocardiographic evaluation, parameters such as improvement in the LVEF, and a decrease in LV end-systolic diameter and LV end-diastolic diameter all favoured the active group, although again in a statistically non-significant manner. The interpretation of these differences should be tempered by the fact that the study is small and recruitment was in a selected group of hospitals, mostly advanced medical centres in each country.

The combination of hydralazine and isosorbide dinitrate has been shown to reduce mortality, as compared with placebo, in patients with mild to moderate HF treated with digoxin and diuretics.[9] In V-HeFT II, enalapril improved survival to a greater extent than hydralazine and isosorbide dinitrate at 2 years, but the difference between the treatment groups was attenuated by the end of follow-up.[10] In A-HeFT, the fixed dose combination of hydralazine and isosorbide dinitrate improved survival, as compared with placebo (6.2% vs. 10.2%, HR 0.57, $P = 0.01$)[11] in African

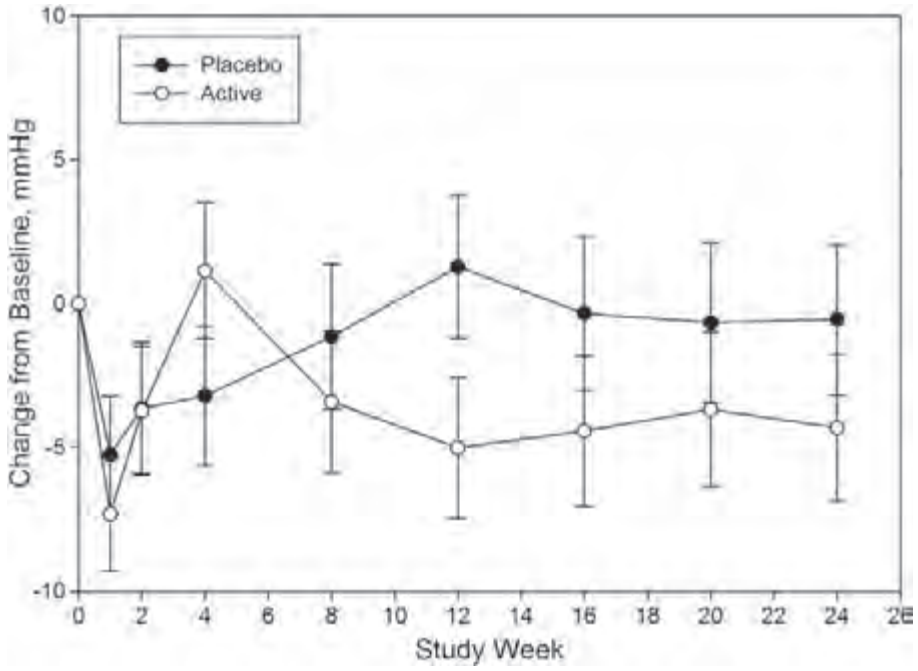

Figure 4 Changes in systolic blood pressure.

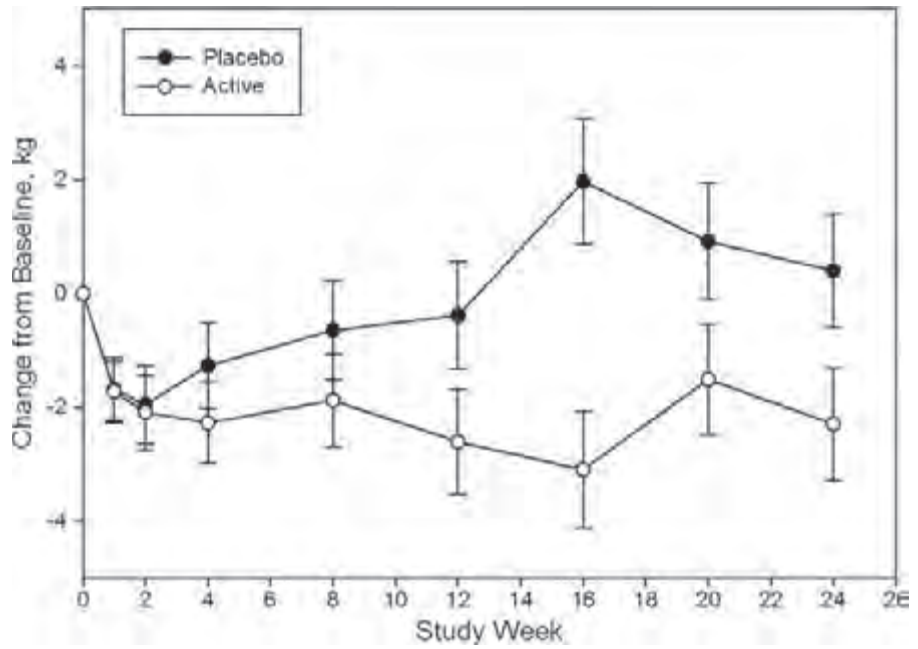

Figure 5 Changes in weight.

American patients. The rate of first HF hospitalization was also reduced in the hydralazine and isosorbide dinitrate group (16.4% vs. 24.4%, $P = 0.001$). Comparing the A-HeFT and BA-HEF studies highlights some important points, although one has to bear in mind that A-HeFT recruited chronic HF patients while BA-HEF recruited patients with AHF. Despite the above, the age of the patients was similar between the two studies (mid-50s). However, patients in A-HeFT were on average ~20 kg heavier than patients in BA-HEF. This may explained by the fact that patients in A-HeFT had a higher prevalence of diabetes mellitus and IHD as compared

Table 3 Changes in renal function markers

Measure	Statistic	Placebo ($n = 65$)	HYIS ($n = 68$)	Treatment effect (95% CI)[a]	*P*-value
Creatinine, μmol/L					
Baseline	Mean (SD)	106.20 (30.38)	120.08 (54.12)		
	Median (Q1, Q3)	104.0 (82.0, 125.0)	105.2 (88.4, 140.0)		
Change to week 24	Mean (SD)	4.50 (26.18)	1.78 (35.44)		
	Geometric mean (95% CI)	1.04 (0.98, 1.09)	1.01 (0.95, 1.09)	1.00 (0.92, 1.09)	0.9893
	Median (Q1, Q3)	0.0 (−8.5, 16.9)	0.0 (−14.6, 22.9)		
BUN, mmol/L					
Baseline	Mean (SD)	7.20 (3.40)	7.52 (4.76)		
	Median (Q1, Q3)	6.70 (4.60, 9.06)	6.53 (4.20, 8.50)		
Change to week 24	Mean (SD)	0.48 (3.71)	0.03 (4.99)		
	Geometric mean (95% CI)	1.06 (0.93, 1.22)	0.93 (0.81, 1.05)	0.87 (0.73, 1.03)	0.1082
	Median (Q1, Q3)	0.00 (−1.60, 2.59)	0.00 (−2.10, 1.20)		
eGFR, mL/min/1.73 m^2					
Baseline	Mean (SD)	79.21 (30.16)	73.41 (30.02)		
	Median (Q1, Q3)	74.56 (61.15, 90.70)	70.61 (51.37, 90.89)		
Change to week 24	Mean (SD)	−3.05 (20.11)	3.23 (41.50)	3.7 (−6.8, 14.3)	0.4865
	Median (Q1, Q3)	0.00 (−14.26, 5.15)	0.0 (−10.54, 16.01)		

BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; HYIS, hydralazine/isosorbide dinitrate.
[a]Treatment effect for creatinine and BUN is presented as the geometric least squares mean ratio. Treatment effect for eGFR is presented as the least squares mean difference.

Table 4 Changes in echocardiographic parameters

Measure	Statistic	Placebo ($n = 65$)	HYIS ($n = 68$)	LS mean difference (95% CI)	*P*-value
Ejection fraction, %					
Baseline	Mean (SD)	23.8 (9.07)	25.3 (11.26)		
	Median (Q1, Q3)	24.0 (18.0, 30.0)	25.0 (15.0, 34.0)		
Change to week 24	Mean (SD)	8.0 (14.18)	8.0 (14.13)	0.3 (−4.6, 5.1)	0.9187
	Median (Q1, Q3)	6.5 (0.0, 19.5)	4.0 (0.0, 19.5)		
Left ventricular size systole, mm					
Baseline	Mean (SD)	55.8 (10.72)	55.8 (10.71)		
	Median (Q1, Q3)	55.0 (50.0, 62.3)	56.0 (46.0, 63.3)		
Change to week 24	Mean (SD)	−2.2 (8.62)	−4.2 (9.58)	−2.0 (−5.2, 1.2)	0.2189
	Median (Q1, Q3)	0.0 (−7.0, 1.0)	−3.5 (−11.0, 0.0)		
Left ventricular size diastole, mm					
Baseline	Mean (SD)	62.7 (11.01)	63.1 (10.36)		
	Median (Q1, Q3)	63.0 (57.0, 71.0)	62.7 (55.1, 69.5)		
Change to week 24	Mean (SD)	2.1 (10.12)	1.0 (10.76)	−1.1 (−4.6, 2.5)	0.5502
	Median (Q1, Q3)	0.0 (−3.0, 5.0)	0.0 (−3.0, 1.0)		

CI, confidence interval; HYIS, hydralazine/isosorbide dinitrate; LS, least squares.

with BA-HEF. On the other hand, patients in BA-HEF had a higher incidence of valvular heart disease possibly due to a higher incidence of rheumatic heart disease. They also received on average less diuretics, beta-blockers, and aldosterone blockers at screening, although this may be in part related to the fact that some had new-onset HF, as reflected by the lower NYHA class at the same time (*Table 1*). Interestingly, in line with the findings from the THESUS registry,[7] patients in both studies were relatively young (mid-50s), had low prevalence of AF and IHD, and almost identical LVEF and LV end-diastolic diameter (*Table 1*).

Despite the encouraging results of A-HeFT, the THESUS-HF data show that patients in Africa are rarely treated with a combination of hydralazine and nitrates, or the fixed-dose combination BiDil that was used in A-HeFT, since this preparation is unavailable in Africa. The efficacy of combination hydralazine and isosorbide dinitrate is uncertain in Africans when given as individual generic agents. Finally, hydralazine and isosorbide dinitrate had not been evaluated in AHF.

There are a number of reasons for the poor recruitment into this study. There were only 21.5% of screened patients who were eligible for entry into the study, which reflects the difficulty in

recruiting patients for AHF trials in general. Screening failures were mostly due to renal and hepatic dysfunction, low BP, and procedural difficulties. Therefore, there was a need to screen 2500 patients to achieve the original sample size of 500 patients, which was not achieved due to the low screening at the enrolling sites and because some of the originally planned sites never screened patients at all.

Although other studies in which more sites were activated[12] have been able to reach their enrolment targets, this double-blind prospective randomized study seems to have been challenging for investigators, as have been other AHF studies of this kind. Many of the centres that participated in the BA-HEF study had limited clinical research facilities such as Good Clinical Practice-trained nurses and monitors, a dedicated research office or research equipment, and clinical staff with dedicated time to perform research. These factors made the recruitment of patients within the specified time interval extremely challenging. Obtaining ethics approval for centres that had limited experience with a placebo-controlled, multicentre randomized trial was a major challenge, causing delays of up to 2 years at some sites. Registries which do not have these short recruitment time intervals, or give study medication, are still possible under these circumstances, but require enthusiasm and large investment of after-hours time, as the recently published REMEDY study on rheumatic heart disease,[13] The Heart of Soweto Study,[14] and THESUS-HF[7] have demonstrated.

The shortage of trained physicians and cardiologists, plus inadequate specialized cardiac facilities and equipment, coupled with low levels of patient and public awareness, led to many patients not having ready access to basic diagnostic facilities such as electrocardiography and echocardiography, causing a delay in recruitment. It is therefore imperative that the research and developmental objectives be specifically focused and tailored towards those disease entities that are highly prevalent on the African continent (e.g. HF) and upon issues and obstacles in regard to documenting their epidemiology, treatment, and prevention.

As stated above, a cautious interpretation of the study results is warranted. However, this is the first study to examine the administration of the HYIS combination in patients with AHF. The limited results of the study suggest that HYIS treatment may be associated with an early decrease in cardiovascular mortality but offset by an increase in non-cardiovascular mortality and HF readmissions. A trend towards an increase in non-cardiovascular mortality while cardiovascular mortality decreases was observed in recent years in HF studies, although not to the point of a lack of decrease in all-cause mortality.[15] Nonetheless, the effects observed raise an important related question of what the effects of HYIS combination would be in all patients with AHF regardless of race and geographical region. As no new effective therapies have been developed in AHF in recent decades, would it be possible that some of the effects observed here may be replicated in larger and more diverse populations?

Limitations

The BA-HEF study enrolled patients in almost the same centres as in the THESUS-HF study and, as such, shares certain limitations with the original cohort. The majority of the patients were recruited in a limited number of hospitals—mainly in Kenya, Mozambique, Nigeria, South Africa, and Uganda. As the study had to be terminated early, it was underpowered. Loss to follow-up and missing laboratory data and assessments of clinical signs were higher than in studies conducted in other regions.

Conclusions

Extensive investment in research facilities in a number of African countries is needed which would allow randomized controlled studies for non-communicable diseases, including AHF studies.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics of the study population by country.

Acknowledgements

The authors would like to thank Dr Ameet Nathwani of Novartis Switzerland and Sandoz South Africa for manufacturing and supplying the study drug and matching placebo, free of charge.

Conflict of interest: none declared.

Appendix

The Steering Committee included: Professor Sliwa, Professor Damasceno, Professor Mayosi, Dr Ojii, Dr Mondo, Dr Ogah, Dr Sani, Dr Davison, and Dr. Cotter.

The Data Monitoring Committee included: Professor Adrian A. Voors, Professor Justin Ezekowitz, Professor Faiez Zanad, and the DMC statistician Professor Jan Tijssen.

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5 Chapter 5: The predictors of readmission and mortality in acute heart failure in sub Saharan Africa: results from THESUS-HF registry

5.1 Introduction

Patients with heart failure (HF) are at high risk for mortality and rehospitalization in the early period after hospital discharge. Identification of predictors of outcomes is needed for risk stratification of HF patients. Patient management requires an understanding of risk of future events to make appropriate decisions about acuity of care (eg, admission to an intensive care unit versus a less monitored setting), to triage patients among available therapies, and to plan hospital discharge and intensity of follow up. [104]

Although there has been several publications on long-term prognostic factors in CHF, [105,106] little has been done to aid in the risk stratification of patients presenting with exacerbations of decompensated heart failure. [107,108]

Acute heart failure exacts a heavy social and economic burden on families and society in Africa. The understanding of the causes of re-admission and death is especially important in African population and may be relevant to other developing regions of the world.

In this chapter, we present the patient characteristics associated with 60-day re-admission or death and 180-day mortality among patients admitted with AHF and enrolled in the THESUS-HF registry

Our results showed that the main predictors of 60-day re-admission or death in a

model excluding the geographic region were a history of malignancy, severe lung disease, admission systolic blood pressure, and signs of congestion (rales) as well as kidney function (BUN). In a model including region, the Southern region had a higher risk. Predictors of 180-day mortality included malignancy, severe lung disease, smoking history, systolic blood pressure, heart rate, and symptoms and signs of congestion (orthopnoea, peripheral oedema and rales) at admission, kidney dysfunction (BUN), anaemia, and HIV positivity.

This chapter is presented as a published research paper below, in the European Heart Journal.

Sliwa K, Davison BA, Mayosi BM, Damasceno A**, Sani M,** Ogah O, Mondo C, Ojji D, Dzudie A, Koum Koum C, Suliman A, Schrueder N, Yonga G, Ba, SA, Maru F, Alemayehu B, Edwards C and Cotter G. Readmission and Death after an acute heart falure event: predictors and oputcomes in sub-Saharan Africa: results from the THESUS- HF registry. Eur Heart J. 2013 Oct; 34(40):3151-9. doi: 10.1093/eurheartj/eht393. Epub 2013 Sep 18.

Statement of originality document: Please see Appendix

European Heart Journal (2013) **34**, 3151–3159
doi:10.1093/eurheartj/eht393

Readmission and death after an acute heart failure event: predictors and outcomes in sub-Saharan Africa: results from the THESUS-HF registry

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Received 10 March 2013; revised 4 August 2013; accepted 28 August 2013; online publish-ahead-of-print 18 September 2013

Aims Contrary to elderly patients with ischaemic-related acute heart failure (AHF) typically enrolled in North American and European registries, patients enrolled in the sub-Saharan Africa Survey of Heart Failure (THESUS-HF) were middle-aged with AHF due primarily to non-ischaemic causes. We sought to describe factors prognostic of re-admission and death in this developing population.

Methods and results Prognostic models were developed from data collected on 1006 patients enrolled in THESUS-HF, a prospective registry of AHF patients in 12 hospitals in nine sub-Saharan African countries, mostly in Nigeria, Uganda, and South Africa. The main predictors of 60-day re-admission or death in a model excluding the geographic region were a history of malignancy and severe lung disease, admission systolic blood pressure, heart rate and signs of congestion (rales), kidney function (BUN), and echocardiographic ejection fraction. In a model including region, the Southern region had a higher risk. Age and admission sodium levels were not prognostic. Predictors of 180-day mortality included malignancy, severe lung disease, smoking history, systolic blood pressure, heart rate, and symptoms and signs of congestion (orthopnoea, peripheral oedema and rales) at admission, kidney dysfunction (BUN), anaemia, and HIV positivity. Discrimination was low for all models, similar to models for European and North American patients, suggesting that the main factors contributing to adverse outcomes are still unknown.

Conclusion Despite the differences in age and disease characteristics, the main predictors for 6 months mortality and combined 60 days re-admission and death are largely similar in sub-Saharan Africa as in the rest of the world, with some exceptions such as the association of the HIV status with mortality.

Keywords Heart failure • Prognosis • sub-Saharan Africa

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Introduction

Acute heart failure (AHF) is one of the most common reasons for admission to hospital, and a major driver for health-related cost globally. Its prevalence is shown to be high and outcomes dire in North America,[1] Europe,[2] South America,[3] Southeast Asia,[4] and recently also in sub-Saharan Africa.[5]

Despite the huge impact of this disease until recently little progress has been made in characterizing the pathophysiology of the disease. The 2012 European Society of Cardiology (ESC) guidelines on acute and chronic heart failure[6] highlight the lack of evidence-based therapy for AHF compared with the therapeutic options for chronic heart failure. Models examining predictors of outcomes such as short-term re-admission and death have very low ability to discriminate between those with and without the outcome with *c*-indexes ranging from 0.6 to 0.7,[7–9] where 0.5 represents chance and 1.0 perfect discrimination. This lack of understanding of pathophysiology and predictors of outcome in AHF is at the core of the lack of progress in its treatment with available therapies (diuretics and nitrates), such that outcomes have been largely unchanged over the last 30–40 years.[10]

Acute heart failure exacts a heavy social and economic burden on families and society in Africa. Contrary to North America and Europe where AHF affects patients with an average age of >70 years old,[1] the THESUS-HF registry[5] has shown that in sub-Saharan Africa the disease affects men and women in the most productive years of life, at an average age of 52.3 years and is mostly caused by hypertension and not ischaemic heart disease. Hence, understanding the causes for re-admission and death is especially important in this African population and may be relevant to other developing regions of the world.

In this work, we identify patient characteristics associated with 60-day re-admission or death and 180-day mortality in a cohort of 1006 African patients admitted with AHF and enrolled in the THESUS-HF registry.

Methods

Patients and data collected

THESUS-HF[5] was a prospective, multicentre, international observational survey conducted in 12 hospitals from 9 countries in the southern, eastern, central, and western regions of sub-Saharan Africa. All patients were recruited during an admission for AHF, mostly in Nigeria, Uganda, and South Africa. Methods and results have been previously described in detail.[5] In brief, from July 2007 to June 2010 patients admitted with dyspnoea and diagnosed with AHF based on symptoms and signs (including dyspnoea, orthopnoea, dyspnoea on exercise, rales, oedema, jugular venous pulse, and oxygen saturation) and who provided written informed consent were enrolled into the study. The diagnosis was supported by echocardiographical findings and was confirmed by a cardiologist. Exclusion criteria included acute ST elevation myocardial infarction, severe renal failure (patients on dialysis or creatinine >4 mg/dL), nephrotic syndrome, or hepatic failure. Approval was obtained from the ethics committee of each participating institution and the study conformed to the principles of the Declaration of Helsinki.

Detailed data collected at admission onto standardized case report forms included medical history, medication use, laboratory values, and physical examination with symptoms and signs of heart failure. Echocardiography and electrocardiography were also performed. Human immunodeficiency virus testing was performed as clinically indicated. Patients were followed either by clinic visit or telephone contact through 6 months for the occurrence of re-admissions and death. As described in the main report, patients were classified as having either an emerging or endemic cause of heart failure. Endemic causes included rheumatic heart disease, cardiomyopathies, and infective causes, while emerging causes included hypertension and ischaemic heart disease.

Statistical methods

Cox regression models were constructed considering the time from admission to the first event; times for patients without the event of interest were censored at the earlier of the last date the patient was known to be alive or the period of interest. Prognostic models were constructed for the two outcomes of interest considering candidate predictors chosen based on data available in THESUS-HF, variables found to be predictive in other AHF studies, and clinical judgment. Participating countries were grouped into three regions: East which comprised Sudan ($n = 72$), Ethiopia ($n = 10$), Kenya ($n = 32$), and Uganda ($n = 154$); West which comprised Senegal ($n = 15$), Nigeria ($n = 425$), and Cameroon ($n = 90$); and South which comprised South Africa ($n = 132$) and Mozambique ($n = 76$). Because region was found to be significantly associated with re-admission or death, and because regional cultural and medical practice patterns might affect admission, we also constructed a model examining only patient clinical characteristics.

The linearity of association between each continuous predictor and each outcome was assessed using restricted cubic splines with four 'knots' with a test of the significance of the non-linear terms.[11] Where the association was non-linear, a readily interpreted transformation was chosen through examination of plots of the predicted log hazard ratio against the value of the predictor and changes in Akaike's information criterion. If little information was lost, the same transformation was used to model both outcomes. Multiple imputation assuming multivariate normality (SAS PROC MI) was used to handle missing values. The imputation model included all covariates under consideration for the multivariable models. The ranges of imputed values were restricted to the ranges of the observed values. Seven imputation data sets were used. Parameter estimates were averaged across these data sets using Rubin's algorithm[12] (SAS PROC MIANALYZE). SAS version 9.2 (SAS Institute, Inc, Cary, NC, USA) was used for the analyses.

We constructed a multivariable model for each of the outcomes from the candidate predictors listed in *Table 1* (except those effects that were dropped), with continuous variables included using the model forms indicated in *Tables 2–4*. For the 60-day composite endpoint, one model was assessed with the inclusion of region as a predictor and one excluding region. Backwards selection was performed in each of the imputed data sets, with the criterion for staying at $P = 0.10$. Predictors that were significant in at least four of the imputed data sets were kept in the reduced model. The discrimination of the models was evaluated using the c-index.[13] The model fit was assessed visually using calibration plots[11] which were generated from the stacked imputation data sets.[14] In these plots, patients were grouped by deciles of predicted risk, and the mean predicted risk for each group was compared with the Kaplan–Meier estimate of risk in these same groups.

Results

Of the 1006 patients included in the THESUS-HF database, one patient was excluded who had unreasonable data pertaining to both outcomes (i.e. subject had a date of death listed before admission) giving 1005 patients for this analysis. Of the 1006 patients enrolled 430 were enrolled in Nigeria, 154 in Uganda and 132 in South Africa. Patients were followed a median of 180 days.

Table 1 Candidate predictors for re-admission and death

Variable	*N*	*n*	Distribution (%) for dichotomous; 25th %ile, median, 75th %ile for continuous	% missing	Comments
Hx of DM	1004	114	(11.4)	0.2	
Hx of IHD	1004	82	(8.2)	0.2	
Valvular disease	1000	272	(27.2)	0.6	
HIV positive	992	65	(6.6)	1.4	
Hypertension	1002	556	(55.5)	0.4	
Hyperlipidaemia	981	90	(9.2)	2.5	
HX of stroke	1005	25	(2.5)	0.1	
HX of PVD	1003	12	(1.2)	0.3	
Current or former smoker	1002	98	(9.8)	0.4	
Malignancy	1003	13	(1.3)	0.3	
Hx of depression	1004	33	(3.3)	0.2	
Hx of dementia	1004	22	(2.2)	0.2	
Hx of atrial fibrillation	998	184	(18.4)	0.8	
Hx of pericardial Disease	1000	53	(5.3)	0.6	
Hx of Cardiomyopathy	994	416	(41.8)	1.2	
Hx of cor pulmonale	995	72	(7.2)	1.1	
Age, years	996		39, 55, 67	1.0	
Male sex	1005	494	(49.2)	0.1	
White race	999	15	(1.5)	0.7	Dropped from consideration as there were no events for either outcome in 15 white subjects
Ejection fraction, %	930		27, 38, 50	7.6	
BMI, kg/m^2	968		20.9, 24.0, 28.0	3.8	Extreme values of 214.5 and 121.4 set to missing for analysis
BUN, mg/dL	971		16.5, 26.6, 42.0	3.5	Values <6 set to missing
Creatinine, mg/dL	970		0.89, 1.12, 1.5	3.6	Values <0.4 set to missing
Glucose, mg/dL	878		84.0, 93.7, 117.0	12.7	
Haemoglobin, g/dL	967		10.7, 12.3, 13.7	3.9	
Lymphocytes, %	839		20.0, 30.0, 39.6	16.6	
Sodium, mmol/L	946		131.0, 135.8, 139.1	6.0	
Cholesterol, mg/dL	649		124.0, 152.1, 187.0	35.5	Not measured in large proportion of study population
Total WBC, /mm^3 or /cumm or/μL or /mcL	963		5200, 6800, 8980	4.3	
Systolic BP, mmHg	994		106, 126.5, 150	1.2	
Diastolic BP, mmHg	992		70, 80, 100	1.4	Collinear with systolic BP. Dropped from consideration
Heart rate, b.p.m.	997		90, 104, 116	0.9	
Respiration, breaths/min	989		26, 29, 34	1.7	
Orthopnoea, (0/1 vs. 2/3)	838	741	(88.4)	16.7	
Peripheral oedema, (0/1 vs. 2/3)	990	665	(67.2)	1.6	
Rales, (0/1 vs. 2/3)	880	565	(64.2)	12.5	
lifestyle (emerging = 1, endemic = 0)	980	507	(51.7)	2.6	
Region	1006		East: 268, South: 208, West: 530	0	

Ninety-five patients died and 74 were readmitted through 60 days; 138 patients experienced a death or re-admission through 60 days, where the first event was re-admission for 74 patients and death for 64 patients. A total of 151 patients died through 180 days after admission. A total of 38 candidate predictors were considered. The distribution and proportion of unavailable values for each predictor are given in *Table 1*. A total of 522 (51.9%) patients were missing at least one candidate variable when cholesterol was not included as a predictor; one variable was missing for 284 patients, two for 162 patients, three for 72 patients, and four or more for 140 patients. We also considered cholesterol as a predictor, although it is measured only when clinically indicated in African patients with AHF. With the inclusion of

Table 2 Models for all-cause death or re-admission through 60 days

Predictor	HR for a change of	Univariable models		Multivariable model	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Hx of DM	Yes/no	1.29 (0.81, 2.08)	0.2862		
Hx of IHD	Yes/no	1.00 (0.55, 1.81)	0.9948		
Valvular disease	Yes/no	1.04 (0.72, 1.52)	0.8275		
HIV positive	Yes/no	1.57 (0.88, 2.80)	0.1241		
Hypertension	Yes/no	0.86 (0.62, 1.20)	0.3756		
Hyperlipidaemia	Yes/no	0.40 (0.17, 0.95)	0.0373	0.47 (0.20, 1.12)	0.0891
HX of stroke	Yes/no	0.27 (0.04, 1.98)	0.1984		
HX of PVD	Yes/no	1.13 (0.27, 4.66)	0.8644		
Current or former smoker	Yes/no	0.76 (0.41, 1.43)	0.3995		
Malignancy	Yes/no	5.07 (2.25, 11.45	<0.0001	5.04 (2.19, 11.56)	0.0001
Hx of depression	Yes/no	1.21 (0.49, 2.97)	0.6831		
Hx of dementia	Yes/no	0.92 (0.29, 2.92)	0.8933		
Hx of atrial Fibrillation	Yes/no	1.34 (0.90, 1.99)	0.1509		
Hx of pericardial disease	Yes/no	1.29 (0.67, 2.47)	0.4423		
Hx of cardiomyopathy	Yes/no	0.96 (0.68, 1.35)	0.8133		
Hx of cor plmonale	Yes/no	2.50 (1.57, 4.00)	0.0001	1.75 (1.07, 2.87)	0.0268
Age, years	10	0.95 (0.87, 1.04)	0.2443		
Male Sex	Yes/no	1.16 (0.83, 1.63)	0.3756		
Ejection fraction, %[a]	50 vs. 27	0.94 (0.73, 1.21)	0.0523	0.89 (0.79, 1.14)	0.1355
BMI, kg/m^2	5	1.04 (0.90, 1.20)	0.6127		
BUN, mg/dL[a]	Doubling	1.39 (1.18, 1.63)	<0.0001	1.46 (1.23, 1.73)	<0.0001
Creatinine, mg/dL[a]	1.55 vs. 0.90	1.40 (1.07, 1.83)	0.0095		
Glucose, mg/dL	10	0.99 (0.95, 1.03)	0.5489		
Haemoglobin, g/dL	1	0.92 (0.86, 0.99)	0.0238		
Lymphocytes, %	5	0.96 (0.90, 1.03)	0.2275		
Sodium, mmol/L	5	0.87 (0.77, 0.98)	0.0263		
Total WBC, /mm^3 or /cumm or /μL or /mcL[a]	Doubling	1.10 (0.84, 1.43)	0.4833		
Cholesterol, mg/dL	10	0.98 (0.94, 1.02)	0.2423		
Systolic BP, mmHg	10	0.91 (0.86, 0.96)	0.0009	0.91 (0.86, 0.97)	0.0017
Heart rate, b.p.m.	5	1.04 (1.00, 1.08)	0.0300		
Respiration, breaths/min	5	1.07 (0.97, 1.18)	0.1836		
Orthopnoea[b]	(2/3 vs. 0/1)	1.78 (0.89, 3.56)	0.1033		
Peripheral oedema[c]	(2/3 vs. 0/1)	1.60 (1.08, 2.37)	0.0194		
Rales[d]	(2/3 vs. 0/1)	2.16 (1.38, 3.38)	0.0008	2.18 (1.36, 3.50)	0.0012
Heart failure cause[e]	(emerging = 1, endemic = 0)	0.78 (0.56, 1.09)	0.1497		
Region	(South vs. West)	1.32 (0.89, 1.94)	0.0141	1.83 (1.21, 2.78)	0.0025
Region	(East vs. West)	0.62 (0.39, 0.97)		0.78 (0.48, 1.27)	
C-statistic (95% confidence interval)				0.6986 (0.6521–0.7451)	

[a]Appropriate transformation used due to the non-linear relationship between predictor and outcome.
[b]Orthopnoea defined as: 0 = none, +1 = 1 pillow (10 cm), +2 = 2 pillow (20 cm), +3 = 3 pillow (>30 cm).
[c]Peripheral oedema defined as: 0, complete absence of skin indentation with mild digital pressure in all dependent areas; 1+, indentation of skin that resolves over 10–15 s; 2+, identation of skin is easily created with limited pressure and disappears slowly (15–30 s or more); 3+, large areas of indentation easily produced and slow to resolve (.30 s).
[d]Rales defined as: 0, no rales after clearing with cough; 1, moist or dry rales heard in lowerone-third of 1 or both lung fields that persist after cough; 2, moist or dry rales heard throughout the lower half to two-thirds of 1 or both lung fields; 3, moist or dry rales heard throughout both lung fields.
[e]Endemic causes included rheumatic heart disease, cardiomyopathies, and infective causes, while emerging causes included hypertension and ischaemic heart disease.

cholesterol 646 (64.3%) of the patients were missing a value for at least one predictor. Models were run for each outcome including and excluding cholesterol as a predictor. Despite the high number of patients with unavailable baseline cholesterol, the variables that stayed in the model for the outcomes were the same whether or not cholesterol was included.

Univariable associations with the composite outcome, and the final multivariable models with and without consideration of the

Table 3 Models for all-cause death or re-admission through 60 days, excluding region

Predictor	HR for a change of	Univariable models		Multivariable model	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Hx of DM	Yes/no	1.29 (0.81, 2.08)	0.2862		
Hx of IHD	Yes/no	1.00 (0.55, 1.81)	0.9948		
Valvular disease	Yes/no	1.04 (0.72, 1.52)	0.8275		
HIV positive	Yes/no	1.57 (0.88, 2.80)	0.1241		
Hypertension	Yes/no	0.86 (0.62, 1.20)	0.3756		
Hyperlipidaemia	Yes/no	0.40 (0.17, 0.95)	0.0373	0.49 (0.21, 1.19)	0.1156
HX of stroke	Yes/no	0.27 (0.04, 1.98)	0.1984		
HX of PVD	Yes/no	1.13 (0.27, 4.66)	0.8644		
Current or former smoker	Yes/no	0.76 (0.41, 1.43)	0.3995		
Malignancy	Yes/no	5.07 (2.25, 11.45)	<0.0001	4.31 (1.89, 9.82)	0.0005
Hx of depression	Yes/no	1.21 (0.49, 2.97)	0.6831		
Hx of dementia	Yes/no	0.92 (0.29, 2.92)	0.8933		
Hx of atrial Fibrillation	Yes/no	1.34 (0.90, 1.99)	0.1509		
Hx of pericardial disease	Yes/no	1.29 (0.67, 2.47)	0.4423		
Hx of cardiomyopathy	Yes/no	0.96 (0.68, 1.35)	0.8133		
Hx of cor pulmonale	Yes/no	2.50 (1.57, 4.00)	0.0001	2.03 (1.24, 3.32)	0.0048
Age, years	10	0.95 (0.87, 1.04)	0.2443		
Male sex	Yes/no	1.16 (0.83, 1.63)	0.3756		
Ejection fraction, %[a]	50 vs. 27	0.94 (0.73, 1.21)	0.0523	0.97 (0.75, 1.26)	0.0981
BMI, kg/m^2	5	1.04 (0.90, 1.20)	0.6127		
BUN, mg/dL[a]	Doubling	1.39 (1.18, 1.63)	<0.0001	1.42 (1.19, 1.68)	<0.0001
Creatinine, mg/dL[a]	1.55 vs. 0.90	1.40 (1.07, 1.83)	0.0095		
Glucose, mg/dL	10	0.99 (0.95, 1.03)	0.5489		
Haemoglobin, g/dL	1	0.92 (0.86, 0.99)	0.0238		
Lymphocytes, %	5	0.96 (0.90, 1.03)	0.2275		
Sodium, mmol/L	5	0.87 (0.77, 0.98)	0.0263		
Total WBC, /mm^3 or /cumm or /μL or /mcL[a]	Doubling	1.10 (0.84, 1.43)	0.4833		
Cholesterol, mg/dL	10	0.98 (0.94, 1.02)	0.2423		
Systolic BP, mmHg	10	0.91 (0.86, 0.96)	0.0009	0.92 (0.87, 0.98)	0.0048
Heart rate, b.p.m.	5	1.04 (1.00, 1.08)	0.0300	1.04 (1.00, 1.08)	0.0723
Respiration, breaths/min	5	1.07 (0.97, 1.18)	0.1836		
Orthopnoea[b]	(2/3 vs. 0/1)	1.78 (0.89, 3.56)	0.1033		
Peripheral oedema[c]	(2/3 vs. 0/1)	1.60 (1.08, 2.37)	0.0194		
Rales[d]	(2/3 vs. 0/1)	2.16 (1.38, 3.38)	0.0008	2.04 (1.31, 3.16)	0.0016
Heart failure cause[e]	(emerging = 1, endemic = 0)	0.78 (0.56, 1.09)	0.1497		
C-statistic (95% confidence interval)				0. 6826 (0.6375–0.7294)	

[a]Appropriate transformation used due to the non-linear relationship between predictor and outcome.
[b]Orthopnoea defined as: 0 = none, +1 = 1 pillow (10 cm), +2 = 2 pillow (20 cm), +3 = 3 pillow (>30 cm).
[c]Peripheral oedema defined as: 0, complete absence of skin indentation with mild digital pressure in all dependent areas; 1+, indentation of skin that resolves over 10–15 s; 2+, indentation of skin is easily created with limited pressure and disappears slowly (15–30 s or more); 3+, large areas of indentation easily produced and slow to resolve (.30 s).
[d]Rales defined as: 0, no rales after clearing with cough; 1, moist or dry rales heard in lowerone-third of 1 or both lung fields that persist after cough; 2, moist or dry rales heard throughout the lower half to two-thirds of 1 or both lung fields; 3, moist or dry rales heard throughout both lung fields.
[e]Endemic causes included rheumatic heart disease, cardiomyopathies, and infective causes, while emerging causes included hypertension and ischaemic heart disease.

geographic region are given in *Tables 2* and *3*, respectively. Adjusted for geographic region malignancy, cor pulmonale, higher admission BUN level, and presence of rales were found to significantly increase the risk of death or re-admission within 60 days, while hyperlipidaemia, and higher systolic blood pressure reduced the risk (*Table 2*). Unlike for other continuous predictors, the association of ejection fraction with the log hazard ratio was non-linear, with risk increasing for patients with ejection fraction both less than and greater than ~40%. Patients enrolled in Southern centres were at higher risk of the composite outcome, while those enrolled in Eastern centres were at lower risk, compared with those enrolled in Western centres. Considering region, the c-index for the

Table 4 Models for all-cause death through 180 days

Predictor	HR for a change of	Univariable models		Multivariable model	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Hx of DM	Yes/no	1.25 (0.80, 1.97)	0.3260		
Hx of IHD	Yes/no	0.56 (0.27, 1.15)	0.1121		
Valvular disease	Yes/no	1.05 (0.73, 1.51)	0.7882		
HIV positive	Yes/no	1.98 (1.20, 3.29)	0.0081	1.62 (0.94, 2.78)	0.0805
Hypertension	Yes/no	0.76 (0.55, 1.04)	0.0859		
Hyperlipidaemia	Yes/no	0.43 (0.20, 0.96)	0.0382		
HX of stroke	Yes/no	0.77 (0.24, 2.43)	0.6544		
HX of PVD	Yes/no	0.92 (0.22, 3.79)	0.9074		
Current or former smoker	Yes/no	0.57 (0.29, 1.12)	0.1050	0.51 (0.25, 1.03)	0.0592
Malignancy	Yes/no	4.26 (1.76, 10.33)	0.0014	3.00 (1.22, 7.35)	0.0166
Hx of depression	Yes/no	1.16 (0.47, 2.85)	0.7474		
Hx of dementia	Yes/no	1.48 (0.61, 3.63)	0.3883		
Hx of atrial fibrillation	Yes/no	1.17 (0.79, 1.74)	0.4371		
Hx of pericardial disease	Yes/no	0.89 (0.43, 1.81)	0.7384		
Hx of cardiomyopathy	Yes/no	1.18 (0.86, 1.63)	0.3060		
Hx of Cor pulmonale	Yes/no	2.14 (1.33, 3.44)	0.0017	1.99 (1.22, 3.24)	0.0057
Age, years	10	0.93 (0.85, 1.01)	0.0845		
Male sex	Yes/no	1.08 (0.78, 1.49)	0.6409	1.38 (0.97, 1.96)	0.0699
Ejection fraction, %	5	0.96 (0.92, 1.02)	0.1657		
BMI, kg/m^2	5	1.01 (0.88, 1.16)	0.9101		
BUN, mg/dL[a]	Doubling	1.27 (1.08, 1.50)	0.0033		
Creatinine, mg/dL[a]	1.55 vs. 0.90	1.37 (1.14, 1.65)	0.0020	1.36 (1.12, 1.64)	0.0051
Glucose, mg/dL	10	0.98 (0.95, 1.02)	0.3820		
Haemoglobin, g/dL	1	0.91 (0.85, 0.97)	0.0050	0.93 (0.87, 1.00)	0.0488
Lymphocytes, %	5	1.00 (0.93, 1.07)	0.9657		
Sodium, mmol/L	5	0.87 (0.78, 0.99)	0.0294		
Cholesterol, mg/dL	10	0.95 (0.91, 0.99)	0.0282		
Total WBC, /mm^3 or /cumm or /μL or /mcL[a]	Doubling	1.14 (0.89, 1.46)	0.3060		
Systolic BP, mmHg	10	0.86 (0.81, 0.91)	<0.0001	0.86 (0.81, 0.91)	<0.0001
Heart rate, b.p.m.[a]	116 vs. 90	1.29 (0.99, 1.67)	0.0165	1.34 (1.01, 1.81)	0.0845
Respiration, breaths/min	5	1.02 (0.93, 1.13)	0.6641		
Orthopnoea[b]	(2/3 vs. 0/1)	2.69 (1.30, 5.56)	0.0079	1.86 (0.85, 4.08)	0.1194
Peripheral oedema[c]	(2/3 vs. 0/1)	2.26 (1.50, 3.40)	<0.0001	1.91 (1.23, 2.97)	0.0043
Rales[d]	(2/3 vs. 0/1)	2.11 (1.41, 3.18)	0.0003	1.60 (1.03, 2.50)	0.0380
Heart failure cause[e]	(emerging = 1, endemic = 0)	0.72 (0.52, 0.99)	0.0431		
Region	(South vs. West)	1.21 (0.84, 1.76)	0.0042		
Region	(East vs. West)	0.53 (0.34, 0.83)			
C-statistic (95% confidence interval)				0.7231 (0.6849–0.7451)	

[a]Appropriate transformation used due to the non-linear relationship between predictor and outcome.
[b]Orthopnoea defined as: 0 = none, +1 = 1 pillow (10 cm), +2 = 2 pillow (20 cm), +3 = 3 pillow (>30 cm).
[c]Peripheral oedema defined as: 0, complete absence of skin indentation with mild digital pressure in all dependent areas; 1+, indentation of skin that resolves over 10–15 s; 2+, indentation of skin is easily created with limited pressure and disappears slowly (15–30 s or more); 3+, large areas of indentation easily produced and slow to resolve (.30 s).
[d]Rales defined as: 0, no rales after clearing with cough; 1, moist or dry rales heard in lowerone-third of 1 or both lung fields that persist after cough; 2, moist or dry rales heard throughout the lower half to two-thirds of 1 or both lung fields; 3, moist or dry rales heard throughout both lung fields.
[e]Endemic causes included rheumatic heart disease, cardiomyopathies, and infective causes, while emerging causes included hypertension and ischaemic heart disease.

multivariable model was 0.70, indicating a moderate degree of discrimination (*Table 2*). The same multivariable predictors were obtained when region was not considered, except that heart rate also entered the model (*Table 3*). The *C*-index for this multivariable model (0.68) was slightly less than for that including region.

Univariable associations and the multivariable model of death through 180 days are given in *Table 4*. Known HIV positivity, malignancy, cor pulmonale, male sex, lower haemoglobin, lower systolic blood pressure, and presence of orthopnoea, peripheral oedema, and rales were found to increase risk, while current or former

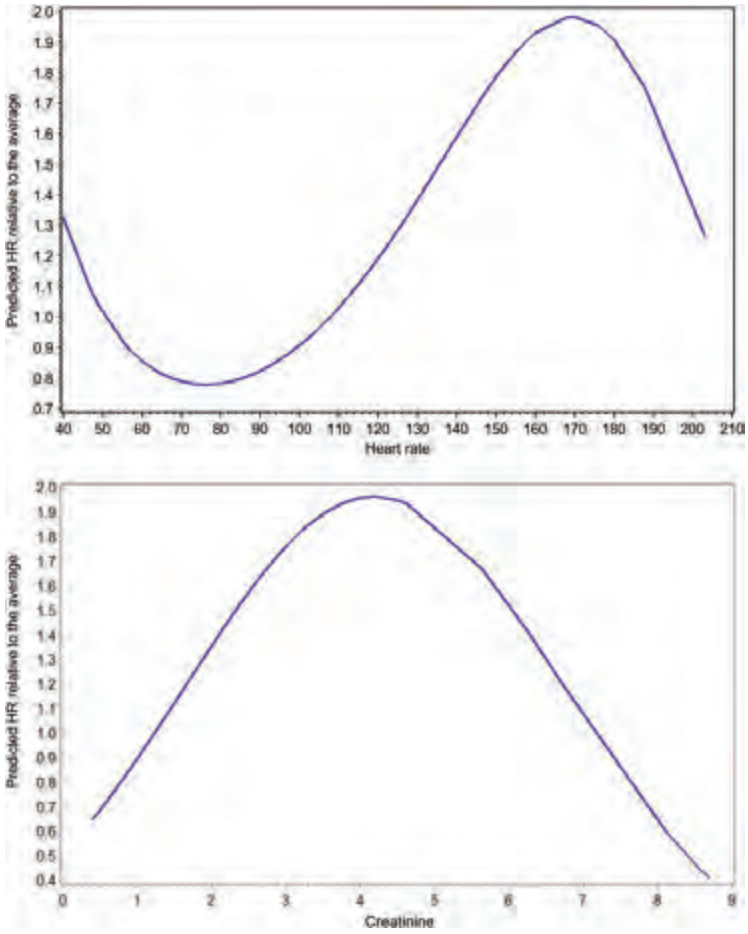

Figure 1 Non-linear associations of continuous predictors with all-cause death through 180 days.

smoking reduced risk (*Table 4*). The associations of creatinine and heart rate with the log hazard ratio for mortality were non-linear (*Figure 1*). Patients with a higher heart rate were generally at increased risk; while the model-predicted risk appears to fall again, this is likely because of undue influence of a few patients with extreme heart rates (six patients with HR >170 b.p.m.). The model-predicted association with creatinine was an apparent inverted U shape with patients with creatinine levels of ~1.9 mg/dL at highest risk; risks appear to decrease with values >4 mg/dL; however, very few (32) patients had these extreme values. The *C*-index for the multivariable model was 0.72.

Calibration plots, comparing observed event rates with those predicted by the models, are given in *Figure 2* for death or re-admission through Day 60 (with, *Figure 2A*, and without, *Figure 2B* consideration of region) and in *Figure 3* for mortality through Day 180. Risks predicted by the models were generally close to those observed among patients grouped by deciles of predicted risk.

Discussion

The current manuscript is an analysis of the THESUS registry.[5] As previously noted the main finding of the THESUS registry points to the fact that patients who present with AHF in sub-Saharan Africa are younger, less have ischaemic heart disease or risk factors for ischaemic heart disease (such as smoking) and many more have valvular (mostly rheumatic) heart disease and are hypertensive. As has been found in other studies,[7–9] the main predictors of either re-admission or death in the model that excludes region (*Table 3*) are a history of malignancy and severe lung disease, admission systolic blood pressure, heart rate and signs of congestion (rales), kidney function (BUN), and echocardiographic ejection fraction. In the model in which region has been included (*Table 2*), the Southern African region seems to confer a higher risk of re-admission suggesting that cultural and health economics-related factors may contribute to the decision to re-admit a patient after an AHF event, as opposed to outpatient clinic treatment. Interestingly, some factors that routinely contribute to similar models in North America and Europe have a lesser role in sub-Saharan Africa. These should be confirmed in further studies in potentially larger number of patients and more hospitals. Most notably age and sodium levels at admission may have potentially less of a predictive effect in sub-Saharan Africa. Age may have a lesser role in this population because these patients are almost 20 years younger on average than AHF patients in North American and European registries. Sodium may play a lesser role

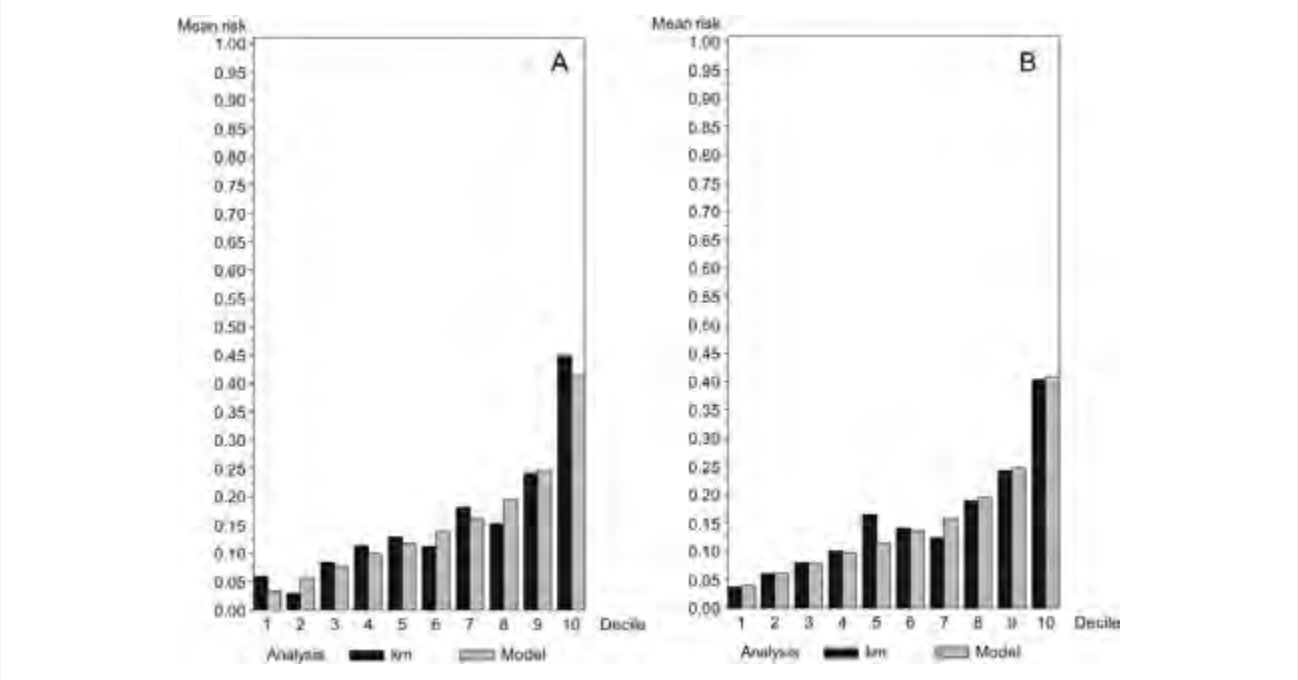

Figure 2 (*A*) Calibration plot for multivariable model for all-cause death or re-admission through 60 days. Model including region. (*B*) Calibration plot for multivariable model for all-cause death or re-admission through 60 days. Model excluding region.

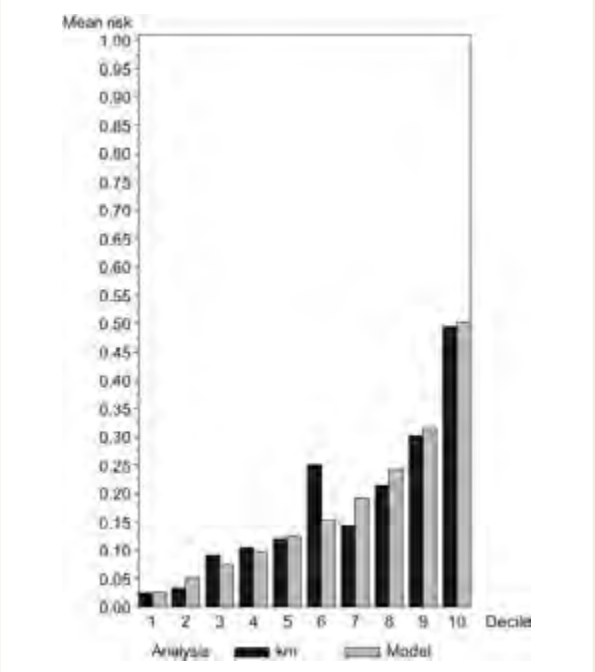

Figure 3 Calibration plot for multivariable model for all-cause death through Day 180.

since most patients are young and the most common cause of heart failure is hypertension which may be associated with less neurohormonal activation than end-stage ischaemic cardiomyopathies which are more prevalent in North America and Europe, especially among the sickest AHF patients who are more commonly re-admitted after discharge.

The main predictors of 180-day mortality include malignancy, severe lung disease, smoking history, systolic blood pressure, heart rate, and symptoms and signs of congestion (orthopnoea, peripheral oedema, and rales) at admission, kidney dysfunction (BUN), anaemia, and being HIV positive. Again, many of these predictors are the same as those reported in similar studies in North America and Europe, although some notable differences are apparent. Again, the interpretation of these differences should be tempered by the fact that the study is relatively small and was recruited in a selected group of hospitals, mostly advance medical centres in each country. The role of HIV positivity as a predictor of adverse outcome is important. Sodium was not found to be a predictor of mortality in the current study (as is the case of re-admission and death), suggesting again that neurohormonal activation involving the renin–angiotensin system may have a lesser role in the HF process in sub-Saharan Africa, a finding in line with the reduced efficacy of ACEi in African Americans,[15] suggesting that other therapies such as combination of hydralazine and nitrates should be further explored in this population. Finally, the association of smoking with less adverse outcome may relate to the diagnosis of AHF being wrong and the breathlessness was due to lung disease, and this misdiagnosis led to the associated cigarette smoking being seen as conferring survival advantage.

Similar to other studies in which short-term re-admission and death and intermediate-term mortality were modelled in AHF the strength of the predictive models are modest with *C*-indexes in the range of 0.68–0.72. These *C*-indexes suggest that although some of the variability in outcomes can be explained by the factors examined,

other causes for re-admission and death after an AHF are still unknown in sub-Saharan Africa as in the rest of the world.

Limitations

The present study is an analysis of the patients enrolled in the THESUS-HF study and as such shares certain limitations with the original cohort. The majority of the patients were recruited in a limited number of hospitals mainly in Nigeria, Uganda, and South Africa. Most importantly loss to follow-up and missing laboratory data and clinical signs assessments were higher than in studies conducted in other regions. Loss to follow-up is common in the population studied due to a number of factors such as working opportunities if still well (migrant workers), or need to be taken care of if not well. Some tests are not performed as routinely in these institutions as in institutions participating in other studies. Secondly, this registry has been performed in selected centres and may represent only AHF patients seen in specialized centres. Thirdly, HIV infection has emerged as an important factor that predicts outcome in patients with AHF in sub-Saharan Africa. Future studies should aim not only to ensure testing of cases for heart failure, but also explore the contribution of degree of immunosuppression (by CD4+ T cell count testing), and the impact of anti-retroviral therapy. Finally, a larger sample size with significant numbers of participants at each site will be needed to provide valid comparisons between patients from various countries in Africa. The small size of the database obviated a split-sample approach to model validation; validation in another sub-Saharan African cohort would provide greater confidence in the findings.

Conclusions

Despite being one of the most common causes for hospital admissions both globally and in sub-Saharan Africa, our knowledge of the pathophysiology of AHF is limited. In the present study, the predictive models for 60-day re-admission or death and 180-day mortality are of the modest predictive value suggesting that some of the factors contributing to the morbidity and mortality in AHF are unknown. For the most part, the main predictors for these adverse outcomes are similar in sub-Saharan Africa as in the rest of the world although with some notable exceptions such as the association of the HIV status with mortality and lack of prediction by sodium on both re-admission and deaths.

Funding

This study was supported by Momentum Research, Inc.

Conflict of interest: none declared.

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6 Chapter 6: Symptoms and signs of heart failure at admission and discharge and outcomes in the Sub-Saharan Acute Heart Failure (THESUS-HF) registry

6.1 Introduction

Because of their importance symptoms and signs of HF have been the mainstay of assessments aimed at determining the severity of disease, as well as response to therapy in patients admitted for AHF. Such assessments are done at least daily in hospitals all over the world. However, their importance and additive value to other characteristics have been debated. The challenge relates to both the exact symptoms and signs to be assessed which vary widely around the world, as well as variability in severity determination driven by different standards and differences between assessors.[474]

The Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) investigators[474] conducted an analysis of outcomes in patients admitted with AHF and determined that more congestion at discharge predicted more adverse outcomes, after adjusting for baseline characteristics, suggesting that non-resolution of symptoms and signs of HF during a AHF admission may be a strong marker for adverse outcome. However, the EVEREST study was limited to patients with AHF due to systolic dysfunction who met the strict inclusion and exclusion criteria of the study. The value of assessing changes in symptoms and signs of HF was not previously assessed in more real life AHF patients and, specifically, in patients in Sub-Saharan Africa. We sought to determine

the relation between symptoms and signs of congestion and prognosis in African patients with AHF.

6.2 Methods

The data were collected in the THESUS study, a prospective, multicenter, international observational survey of AHF in 12 cardiology centers, from 9 countries in sub-Saharan Africa. [36]

Details of data collection have been previously described.[3] Symptoms and signs of heart failure, including oxygen saturation, degree of edema and rales, body weight and levels of orthopnea were assessed at admission and on days 1, 2, and 7 (or on discharge if earlier). Changes in dyspnea and well-being relative to admission were assessed on days 1, 2, and 7 (or on discharge if earlier). These assessments were done using structured scales as shown in Table 6.1. Oxygen saturation was assessed using pulse oximeters available at the sites and respiratory rate was defined as respiratory cycles per minute counted over at least 1 minute.

Table 6.1 Structured scale used in assessing symptoms and signs of heart failure at admissions, days 1, 2, 7 (or discharge if earlier)

Symptoms							
Parameter	Grading						
Changes in Dyspnea	+3= Markedly better	+2 = Moderately better	+1 = Minimally better	0 = No change	-1 Minimally worse	-2 = Moderately Worse	- 3 Markedly worse
Changes in patients well being	+3= Markedly better	+2 = Moderately better	+1 = Minimally better	0 = No change	-1 Minimally worse	-2 = Moderately Worse	- 3 Markedly worse
Orthopnea (number of pillow used by the patient	0= None	+1 = 1 pillow (10 cm)	+2 = 2 pillow (20 cm)	+3 = 3 pillow (>30 cm).			
Signs							
Parameter	Grading						
Severity of Oedema	0: no skin indentation with mild digital pressure	1+: Indentation of skin that resolves over 10–15 seconds	2+: Indentation easily produced and goes slowly (15–30 seconds)	3+: Large areas of indentation easily produced and slow to resolve (> 30 seconds).			
Presence of Rales	0: No rales after clearing with cough	1: Moist or dry rales heard in lower ⅓ of 1 or both lung fields that persist after cough	2: Moist or dry rales heard throughout the lower half to ⅔ of 1 or both lung fields	3: Moist or dry rales heard throughout both lung fields.			

6.2.1 Statistical Analysis

Data were analyzed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Symptoms and signs and their changes were analyzed on a continuous scale with summary statistics (mean, SD, median, min, and max) provided.

Cox regression models were constructed to examine univariable and multivariable associations of baseline symptoms and signs and changes from baseline to day 7 (or discharge) with all-cause death through day 180 and a composite endpoint of all-cause death or readmission through 60 days. The time to first event from admission was used. Patients with no event were censored at the earlier of the last date the patient was known to be alive or the period of interest. Linearity was assessed for each sign/symptom change that was included as a potential predictor, using restricted cubic splines (RCS) with 4 'knots' and examining the significance of the non-linear terms. None of the predictors were found to have a significantly non-linear association with either outcome so each predictor was entered as a linear term.

Multivariable models were adjusted for clinical covariates included in multivariable prognostic models in the overall THESUS-HF registry. [475] For the outcome all-cause death or readmission to 60 days, these included history of hyperlipidemia, malignancy, or cor pulmonale, systolic BP, left ventricular ejection fraction, oxygen saturation, rales, blood urea nitrogen, and region. For the outcome all-cause death to day 180, clinical covariates included sex, history of malignancy, cor pulmonale, smoking, human immunodeficiency virus, systolic blood pressure (BP), heart rate, oxygen saturation, orthopnea, rales, edema, creatinine, and hemoglobin. Multiple imputations using seven imputed datasets and assuming multivariate normality was used to handle missing values. Backwards elimination among the symptoms and signs and their changes was then

performed on each imputation dataset, which also included adjustment for the baseline value of each sign/symptom change in the model. Predictors that remained in ≥ 4 of the imputation datasets after backwards selection with a $p < 0.1$ were then included in the final model. Change values found to be predictive after model selection included an adjustment for the baseline value in the final model if the baseline value was not already included from the original prognostic model. Bootstrapping methods were used to examine the difference in c-statistics when the changes of symptoms and signs that were found to be predictive of outcome were added to the original prognostic model.

6.3 Results

There were a total of 1006 patients in the THESUS HF registry. Twenty-three subjects who died during the index hospitalization before day 7 and five patients who were censored before day 7, and did not have day7/discharge data, were excluded from the multivariable models. The mean (SD) age of the patients was 52.4 (18.3) years, 498 (51.0%) were women, and the predominant race was black African 961 (99.0%). Left ventricular EF (LVEF) was 39.4 ± 16.4%.

The majority of patients had data on changes in dyspnea, general well-being, edema, rales, and respiratory rate, while a lower proportion had data on changes in orthopnea, oxygen saturation, and weight (Tables 2 and 3).

Changes in symptoms and signs of HF from baseline to day 2 and to discharge/day 7 are presented in Table 6.2 for patients who had changes available at both follow-up time points. The symptoms of dyspnea as well as general well-being improved, compared to admission at both day 2 and day 7 or discharge. For the most part, patients had significant improvements in symptoms and signs of HF during this time period.

The final signs of HF at day 7/discharge are presented in Table 6.3. It shows that the patients have their symptoms improved with medians of absent rales and oedema among them. The mean respiratory rate was 20 cycles per minute and the mean oxygen saturation was 98%. In general signs of HF in day 7/discharge were mild.

Table 6.2 Summary of changes in heart failure symptoms and signs from baseline to day 2 and the earlier of day 7 or discharge

HF sign or symptom	Statistic	Change from baseline to Day 2*	Change from Baseline to Day 7 or Discharge*
Dyspnea† (-3 to +3)	N Mean (STD) Median (Min, Max)	918 0.40 (1.54) 1 (-3, 3)	918 1.84 (1.13) 2 (-3, 3)
General well being†(-3 to +3)	N Mean (STD) Median (Min, Max)	913 0.51 (1.48) 1 (-3, 3)	913 1.98 (1.08) 2 (-3, 3)
Orthopnea (0 to +3)	N Mean (STD) Median (Min, Max)	780 -0.94 (0.79) -1 (-3, 2)	780 -1.53 (0.90) -2 (-3 , 3)
Edema (0 to 3+)	N Mean (STD) Median (Min, Max)	918 -0.80 (0.61) -1 (-3, 0)	918 -1.43 (0.92) -2 (-3, 2)
Rales (0 to 3)	N Mean (STD) Median (Min, Max)	838 -0.89 (0.65) -1 (-3, 2)	838 -1.43 (0.87) -1 (-3, 1)
Respiration Rate, breaths per minute	N Mean (STD) Median (Min, Max)	920 -6.52 (7.42) -6 (-48, 76)	920 -9.32 (7.93) -8 (-50, 49)
Oxygen Saturation, %	N Mean (STD) Median (Min, Max)	583 3.17 (5.86) 2 (-20 , 59)	583 3.95 (6.12) 3 (-14 , 58)
Weight, kg	N Mean (STD) Median (Min, Max)	596 -1.78 (1.60) -1.3 (-12, 8)	596 -3.74 (3.29) -3 (-25, 19)

*Restricted to patients having reported values at baseline, day 2 and day 7/discharge
†Restricted to patients having reported values at day 2 and day 7/discharge (reported value is relative to admission)

Table 6.3 Heart failure symptoms and signs at the earlier of day 7 or discharge

Dyspnea (-3 to +3)	**N** **Mean (STD)** **Median** **(Min, Max)**	**932** **1.84 (1.14)** **2** **(-3, 3)**
General well-being (-3 to +3)	N Mean (STD) Median (Min, Max)	929 1.97 (1.09) 2 (-3, 3)
Orthopnea (0 to +3)	N Mean (STD) Median (Min, Max)	946 0.77 (0.77) 1 (0, 3)
Edema (0 to 3+)	N Mean (STD) Median (Min, Max)	942 0.40 (0.64) 0 (0, 3)
Rales (0 to 3)	N Mean (STD) Median (Min, Max)	855 0.26 (0.51) 0 (0, 3)
Respiration Rate, breaths per minute	N Mean (STD) Median (Min, Max)	946 21.55 (5.01) 20 (11, 99)
Oxygen Saturation, %	N Mean (STD) Median (Min, Max)	635 97.06 (2.89) 98 (74, 100)
Weight, kg	N Mean (STD) Median (Min, Max)	667 64.23 (16.86) 61.5 (19, 150)

Univariable associations of baseline heart failure symptoms and signs with clinical outcomes are shown in Table 6.4. Rales and, to a lesser extent, respiratory rate and oxygen saturation were predictive of death or HF hospitalization through day 60 while oedema, rales, and respiratory rate strongly predicted death through day 180.

Table 6.4 Univariable associations of baseline heart failure symptoms and signs with clinical outcomes

Variable	Death or HF readmission through day 60		Death through day 180	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Orthopnea*	1.07 (0.84, 1.35)	0.5948	1.14 (0.91, 1.41)	0.2495
Edema*	1.22 (0.92, 1.61)	0.1704	1.60 (1.23, 2.07)	0.0004
Rales*	1.53 (1.14, 2.04)	0.0042	1.79 (1.36, 2.35)	<.0001
Respiration Rate†	1.04 (1.00, 1.08)	0.0502	1.08 (1.04, 1.12)	<.0001
Oxygen Saturation†	0.94 (0.89, 1.01)	0.0758	0.96 (0.90, 1.02)	0.1832
Weight†	0.99 (0.93, 1.05)	0.7244	1.00 (0.95, 1.06)	0.9168

*Adjusted for baseline dichotomized value (2/3 vs. 0/1)
†Adjusted for baseline value

Multivariable associations of symptoms and signs at admission and their changes to day 7/discharge with death or HF hospitalization through day 60, and with death through day 180 are presented in Tables 6.5 and 6.6, respectively. Baseline rales, baseline oxygen saturation and changes to day 7 or discharge in general well-being predicted death or HF hospitalization through day 60. For death through day 180, baseline orthopnea, rales, oedema and oxygen saturation and changes to day 7 or discharge in respiratory rate, and general well-being were predictive of the outcome.

Table 6.5 Multivariable associations of baseline heart failure symptoms and signs and their changes to day 7 or discharge with death or heart failure readmission through 60 days

Parameter	Unit Change	HR	95% CI	P-value
Hyperlipidemia	Yes/No	0.39	(0.14, 1.05)	0.0638
Malignancy	Yes/No	4.71	(1.69, 13.09)	0.0031
Cor Pulmonale	Yes/No	1.46	(0.81, 2.65)	0.2113
Ejection Fraction, %*	50 vs. 27	0.94	(0.69, 1.26)	0.4126
BUN, mg/dL†	Doubling	1.40	(1.15, 1.70)	0.0006
Systolic BP, mmHg	10	0.94	(0.89, 1.00)	0.0670
Baseline Rales	(2/3 vs. 0/1)	2.30	(1.33, 3.98)	0.0032
Region	(South vs. West)	1.55	(0.96, 2.50)	0.0302
Region	(East vs. West)	0.69	(0.40, 1.18)	
Baseline Oxygen Saturation, %	1	0.94	(0.87, 1.01)	0.1189
Change in Oxygen Saturation to Discharge/Day 7	1	0.95	(0.88, 1.04)	0.2745
Change in General Well-Being to Discharge/Day 7	1	0.83	(0.70, 0.98)	0.0327
Bias Corrected C-Statistic (95% CI)		**0.6922 (0.6496, 0.7348)**		

*Non-linear association with outcome; HR for the 75th versus 25th percentile of the distribution presented.†Log-transformed.

Table 6.6 Multivariable associations of baseline heart failure symptoms and signs and their changes to day 7 or discharge with death through 180 days

Parameter	Unit Change	HR	95% CI	P-value
HIV Positive	Yes/No	1.75	(0.97, 3.15)	0.0619
Current/Former Smoker	Yes/No	0.54	(0.26, 1.10)	0.0898
Malignancy	Yes/No	3.42	(1.04, 11.23)	0.0430
Cor Pulmonale	Yes/No	1.51	(0.84, 2.70)	0.1661
Male	Yes/No	1.34	(0.91, 1.97)	0.1431
Creatinine, mg/dL*	1.54 vs. 0.89	1.42	(1.13, 1.78)	0.0085
Hemoglobin, g/dL	1	0.90	(0.83, 0.97)	0.0042
Systolic BP, mmHg	10	0.89	(0.83, 0.95)	0.0003
Heart Rate, bpm*	116 vs. 90	1.57	(1.07, 2.30)	0.1230
Orthopnea (Baseline)	(2/3 vs. 0/1)	1.75	(0.91, 5.64)	0.0783
Edema (Baseline)	(2/3 vs. 0/1)	1.75	(1.05, 2.91)	0.0321
Rales (Baseline)	(2/3 vs. 0/1)	1.83	(1.09, 3.08)	0.0226
Baseline Oxygen Saturation	1	0.94	(0.88, 1.01)	0.0921
Change in Oxygen Saturation to Discharge/Day 7	1	0.95	(0.89, 1.03)	0.1995
Baseline Respiration Rate	1	1.01	(0.97, 1.06)	0.6093
Change in Respiration Rate to Discharge/Day 7	1	1.06	(1.01, 1.11)	0.0269
Change in General Well Being Discharge/Day 7	1	0.77	(0.65, 0.92)	0.0032
Bias Corrected C-Statistic (95% CI)		**0.7392 (0.7040, 0.7745)**		

*Non-linear association with outcome; HR for the 75th versus 25th percentile of the distribution presented.

The addition of signs and symptoms add incremental prognostic information beyond other clinical variables previously found to be predictive of these outcomes. [475] The C-index for the model for all-cause 180-day mortality significantly improved from 0.69 to 0.74, an increase of 0.05 (95% CI 0.02-0.08), and for 60-day HF readmission or death significantly improved from 0.64 to 0.69, an increase of 0.05 (95% CI 0.01-0.08).

6.4 Discussion

Symptoms and signs of HF assessed at admission and thereafter daily to discharge have been the mainstay of assessment and follow-up for patients admitted for AHF. The main purpose of these repeat assessments is to determine the severity of the patients' symptoms and the main reason patients seek medical help and are admitted - leading to changes in medical therapy, mainly targeting symptom relief.

The addition of symptoms and signs of HF during admission to the models predicting readmission or death resulted in significant improvement in C-indexes, suggesting that important additional information was added, improving our ability to discriminate between patients with good and bad outcomes. This result is in line with the analysis of the EVEREST study, [474] which found similar strong associations between lack of improvement of symptoms and signs of HF and adverse outcomes in patients admitted for AHF who have systolic dysfunction. Interestingly, the symptoms and signs that were found to be most predictive are somehow different from what would have been traditionally believed to be of importance. For instance the model generated in the EVEREST study combined three parameters – orthopnea, JVP and pedal edema.

Although JVP was not systematically collected in the THESUS-HF registry, rales and edema were found in the current study to be independently predictive of mortality (as

compared to orthopnea and edema in EVEREST). The presence of rales depicts raised left-sided filling pressure and resultant alveolar oedema while leg oedema, which is the simplest sign of right-sided congestion, reflects elevation of right atrial pressure. [476,477] Damy and colleagues found that having right- and left-sided congestion was associated with a worse prognosis than having either side alone, perhaps reflecting more severe congestion. [478] This was independent of other factors. In a post-hoc analysis of patients enrolled in the Atrial Fibrillation and Congestive Heart Failure (AFCHF) trial to evaluate the prognostic value of baseline physical examination findings, including elevated JVP, third heart sound, rales and peripheral edema, in patients with systolic heart failure, Caldentey et al [479] confirmed that physical signs of congestion, defined by any of the 4 physical findings, is associated with increased mortality and heart failure–related hospitalizations.

In addition the THESUS-HF registry found two other important variables to be predictive of outcomes. First, oxygen saturation, which may be an accurate measure of congestion. Second, patient reported general well-being, which may be an accurate way to gauge congestion and the overall severity of heart failure, may add important information on severity of disease.

Because AHF affects pulmonary function, [396] gas exchange can be altered even in mild forms. The finding of oxygen saturation predicting outcome was in accordance with previous trials, which showed a close correlation between the defects in gas exchange and the severity of AHF or the pulmonary capillary wedge pressures. [480] Hypoxemia in AHF can be explained by an increase in veno-arterial shunting and ventilation perfusion imbalance. [396,481] It is however important to note that the accuracy of pulse oximetry may

decrease in special situations such as severe hypoxemia, anemia, acidosis, pigmentation, low perfusion states, and the use of vasoactive drugs.[482,483]

The addition of these variables had a small yet significant effect on the C-indexes of the models, suggesting that the addition of symptoms and signs assessment improves our ability to risk stratify patients with AHF, albeit to a small degree. This limited additional value may relate to the value of other variables now routinely collected in AHF patients, such as medical history and laboratory evaluation, or to the possibility that severity of congestion may not be as strong a predictor of outcome in AHF as previously hypothesized.

Symptoms and signs of congestion are important in assessment and prognostication of AHF patients and interventions to treat congestion are class I recommendations for both acute and chronic management of heart failure.[48]

The THESUS-HF study enrolled patients with AHF in Sub-Saharan Africa and therefore the conclusions may be limited by the patient population, which was younger and had more hypertension and rheumatic heart disease-driven AHF. Furthermore, the study was small (approximately 1,000 patients were enrolled), follow-up was not complete and the investigators assessment of symptoms and signs of HF was only partially standardized.

6.5 Conclusion

In patients with AHF from Sub-Saharan Africa, symptoms and signs of HF improved over time and repeat assessments of these symptoms and signs of HF are a valuable tool in predicting patients' outcomes. Simple assessments including edema, rales, oxygen saturation, respiratory rate and asking the patient about general well-being seem to add significant prognostic value to baseline characteristics and lab values.

7 Chapter 7: Echocardiographic predictors of outcome in Acute Heart failure patients in Sub-Saharan Africa: Insights from THESUS-HF

7.1 Introduction

Recent data clearly indicate that HF is an important health care problem in Africa, where it is estimated to constitute about 3–7 % of all medical admissions. The causes of HF in Africa are different from those outside of Africa. [150] The recent THESUS-HF registry[36] showed that in sub-Saharan Africa, the disease affects men and women in the most productive years of life, at an average age of 52 years. Furthermore, HF in Africa is mostly caused by hypertension and not by CAD, as is seen in Western countries.[83]

Patients with HF are heterogeneous in terms of risk of cardiac death and re-admission for decompensated HF. Therefore, assessment of prognosis is a fundamental step in individual patient management. Analysis of clinical variables has helped in identifying the most significant predictors of mortality in the HF population.[484]

Echocardiography has become the gold standard for the evaluation of patients with heart failure because it is an inexpensive, highly reproducible, widely available, and relatively extensive method for assessing left ventricular systolic and diastolic function.[485]In fact, the recent HF guidelines of the European Society of Cardiology state that ”echocardiography is the method of choice in patients with suspected HF for reasons of accuracy, availability (including portability), safety, and cost.”[42]

More than 20 echocardiographic parameters have been proposed as predictors of outcome in HF patients in a number of clinical studies. [486] However, the role of echocardiography

in the assessment and risk stratification of acute HF has been less clear. Some small studies have found little correlation between echocardiographic and hemodynamic variables in acute HF, and little change in these variables from admission to follow up. [487] In large registries and trials, echocardiographic parameters were not found in many cases to be associated with outcomes. [488] Therefore, it is not clear which echocardiographic variables are of importance in patients with acute HF. [484,489]

THESUS-HF[36] provides a unique opportunity to study the echocardiographic predictors of outcome in patients admitted with acute HF in this part of the world. To our knowledge, no similar study has been previously published in Africans with acute HF.

7.2 Methods

THESUS-HF was a prospective, multicenter, international observational survey of acute HF in 12 cardiology centers from 9 countries sub-Saharan Africa. [36] All participating centers had a physician trained in clinical cardiology and echocardiography.

Details of data collection have been previously described in chapter 3.

7.2.1 Echocardiography

Echocardiographic procedures, and measurements were performed according to the American Society of Echocardiography (ASE) Guidelines. [468] M-mode echocardiograms were derived from 2D images. The M-mode cursor on the 2D scan was moved to specific areas of the heart to obtain measurements, according to the recommendation of the committee on M-mode standardization of the ASE. Doppler indices of left ventricular (LV) diastolic filling were obtained. Complete Doppler studies were performed according to the recommendations of the ASE (Figure 7.1). From the M-mode measurements, LV dimensions and function (LV ejection fraction) were derived. LV mass was calculated using the recommended method from the ASE: 1.04 ([LVIDD + PWTD + IVSTD]^3-

$[LVIDD]^3$) -13,6 g.[490]

For diastolic function, left atrial (LA) size (both antero–posterior diameter and planimetry) and pulse wave mitral valve (MV) inflow (early and late peak diastolic velocities which measure the E/A ratio and the deceleration time and MV A-wave duration) were measured. Echocardiography examinations also included assessment of valvular architecture, a semi-quantitative estimate of the severity of valvular regurgitation, and determination of presence of pericardial effusion. Other abnormalities, such as evidence of pulmonary arterial hypertension, were also noted.

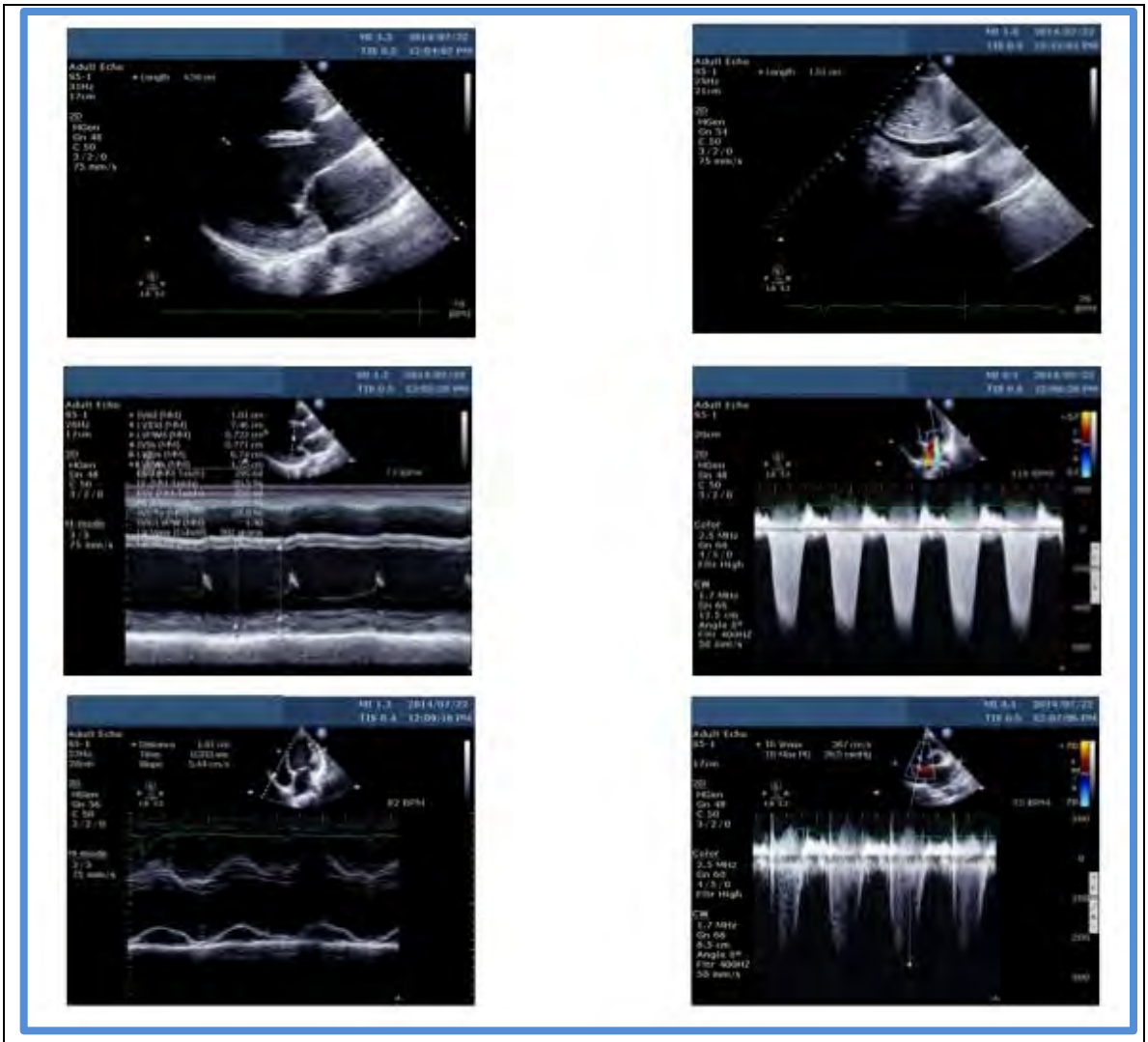

Figure 7.1 Echocardiography images depicting methods of echo assessment in study

7.2.2 Statistical Methods and Modeling

Patients whose echocardiograph was performed within 4 weeks prior to and 2 weeks post enrollment were included in this analysis. Continuous parameters are summarized by the mean and standard deviation, and categorical parameters by absolute and relative frequencies.

For patients who had their E/A ratios recorded, Grade 1 was defined as E/A < 0.8, Grade 2 as E/A between 0.8 and 1.5, and Grade 3 as E/A ratio > 1.5. If a patient had a missing

E/A ratio then the grade was defined using the E-wave deceleration time as follows: Grade 1 as E-wave > 200 msec, Grade 2 as E-wave between 160 msec and 200 msec, and Grade 3 as E-wave < 160 msec.

The associations between echo parameters and clinical outcomes were examined using Cox regression models. The univariable associations between each predictor and outcome were examined. The linearity of associations between continuously distributed predictors and each outcome was assessed using restricted cubic splines with 4 knots with a test of the significance of the non-linear terms. If the association was non-linear, a readily interpretable transformation was chosen through examination of plots of the predicted log hazard ratio against the value of the predictor and changes in Akaike's Information Criterion. For the outcome of 180-day mortality, the associations with creatinine, heart rate, and posterior wall thickness were all significantly non-linear. We chose to model creatinine as a quadratic polynomial, and heart rate and posterior wall thickness using linear splines with one knot where the association between predictor and outcome appeared to change.

Univariable associations between echo parameters and outcomes are presented for the whole analysis population as well as by key diagnosis groups. Diagnoses were grouped as hypertension, cardiomyopathy, valvular, and others. Valvular was defined as having rheumatic heart disease or at least one of the following classified as severe: aortic stenosis or regurgitation, mitral stenosis or regurgitation. To assess whether an association between an echo parameter and outcomes differed by diagnosis group, we tested for the significance of the diagnosis-by-echo parameter interaction term in the Cox regression model for the outcome.

The number of events in the analysis population limited development of multivariable models for 180-day mortality and 60-day death or readmission. Because of this, we chose a few echo parameters in addition to predictors known to be associated with each outcome in this study population.

Multiple imputations were used with a method that assumes multivariate normality (SAS PROC MI) to handle missing values. The imputation model included all covariates under consideration for the multivariable models. The ranges of imputed values were restricted to the ranges of the observed values. Seven imputation datasets were used. Parameter estimates were averaged across these datasets using Rubin's algorithm (SAS PROC MIANALYZE). Backwards selection was used in each of the seven imputation datasets, with the criterion for staying at $p<0.10$. Predictors that were significant in the majority of the imputed datasets were kept in the final model. SAS release 9.2 (SAS Institute, Cary, NC, USA) was used for analyses.

7.3 Results

There were a total of 1006 patients in the THESUS-HF registry of whom 954 had an echocardiogram performed within 4 weeks before to 2 weeks after enrollment. Among these 954 patients, the mean ± SD age of the patients was 52.3 ±18.2 years, 469 (49.2%) were men, the predominant race was black African (99.1%), 11.4% of patients had diabetes mellitus and 9.0% had hyperlipidemia. The mean + SD left ventricular EF was 39.4 ± 16.4%, the initial systolic blood pressure was 130.7 ± 33.5 mm Hg, and heart rate was 104 ± 21.4 beats per minute. (Table 7.1).

Table 7.1 Patients' characteristics, overall and by LV ejection fraction

Patient characteristics	Overall n = 954	LV Ejection Fraction <50 n = 654	LV Ejection Fraction ≥ 50 n = 243	P-value
Age, years, mean ± SD	52.3 ± 18.24	52.3 ± 17.64	53.0 ± 19.58	0.62
Male sex, n (%)	469 (49.2%)	342 (52.3%)	101 (41.7%)	0.0050
Black Africans, n (%)	939 (99.1%)	646 (99.1%)	242 (99.6%)	0.68
Hypertension, n (%)	532 (56.0%)	369 (56.7%)	138 (57.0%)	0.93
Hyperlipidemia, n (%)	84 (9.0%)	58 (9.1%)	23 (9.6%)	0.80
History of Smoking, n (%)	93 (9.8%)	64 (9.8%)	17 (7.1%)	0.20
Malignancy, n (%)	13 (1.4%)	10 (1.5%)	3 (1.2%)	1.00
History of Cor Pulmonale, n (%)	67 (7.1%)	34 (5.2%)	30 (12.4%)	0.0002
Diabetes Mellitus, n (%)	109 (11.4%)	72 (11.0%)	26 (10.7%)	0.88
Peripheral edema, n (%)	631 (67.1%)	448 (69.6%)	146 (60.8%)	0.014
Rales, n (%)	533 (63.8%)	382 (65.3%)	130 (59.6%)	0.14
Body Mass Index, kg/m2, mean ± SD	24.9 ± 5.84	24.8 ± 5.62	24.7 ± 6.10	0.82
Systolic Blood Pressure, mm Hg, mean ± SD	130.7 ± 33.51	127.9 ± 32.16	137.2 ± 36.35	0.0006
Diastolic Blood Pressure, mm Hg, mean ± SD	84.5 ± 21.04	84.0 ± 20.52	85.5 ± 22.04	0.34
Heart Rate, BPM, mean ± SD	104.0 ± 21.35	105.0 ± 21.02	101.1 ± 22.69	0.016
LVEF %, mean ± SD	39.4 ± 16.43	31.8 ± 10.04	60.6 ± 9.65	<.0001
Creatinine level, mg/dL, mean ± SD	1.4 ± 0.99	1.4 ± 0.99	1.3 ± 1.07	0.54
BUN, mg/dL, mean ± SD	34.7 ± 31.59	35.1 ± 29.58	35.9 ± 38.35	0.79
Sodium level, mEq/L, mean ± SD	135.2 ± 6.57	135.0 ± 6.72	135.5 ± 6.3	0.27
eGFR, ml/min/1.73m2, mean ± SD	84.4 ± 47.91	81.7 ± 44.08	90.8 ± 57.97	0.032
Hemoglobin, g/dL, mean ± SD	12.1 ± 2.41	12.3 ± 2.30	11.8 ± 2.64	0.019
Glucose level, mg/dL, mean ± SD	109.8 ± 49.92	110.4 ± 51.95	106.1 ± 41.93	0.22
Prior medication use, n (%)				
ACE inhibitor	180 (32.4%)	134 (34.9%)	40 (24.8%)	0.022
Loop diuretics	215 (39.4%)	152 (40.1%)	57 (36.5%)	0.44
b-blockers	97 (17.9%)	69 (18.3%)	26 (16.7%)	0.65
Digoxin	103 (18.9%)	80 (21.1%)	22 (13.9%)	0.053

Hydralazine	3 (0.6%)	2 (0.5%)	1 (0.6%)	1.00
Nitrates	10 (1.8%)	8 (2.1%)	2 (1.3%)	0.73
Aldosterone Inhibitor	101 (18.5%)	77 (20.4%)	22 (13.8%)	0.075
Statins	27 (5.0%)	18 (4.8%)	9 (5.7%)	0.68
Aspirin	122 (22.2%)	91 (24.0%)	29 (18.1%)	0.13
Anticoagulants	31 (5.7%)	22 (5.9%)	7 (4.4%)	0.49
Etiology heart failure, n (%)				
Hypertensive CMP	380 (40.9%)	274 (42.5%)	86 (37.6%)	
Idiopathic Dilated CMP	129 (13.9%)	120 (18.6%)	2 (0.9%)	
Rheumatic heart disease	133 (14.3%)	75 (11.6%)	55 (24.0%)	
Ischemic heart disease	71 (7.6%)	57 (8.8%)	10 (4.4%)	
Peripartum cardiomyopathy	72 (7.8%)	59 (9.2%)	2 (0.9%)	
Pericardial effusion tamponade	45 (4.8%)	22 (3.4%)	23 (10.0%)	
HIV cardiomyopathy	22 (2.4%)	12 (1.9%)	8 (3.5%)	
Endomyocardial fibrosis	11 (1.2%)	2 (0.3%)	8 (3.5%)	
Other	66 (7.1%)	24 (3.7%)	35 (15.3%)	

ACE, angiotensin converting enzyme; BUN, blood urea nitrogen; CMP, cardiomyopathy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction

Heart failure was most commonly due to hypertension (n=380 [40.9%]) followed by rheumatic valvular heart disease (n=133 [14.3%]) and idiopathic dilated cardiomyopathy (n=129 [13.9%]). Ischemic heart failure was present in only 71 (7.6%) patients (Table 1). The distribution and proportion of missing values for each echocardiographic parameter are presented in Table 7.2. LVEF was available for 897 patients and was missing for 6.0% of patients. LVEF was < 50% in 654 (73%) patients and ≥ 50% in 243 (27%) patients. Patients' characteristics according to LVEF are presented in Table 7.1. Patients with HFrEF had higher proportions of males and peripheral oedema, and lower systolic pressure, higher heart rate, and lower estimated glomerular filtration rate, on average.

Table 7.2 Distribution and proportion of missing values for each echocardiographic parameter

Echocardiographic parameter	N (% missing)	Min, 25th, Median, 75th, Max for continuous n (%) for dichotomous
Heart rate	753 (21.07%)	30.00, 84.00, 94.00, 104.00, 177.00
LVEDD (mm)	946 (0.84%)	27.00, 50.00, 58.00, 65.00, 104.00
LVESD (mm)	943 (1.15%)	14.00, 37.00, 47.00, 55.00, 95.00
IVSd (mm)	927 (2.83%)	3.00, 9.00, 11.00, 13.00, 25.00
PWTd (mm)	904 (5.24%)	3.00, 9.00, 10.15, 12.90, 22.00
LV mass	902 (5.45%)	42.17, 186.79, 256.15, 335.05, 914.37
LV Ejection Fraction (%)	897 (5.97%)	10.00, 26.90, 38.00, 50.00, 78.00
Left Atrial size (A- P) (mm)	910 (4.61%)	21.80, 41.00, 47.00, 53.00, 87.00
Left Atrial size (Planimetry) mm2	528 (44.65%)	526.00, 2200.00, 2620.00, 3260.00, 6840.00
E/A ratio	651 (31.76%)	0.08, 0.98, 1.64, 2.42, 37.88
E wave deceleration time (ms)	758 (20.55%)	10.00, 100.00, 130.00, 171.00, 1212.00
MV A-wave duration	535 (43.92%)	24.00, 100.00, 123.00, 150.00, 540.00
Mitral Valve E/A ratio grades		
Grade 1: Impaired relaxation	784 (17.82%)	144 (18.37%)
Grade 2: Pseudonormal		204 (26.02%)
Grade 3: Restrictive Filling		436 (55.61%)
Aortic Stenosis (moderate –severe)	930 (2.52%)	24 (2.58%)
Aortic regurgitation (moderate –severe)	938 (1.68%)	83 (8.85%)
Mitral Stenosis (moderate – severe)	920 (3.56%)	51 (5.54%)
Mitral regurgitation (moderate – severe)	945 (0.94%)	366 (38.73%)
Tricuspid regurgitation (moderate-severe)	943 (1.15%)	266 (28.21%)

LV – left ventricle; LVEDD – left ventricular end diastolic diameter; LVESD – left ventriculat end systolic diameter; IVSd – interventricular septum in diastole; PWTd – posterior wall thickness in diastole; LV- left ventricle; MV – mitral valve; A-P – antero-posterior.

Univariable associations between the echo predictors and the outcomes by diagnosis groups (hypertensive heart disease, valvular heart disease and other) suggest that none of the associations of echo parameters with outcomes differed significantly among the diagnostic groups (Tables 7.3 and 7.4).

Table 7.3 Univariable associations between echo predictors and 60-day mortality or readmission by diagnosis groups

Echocardiographic parameter	Hypertensive CMP n=338		Valvular n=217		Other n=399		Interaction p-value
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	
LVEDD (mm)	0.98 (0.95, 1.01)	0.15	1.02 (0.99, 1.05)	0.29	1.01 (0.99, 1.03)	0.49	0.17
LVESD (mm)	0.98 (0.96, 1.00)	0.087	1.01 (0.98, 1.04)	0.47	1.00 (0.98, 1.02)	0.92	0.20
IVSd (mm)	0.98 (0.89, 1.09)	0.76	0.98 (0.88, 1.10)	0.77	0.93 (0.85, 1.02)	0.12	0.64
PWTd (mm)	1.03 (0.91, 1.15)	0.68	0.97 (0.85, 1.10)	0.59	0.93 (0.84, 1.04)	0.19	0.47
LV mass	1.00 (1.00, 1.00)	0.44	1.00 (1.00, 1.00)	0.63	1.00 (1.00, 1.00)	0.59	0.62
LV Ejection Fraction (%), per 5% increment	1.07 (0.97, 1.18)	0.16	0.99 (0.89, 1.11)	0.86	0.99 (0.91, 1.08)	0.82	0.42
Left Atrial size (A-P) (mm)	1.02 (0.97, 1.06)	0.46	1.01 (0.98, 1.05)	0.57	1.00 (0.97, 1.03)	0.97	0.83
Left Atrial size (Planometry) mm2	1.00 (1.00, 1.00)	0.083	1.00 (1.00, 1.00)	0.49	1.00 (1.00, 1.00)	0.055	0.73
E/A ratio per doubling	0.93 (0.65, 1.31)	0.67	1.67 (0.75, 3.75)	0.21	1.15 (0.85, 1.55)	0.37	0.35

E wave deceleration time (ms)	1.00 (0.99, 1.00)	0.65	1.00 (0.99, 1.00)	0.24	1.00 (0.99, 1.01)	0.73	0.77
Mitral Valve A-wave duration	1.01 (1.00, 1.02)	0.25	1.01 (1.00, 1.01)	0.049	0.99 (0.99, 1.00)	0.17	0.056
Mitral Valve E/A ratio grades							
Grade 1: Impaired relaxation	(reference group)	0.32	(reference group)	--	(reference group)	0.63	0.18
Grade 2: Pseudo-normal	1.63 (0.66, 3.98)		--		0.78 (0.29, 2.09)		
Grade 3: Restrictive Filling	0.93 (0.39, 2.18)		--		1.13 (0.49, 2.58)		

IVSd, interventricular septal thickness in diastole; LV, left ventricle; LVEDD, left ventricular end diastolic diameter, LVESD, left ventricular end systolic diameter, PWTd, posterior wall thickness in diastole. Note: HRs are for an increment of 1 unit in the predictor unless otherwise noted. Valvular group defined as rheumatic heart disease or having severe mitral stenosis/regurgitation, aortic stenosis/regurgitation.

Table 7.4 Univaraiable associations between echo predictors and 180-day mortality by diagnosis groups

Echocardiographic parameter	Hypertensive CMP n=338		Valvular n=217		Other n=399		Interaction p-value
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	
LVEDD (mm)	0.98 (0.96, 1.01)	0.25	1.01 (0.98, 1.04)	0.47	1.02 (1.00, 1.04)	0.12	0.17
LVESD (mm)	0.99 (0.96, 1.01)	0.28	1.01 (0.99, 1.04)	0.32	1.01 (0.99, 1.03)	0.19	0.20
IVSd (mm)	0.95 (0.85, 1.06)	0.34	0.99 (0.89, 1.09)	0.80	0.91 (0.84, 1.00)	0.041	0.50
PWTd (mm)							
≤ 9 mm	0.58 (0.42, 0.80)	0.0011	0.79 (0.57, 1.10)	0.32	0.82 (0.67, 1.00)	0.072	0.30
> 9 mm	1.73 (1.16, 2.59)		1.38 (0.91, 2.11)		1.19 (0.88, 1.62)		
LV mass	1.00 (0.99, 1.00)	0.097	1.00 (1.00, 1.00)	0.85	1.00 (1.00, 1.00)	0.62	0.36
LV Ejection Fraction (%), per 5% increment	1.00 (0.90, 1.11)	0.99	0.95 (0.85, 1.06)	0.36	0.93 (0.86, 1.02)	0.11	0.59
Left Atrial size (A- P) (mm)	0.99 (0.94,	0.52	1.01 (0.97,	0.79	0.99 (0.96,	0.63	0.79

	1.03)		1.04)		1.02)		
Left Atrial size (Planimetry) mm2	1.00 (1.00, 1.00)	0.70	1.00 (1.00, 1.00)	0.78	1.00 (1.00, 1.00)	0.34	0.72
E/A ratio, per doubling	1.03 (0.74, 1.43)	0.89	2.07 (1.01, 4.26)	0.049	1.13 (0.86, 1.49)	0.38	0.21
E wave deceleration time (ms)	1.00 (0.99, 1.00)	0.23	1.00 (1.00, 1.00)	0.42	1.00 (0.99, 1.00)	0.15	0.68
Mitral Valve A-wave duration	1.00 (0.99, 1.01)	0.63	1.01 (1.00, 1.01)	0.12	1.00 (0.99, 1.01)	0.47	0.26
Mitral Valve E/A ratio grades							
Grade 1: Impaired relaxation	(reference group)	0.50	(reference group)	0.14	(reference group)	0.20	0.27
Grade 2: Pseudonormal	1.63 (0.67, 3.98)		0.82 (0.07, 8.99)		2.71 (0.91, 8.04)		
Grade 3: Restrictive Filling	1.14 (0.50, 2.61)		3.01 (0.40, 22.68)		2.16 (0.76, 6.15)		

IVSd, interventricular septal thickness in diastole; LV, left ventricle; LVEDD, left ventricular end diastolic diameter, LVESD, left ventricular end systolic diameter, PWTd, posterior wall thickness in diastole. Note: HRs are for an increment of 1 unit in the predictor unless otherwise noted Valvular group defined as rheumatic heart disease or having severe mitral stenosis/regurgitation, aortic stenosis/regurgitation.

Univariable associations of echo predictors with 60-day death or readmission and with 180-day death are shown in Tables 7.5 and 7.6, respectively. Heart rate and left atrial size were associated with death or readmission within 60 days. Heart rate, left ventricular posterior wall thickness, and presence of aortic stenosis were associated with the risk of death through 180 days.

Table 7.5 Univariable associations between echo predictors and 60 day mortality/readmission

Echocardiographic parameter	Hazard Ratio (95% CI)	p-value
Heart rate, per increment of 5	1.07 (1.02, 1.13)	0.0088
LVEDD (mm)	1.00 (0.99, 1.02)	0.81
LVESD (mm)	1.00 (0.98, 1.01)	0.63
IVSd (mm)	0.96 (0.91, 1.01)	0.14
PWTd (mm)	0.97 (0.91, 1.03)	0.34
LV mass	1.00 (1.00, 1.00)	0.63
LV Ejection Fraction (%), per 5% increment	1.02 (0.96, 1.07)	0.58
Left Atrial size (A- P) (mm)	1.01 (0.99, 1.03)	0.57
Left Atrial size (Planometry) mm2	1.00 (1.00, 1.00)	0.030
E/A ratio, per doubling	1.07 (0.86, 1.34)	0.53
E wave deceleration time (ms)	1.00 (0.99, 1.00)	0.13
MV A-wave duration	1.00 (1.00, 1.01)	0.43
Mitral Valve E/A ratio grades		
Grade 1: Impaired relaxation	(reference group)	0.61
Grade 2: Pseudo-normal	1.07 (0.55, 2.06)	
Grade 3: Restrictive Filling	1.28 (0.72, 2.26)	

Aortic Stenosis		
None, Mild	(reference group)	0.69
Moderate	1.83 (0.45, 7.41)	
Severe	0.90 (0.22, 3.65)	
Aortic regurgitation		
None, Mild	(reference group)	0.072
Moderate	1.20 (0.61, 2.36)	
Severe	2.42 (1.13, 5.19)	
Mitral Stenosis		
None, Mild	(reference group)	0.50
Moderate	1.56 (0.58, 4.22)	
Severe	0.64 (0.20, 2.00)	
Mitral regurgitation		
None, Mild	(reference group)	0.95
Moderate	0.95 (0.63, 1.41)	
Severe	1.03 (0.60, 1.76)	
Tricuspid regurgitation		
None, Mild	(reference group)	0.23
Moderate	1.41 (0.94, 2.11)	
Severe	1.21 (0.66, 2.21)	

IVSd, interventricular septal thickness in diastole; LV, left ventricle; LVEDD, left ventricular end diastolic diameter, LVESD, left ventricular end systolic diameter, PWTd, posterior wall thickness in diastole. Note: HRs are for an increment of 1 unit in the predictor unless otherwise noted

Table 7.6 Univariable associations between echo predictors and 180 day mortality

Echocardiographic parameter	Hazard Ratio (95% CI)	p-value
Heart rate		
≤ 80 bpm, per change of 5	0.90 (0.76, 1.06)	0.0001
> 80 bpm, per change of 5	1.25 (1.03, 1.52)	
LVEDD (mm)	1.01 (0.99, 1.02)	0.39
LVESD (mm)	1.01 (0.99, 1.02)	0.38
IVSd (mm)	0.94 (0.89, 0.99)	0.025
PWTd (mm)		
≤ 9 mm	0.77 (0.67, 0.89)	0.0009
> 9 mm	1.32 (1.08, 1.61)	
LV mass	1.00 (1.00, 1.00)	0.22
LV Ejection Fraction (%), per 5% increment	0.96 (0.91, 1.01)	0.12
Left Atrial size (A- P) (mm)	1.00 (0.98, 1.01)	0.64
Left Atrial size (Planimetry) mm2	1.00 (1.00, 1.00)	0.50
E/A ratio, per doubling	1.13 (0.92, 1.39)	0.23
E wave deceleration time (ms)	1.00 (0.99, 1.00)	0.070
MV A-wave duration	1.00 (1.00, 1.01)	061
Mitral Valve E/A ratio grades		
Grade 1: Impaired relaxation	(reference group)	0.19
Grade 2: Pseudonormal	1.77 (0.92, 3.38)	
Grade 3: Restrictive Filling	1.67 (0.92, 3.03)	
Aortic Stenosis		

None, Mild	(reference group)	0.039
Moderate	3.60 (1.33, 9.74)	
Severe	0.83 (0.21, 3.36)	
Aortic regurgitation		
None, Mild	(reference group)	0.096
Moderate	0.93 (0.46, 1.90)	
Severe	2.30 (1.07, 4.92)	
Mitral Stenosis		
None, Mild	(reference group)	0.89
Moderate	0.99 (0.31, 3.10)	
Severe	0.79 (0.29, 2.12)	
Mitral regurgitation		
None, Mild	(reference group)	0.87
Moderate	0.92 (0.62, 1.34)	
Severe	1.05 (0.63, 1.74)	
Tricuspid regurgitation		
None, Mild	(reference group)	0.53
Moderate	1.26 (0.85, 1.86)	
Severe	1.04 (0.57, 1.89)	

IVSd, interventricular septal thickness in diastole; LV, left ventricle; LVEDD, left ventricular end diastolic diameter, LVESD, left ventricular end systolic diameter, PWTd, posterior wall thickness in diastole. Notes. HRs are for an increment of 1 unit in the predictor unless otherwise noted

The multivariable models suggest LVESD, IVSd, PWTd, left atrial size, E/A ratio do not add significantly to prediction of 60-day death or readmission, while left ventricular posterior wall thickness added to clinical variables in the prediction of 180-day mortality (Tables 7.7 and 7.8).

Table 7.7 Univariable and multivariable Cox regression models for 60-mortality or readmission

Predictors		**Univariable Models**			**Multivariable Model**			**Reduced Multivariable Model**		
	HR for a change of	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Baseline predictors										
Malignancy	Yes vs. No	5.09	(2.25, 11.52)	<.0001	5.16	(2.23, 11.92)	0.0001	5.13	(2.24, 11.77)	0.0001
Hx Cor Pulmonale	Yes vs. No	2.60	(1.61, 4.19)	<.0001	1.88	(1.11, 3.17)	0.018	1.99	(1.21, 3.25)	0.0064
log2BUN	Doubling	1.44	(1.22, 1.71)	<.0001	1.49	(1.23, 1.79)	<.0001	1.47	(1.23, 1.77)	<.0001
Systolic BP	10	0.92	(0.87, 0.97)	0.0035	0.92	(0.87, 0.98)	0.0083	0.91	(0.87, 0.97)	0.0019
Rales	(2/3 vs. 0/1)	2.43	(1.55, 3.80)	0.0001	2.40	(1.49, 3.89)	0.0004	2.39	(1.48, 3.86)	0.0004
Region	(South vs. West)	1.26	(0.85, 1.88)	0.012	1.73	(1.13, 2.67)	0.0052	1.71	(1.11, 2.61)	0.0040

Region	(East vs. West)	0.56	(0.35, 0.91)		0.73	(0.43, 1.23)		0.70	(0.42, 1.15)	
Echo predictors										
LVESD, mm	1	1.00	(0.98, 1.01)	0.58	0.99	(0.97, 1.00)	0.17			
IVSd, mm	1	0.96	(0.91, 1.01)	0.13	0.98	(0.89, 1.08)	0.66			
PWTd, mm	1	0.97	(0.91, 1.03)	0.28	0.99	(0.89, 1.10)	0.89			
Left Atrial Size (A-P), mm	1	1.00	(0.99, 1.02)	0.62	1.01	(0.99, 1.03)	0.49			
E/A ratio	Doubling	1.07	(0.86, 1.34)	0.51	1.06	(0.84, 1.33)	0.64			
E wave deceler. time, ms	1	1.00	(1.00, 1.00)	0.29	1.00	(1.00, 1.00)	0.50			

BP, blood pressure; BUN, blood urea nitrogen; Hx, history, IVSd, interventricular septal thickness in diastole; LV, left ventricle; LVEDD, left ventricular end diastolic diameter, LVESD, left ventricular end systolic diameter, PWTd, posterior wall thickness in diastole

Table 7.8 Univariable and multivariable Cox regression models for 180 mortality

Predictors		**Univariable Models**			**Multivariable Model**			**Reduced Multivariable Model**		
	HR for a change of	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Baseline predictors										
Malignancy	Yes vs. No	4.29	(1.76, 10.43)	0.0013	3.65	(1.47, 9.06)	0.0054	3.63	(1.47, 8.99)	0.0054
Hx Cor Pulmonale	Yes vs. No	2.07	(1.26, 3.40)	0.0042	1.89	(1.10, 3.23)	0.021	2.06	(1.24, 3.43)	0.0057
Hemoglobin	1	0.89	(0.84, 0.96)	0.0011	0.93	(0.86, 1.00)	0.038	0.92	(0.86, 0.99)	0.029
Creatinine*	1.55 vs. 0.89	1.43	(1.18, 1.73)	0.0004	1.45	(1.19, 1.77)	0.0006	1.43	(1.18, 1.74)	0.0009
Systolic BP	10	0.87	(0.82, 0.92)	<.0001	0.86	(0.81, 0.92)	<.0001	0.87	(0.82, 0.92)	<.0001
Peripheral Edema	(2/3 vs. 0/1)	2.47	(1.60, 3.83)	<.0001	1.83	(1.15, 2.90)	0.011	1.75	(1.11, 2.76)	0.015
Rales	(2/3 vs. 0/1)	2.35	(1.52, 3.63)	0.0001	1.89	(1.20, 2.97)	0.0059	1.85	(1.18, 2.91)	0.0074
Echo predictors										

LVESD, mm	1	1.01	(0.99, 1.02)	0.38	0.99	(0.98, 1.01)	0.39			
IVSd, mm	1	0.94	(0.89, 0.99)	0.025	1.01	(0.93, 1.11)	0.74			
PWTd, mm										
≤ 9	1	0.78	(0.67, 0.90)	0.0008	0.77	(0.64, 0.92)	0.0039	0.79	(0.68, 0.91)	0.0019
> 9	1	1.01	(0.93, 1.10)	0.82	1.05	(0.93, 1.18)	0.44	1.06	(0.97, 1.16)	0.17
Left Atrial Size (A-P), mm	1	1.00	(0.98, 1.01)	0.69	0.99	(0.97, 1.01)	0.56			
E/A ratio	Doubling	1.07	(0.89, 1.27)	0.48	1.08	(0.89, 1.32)	0.44			
Ewave deceleration time, ms	1	1.00	(1.00, 1.00)	0.15	1.00	(1.00, 1.00)	0.86			

* Creatinine was modeled as a quadratic polynomial. BP, blood pressure; Hx, history, IVSd, interventricular septal thickness in diastole; LVESD, left ventricular end systolic diameter, PWTd, posterior wall thickness in diastole

7.4 Discussion

A thorough and complete echocardiographic examination has been shown to be a useful diagnostic test in the evaluation of patients with HF.[491]Although it is widely used to evaluate cardiac structure and function in patients with HF, few data are available regarding its ability to predict outcomes. [492] In the case of acute HF, the precise association of LVEF with cardiovascular outcomes in patients with acute decompensated HF is controversial. [112] Because the LVEF measure is load-dependent and varies with hemodynamic status, it may underestimate or overestimate true myocardial function in various pathophysiologic conditions and precipitants of acute decompensation. A prospective study reported that LVEF was weakly correlated with hemodynamic measures and clinical outcomes in patients with acute HF.[493]

Various therapeutic interventions can reduce the risk of readmissions and death in patients admitted with HF. Therefore, identification of patients at the highest risk of readmission or death could help provide targeted cost-effective interventions. Although several studies have assessed potential echocardiographic predictors, the results have been inconsistent. [494,495] A large number of variables can be measured or calculated by echocardiographic and Doppler imaging. Thus, it is not clear which echocardiographic measurements provide independent prognostic information.

In the current study, echocardiographic parameters showed only limited associations between echocardiographic measures and outcomes. Heart rate (which can be obtained by simple physical examination) and left atrial size were associated with death or readmission within 60 days, and left ventricular posterior wall thickness and presence of

aortic stenosis were associated with the risk of death through 180 days. In agreement with the results of the PROTECT study modeling, [488] LVEF was not associated with 60-day death or readmission or with 180 day mortality. This finding contrasts data from the ESCAPE study, where echocardiographic measures of LV size and function did change from baseline to follow up and were associated with some outcomes. [496] However, the ESCAPE study enrolled patients with end stage cardiomyopathy who had very significant LV dysfunction at baseline. These patients are different from the majority of acute HF patients, particularly those enrolled in the THESUS registry. The results of the current study confirming the preliminary findings of Gandhi et al[487] and the retrospective analysis of PROTECT study[488] raised the question of why in the general population of patients admitted for acute HF, echocardiographic measures of left ventricular function and size are not associated with outcomes. This puzzling finding suggests that the pathophysiology of acute HF may differ from that of chronic HF by being less dependent on systolic function and, as suggested by Gandhi et al, [487] more driven by factors that cause cardiac and vascular stiffening manifesting as diastolic dysfunction

Left ventricular hypertrophy (LVH) is a recognized complication of systemic hypertension and the best-studied marker of hypertensive heart disease. [497] LVH strongly predicts cardiovascular morbidity and mortality in hypertensive patients, and is an independent risk factor for overall cardiovascular mortality and morbidity. [498] It is known to cause a reduction in myocardial coronary reserve, which predisposes to myocardial ischaemia and left ventricular dysfunction, thereby causing increased incidence of coronary heart disease among hypertensives. [499] This finding should encourage increased efforts for screening and treatment of young hypertensive patients, in Africa and

throughout the world, to prevent the progression of hypertension to LVH. The increased risk of patients with severe valvular heart disease, particularly aortic stenosis, is well documented; [500] the confirmation in the current study of the increased risk of these patients when admitted for acute HF is important, adding to the evidence encouraging a low threshold for evaluation and treatment of patients with suspected aortic stenosis.

Left atrial enlargement has been increasingly suggested in recent years to be an important indicator of increased risk for an adverse clinical outcome. Left atrial enlargement may serve as an indicator for persistent increased pressure within the cardiovascular system, possibly representing longer term changes, such as the role of HbA1c in diabetes mellitus. Furthermore, the left atrium modulates left ventricular filling and cardiovascular performance by functioning as a reservoir for pulmonary venous return during ventricular systole, a conduit for pulmonary venous return during early ventricular diastole, and a booster pump that augments ventricular filling during late ventricular diastole. Therefore, left atrial enlargement (and possibly associated dysfunction) may play an important role not only in the marking of cardiovascular dysfunction but also in its enhancement. The finding that left atrial size is associated with adverse outcomes begs the question of why measures of diastolic dysfunction were not predictive of such adverse outcomes in the current cohort. Although the reasons for that cannot be ascertained given the limitations of the study (see below), it is possible that as described by Gandhi et al[487] measures of diastolic dysfunction improve rapidly after admission in patients with acute HF. Because the echocardiographic evaluations performed in the current study were not done close to the time of admission in many patients, the worst measures may have been missed. It is also possible that some specific characteristics of the patient population may have

contributed to this lack of association.

Increased resting heart rate is a known predictor for cardiovascular mortality and morbidity in a variety of cardiovascular diseases, including heart failure. [501] In patients with reduced LVEF, with or without signs or symptoms of HF, high heart rate has predicted adverse outcomes, irrespective of other known risk factors. [502] Several pathophysiologic mechanisms, including blunting of the force-frequency relationship, the induction of myocardial ischemia, precipitation of rhythm disturbances, and acceleration of atherosclerosis have been proposed to explain the association between higher heart rate and worse outcomes in patients with HF. [501] Higher heart rate might also be a marker of greater neurohormonal activation. The SHIFT study showed that heart rate is important in the pathophysiology of HF with reduced LVEF, and that heart rate reduction per se is a mechanism responsible for improvement of clinical outcomes. [503] The CHARM investigators also found that the value of resting heart rate in predicting worse outcomes was independent of baseline left ventricular systolic function in heart failure. [504] A higher heart rate was associated with a greater risk of HF hospital stay, both in patients with reduced and preserved LVEF in a post hoc analysis of the DIG (Digitalis Investigation Group) trial. In predicting mortality, however, higher heart rate was only significant in patients with a reduced LVEF.[505]

Similar to our findings, left atrial size or its surrogates have been shown to predict HF hospitalization and death in other studies. [506] Left atrial size predicts death among high-risk groups, such as patients with dilated cardiomyopathy, LV dysfunction, atrial arrhythmias, acute myocardial infarction as well as in in the general population.[507]

Left atrial size, aortic stenosis, heart rate, and measures of hypertrophy had some value in

predicting outcome in our cohort. This may suggest that early diagnosis and treatment of hypertension and valvular heart disease in Sub Saharan Africa should be emphasized to improve outcome.

Our data should be interpreted in the context of their limitations. Unobserved variables may have confounded the results. Not all echocardiographic parameters were available in all patients, limiting the number of parameters for analysis. The variable timing of the echocardiogram, and inter-observer variability may have affected the specific results obtained. Furthermore, the number of events was small. Thus, both the variable selection and the parameter estimates for the selected variables are subject to instability. We also looked at echo predictors of acute heart failure from various causes. Even though, there is no statistically significant interaction between the echo variables, different conditions and outcomes, there could still be dilutional effect of grouping heterogeneous conditions together. Finally, our results are drawn from a population of young acute HF patients predominantly with systolic dysfunction. Consequently, these findings may not apply to older patients or to those with preserved LVEF.

7.5 Conclusions

In accordance with previous studies, echocardiographic variables, especially those of left ventricular size and function, were found to have little or no additional predictive value in patients admitted for acute HF. Left atrial size was associated with death or readmission within 60 days while left ventricular posterior wall thickness, and presence of aortic stenosis were associated with the risk of death through 180 days. There is need for further studies of echocardiographic evaluation, especially when performed closer to the acute

event, to further elucidate the pathophysiology and risk stratification of patients with acute HF.

8 Chapter 8: Renal Dysfunction in African patients with acute heart failure

8.1 Introduction

Studies from Europe and North America have shown that more than half of the patients hospitalized for heart failure have some degree of impairment of renal function, and moderate to severe impairment has been reported in 30–35% of cases .[508]

An association between impaired renal function and unfavorable outcomes has also been reported in HF patients. [358] In addition hospitalization for acute heart failure is also associated with further WRF in 30–50% of patients. [116,509]

Patients with WRF have been shown to have longer lengths of stay, higher in-hospital costs, increased in-hospital mortality, and greater likelihood of readmission. [358]

In this chapter, we describe the prevalence, predictors and clinical outcome of renal dysfunction in younger, mainly hypertensive AHF patients in sub-Saharan Africa enrolled in the THESUS-HF registry.

We found one third of the patients had renal dysfunction on admission in this cohort. WRF during hospitalization was detected in 53 (9.8 %) of 543 patients with a follow-up creatinine value, and was independently associated with the Western sub-Saharan region, body mass index, and the presence of rales. WRF was an independent predictor of death or readmission over 60 days and all-cause death over 180 days

This chapter in presented as a published research paper in the European Journal of Heart Failure.

Sani MU, Davison BA, Cotter G, Sliwa K, Edwards C, Liu L, Damasceno A, Mayosi BM, Ogah OS , Mondo C, Dzudie A, Ojji DB , Voors AA . Renal dysfunction in African patients with acute heart failure . Eur J Heart Fail. 2014 Jul;16(7):718-28. doi: 10.1002/ejhf.103. Epub 2014 Jun 24.

European Journal of Heart Failure (2014)
doi:10.1002/ejhf.103

Renal dysfunction in African patients with acute heart failure

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Received 30 December 2013; revised 10 March 2014; accepted 14 March 2014

Aims In Western countries with typically elderly ischaemic acute heart failure patients, predictors and clinical outcome of renal dysfunction and worsening renal function are well described. However, the prevalence, predictors and clinical outcome of renal dysfunction in younger, mainly hypertensive acute heart failure patients from Africa, have not been described.

Methods and results From 1006 patients enrolled in the sub-Saharan Africa Survey of Heart Failure (THESUS-HF), renal function was determined by the estimated glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) formula. Worsening renal function was defined as an increase in creatinine $\leq$0.3 mg/dL (26.5 μmol/L) from baseline to day 7/discharge. The mean (SD) age of the patients was 52.4 (18.2) years, 481 (50.8%) were women and the predominant race was black African [932 of 946 (98.5%)]. Heart failure was most commonly a result of hypertension ($n = 363$, 39.5%) and only 7.8% had ischaemic heart failure. At hospital admission, 289 patients (30.6%) had an estimated glomerular filtration rate $\leq$60 ml/min.1.73m^2. Worsening renal function during hospitalization was detected in 53 (9.8 %) of 543 patients with a follow-up creatinine value, and was independently associated with the Western sub-Saharan region, body mass index, and the presence of rales. Worsening renal function was an independent predictor of death or readmission over 60 days [multivariable hazard ratio = 2.06 (1.10, 3.38); $P = 0.023$] and all-cause death over 180 days [multivariable hazard ratio = 1.92 (1.08, 3.38); $P = 0.025$].

Conclusions Renal dysfunction is also prevalent in younger non-ischaemic acute heart failure patients in Africa, but worsening renal function is less prevalent and has different predictors compared with Western cohorts. Nevertheless, worsening renal function is strongly and independently related with clinical outcome.

Keywords Africa • Outcome • Prognosis • Renal dysfunction • Worsening renal function

Introduction

Heart failure is generally considered a typical disease of Western countries. However, recent data clearly indicate that heart failure is also an important health-care problem in Africa, where it is estimated to contribute about 3–7% of all medical admissions.[1,2] The causes of heart failure in Africa are different from those outside of Africa. The recent sub-Saharan Africa Survey of Heart Failure (THESUS-HF) registry[3] showed that in sub-Saharan Africa the disease affects men and women in the most productive years of life, at an average age of 52 years and is mostly caused by hypertension and not ischaemic heart disease, as is seen in Western countries.[4] Other studies have confirmed that hypertension accounts for more than half of cases, followed by cardiomyopathies and rheumatic

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heart disease.[5] In a recent study from Abuja, Nigeria, hypertension was the cause of heart failure in 64% of patients.[6] In addition, the patients mostly present in late stages of heart failure [New York Heart Association (NYHA) class III and class IV], which may significantly worsen prognosis and increase morbidity and mortality.

Studies from Europe and North America have shown that more than half of the patients hospitalized for heart failure have some degree of impairment of renal function, and moderate to severe impairment has been reported in 30–35% of cases.[7–10] Hospitalization for acute heart failure is also associated with further worsening renal function (WRF) in 30–50% of patients, depending on the definition used.[8,9] Typical predictors of WRF in these patients are baseline chronic kidney disease, history of hypertension and diabetes, age, and use of diuretics.[11]

However, the prevalence, predictors and clinical outcome of renal dysfunction in younger, mainly hypertensive acute heart failure (AHF) patients in sub-Saharan African are not known. We therefore studied renal dysfunction at admission and WRF, the association between WRF and 180-day mortality, and 60-day death/readmission in a cohort of 1006 African patients admitted with AHF and enrolled in the THESUS-HF registry.

Methods

THESUS-HF[3] was a prospective, multicentre, international observational survey conducted in 12 hospitals from nine countries in the southern, eastern, central, and western regions of sub-Saharan Africa. All patients were recruited during an admission for AHF, mostly in Nigeria, Uganda, and South Africa. Methods and results have been described in detail previously.[3] In brief, from July 2007 to June 2010 patients admitted with dyspnoea and diagnosed with AHF based on symptoms and signs (including dyspnoea, orthopnoea, dyspnoea on exercise, rales, oedema, jugular venous pulse, and oxygen saturation), and who provided written informed consent, were enrolled into the study. The diagnosis was supported by echocardiographic findings and was confirmed by a cardiologist. Approval was obtained from the ethics committee of each participating institution and the study conformed to the principles of the Declaration of Helsinki.

Detailed data collected on standardized case report forms at admission included medical history, medication use, laboratory values, and physical examination with symptoms and signs of heart failure. Echocardiography and electrocardiography were also performed. Human immunodeficiency virus testing was performed as clinically indicated. Patients were followed either by clinic visit or telephone contact over 6 months for the occurrence of readmissions and death. As described in the main report, patients were classified as having either an emerging or endemic cause of heart failure. Endemic causes included rheumatic heart disease, cardiomyopathies, and infective causes, while emerging causes included hypertension and ischaemic heart disease.

Renal function and worsening renal function

Patients presenting with heart failure are routinely checked for renal dysfunction at presentation. More detailed investigations and follow up on previous tests are based on indications and availability of resources. The estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula ($186.3 \times (\text{serum creatinine (mg/dl)})^{-1.154} \times \text{age}^{-0.203} \times (0.742$ if female$) \times (1.212$ if black African) (mL/min.1.73 m^2).[12,13] Worsening renal function was defined as an absolute increase in creatinine $\geq$0.3 mg/dL (26.5 μmol/l)[14,15] from baseline to the earlier of day 7 or hospital discharge.

The relation between clinical variables, renal function and worsening renal function was evaluated. Finally, we examined clinical outcomes of patients with worsening renal function and its prognostic significance.

Statistical methods

Means ± standard deviations (SD) are presented for continuous variables, and absolute and relative frequencies for categorical variables. Differences in continuous variables between groups were compared using two-sample *t*-tests, or one-way ANOVA tests where there were more than two groups. Categorical variables were compared using chi-square tests or Fisher's exact tests where at least one group had an absolute frequency <5. To evaluate the predictors of WRF, we first examined the univariable associations between each covariate and WRF. Patients with baseline and follow-up creatinine values at day 7 (or discharge) were included in this analysis. The linearity of association between each continuously distributed predictor and WRF was assessed using restricted cubic splines (RCS) with four 'knots' with a test of the significance of the non-linear terms. Where the association was non-linear, a readily interpretable transformation was chosen through examination of plots of the predicted log hazard ratio against the value of the predictor and changes in Akaike's Information Criterion (AIC). The only non-linear predictor was body mass index (BMI). A linear spline was chosen with a single knot at 18.5 kg/m^2 (the lower cut-off for a normal BMI).

SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for analyses. Multiple imputations were used with a method that assumes multivariate normality (SAS PROC MI) to handle missing values. The imputation model included all covariates under consideration for the multivariable models. The ranges of imputed values were restricted to the ranges of the observed values. Seven imputation datasets were used. Parameter estimates were averaged across these datasets using Rubin's algorithm (SAS PROC MIANALYZE). With only 53 WRF events, the number of predictors that could be entered into a multivariable model was limited. We selected predictors that had a strong univariable association with WRF and used backwards selection in each of the seven imputation datasets, with the criterion for staying $P < 0.10$. Predictors that were significant in the majority of the imputed datasets were kept in the final model.

We assessed the associations between WRF and clinical outcomes using a two-sided two-sample *t*-tests for length of initial hospital stay and a log-rank test for time-to-event outcomes. The associations between WRF and 60-day death or readmission and 180-day mortality were then assessed after adjusting for predictors known to be associated with each outcome in this study population (no backwards selection was done here).[16]

Results

There were a total of 1006 patients in the THESUS-HF registry. Serum creatinine on admission was available in 964 (96%) of the 1006 patients. The mean (SD) age of the patients was 52.4

Table 1 Patient characteristics by estimated glomerular filtration rate (eGFR)

Patient characteristics	eGFR ≤ 30, *n* = 67	eGFR 30–≤60, *n* = 222	eGFR 60–≤90, *n* = 325	eGFR >90, *n* = 332	Total, *N* = 946	*P*-value*
Age, years, mean ± SD, median (25% Q, 75% Q)	57.4 ± 16.06, 60.0 (46.0, 69.0)	58.2 ± 16.88, 60.0 (49.0, 70.0)	51.4 ± 17.10, 51.0 (39.0, 65.0)	48.5 ± 19.40, 49.0 (31.5, 65.0)	52.4 ± 18.23, 55.0 (39.0, 67.0)	<0.0001
Male sex, *n* (%)	32 (47.8%)	102 (46.0%)	160 (49.2%)	171 (51.5%)	465 (49.2%)	0.64
Black Africans, *n* (%)	65 (97.0%)	217 (97.8%)	319 (98.2%)	331 (99.7%)	932 (98.5%)	0.066
Hypertension, *n* (%)	54 (80.6%)	144 (65.2%)	171 (52.9%)	144 (43.5%)	513 (54.5%)	<0.0001
Hyperlipidaemia, *n* (%)	13 (21.0%)	17 (7.8%)	35 (10.9%)	22 (6.8%)	87 (9.2%)	0.0032
History of smoking, *n* (%)	2 (3.0%)	18 (8.1%)	32 (9.9%)	39 (11.8%)	91 (9.7%)	0.11
Malignancy, *n* (%)	0 (0.0%)	7 (3.2%)	4 (1.2%)	1 (0.3%)	12 (1.3%)	0.033
History of cor pulmonale, *n* (%)	3 (4.6%)	14 (6.4%)	25 (7.7%)	23 (7.0%)	65 (6.9%)	0.86
History of atrial fibrillation, *n* (%)	9 (13.6%)	55 (25.0%)	58 (17.9%)	56 (17.1%)	178 (18.8%)	0.059
Diabetes mellitus, *n* (%)	18 (26.9%)	33 (14.9%)	29 (9.0%)	29 (8.7%)	109 (11.5%)	<0.0001
Peripheral oedema, *n* (%)	56 (86.2%)	158 (72.2%)	202 (63.5%)	208 (63.2%)	624 (67%)	0.0006
Rales, *n* (%)	41 (75.9%)	138 (70.4%)	168 (60.0%)	174 (59.0%)	521 (63.2%)	0.0088
Body mass index, kg/m^2, mean ± SD, median (25% Q, 75% Q)	27.7 ± 7.27, 27.4 (22.51, 32.59)	25.5 ± 5.39, 25.4 (21.96, 28.76)	24.6 ± 5.76, 23.7 (20.75, 27.52)	24.3 ± 5.77, 23.4 (20.75, 27.19)	25.0 ± 5.86, 24.0 (20.91, 28.09)	<0.0001
Systolic blood pressure, mmHg, mean ± SD, median (25% Q, 75% Q)	144.4 ± 42.56, 140.0 (112.1, 170.0)	132.9 ± 35.84, 130.0 (106.0, 160.0)	128.6 ± 31.82, 122.5 (105.5, 150.0)	125.7 ± 29.33, 120.0 (103.0, 140.0)	129.7 ± 33.15, 124.0 (105.0, 150.0)	0.0001
Diastolic blood pressure, mmHg, mean ± SD median (25% Q, 75% Q)	89.5 ± 22.36, 90.0 (70.0, 104.0)	85.8 ± 21.89, 85.0 (70.0, 100.0)	84.4 ± 21.46, 80.0 (70.0, 100.0)	81.3 ± 18.92, 80.0 (70.0, 90.0)	84.0 ± 20.87, 80.0 (70.0, 100.0)	0.0076
Heart Rate, bpm, mean ± SD median (25% Q, 75% Q)	97.3 ± 17.92, 100.0 (88.0, 109.0)	106.0 ± 22.63, 105.0 (91.0, 120.0)	103.6 ± 21.83, 104.0 (90.0, 116.0)	103.3 ± 21.33, 100.0 (88.0, 116.0)	103.6 ± 21.66, 104.0 (90.0, 116.0)	0.036
LVEF %, mean ± SD median (25% Q, 75% Q)	40.7 ± 15.62, 40.0 (29.0, 52.5)	38.8 ± 15.56, 39.0 (27.0, 48.0)	37.2 ± 15.51, 35.0 (25.0, 46.0)	41.1 ± 17.41, 40.0 (28.0, 55.0)	39.2 ± 16.27, 38.0 (27.0, 50.0)	0.024
LVEF <40%, *n* (%)	29 (3.3%)	108 (12.3%)	179 (20.4%)	149 (17.0%)	465 (53.0%)	0.068
Creatinine level, µmol/L, mean ± SD, median (25% Q, 75% Q)	385.6 ± 166.40, 342.6 (267.00, 495.04)	153.4 ± 38.85, 145.9 (125.98, 174.00)	103.0 ± 16.85, 102.0 (89.30, 114.92)	69.4 ± 15.97, 70.7 (60.84, 79.56)	123.0 ± 93.43, 99.0 (78.0, 132.6)	<0.0001
BUN, µmol/L, mean ± SD, median (25% Q, 75% Q)	32.3 ± 23.89, 23.4 (18.21, 36.70)	15.1 ± 9.11, 12.6 (9.30, 18.92)	10.4 ± 8.18, 8.2 (5.60, 12.50)	8.5 ± 5.22, 7.4 (4.60, 10.71)	12.4 ± 11.36, 9.4 (6.00, 14.55)	<0.0001
Sodium level, mmol/L, mean ± SD, median (25% Q, 75% Q)	132.7 ± 7.91, 133.0 (128.0, 138.0)	135.2 ± 6.88, 135.0 (131.2, 140.0)	135.3 ± 6.42, 136.0 (132.0, 129.0)	135.2 ± 6.35, 136.0 (131.0, 140.0)	135.07 ± 6.65, 135.2 (131.0, 139.0)	0.030
eGFR, mL/min.1.73m^2, mean ± SD, median (25% Q, 75% Q)	18.6 ± 7.04, 18.4 (12.96, 24.51)	47.2 ± 8.59, 48.4 (40.48, 54.32)	75.3 ± 8.44, 75.28 (68.08, 82.63)	129.8 ± 49.36, 114.8 (101.64, 141.60)	83.8 ± 47.77, 76.9 (54.55, 103.77)	<0.0001

Table 1 Continued

Patient characteristics	eGFR ≤ 30, *n* = 67	eGFR 30–≤60, *n* = 222	eGFR 60–≤90, *n* = 325	eGFR >90, *n* = 332	Total, *N* = 946	*P*-value*
Haemoglobin, g/L, mean ± SD	107.7 ± 26.46,	120.8 ± 24.33,	126.1 ± 22.24,	123.7 ± 21.40,	122.7 ± 23.23,	<0.0001
median (25% Q, 75% Q)	107.0 (87.0, 122.0)	120.0 (104.5, 137.0)	126.9 (113.0, 140.0)	126.0 (110.0, 137.0)	123.0 (109.0, 138.0)	
Glucose level, mmol/L,	6.1 ± 2.70,	6.3 ± 3.15,	6.2 ± 2.69,	6.0 ± 2.55,	6.11 ± 2.76,	0.61
mean ± SD, median (25% Q, 75% Q)	5.30 (4.60, 6.49)	5.18 (4.66, 6.30)	5.28 (4.80, 6.66)	5.22 (4.60, 6.49)	5.22 (4.70, 6.52)	
Previous medication use, *n* (%)						
ACE inhibitor	19 (40.4%)	34 (30.1%)	67 (37.0%)	59 (27.2%)	179 (32.1%)	0.11
Loop diuretics	25 (53.2%)	37 (33.6%)	88 (49.7%)	69 (32.2%)	219 (40%)	0.0005
β-Blockers	9 (19.1%)	24 (21.8%)	37 (21.5%)	27 (12.6%)	97 (17.8%)	0.075
Digoxin	7 (15.2%)	14 (12.5%)	42 (23.7%)	40 (18.7%)	103 (18.8%)	0.11
Hydralazine	1 (2.2%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	3 (0.5%)	0.064
Nitrates	1 (2.2%)	3 (2.7%)	5 (2.9%)	1 (0.5%)	10 (1.8%)	0.17
Aldosterone Inhibitor	7 (14.9%)	28 (25.2%)	38 (21.7%)	31 (14.6%)	104 (19%)	0.076
Statins	4 (8.9%)	8 (7.1%)	9 (5.2%)	6 (2.8%)	27 (5%)	0.13
Aspirin	14 (30.4%)	27 (23.9%)	41 (23.3%)	41 (19.1%)	123 (22.4%)	0.35
Anticoagulants	5 (11.4%)	5 (4.4%)	14 (8.0%)	11 (5.2%)	35 (6.4%)	0.28
Aetiology of heart failure						
Hypertensive CMP, *n* (%)	37 (56.9%)	96 (45.1%)	114 (36.0%)	116 (35.7%)	363 (39.5%)	
Idiopathic dilated CMP, n (%)	7 (10.8%)	30 (14.0%)	43 (13.6%)	56 (17.2%)	136 (14.8%)	
Rheumatic heart disease, *n* (%)	5 (7.7%)	27 (12.7%)	55 (17.4%)	50 (15.4%)	137 (14.9%)	
Ischaemic heart disease, *n* (%)	4 (6.2%)	24 (11.3%)	27 (8.5%)	17 (5.2%)	72 (7.8%)	
Peripartum cardiomyopathy, *n* (%)	1 (1.5%)	11 (5.2%)	31 (9.8%)	27 (8.3%)	70 (7.6%)	
Pericardial effusion tamponade, *n* (%)	5 (7.7%)	9 (4.2%)	17 (5.4%)	11 (3.4%)	42 (4.8%)	
HIV cardiomyopathy, *n* (%)	4 (6.2%)	3 (1.4%)	7 (2.2%)	9 (2.8%)	23 (2.5%)	
Endomyocardial fibrosis, *n* (%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	11 (3.4%)	13 (1.4%)	
Other, *n* (%)	2 (3.1%)	13 (6.1%)	21 (6.6%)	28 (8.6%)	64 (7.0%)	
Region						
East	14 (20.9%)	61 (27.5%)	99 (30.5%)	91 (27.4%)	265 (28.0%)	0.25
South	12 (17.9%)	47 (21.2%)	77 (23.7%)	62 (18.7%)	198 (20.9%)	
West	41 (61.2%)	114 (51.4%)	149 (45.9%)	179 (53.9%)	483 (51.1%)	

BUN, blood urea nitrogen; CMP, cardiomyopathy; HIV, human immunodeficiency virus ;LVEF, left ventricular ejection fraction. *P-value for categorical variables from Chi-square test or Fisher's exact test if at least one cell count <5 P-value for continuous variables from ANOVA.

Table 2 Baseline characteristics of patients with and without a follow-up creatinine value

Baseline characteristic	Patients with FU creatinine, $N = 543$	Patients with BL creatinine, but no FU, $N = 441$	*P*-value*
Age, mean (SD) median (25%Q, 75%Q)	49.8 (17.45) 51.0 (36.0, 64.0)	55.4 (18.82) 75.0 (41.0, 70.0)	<0.0001
Male sex, *n* (%)	264 (48.6%)	218 (49.5%)	0.77
Black Africans, *n* (%)	532 (98.0%)	430 (99.1%)	0.20
Hypertension, *n* (%)	286 (52.8%)	257 (58.7%)	0.0643
Hyperlipidaemia, *n* (%)	49 (9.2%)	41 (9.7%)	0.789
History of smoking, *n* (%)	53 (9.8%)	44 (10.0%)	0.91
Malignancy, *n* (%)	3 (0.6%)	9 (2.1%)	0.034
History of cor pulmonale	38 (7.1%)	30 (6.8%)	0.88
Diabetes, *n* (%)	64 (11.8%)	50 (11.4%)	0.83
Peripheral oedema, *n* (%)	371 (69.0%)	279 (64.7%)	0.16
Rales, *n* (%)	340 (70.7%)	210 (55.3%)	<0.0001
BMI, kg/m^2 mean (SD), median (25%Q, 75%Q)	24.6 (5.93), 23.4 (20.70, 27.68)	25.2 (5.68), 24.6 (21.36, 28.65)	0.12
SBP, mmHg, mean (SD), median (25%Q, 75%Q)	127.7 (34.24), 120.0 (102.0, 150.0)	133.8 (32.80), 130.0 (110.0, 152.5)	0.0051
DBP, mmHg, mean (SD), median (25%Q, 75%Q)	83.2 (20.86), 80.0 (70.0, 100.0)	85.6 (21.15), 82.0 (70.0, 100.0)	0.075
Heart Rate, bpm mean (SD), median (25%Q, 75%Q)	106.0 (21.28), 108.0 (92.0, 120.0)	100.7 (21.79), 100.0 (88.0, 113.0)	0.0001
LVEF (%), mean (SD), median (25%Q, 75%Q)	37.7 (15.75), 36.0 (25.0, 47.0)	41.7 (16.93), 40.0 (29.0, 55.0)	0.0002
LVEF <40%, *n* (%)	289 (32.5%)	182 (20.5%)	0.006
Creatinine, μmol/L, mean (SD), median (25%Q, 75%Q)	124.0 (84.49), 103.0 (79.56, 136.18)	121.9 (101.94), 95.5 (70.72, 129.00)	0.73
BUN, mmol/L, mean (SD), median (25%Q, 75%Q)	12.6 (9.80), 10.0 (6.10, 15.35)	12.6 (13.36), 8.9 (5.72, 14.21)	0.94
Sodium, mmol/L, mean (SD), median (25%Q, 75%Q)	134.3 (6.56), 135.0 (130.0, 138.6)	136.2 (6.60), 136.2 (132.0, 140.0)	<0.0001
eGFR,ml/min.1.73m^2, mean (SD), median (25%Q, 75%Q)	79.3 (38.79), 76.2 (52.71, 98.19)	89.3 (56.38), 78.5 (57.03, 106.88)	0.0020
Haemoglobin, g/L, mean (SD), median (25%Q, 75%Q)	117.6 (23.84), 120.0 (103.0, 132.5)	127.5 (23.15), 129.0 (115.0, 143.0)	<0.0001
Glucose, mmol/L, mean (SD), median (25%Q, 75%Q)	6.3 (3.18), 5.3 (4.52, 6.79)	5.8(2.00), 5.2 (4.72, 6.19)	0.0039
Medication use (1-month before)			
ACE inhibitor, *n* (%)	89 (37.2%)	95 (28.2%)	0.022
Loop diuretics, *n* (%)	103 (43.6%)	120 (36.4%)	0.081
Beta blockers, *n* (%)	44 (18.6%)	56 (17.2%)	0.68
Digoxin, *n* (%)	48 (20.1%)	58 (17.7%)	0.47
Hydralazine, *n* (%)	3 (1.3%)	0 (0.0%)	0.074
Nitrates, *n* (%)	8 (3.4%)	2 (0.6%)	0.021
Aldosterone inhibitor, *n* (%)	57 (24.2%)	51 (15.5%)	0.0099
Statins, *n* (%)	21 (8.9%)	7 (2.2%)	0.0003
Aspirin, *n* (%)	71 (29.8%)	55 (16.7%)	0.0002
Anticoagulants, *n* (%)	24 (10.1%)	11 (3.4%)	0.0011
Aetiology of heart failure			
Endomyocardial fibroelastosis	9 (1.7%)	4 (0.9%)	
HIV CMP	10 (1.9%)	13 (3.0%)	
Hypertensive CMP	201 (37.9%)	184 (43.0%)	
Idiopathic dilated CMP	81 (15.3%)	55 (12.9%)	
Ischemic heart disease	37 (7.0%)	40 (9.4%)	
Pericardial effusion /tamponade	31 (5.9%)	14 (3.3%)	
Peripartum CMP	46 (8.7%)	26 (6.1%)	
Rheumatic heart disease	79 (14.9%)	59 (13.8%)	
Other	36 (6.8%)	33 (7.7%)	

Table 2 Continued

Baseline characteristic	Patients with FU creatinine, $N = 543$	Patients with BL creatinine, but no FU, $N = 441$	*P*-value*
Region			
East	99 (70.7%)	168 (38.1%)	<0.0001
South	143 (26.3%)	64 (14.5%)	
West	301 (55.4%)	209 (47.4%)	
Country			
Cameroon	10 (1.8%)	77 (17.5%)	
Ethiopia	9 (1.7%)	1 (0.2%)	
Kenya	17 (3.1%)	15 (3.4%)	
Mozambique	72 (13.3%)	4 (0.9%)	
Nigeria	285 (52.5%)	125 (28.3%)	
Senegal	6 (1.1%)	7 (1.6%)	
South Africa	71 (13.1%)	60 (13.6%)	
Sudan	68 (12.5%)	4 (0.9%)	
Uganda	5 (0.9%)	148 (33.6%)	

BL, baseline; FU, follow up; BMI, body mass index; SBP, systolic blood pressure, DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CMP, cardiomyopathy; HIV, human immunodeficiency virus.
*P-value is from two-sided *t*-tests for continuous variables, or chi-square tests for categorical variables (Fisher's exact if at least one cell count is <5).

Table 3 Clinical outcomes in patients with and without a follow-up creatinine value

	Patients with BL and FU creatinine, $N = 523$	Patients with BL creatinine, but no FU. $N = 441$	*P*-value*
Length of initial hospital stay (days), mean(SD), median (25% Q, 75% Q)	10.2 (10.83), 8.0 (6.0, 11.0)	8.1 (7.34), 7.0 (4.0, 9.0)	0.0009
Initial hospitalization mortality, *n* (%)	22 (15.1%)	15 (5.8%)	0.91
Rehospitalization to day 60, *n* (%)	45 (10.4%)	23 (6.6%)	0.070
Death to day 60, *n* (%)	50 (10.6%)	36 (9.3%)	0.66
Death of readmission to day 60, *n* (%)	77 (16.5%)	47 (12.3%)	0.13
Death to day 180, *n* (%)	90 (20.4%)	50 (13.5%)	0.029

BL, baseline; FU, follow up.
*P-value is from two-sided t-test for length of stay (LOS), log-rank test for time to event outcomes. %'s represent Kaplan-Meier event rates for time to event outcomes.

(18.2) years, 481 (50.8%) were women, and the predominant race was black African (98.5%).[3]

The comorbid conditions present were 11.5% of patients with diabetes, 18.8% with atrial fibrillation, 9.2% with hyperlipidaemia and 15.2% with anaemia. Left ventricular ejection fraction (LVEF) was 39.2 ± 16.3%, with 465 (53.0%) of patients with an LVEF of less than 40%. The initial systolic blood pressure was 129.7 ± 33.2 mmHg and heart rate was 103.6 ± 21.7 bpm.

Heart failure was most commonly caused by hypertension ($n = 363$, 39.5%) followed by idiopathic dilated cardiomyopathy ($n = 136$, 14.8%) and rheumatic valvular heart disease ($n = 137$, 14.9%). Ischaemic heart failure was present in only 72 (7.8%) of the patients.

Mean creatinine at admission was 123.0 ± 93.43 μmol/L [median 99.0 μmol/L, interquartile range (IQR) 78.0–132.6 μmol/L] and eGFR was 83.8 ± 47.8 mL/min.1.73m^2 (median 76.9 mL/min, IQR 54.6–103.8 mL/min.1.73m).

Table 1 shows the patients characteristic according to the eGFR. They were categorized as follows: eGFR ≤ 30 mL/min.1.73m^2, $30-\leq 60$ mL/min.1.73m^2, $60-\leq 90$ mL/min.1.73m^2 and >90 mL/min.1.73m^2. Patients with a lower eGFR (≤ 60 ml/min.1.73m^2; $n = 289$, 30.6%) were significantly older and had more hypertension, diabetes, and hyperlipidaemia. They also showed more evidence of congestion (rales and peripheral oedema), and had higher body mass indices. Laboratory results showed that they had higher creatinine and blood urea nitrogen and lower haemoglobin levels.

Five hundred and forty-three (53%) patients had baseline and follow-up creatinine. This group was significantly younger, had more evidence of congestion (rales), a higher heart rate, and lower eGFR, LVEF, and haemoglobin levels compared with those with only a baseline value. They were also more likely to receive renin–angiotensin aldosterone system inhibition ($n = 453$; *Table 2*).

Table 4 Characteristics of patients with and without worsening renal function (WRF)

Patient characteristics	WRF, *N* = 53	no WRF, *N* = 470	Total, *N* = 523	*P*-value*
Age, years, mean ± SD median (25% Q, 75% Q)	50.6 ± 15.71 55.0 (40.0, 63.0)	50.0 ± 17.64 51.0 (36.0, 65.0)	50.1 ± 17.44 51.0 (36.0, 64.0)	0.82
Male sex, *n* (%)	30 (56.6%)	223 (47.5%)	253 (48.4%)	0.21
Black Africans, *n* (%)	52 (98.1%)	461 (98.1%)	513 (98.1%)	1.00
Hypertension, *n* (%)	30 (56.6%)	239 (51.0%)	269 (51.5%)	0.44
Hyperlipidaemia, *n* (%)	4 (7.8%)	44 (9.5%)	48 (9.3%)	1.0
History of smoking, *n* (%)	4 (7.5%)	46 (9.8%)	50 (9.6%)	0.81
Malignancy, *n* (%)	0 (0.0%)	3 (0.6%)	3 (0.6%)	1.0
History of cor pulmonale, *n* (%)	6 (11.3%)	31 (6.7%)	37 (7.2%)	0.22
History of atrial fibrillation, *n* (%)	6 (11.3%)	86 (18.4%)	92 (17.7%)	0.20
Diabetes mellitus, *n* (%)	6 (11.3%)	56 (11.9%)	62 (11.9%)	0.90
Peripheral oedema, *n* (%)	43 (81.1%)	312 (67.1%)	355 (68.5%)	0.037
Rales, *n* (%)	43 (91.5%)	281 (67.7%)	324 (70.1%)	<.0001
Body mass index, kg/m^2, mean ± SD, median (25% Q, 75% Q)	27.0 ± 7.85 25.5 (21.37, 32.72)	24.5 ± 5.69 23.4 (20.70, 27.52)	24.7 ± 5.99 23.5 (20.72, 27.77)	0.024
Systolic blood pressure, mmHg, mean ± SD, median (25% Q, 75% Q)	133.9 ± 39.15, 130.0 (105.0, 150.0)	125.8 ± 32.14, 120.0 (100.0, 145.0)	126.7 ± 32.97, 120.0 (101.0, 146.5)	0.15
Diastolic blood pressure, mmHg, mean ± SD, median (25% Q, 75% Q)	86.1 ± 25.27, 84.0 (70.0, 100.0)	82.3 ± 19.86, 80.0 (70.0, 96.0)	82.7 ± 20.49, 80.0 (70.0, 97.0)	0.29
Heart rate, Bpm, mean ± SD, median (25% Q, 75% Q)	105.26 ± 17.22, 107.0 (92.0, 114.0)	105.77 ± 21.75, 108.0 (90.0, 120.0)	105.7 ± 21.32, 108.0 (92.0, 120.0)	0.84
LVEF %, mean ± SD, median (25% Q, 75% Q)	39.1 ± 14.98, 39.0 (26.70, 50.30)	37.2 ± 15.79, 35.0 (25.0, 45.0)	37.4 ± 15.71, 35.0 (25.0, 47.0)	0.43
LVEF % <40, *n* (%)	27 (5.3%)	262 (51.6%)	289 (56.9%)	0.45
Creatinine level, μmol/L, mean ± SD, median (25% Q, 75% Q)	120.8 ± 82.49, 101 (79.56, 129.97)	124.4 ± 84.79, 103.8 (79.56, 136.97)	124.0 ± 84.49, 103.0 (79.56, 136.18)	0.77
BUN, mmol/L, mean ± SD, median (25% Q, 75% Q)	12.2 ± 6.77, 11.06 (6.80, 15.89)	12.3 ± 9.59, 9.9 (6.00, 14.98)	12.29 ± 9.34, 10.0 (6.1, 15.0)	0.95
Sodium level, mmol/L, mean ± SD, median (25% Q, 75% Q)	134.0 ± 6.39, 134.0 (129.5, 138.0)	134.4 ± 6.61, 135.0 (130.0, 139.0)	134.4 ± 6.58, 135.0 (130.0, 139.0)	0.71
eGFR, ml/min.1.73m^2, mean ± SD, median (25% Q, 75% Q)	86.2 ± 44.30, 77.2 (60.57, 106.17)	78.5 ± 38.09 75.9 (52.71, 96.66)	79.3 ± 38.79 76.2 (52.71 98.19)	0.17
Haemoglobin, g/L, mean ± SD, median (25% Q, 75% Q)	117.9 ± 24.31, 120.0 (105.0, 132.0)	118.7 ± 22.66, 120.0 (105.0, 133.0)	118.7 ± 22.81, 120.0 (105.0, 133.0)	0.80
Glucose level, mg/dL, mean ± SD, median (25% Q, 75% Q)	5.9 ± 2.59, 5.20 (4.70, 6.19)	6.4 ± 3.28, 5.38 (4.60, 6.92)	6.4 ± 3.22, 5.3 (4.60, 6.83)	0.25
Previous medication use, *n* (%)				
ACE inhibitor	9 (37.5%)	77 (36.7%)	86 (36.8%)	0.94
Loop diuretics	13 (54.2%)	87 (42.0%)	100 (43.3%)	0.26
β-Blockers	4 (16.7%)	37 (17.8%)	41 (17.7%)	1.0
Digoxin	6 (25.0%)	40 (19.0%)	46 (19.7%)	0.49
Hydralazine	0 (0.0%)	3 (1.4%)	3 (1.3%)	1.0
Nitrates	0 (0.0%)	8 (3.8%)	8 (3.5%)	1.0
Aldosterone Inhibitor	6 (25.0%)	49 (23.8%)	55 (23.9%)	0.90
Statins	2 (8.7%)	18 (8.6%)	20 (8.6%)	1.0
Aspirin	7 (29.2%)	62 (29.7%)	69 (29.6%)	0.96
Anticoagulants	2 (8.3%)	22 (10.6%)	24 (10.4%)	1.0
Aetiology heart failure				
Hypertensive CMP, *n* (%)	21 (41.2%)	167 (36.4%)	188 (36.0%)	
Idiopathic dilated CMP, *n* (%)	9 (17.7%)	72 (15.7%)	81 (15.5%)	
Rheumatic heart disease, *n* (%)	8 (15.7%)	71 (15.5%)	79 (15.1%)	
Ischaemic heart disease, *n* (%)	3 (5.9%)	32 (7.0%)	35 (6.7%)	
Peripartum cardiomyopathy, *n* (%)	3 (5.9%)	43 (9.4%)	46 (8.8%)	
Pericardial effusion tamponade, *n* (%)	3 (5.9%)	25 (5.5%)	28 (5.4%)	
HIV cardiomyopathy, *n* (%)	2 (3.9%)	8 (1.7%)	10 (1.9%)	
Endomyocardial fibrosis, *n* (%)	0 (0.0%)	9 (2.0%)	9 (1.7%)	
Other, *n* (%)	2 (3.9%)	32 (7.0%)	34 (6.1%)	
Region				
East	5 (9.4%)	93 (19.8%)	98 (18.7%)	0.048
South	11 (20.8%)	129 (27.5%)	140 (26.8%)	
West	37 (69.8%)	248 (52.8%)	285 (54.5%)	

ACE, angiotensin converting enzyme; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction.
*P-value for categorical variables from chi-square test or Fisher's exact test if at least one cell count <5 *P*-value for continuous variables from ANOVA.

Table 5 Predictors of worsening renal function

Predictor	Unit increase	Univariable models		Multivariable model	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Baseline Creatinine, μmol/L	88.4	0.95 (0.69, 1.31)	0.7720	0.77 (0.53, 1.11)	0.16
History of cor pulmonale	Yes vs. No	1.73 (0.68, 4.41)	0.2497		
Male sex	Male vs. Female	1.45 (0.82, 2.56)	0.2079	1.81 (0.97, 3.39)	0.062
BMI, ≤18.5 kg/m^2	5	0.10 (0.02, 0.42)	0.0018	0.06 (0.01, 0.29)	0.0005
BMI, >18.5 kg/m^2	5	1.58 (1.27, 1.98)	<0.0001	1.78 (1.39, 2.28)	<0.0001
History of atrial fibrillation	Yes vs. No	0.57 (0.23, 1.36)	0.2050		
Systolic blood pressure,, mmHg	10	1.07 (0.99, 1.16)	0.0908		
Peripheral oedema	2/3 vs. 0/1	2.13 (1.04, 4.38)	0.0395		
Rales	2/3 vs. 0/1	3.50 (1.48, 8.28)	0.0043	3.56 (1.38, 9.17)	0.0088
Region	South vs. West	0.57 (0.28, 1.16)	0.0559	0.60 (0.27, 1.35)	0.060
	East vs. West	0.36 (0.14, 0.94)		0.31 (0.11, 0.87)	

BMI, body mass index; CI, confidence interval; OR, odds ratio.

Patients with a follow-up creatinine value also had a longer length of stay, and had a higher rate of readmission and death (*Table 3*). In particular, a higher proportion of patients with follow-up creatinine values than without follow-up creatinine values died in-hospital (22 or 15.1% versus 15 or 5.8%).

Worsening renal function was evident in 53 (9.8%) patients with follow-up creatinine values available. The characteristics of patients with and without WRF are shown in *Table 4*. Patients with WRF were essentially similar to those without WRF in their characteristics, except that they had more evidence of congestion (peripheral oedema and rales).

Univariable and multivariable predictors of worsening renal function are presented in *Table 5*. Upon multivariable adjustment, significant predictors of WRF were BMI, the presence of rales, and geographic region. The risk of WRF decreased with increasing BMI until approximately 18.5 kg/m^2, above which the risk increased with increasing BMI.

Clinical outcomes by the occurrence of WRF are shown in *Table 6*. Those with WRF had a similar length of hospital stay as those without WRF, but a higher rate of 60-day mortality or readmission and a higher 180-day mortality rate. *Figure 1* is a Kaplan–Meier plot of cumulative incidence of death by worsening renal function to day 180.

Univariable and multivariable models predicting clinical outcome are presented in the Supporting Information *Tables S1* and *S2*. After multivariable adjustment for other prognostic factors, worsening renal function was an independent predictor of death or readmission over 60 days [adjusted hazard ratio (HR) = 2.06 (1.10, 3.82); $P = 0.023$] and all-cause death over 180 days [adjusted HR = 1.92 (1.08, 3.38); $P = 0.025$].

Table 6 Patient outcome by worsening renal function (WRF)

	WRF, *N* = 53	No WRF, *N* = 470	*P*-value*
Length of initial hospital stay (days), mean(SD), median (25% Q, 75% Q)	10.3 (7.08), 8.0 (6.5, 12.0)	10.2 (11.16), 8.0 (6.0, 11.0)	0.93
Initial hospitalization mortality, *n* (%)	5 (18.8%)	17 (14.6%)	0.10
Rehospitalization to day 60, *n* (%)	6 (14.5%)	39 (10.0%)	0.39
Death to day 60, *n* (%)	11 (22.8%)	39 (9.2%)	0.0034
Death or readmission to day 60, *n* (%)	13 (26.9%)	64 (15.3%)	0.032
Death to day 180, n (%)	15 (32.0%)	75 (19.1%)	0.020

WRF: ≥0.3 mg/dL (26.5 μmol/l) increase in creatinine compared with baseline.
*p-value is from two-sided t-test for LOS, log-rank test for time to event outcomes.

Discussion

Our study is the first multicentre registry from sub-Saharan Africa that provides insight into the prevalence, predictors, and clinical outcome of the renal dysfunction in AHF patients on this continent. The major findings of this study were that renal dysfunction was also frequently found at hospital admission for heart failure in this younger, mostly non-ischaemic patients. Although data for WRF was available in half of the patients studied, it was less prevalent and has different predictors compared with Western cohorts. Nevertheless, WRF was strongly and independently related to clinical outcome.

The prevalence of renal dysfunction (31% of patients with a eGFR <60 mL/min/1.73m^2) in our cohort was similar to Western countries,[7–10,17] despite younger age. This relatively high prevalence might be related to the large number of patients with hypertensive heart failure, as the deleterious effects of hypertension on the kidneys are well known. In addition, AHF affects the haemodynamic and neurohormonal milieu, which leads to functional impairment or permanent kidney damage, regardless of the

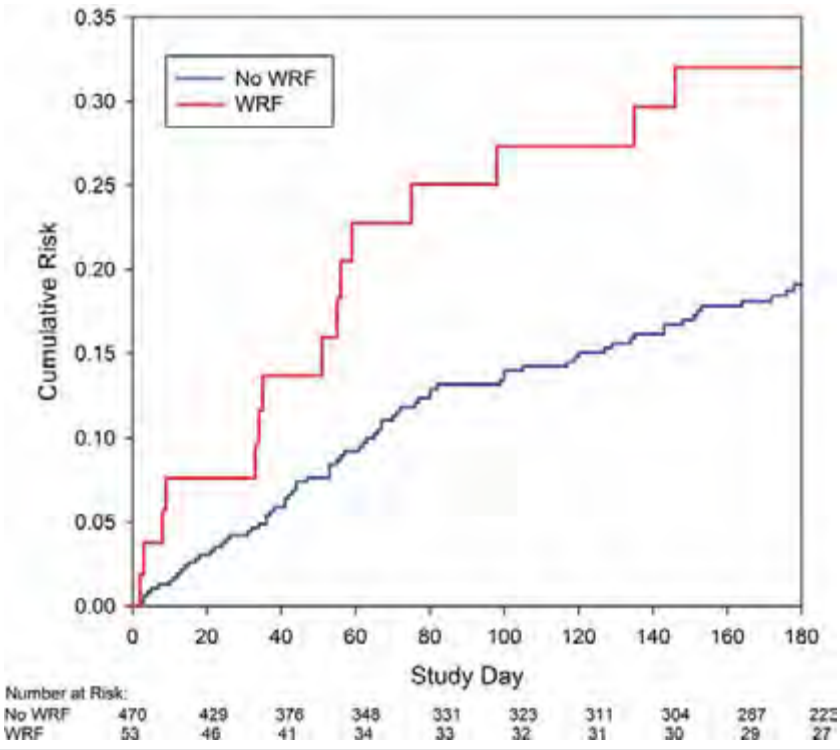

Figure 1 Kaplan–Meier plot of cumulative incidence of death by worsening renal function (WRF) to day 180.

comorbidities.[18] The presence of comorbidities such as diabetes, atrial fibrillation, and anaemia as well as the serum creatinine values on admission of our patients were similar to those documented in previous studies.[8,15,19] Inglis and co- workers[20] found renal dysfunction in only 12% of African heart failure patients with idiopathic dilated cardiomyopathy, which might be explained by the less deleterious effect of non-hypertension-related heart failure on the kidneys.

Concomitant renal dysfunction is one of the main independent risk factors for prolonged hospitalization, rehospitalization, and short- and long-term mortality in AHF.[21–23] In patients with chronic heart failure, baseline eGFR has been demonstrated to be a stronger predictor for all-cause mortality than LVEF and NYHA functional class.[24] Similarly, a decrease in GFR is directly associated with the rate of in-hospital mortality. In a meta-analysis, Smith *et al.*[7] reported that annual mortality rates were 26% in patients without renal dysfunction, 41% in the patients with any impairment of renal function. and 51% in patients with moderate to severe impairment. Overall, they found that any degree of renal impairment was associated with a 56% increase in relative mortality risk. Renal dysfunction was found to be a predictor of outcome both in heart failure patients with reduced ejection fraction (HFrEF) and heart failure patients with preserved ejection fraction (HFpEF) and was suggested to be a more powerful predictor of outcome in patients with HFpEF.[11]

Although the prevalence of renal dysfunction at baseline was relatively high, worsening renal function was found to be less prevalent than that reported in many previous studies.[8,9,25,26] This is likely to be because our patients were younger, had less previous myocardial infarctions, and probably less atherosclerotic kidneys. Although they had a high prevalence of chronic kidney disease, the kidneys could probably handle acute hypoperfusion better than atherosclerotic kidneys. However, this prevalence may still be an overestimation as there might have been selection in favour of more severe heart failure patients with poorer renal function, in whom renal function was more frequently measured.

The predictors of WRF in this study were BMI, signs of congestion (peripheral oedema and rales) and being in the Western African region. These are different from the factors found by other workers, which include diabetes[15,27,28] elevated systolic blood pressure,[7,27,28] NYHA class,[7,19] tachycardia, and female sex.[25] In a recent updated meta-analysis of WRF and outcomes in heart failure by Damman and colleagues,[11] other predictors found were age, diuretic use, baseline GFR, anaemia, vascular disease/ischaemic heart disease, and LVEF. Only one previous study showed a higher BMI to be a predictor of WRF.[11] We found both lower BMI and higher BMI to be predictors of WRF. Patients with a very low BMI might be cachectic, which carries a poor prognosis by itself, and WRF may be a marker of a poor functional and clinical status of cachectic heart failure patients. We cannot explain why a higher BMI was related to a higher risk of WRF, although it is well known that obese patients tend to hyperfiltrate, which might result in a limited 'spare capacity' when kidneys are challenged with hypoperfusion during an episode of AHF.

Similar to the findings of other studies conducted mostly in Europe and North America,[15,25,29,30] we found that patients who presented with signs of congestion were more likely to develop WRF than those who had a less severe congestion The systemic/pulmonary congestion increases central venous pressure, which is directly transmitted to the renal vein affecting renal perfusion pressure. Different reports have highlighted that higher central venous pressure is associated with decreasing GFR.[17,31,32] In addition, a direct effect on renal perfusion pressure—high renal venous pressure—results in increased intrarenal pressure because the kidney has a tight capsule. This increased pressure causes collapsing of tubules and directly opposes filtration, resulting in decreased GFR.[33] How autoregulation responds to increased renal venous pressure is unknown, although higher levels of intrarenal angiotensin II and activation of the sympathetic nervous system have been proposed, which could indirectly influence arteriolar tone.[34] However, the association between WRF and venous congestion remains complex, as was recently described by Testani and Damman.[35]

In a recent meta-analysis of WRF during renin-angiotensin-aldosterone system (RAAS) inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction by Clark and colleagues,[36] WRF was associated with poorer outcome in both RAAS inhibitor and placebo groups, compared with patients who did not develop WRF. In addition the RAAS inhibitor group, despite having more frequent WRF, was associated with lower overall mortality than the placebo group and that benefit was attained in patients both with and without WRF. This may indicate that WRF by itself is a biased prognosticator.[37] In our study, even though the frequency of WRF is low, there was no difference in RAAS inhibition between those with WRF and those without (angiotensin-converting enzyme inhibition was 36.7% vs. 37.5% , $P = 0.94$; aldosterone inhibition 23.8% vs. 25.0%, $P = 0.9$).

Although the length of hospital stay of our patients was comparable to that found in other European registries,[38−41] there was no difference between those who developed WRF and those who did not. Other studies have shown that the development of WRF is associated with prolonged hospital stay.[15,21] The reason for this difference is not apparent but result from different management strategies in diverse medical centres as well as economic reasons, as in many hospitals in sub-Saharan Africa how long a patient remains on admission is determined by the affordability of the services.

Worsening renal function was an independent predictor of death or readmission over 60 days and all-cause death over 180 days. It has been shown that WRF is associated with a poor prognosis in most previous studies.[8−10,25,42] The cause of WRF in AHF has not been completely elucidated but is thought to result from decreased renal perfusion and venous congestion, while endothelial dysfunction, neurohormonal activation, and inflammation play a mediating role.[31,43] These patients also generally have more severe disease, developing a vicious cycle with more congestion leading to poor renal perfusion and further accelerating the heart failure.

Limitations

The present study is an analysis of the patients enrolled in the THESUS-HF study and as such shares certain limitations with the original cohort.[3] The majority of the patients were recruited in a limited number of hospitals, mainly in Nigeria, Uganda, and South Africa. Most importantly, loss to follow-up, missing laboratory data, and clinical signs assessments were higher than in studies conducted in other regions.

This registry was performed in selected centres and may represent only AHF patients seen in specialized centres. In addition, we did not measure renal haemodynamics or GFR by clearance methods, the eGFR formula used is only a surrogate marker of real GFR, but has been shown to be the most accurate in heart failure.[12] Finally, almost half of the patients do not have follow up creatinine values and as a result, WRF could not be calculated. This calls for caution in interpreting the WRF data.

Conclusion

The present study shows that renal dysfunction is frequently present in younger non-ischaemic AHF patients in Africa. Worsening renal function, although calculated in half of the patients with available follow-up creatinine values, is less prevalent and has different predictors compared with Western cohorts. Nevertheless, in these patients, WRF was associated with the severity of congestion and appeared to be a strong and independent predictor of adverse clinical outcomes.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:
Table S1. Predictors of death or readmission through 60 days
Table S2. Predictors of all-cause death through 180 days

Funding

THESUS-HF was sponsored by Momentum Research, Inc., Durham, NC, USA.

Conflict of interest: none declared

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9 Chapter 9 Prevalence, clinical characteristics and outcomes of valvular atrial fibrillation in a cohort of African patients with acute heart failure: Insights from THESUS-HF Registry

9.1 Introduction

Rheumatic heart disease (RHD) remains an important cause of heart failure in SSA[36,82] and RHD associated with valvular AF is also common on the continent. [510] Among the regions enrolled in Randomized Evaluation of Long-Term Anticoagulation Therapy in atrial fibrillation (AF) (RE-LY- AF), a global prospective registry that enrolled patients presenting to an emergency department with AF, RHD was present in 22% of African patients compared 2% in North American patients. [510]

The risk of AF increases multiple folds in the presence of HF and valvular disease. [511] The prognostic influence of the presence of AF in HF remains controversial, with some studies illustrating an independent adverse effect on mortality. [512,513] In recent metanalysis of 16 studies comprising of more than 50,000 patients with chronic HF, Mamas and colleagues showed that AF was associated with an adverse effect on total mortality. [514]

From a cohort of 1006 African patients admitted with AHF and enrolled in the THESUS-HF registry, we analysed the burden, clinical characteristics and outcomes of AF in general and valvular AF in particular among acute HF patients in Sub Saharan Africa.

9.2 Methods

THESUS-HF was a prospective, multicenter, international observational survey of acute HF in 12 cardiology centers from 9 countries sub-Saharan Africa. [36]

Details of data collection have been previously described in chapter 3. In brief and relevant to this chapter, all ECGs were read centrally at the Momentum Research Inc. by one cardiologist and reviewed by another one. ECGs were analyzed for conduction or rhythm disturbances, evidence of myocardial ischemia/infarction or hypertrophy. AF was defined as either a history of documented AF or a finding of AF on the admission ECG. The information obtained was entered in the database registry together with other clinical data. A detailed echocardiographic assessment of ventricular contractility, valvular structure and function as well as regional wall abnormalities was performed.

9.2.1 Statistical analyses

All data were processed at the central coordinating center at Momentum Research, Durham, North Carolina, USA. Data were analyzed with the use of SAS version 9.3 (SAS Institute, Cary, North Carolina). Summary statistics (mean, SD, median, and 25th and 75th percentiles) are provided for continuous variables and frequencies for categorical variables. Unless otherwise stated, a chi-square test was used for categorical variables, Cochran-Mantel-Haenszel test for ordinal variables, and Wilcoxon test for continuous variables to examine comparisons between groups.

Atrial fibrillation classification was based on subjects either having a history of AF or the presence of AF on an ECG taken at admission. Baseline characteristics by AF status are presented, as well as characteristics between patients with valvular and non-valvular AF.

Comparisons between valvular and non-valvular AF patients are presented to examine differences in the following outcomes: length of index hospitalization, time to first rehospitalization through 60 days, all-cause mortality through 180 days, and the composite endpoint of time to all-cause mortality or rehospitalization through 60 days. For length of index hospitalization, least square means and the difference between least square means are presented. For time-to event outcomes, Cox regression models were used with times for patients without the event of interest being censored at the earlier of the last date the patient was known to be alive or the period of interest for the specific outcome. Kaplan-Meier estimates, hazard ratios and 95% confidence intervals are given with the log rank test used for comparison between groups. Two patients who were classified with AF but were missing valvular-disease status were excluded from tables comparing valvular disease in only those patients with AF. For multivariable modeling these two patients were counted as having neither valvular-AF nor non-valvular AF. Anticoagulation use over time is also presented as the frequency of use by AF and by valvular/non-valvular disease in only those patients with AF by time point.

The prognostic value of valvular and non-valvular AF was examined in multivariable models for the outcomes all-cause mortality through day 180 and the composite endpoint all-cause mortality or rehospitalization through day 60. The multivariable models were adjusted for significant clinical covariates from multivariable prognostic models previously constructed for these outcomes in the overall THESUS-HF registry. [475] To account for missing data, multiple imputations were used with 7 imputed datasets. Rubin's algorithm was used for averaging parameter estimates across the imputed datasets.[515,516]

9.3 Results

There were a total of 1006 patients in the THESUS HF registry. The mean (SD) age of the patients was 52.3 (18.3) years, 511 (50.8%) were women, and the predominant race was black African (98.5%). As reported previously, [517] the primary etiology of heart failure was most commonly hypertension (n=363 [39.5%]) followed by idiopathic dilated cardiomyopathy (n=136[14.8%]) and rheumatic valvular heart disease (n=137[14.9%]), with ischemic heart failure in only 72 (7.8%) patients. Left ventricular EF was 39.5 ± 16.5%, with 606 (65.2%) patients with LVEF less than 45%.

AF was present in 209 (20.8%) of the 1006 patients. In the previous THESUS-HF publication, [36] prevalence was documented to be 18.3% because only those who had AF on the admission ECG were analysed. Table 9.1 shows the baseline patient characteristics by AF status. In both the AF and non-AF groups about 80% of the patients were in NYHA class II or III one month prior to admission. Compared to the patients without AF, the patients with AF were older (mean age 57.1 versus 51.1 years) and more likely to be female (57.4% versus 49.1 %). They also had significantly lower systolic (125 versus 132 mmHg) and diastolic (81 versus 85 mmHg) blood pressures and higher mean heart rates (109 versus 102). The other baseline characteristics were similar in the two groups.

Table 9.1 Baseline patient clinical characteristics by atrial fibrillation status

Variables	Atrial fibrillation N = 209 [1]	No Atrial fibrillation N = 797 [1]	P-Value [2]
Age (years)	57.1 (17.73), 60.0 (46.0, 70.0)	51.1 (18.26), 52.0 (36.0, 65.0)	<.0001
Gender: Females	120 (57.4)	391 (49.1)	0.0328
Country			
Cameroon	27 (12.9)	63 (7.9)	
Ethiopia	3 (1.4)	7 (0.9)	
Kenya	5 (2.4)	27 (3.4)	
Mozambique	20 (9.6)	56 (7.0)	
Nigeria	73 (34.9)	352 (44.2)	0.0508
Senegal	3 (1.4)	12 (1.5)	
South Africa	31 (14.8)	101 (12.7)	
Sudan	9 (4.3)	63 (7.9)	
Uganda	38 (18.2)	116 (14.6)	
Region			
East	55 (26.3)	213 (26.7)	
South	51 (24.4)	157 (19.7)	0.3071
West	103 (49.3)	427 (53.6)	
Black African	203 (97.6)	781 (98.7)	0.2291
BMI (Kg/m2)	24.94 (5.712), 24.73 (21.02, 28.08)	24.85 (5.836), 23.88 (20.83, 27.99)	0.4736
SBP (mmHg)	124.5 (29.86), 120.0 (102.0, 145.0)	131.9 (34.27), 130.0 (108.0, 150.0)	0.0128
DBP (mmHg)	80.6 (19.54), 80.0 (67.0, 90.0)	85.3 (21.19), 82.0 (70.0, 100.0)	0.0032
History of Smoke	14 (6.7)	84 (10.6)	0.0962
History of Diabetes mellitus	15 (7.2)	99 (12.4)	0.0344
HIV test positive	5 (2.4)	60 (7.6)	0.0078

Malignancy	1 (0.5)	12 (1.5)	0.2429
History of Depression	8 (3.8)	25 (3.1)	0.6114
Dementia	7 (3.4)	15 (1.9)	0.1939
No. of AHF admission in the last 12 months	0.33 (0.621), 0.00 (0.00, 1.00)	0.38 (0.812), 0.00 (0.00, 0.00)	0.7840
Heart Rate	109.3 (28.02), 108.0 (90.0, 124.0)	102.2 (19.29), 103.0 (90.0, 114.0)	0.0021
NYHA 1-Month Prior to Admission			
I	21 (13.6)	100 (19.4)	
II	77 (50.0)	226 (43.9)	0.2940
III	47 (30.5)	170 (33.0)	
IV	9 (5.8)	19 (3.7)	
History of Hypertension	110 (52.9)	446 (56.2)	0.3959
Hyperlipidemia	9 (4.5)	81 (10.4)	0.0109
Stroke	7 (3.4)	18 (2.3)	0.3613
Orthopnea			
0	4 (2.3)	23 (3.5)	
1	15 (8.7)	55 (8.3)	0.3764
2	69 (40.1)	289 (43.4)	
3	84 (48.8)	299 (44.9)	
Ischemic heart disease	11 (5.3)	71 (8.9)	0.0849
Valvular disease	92 (44.4)	180 (22.7)	<.0001
Rales			
0	28 (15.9)	93 (13.2)	
1+	47 (26.7)	147 (20.9)	0.1524
2+	70 (39.8)	341 (48.4)	
3+	31 (17.6)	123 (17.5)	
Peripheral Vascular Disease	3 (1.4)	9 (1.1)	0.7072

Anemia	99 (49.0)	390 (51.0)	0.6183
Pericardial disease	9 (4.3)	44 (5.6)	0.4815
Cardiomyopathy	80 (38.8)	336 (42.6)	0.3243
LVEF (%)	42.31 (15.721), 41.90 (31.00, 52.00)	38.74 (16.623), 37.00 (25.40, 50.00)	0.0022
LVEF < 40%	82 (41.6)	405 (55.3)	0.0155
BUN (mg/dL)	33.853 (28.017), 27.450 (17.000, 40.000)	36.048 (34.309), 26.764 (16.806, 42.015)	0.8963
Creatinine (mg/dL)	1.310 (0.7359), 1.136 (0.900, 1.541)	1.414 (1.1182), 1.120 (0.880, 1.500)	0.5950
Glucose (mg/dL)	106.12 (48.532), 93.600 (83.000, 111.60)	110.65 (49.991), 94.000 (84.000, 120.00)	0.3072
eGFR (mL/min/1.73m2)	78.257 (40.114), 70.782 (49.422, 98.271)	84.685 (49.838), 77.735 (55.929, 104.20)	0.0522
Renal dysfunction	10 (5.0)	63 (8.4)	0.1020
Hemoglobin level (g/dL)	12.321 (2.0335), 12.350 (11.400, 13.400)	12.115 (2.5161), 12.200 (10.500, 13.800)	0.3460
Total WBC count (No./µL)	7861.5 (4332.8), 7000.0 (5450.0, 9020.0)	7656.0 (4026.8), 6750.0 (5100.0, 8930.0)	0.3096
Lymphocytes count (%)	30.87 (13.360), 30.70 (21.55, 38.55)	30.18 (13.368), 30.00 (20.00, 39.70)	0.5524
Cholesterol level (mg/dL)	146.49 (43.853), 148.21 (117.00, 168.00)	160.40 (56.197), 153.86 (124.80, 187.21)	0.0154
Triglycerides level (mg/dL)	96.924 (40.492), 92.000 (64.970, 115.70)	108.60 (56.625), 97.900 (71.200, 127.27)	0.0464
Sodium level (mmol/L)	136.23 (6.506), 136.20 (132.00, 140.20)	134.83 (6.627), 135.00 (131.00, 139.00)	0.0097

[1] Mean (SD), Median (first quartile- third quartile) for a continuous variable and frequency (percent) for a categorical variable.
[2] Chi-square test for a categorical variable, CMH for an ordinal variable and Wilcoxon test for a continuous variable.

Ninety-two (44%) of the 207 AF patients had valvular heart disease. Compared with those without valvular disease, these patients were younger (mean age 52 versus 61 years), had lower systolic blood pressure (120 versus 128 mmHg) and higher LVEF (47% versus 38%). Fifty seven percent of them had LVEF ≥45%. Among patients with non-valvular AF, 61% had hypertensive heart disease. The other baseline characteristics were similar in the two groups (Table 9.2).

Table 9.2 Baseline patients clinical characteristics by valvular and non valvular atrial fibrillation

Variables	Valvular Afib N = 92 [1]	Non-Valvular Afib N = 115 [1]	P-Value [2]
Age (years)	52.2 (18.98), 52.0 (38.5, 65.5)	60.8 (15.74), 64.0 (53.0, 72.0)	0.0005
Gender: Females	59 (64.1)	60 (52.2)	0.0838
Country			
Cameroon	7 (7.6)	20 (17.4)	
Ethiopia	0 (0.0)	3 (2.6)	
Kenya	2 (2.2)	3 (2.6)	
Mozambique	6 (6.5)	14 (12.2)	
Nigeria	15 (16.3)	57 (49.6)	<.0001
Senegal	1 (1.1)	2 (1.7)	
South Africa	20 (21.7)	10 (8.7)	
Sudan	8 (8.7)	1 (0.9)	
Uganda	33 (35.9)	5 (4.3)	
Region			
East	43 (46.7)	12 (10.4)	
South	26 (28.3)	24 (20.9)	<.0001
West	23 (25.0)	79 (68.7)	
Black African	91 (98.9)	111 (97.4)	0.4245
BMI (Kg/m2)	24.89 (6.482), 24.76 (20.91, 27.91)	24.90 (5.005), 24.52 (21.23, 28.11)	0.7187
SBP (mmHg)	119.9 (24.39), 112.0 (100.0, 133.0)	127.9 (33.38), 124.5 (108.0, 150.0)	0.0699
DBP (mmHg)	78.4 (17.01), 79.0 (65.0, 90.0)	82.2 (21.29), 80.0 (68.0, 94.0)	0.2521
History of Smoke	7 (7.7)	6 (5.2)	0.4682
History of Diabetes mellitus	5 (5.4)	9 (7.9)	0.4855
HIV test positive	3 (3.4)	2 (1.8)	0.6920

Malignancy	1 (1.1)	0 (0.0)	0.2598
History of Depression	4 (4.4)	4 (3.5)	0.7350
Dementia	3 (3.3)	4 (3.5)	0.9431
No. of AHF admission in the last 12 months	0.40 (0.734), 0.00 (0.00, 1.00)	0.27 (0.506), 0.00 (0.00, 0.00)	0.3873
Heart Rate	111.7 (29.68), 109.0 (92.0, 127.0)	107.4 (26.86), 107.0 (90.0, 120.0)	0.4319
NYHA 1-Month Prior to Admission			
I	12 (15.4)	9 (11.8)	
II	44 (56.4)	33 (43.4)	0.0320
III	20 (25.6)	27 (35.5)	
IV	2 (2.6)	7 (9.2)	
History of Hypertension	38 (41.8)	70 (60.9)	0.0064
Hyperlipidemia	4 (4.6)	4 (3.6)	0.7244
Stroke	3 (3.3)	3 (2.6)	0.7706
Orthopnea			
0	2 (2.5)	2 (2.2)	
1	10 (12.3)	5 (5.6)	0.4206
2	30 (37.0)	38 (42.2)	
3	39 (48.1)	45 (50.0)	
Ischemic heart disease	4 (4.3)	6 (5.2)	0.7719
Valvular disease	92 (100.0)	0 (0.0)	<.0001
Rales			
0	18 (25.4)	10 (9.6)	
1+	16 (22.5)	31 (29.8)	0.0836
2+	25 (35.2)	44 (42.3)	
3+	12 (16.9)	19 (18.3)	
Peripheral Vascular Disease	2 (2.2)	1 (0.9)	0.4235

Anemia	46 (51.7)	51 (45.9)	0.4196
Pericardial disease	3 (3.3)	6 (5.2)	0.5030
Cardiomyopathy	29 (32.2)	50 (43.5)	0.1003
LVEF (%)	47.21 (14.440), 46.00 (40.00, 58.00)	38.20 (15.506), 36.50 (27.00, 45.70)	<.0001
LVEF < 40%	22 (24.7)	59 (55.7)	<.0001
BUN (mg/dL)	32.102 (24.442), 24.369 (16.806, 40.334)	35.694 (30.840), 29.000 (18.487, 40.000)	0.2820
Creatinine (mg/dL)	1.312 (0.7082), 1.171 (0.878, 1.570)	1.316 (0.7660), 1.125 (0.900, 1.544)	1.0000
Glucose (mg/dL)	102.92 (47.079), 91.800 (82.800, 105.20)	108.77 (50.132), 98.600 (84.000, 115.10)	0.1777
eGFR (mL/min/1.73m2)	78.731 (39.738), 74.123 (48.772, 92.796)	77.676 (40.914), 69.039 (49.709, 100.88)	0.7990
Renal dysfunction	4 (4.3)	6 (5.6)	0.6961
Hemoglobin level (g/dL)	12.325 (2.0718), 12.600 (11.000, 13.400)	12.331 (2.0279), 12.300 (11.500, 13.600)	0.7053
Total WBC count (No./µL)	8424.9 (5562.6), 7120.0 (5160.0, 9600.0)	7431.0 (2991.6), 7000.0 (5500.0, 8800.0)	0.6228
Lymphocytes count (%)	29.27 (14.264), 29.60 (18.00, 38.00)	31.79 (12.234), 32.00 (24.00, 38.10)	0.1728
Cholesterol level (mg/dL)	143.77 (41.704), 148.21 (109.20, 171.61)	147.93 (45.413), 143.00 (120.90, 167.71)	0.9203
Triglycerides level (mg/dL)	100.63 (41.320), 91.390 (69.420, 124.60)	93.792 (39.999), 93.000 (62.300, 110.02)	0.4499
Sodium level (mmol/L)	136.63 (6.729), 137.00 (132.20, 141.00)	135.78 (6.314), 136.00 (132.00, 140.00)	0.3750

[1] Mean (SD), Median (first quartile- third quartile) for a continuous variable and frequency (percent) for a categorical variable.
[2] Chi-square test for a categorical variable, CMH for an ordinal variable and Wilcoxon test for a continuous variable.

Anticoagulation prescription rates were low in this cohort of patients and decreased progressively over time. At 6 months only 22% of patients with AF were on oral anticoagulant. For the AF patients, 33% of the patients with valvular AF and 12% of those with non-valvular AF were on anticoagulants at 6 months follow up (Table 9.3). For Aspirin, a greater proportion of patients with AF than without AF were on aspirin 1 month prior to admission (29 versus 20%), but on and after admission the proportions did not differ significantly. At 6 months similar proportions of patients with AF and without AF were on aspirin. Among patients with AF, the proportion on aspirin did not differ significantly except at discharge/day 7 and day 30, when a smaller proportion of patients with valvular AF than with non-valvular were on aspirin (48 versus 62% and 39 versus 67% respectively) (Table 9.3).

Table 9.3 Patients use of anticoagulation and aspirin by time

	1 Month Prior to Admission	Admission	Day 1	Day 2	Disc./Day 7	Day 30	6-Months
Atrial Fibrillation							
Yes (N=209)							
Anticoagulation	16/136 (11.8)	107/205 (52.2)	118/207 (57.0)	124/206 (60.2)	78/204 (38.2)	31/116 (26.7)	22/101 (21.8)
Aspirin	39/135 (28.9)	68/203 (33.5)	68/202 (33.7)	68/201 (33.8)	111/199 (55.8)	67/115 (58.3)	60/102 (58.8)
No (N=797)							
Anticoagulation	19/444 (4.3)	234/786 (29.8)	250/782 (32.0)	255/769 (33.2)	106/744 (14.2)	66/499 (13.3)	22/326 (6.8)
Aspirin	88/443 (19.9)	283/784 (36.1)	290/778 (37.3)	303/767 (39.5)	430/743 (57.9)	303/499 (60.7)	189/327 (57.8)
P-value[1]	0.0013	<0.0001	<0.0001	<0.0001	<0.0001	0.0003	<0.0001
P-value[2]	0.0266	0.4905	0.3422	0.1408	0.5956	0.6269	0.8546
Atrial Fibrillation Subjects							
Valvular (N=92)							
Anticoagulation	12/63 (19.0)	48/91 (52.8)	56/92 (60.9)	60/91 (65.9)	54/90 (60.0)	20/34 (58.8)	15/45 (33.3)
Aspirin	20/63 (31.8)	33/90 (36.7)	32/90 (35.6)	31/89 (34.8)	42/88 (47.7)	13/33 (39.4)	28/46 (60.9)
Non-valvular (N=115)							
Anticoagulation	4/71 (5.6)	58/112 (51.8)	61/113 (54.0)	62/113 (54.9)	23/112 (20.5)	10/81 (12.4)	7/56 (12.5)
Aspirin	18/70 (25.7)	34/111 (30.6)	35/110 (31.8)	36/110 (32.7)	68/109 (62.4)	54/81 (66.7)	32/56 (57.1)
P-value[1]	0.0168	0.8915	0.3217	0.1090	<0.0001	<0.0001	0.0117
P-value[2]	0.4420	0.3667	0.5775	0.7548	0.0394	0.0073	0.7035

1: Chi-square test for comparison of anticoagulation use.
2: Chi-square test for comparison of aspirin use.

As shown in Table 9.4, the mean length of the hospital stay was 1.6 days longer in patients with valvular AF than for patients with non-valvular AF, although this was not statistically significant (p=0.14). The unadjusted risk of 180-day mortality in patients with valvular AF was twice that in patients with non-valvular AF (HR 2.11, 95% CI 1.05-4.24, p=0.032), while the unadjusted risks of 60-day rehospitalization did not differ significantly.

Table 9.4 Outcomes by valvular disease status in patients with atrial fibrillation

Variable	Valvular Atrial Fibrillation (N=92)	Non-Valvular Atrial Fibrillation (N=115)	Effect 95% CI [3]	P-value
Length of Index Hospitalization [1]	11.2	9.6	1.63 (-0.56, 3.83)	0.1438
Rehospitalization through 60 Days [2]	6.0	11.3	0.48 (0.15, 1.52)	0.2046
Death through Day 180 [2]	24.8	13.2	2.11 (1.05, 4.24)	0.0320
Death or Rehospitalization through 60 Days [2]	19.1	15.5	1.32 (0.66, 2.65)	0.4268

[1] LS Means
[2] Kaplan-Meier event rate
[3] Hazard Ratio from cox regression model presented for Rehospitalization, death, and death/Rehospitalization outcome.
LS Means difference presented for length of index hospitalization.

Without adjustment for potential confounding factors, neither valvular nor non-valvular AF was associated with 60-day readmission (Table 9.5), while valvular but not non-valvular AF was associated with 180-day all-cause mortality (Table 9.6). Multivariable models previously developed[475] showed that renal dysfunction, lower blood pressure, congestion and presence of malignancy and history of cor pulmonale were associated with all cause death or readmission within 60 days. Similar factors as well as lower haemoglobin and HIV status were associated with all cause death through 180 days. Multivariable adjustment for these prognostic markers had little effect on the estimated associations of valvular and non-valvular AF with either outcome. Valvular AF was not a significant predictor of all cause death or readmission through day 60 (Figure 9.1) (HR 1.39, 95% CI 0.80-2.42, p=0.24) but was associated with all-cause death through day 180 (HR 1.61, 95% CI 0.99-2.62, p=0.056) (Figure 9.2). On the other hand, non-valvular AF was not a significant predictor of either all cause death or readmission through day 60 (HR 0.99, 95% CI 0.58-1.68, p=0.96) (Figure 9.1) or the outcome all-cause death through day 180 (HR 0.70, 95% CI 0.39-1.26, p=0.23) (Figure 9.2).

Table 9.5 Associations of valvular and non-valvular atrial fibrillation with all-cause death or readmission through 60 days

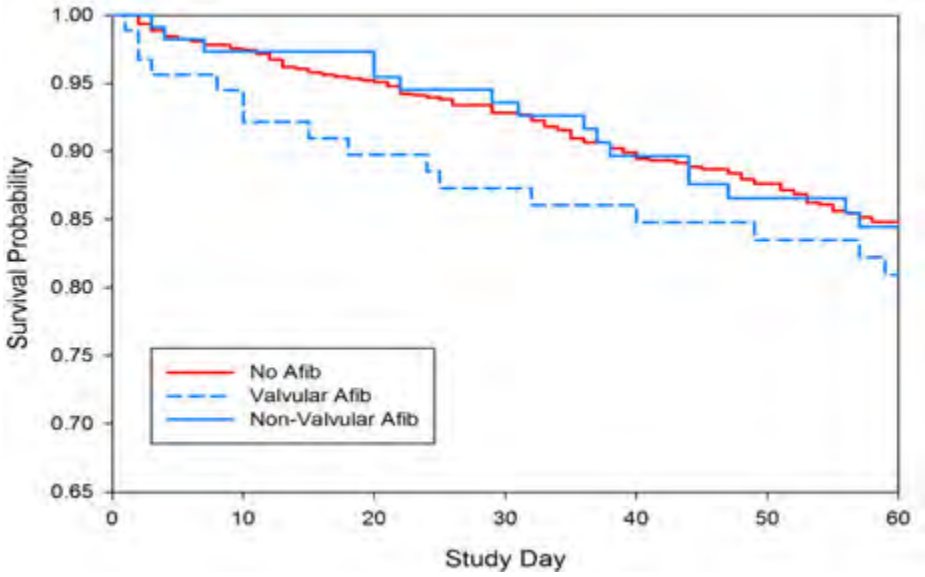
		Unadjusted			Multivariable-adjusted	
Variable	HR for a change of	Hazard ratio 95% CI [1]	P-value		Hazard ratio 95% CI [1]	P-value
Valvular Atrial Fibrillation	**Yes vs. No**	**1.35 (0.80, 2.27)**	**0.2593**		**1.39 (0.80, 2.42)**	**0.2388**
Non-Valvular Atrial Fibrillation	**Yes vs. No**	**0.98 (0.58, 1.65)**	**0.9440**		**0.99 (0.58, 1.68)**	**0.9630**
BUN [2]	Double in BUN	---	---		1.39 (1.17, 1.66)	0.0002
SBP	10 units increase	---	---		0.92 (0.87, 0.98)	0.0050
Malignancy	Yes vs. No	---	---		4.48 (1.96, 10.27)	0.0004
Hx of cor pulmonale	Yes vs. No	---	---		2.03 (1.24, 3.32)	0.0047
Rales	Yes vs. No	---	---		2.12 (1.37, 3.29)	0.0008
Hyperlipidaemia	Yes vs. No	---	---		0.46 (0.19, 1.09)	0.0793
Ejection fraction, % [2]	50 vs. 27	---	---		0.94 (0.72, 1.23)	0.1746

[1] Hazard Ratio from cox regression model

[2] Appropriate transformation used due to the non-linear relationship between predictor and outcome

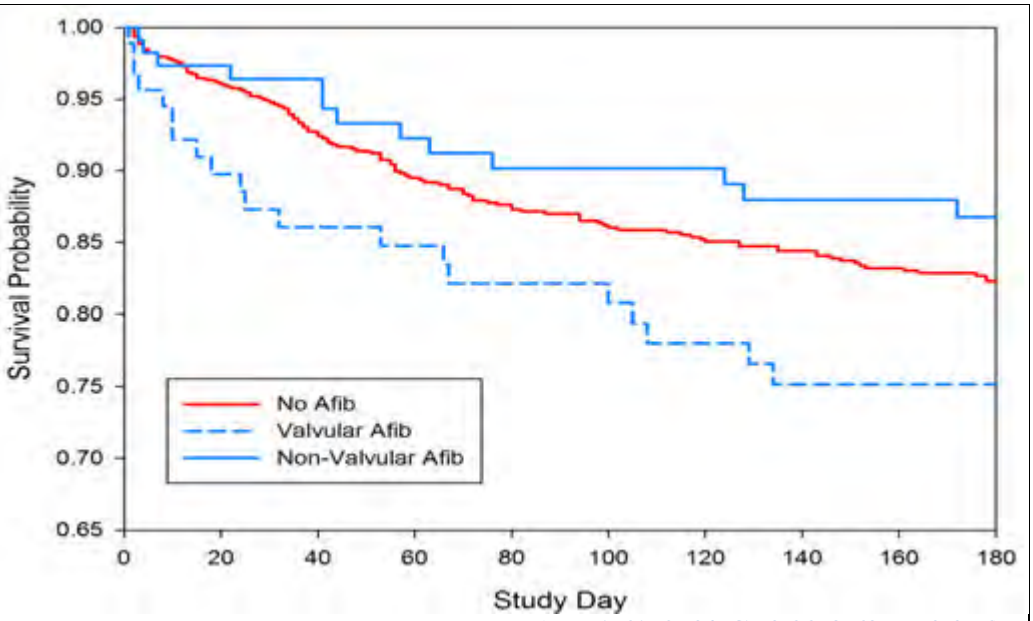
Table 9.6 Associations of valvular and non-valvular atrial fibrillation with all-cause death through 180 days

		Unadjusted			Multivariable-Adjusted	
Variable	HR for a change of	Hazard ratio 95% CI [1]	P-value		Hazard ratio 95% CI [1]	P-value
Valvular Atrial Fibrillation	**Yes vs. No**	**1.61 (1.00, 2.58)**	**0.0475**		**1.61 (0.99, 2.62)**	**0.0563**
Non-Valvular Atrial Fibrillation	**Yes vs. No**	**0.69 (0.39, 1.21)**	**0.1949**		**0.70 (0.39, 1.26)**	**0.2331**
Male sex	Yes vs. No	---	---		1.36 (0.96, 1.92)	0.0859
Hemoglobin, g/dL	1 unit increase	---	---		0.93 (0.87, 1.00)	0.0551
HIV positive	Yes vs. No	---	---		1.82 (1.08, 3.06)	0.0239
Current or former smoker	Yes vs. No	---	---		0.49 (0.24, 0.99)	0.0479
Malignancy	Yes vs. No	---	---		3.05 (1.24, 7.54)	0.0157
Hx of cor pulmonale	Yes vs. No	---	---		2.04 (1.26, 3.30)	0.0038
SBP, mmHg	10 units increase	---	---		0.85 (0.80, 0.90)	<.0001
Orthopnoea	(2/3 vs. 0/1)	---	---		2.32 (1.06, 5.10)	0.0360
Peripheral Oedema	(2/3 vs. 0/1)	---	---		1.76 (1.15, 2.69)	0.0094
Rales	(2/3 vs. 0/1)	---	---		1.71 (1.11, 2.63)	0.0155
Creatinine, mg/dL [2]	1.55 vs. 0.90	---	---		1.37 (1.06, 1.77)	0.0239
[1] Hazard Ratio from cox regression model **[2] Appropriate transformation used due to the non-linear relationship between predictor and outcome**						



(HR 1.39, 95% CI 0.80-2.42, p=0.24)

Figure 9.1 Kaplan Meir Plot: Death or rehospitalization to Day 60.



(HR 1.61, 95% CI 0.99-2.62, p=0.056)

Figure 9.2 Kaplan Meir Plot: Death to day 180.

9.4 Discussion

We found AF to be present in 20.8% of acute HF patients. Forty four percent of the patients with AF had valvular heart disease. Sixty-one percent of the patients with non-valvular AF had hypertension. The presence of AF was not associated with the primary end points, but having valvular AF predicted death through day 180.

To the best of our knowledge, this is the first sub Saharan African study to assess the prevalence and clinical characteristics of AF in patients hospitalized for acute HF. Importantly this study describes an important subpopulation of patients with AF, namely those due to valvular (mostly rheumatic) heart disease, which are still relatively prevalent in sub-Saharan Africa. [97,244,518,321,519]

The prevalence of AF was 21%, which is generally lower than that reported in previous studies, ranging between 23 – 41%.[520-523] Among acutely decompensated HF patients, 20% to 35% will be in AF at presentation. [83] This difference may be due to the fact that in Sub Saharan Africa patients with AHF are younger and have less ischemic heart disease. Indeed in the Heart of Soweto HF cohort, AF occurred in only 6.6% of all 2393 HF cases within the entire study cohort. [518] This however was not in the acute decompensated HF setting.

Rheumatic heart disease is the 3rd commonest cause of HF in the THESUS HF after hypertension idiopathic dilated cardiomyopathy. [36] Almost half of all those with AF in this study had valvular disease compared to 23% in those without AF. Valvular heart disease has long been associated with development of AF. Population based estimates based on Framingham data revealed that valve disease was associated with a 1.8-fold increase of risk of AF in men and a 3.4-fold increased risk in women. [524] Although any

valvular pathology can be related to AF, stenotic left-sided valvular lesions (and in particular rheumatic heart disease) have the highest prevalence rates. Severity of obstruction follows a dose–response relationship: AF prevalence is 9.1% of patients with mild-to-moderate aortic stenosis and 33.7% among those with severe stenosis. [525,526] Likewise, the prevalence of AF varies with the complexity of rheumatic heart disease: from 16% with isolated mitral regurgitation to 29% with isolated mitral stenosis, to 52% with coexisting mitral regurgitation and stenosis, and to 70% with mixed mitral and tricuspid valve disease.[527]

We found low rates of anticoagulation in this cohort. In a prospective study of AF patients in Cameroon, only 34% of patients with an indication for oral anticoagulation received it, [528] similar to 33% of patients with AF received warfarin in the Heart of Soweto study. [518] In this study 52% of our patients with AF received oral anticoagulants. In contrast, a much higher percentage of patients received an anticoagulant in Senegal, where in a retrospective hospital-based study, anticoagulation with warfarin was established in 62% of cases. [529] In the REMEDY registry, [244] 40.7% of patients had indications for oral anticoagulants and they were prescribed in 69.5% of them. The use of oral anticoagulants (OACs) was high in patients with mechanical heart valves (91.6%) and AF (68.6%), but low in those with mitral stenosis in sinus rhythm with either dilated left atrium or left atrial thrombus (20.3%).

A study at a private urban referral teaching hospital in Nairobi, Kenya, found that 80% of patients with AF and a CHADS2 score of 2 received anticoagulation. [530] Similarly, a recent observational multicenter national registry in South Africa indicated that 75% of patients with AF were on warfarin for stroke prevention. [531] We did not collect data on

the quality of anti-coagulation control in this study.

The presence of AF was not associated with all cause death or readmission through 60 days, but having valvular AF predicted death through 180 days. Eapen and colleagues[532] investigated the associations between AF and early outcomes of patients with heart failure. They found AF to be associated with 30-day mortality in patients with preserved EF but not in patients with reduced EF.

Our data should be interpreted in the context of their limitations. The variable timing of the electrocardiogram may have affected the specific results obtained, giving that the ECGs were accepted if they were recorded $\pm$ 2 weeks and not necessarily on admission. Secondly, our results are drawn from a population of young acute HF patients predominantly with systolic dysfunction. Consequently, these findings may not apply to older patients or to those with preserved LVEF. Finally the study was conducted in selected specialized centers, and only patients who consented to the study were enrolled; thus, not all patients admitted with AHF are represented and the study's generalizability may be limited. However, we have increased our understanding of the growing importance of cardiovascular disease in this population, who now suffer from double burden of communicable and non-communicable diseases.

9.5 Conclusion

AF is present in one fifth of sub Saharan African patients with AHF. Almost half of the AF patients have valvular disease (RHD) and are significantly younger. Valvular AF was associated with all-cause death through day 180 but was not a significant predictor of all

cause death or readmission through day 60. The prescription rates of anticoagulation with warfarin were low in this cohort.

10 Chapter 10: NT - Pro BNP and Galectin-3 are Prognostic Biomarkers of Acute Heart failure in sub Saharan Africa: Lessons from the BAHEF Trial.

10.1 Introduction

AHF is a major health issue, accounting for a large proportion of patients admitted to hospitals. Patients with recent hospitalizations for AHF are at high risk for future cardiovascular events and death. [467] African patients with AHF differ from those in the West, in that they are younger in their productive lives, present more acutely, have a more severe disease and higher mortality and have predominantly hypertension and cardiomyopathy rather than ischaemic heart disease. [44,147,171]

BNP and NT Pro BNP are established serum biomarkers for diagnosis and prognosis in acute or chronic HF. [415,426] These peptides have proven utility for confirming the diagnosis of AHF in breathless subjects and are predictive of adverse outcomes. [423] In addition, high levels of natriuretic peptides are associated with recurrent hospitalization and risk of sudden death, [425] and pre discharge BNP level appears to be a strong predictor for identifying subsequent death or hospital admission at 6 months. [426,427]

Gal3 is a novel biomarker that is significantly increased in acute and chronic heart failure, independent of aetiology. [447] While Gal3 shows promise in detecting long-term outcomes, the role of Gal3 levels at admission in diagnosis and early risk stratification in patients with AHFS is undefined. [445,447] Plasma Gal3 appears to be a prognostic marker of HF outcomes such as death and readmissions for HF, [442,443,533,534] and is associated with increased risk for incident HF.[444]

The combination of NT - pro BNP and galectin-3 has also been shown to identify those at greatest death risk among patients with AHF. [442] Patients with the highest quartile of both biomarkers had mortality rates as high as 15% within 10 days of presentation, and twice the 30-day mortality rate versus the cohort with both markers being low.[442]

To the best of our knowledge, the relationship between NT-Pro BNP and galectin 3 and outcome has not been studied in SSA patients with AHF. From pre-specified secondary analyses of the BA-HEF study, which included assays of these biomarkers as part of patients' evaluation and follow up, we set out to describe the association between plasma levels of NT-Pro BNP and galectin 3 and outcomes (CV death or HF hospitalization) through week 24. We also aimed to identify the association between the plasma levels of these biomarkers and LVEF, LVEDD, LVESD, which are markers of LV remodeling; as well as TAPSE, a marker of RV remodeling, in this cohort of AHF patients.

10.2 Methods

The BAHEF study[466] was a prospective, randomized, double-blind, placebo controlled trial comparing the combination of isorsobide dinitrate and hydralazine (HYIS) with placebo. The study aimed to recruit a total of 500 patients from countries in the southern, eastern, central and western regions of sub-Saharan Africa. The rationale and design of BAHEF as well as the details of data collection have been previously described in chapter 3.

10.2.1 Statistical Analysis

The analysis population has been restricted to subjects with available biomarker data and further excluding data from one site in Senegal where major protocol non-compliance had been observed through the course of the BA-HEF study.

Summary statistics for continuous variables may include the number of non-missing observations, mean and standard deviation (SD), median, first and third quartile (Q1, Q3), minimum and maximum, as appropriate. Categorical variables are presented with absolute and/or relative frequencies (percentages). Relative frequencies are based on all non-missing observations for the corresponding variable if not stated otherwise. The summary statistics of the biomarker parameters additionally include the geometric mean and its corresponding 95% confidence interval (CI).

Missing values for the six-minute walk test distance, and for dyspnea and general well-being VAS were imputed by linear interpolation between non-missing observations at the closest visit before and after the missing value occurred. For subjects who died, values at visits following a death were imputed as zero for six-minute walk test distance and as the worst observed value for dyspnea or general well-being VAS. For echocardiographic parameters values following a death were imputed as baseline plus or minus the worst observed change from baseline across all subjects. Clinically implausible values of TAPSE above 50mm have been set to missing for the statistical analysis. Biomarker values below the limit of detection (LOD) have been replaced by 0.5*LOD, and values above the upper limit of quantification (ULOQ) have been replaced by 1.5*ULOQ.

Analysis of Covariance (ANCOVA) methods have been applied to evaluate treatment differences for changes from baseline with treatment effect adjusted for the corresponding baseline values. Results are presented as least square mean differences with 95% CIs and p-value. For the biomarker parameters, ANCOVA was applied on log-transformed values with adjustment for log-transformed baseline values. The resulting

treatment difference is presented as the ratio of the baseline adjusted geometric means with corresponding 95% CIs.

Baseline biomarker values and changes from baseline have been further evaluated for their association with cardiovascular death or rehospitalization for heart failure through week 24 and with cardiovascular death through week 24 as well as with selected echocardiographic parameters. These associations were evaluated by fitting Cox proportional hazards models and presenting hazard ratios, 95% CIs, and p-values. In addition, number of events and the Kaplan-Meier estimate of the event rate are presented for each time-to-event endpoint. For change from week 24 to baseline for six-minute walk test distance, dyspnea VAS, LVEF, LVEDD, LVESD, and TAPSE, linear regression models have been applied to evaluate the association with baseline values as well as with change at week 24 for the two biomarkers. Models evaluating the association with change from baseline have been adjusted for the baseline values of the respective biomarker. Effect sizes are presented as mean differences with 95% CIs and p-values.

All statistical analyses have been performed using SAS® 9.3 (SAS Institute, Inc., Cary, NC, USA).

10.3 Results

The BAHEF trial screened 619 patients from nine centres in 6 African countries (Mozambique, South Africa, Nigeria, Kenya, Uganda and Senegal). Data for 14 randomized patients from one center in Senegal were excluded due to non-compliance with the protocol. Subsequently 133 patients were randomized at the remaining eight centers. The primary reasons for exclusion from the study were (1) lack of test results, e.g., echo or laboratory, available within 96 hours of admission, (2) kidney function too

poor, (3) lack of background treatment with ACEI and/or beta-blocker, and (4) liver function too poor (5) Not eligible due to low blood pressure.

Of the 133 patients randomized, 80 had complete data for biomarkers available for analysis and their baseline characteristics are outlined in Table 10.1. Demographic characteristics of the patients were similar across participating countries. The randomization was blocked by study center. Thus, randomization to the two study arms was balanced within country

Table 10.1 Baseline characteristics of the study population (restricted to biomarker sub set)

Characteristic	Statistic	Overall (N=83)
Age, years	Mean (SD)	53.1 (15.79)
Male sex	%	48.2
Weight, kg	Mean (SD)	76.5 (18.90)
Primary cause of Heart Failure		
Ischemic heart disease	%	4.9
Hypertension	%	65.9
Idiopathic	%	15.9
Valvular Cause	%	1.2
NYHA Class, Screening		
I	%	2.0
II	%	22.4
III	%	53.1
IV	%	22.4
Diabetes	%	9.8
Atrial Fibrillation	%	10.0
Ejection Fraction, Screening	Mean (SD)	24.5(9.87)
LVIDD, cm Screening	Mean (SD)	6.3 (1.1)
Blood pressure		
Systolic	Mean (SD)	132.9 (17.55)
Diastolic	Mean (SD)	87.5 (13.34)
Medication for heart failure		
Diuretic	%	80.0
ACE inhibitor	%	91.3
ARB	%	3.8
Beta Blocker	%	28.8
Carvedilol	%	16.3

Digoxin	%	17.5
Spironolactone	%	10.0
Race		
African or Black	%	74.4
Colored or mixed race	%	23.1
Caucasian or White	%	2.6
Time from presentation to randomization (Hours)	Mean (SD)	63.6 (27.40)

The mean age of the group (restricted biomarker sub set) was 53.1 ± 15.8 years, with 51.8% being females. Seventy four percent were African/Black and 23.15 were coloured or mixed race. The mean period from admission to randomization was 63. 6 ± 27.4 hours. Most of the patients had hypertension (65.9%) and idiopathic dilated cardiomyopathy (15.9%), while ischemic heart disease was present in only 4.9%. Most patients (75.5%) also are in NYHA functional class III and IV. Baseline characteristics were similar in the active and the placebo groups. [466]

The mean LVEF at baseline for the overall group was 24.0 % with no difference between those on HYIS and placebo (Table 10.2). The baseline mean LVEDD was 62.7 ± 8.84 mm while the change from baseline to week 24 was -0.1 ± 10.6 mm. For the LVESD, the mean was 55.8 ± 9.0 mm with a mean change from baseline to week 24 of -6.0 ± 9.51 mm. The mean TAPSE at baseline was 20.9 ± 5.61 with a mean change between baseline and week 24 of 0.3 ± 10.31. There was no difference between HYIS and placebo in terms of change from baseline to week 24 for LVEF, LVEDD, LVESD and TAPSE (Table 10.2).

Table 10.2 Changes from baseline to week 24 in echocardiographic parameter - imputed full analysis set (restricted to biomarker sub set)

Measure	Statistic	Placebo (n=41)	HYIS (n=42)	Overall (n=83)	LS mean difference (95% CI)	P-value
LV Ejection Fraction, %						
Baseline	Mean (SD)	23.3 (8.19)	24.8 (11.13)	24.0 (9.76)		
	Median (Q1, Q3)	24.0 (19.0, 29.0)	24.0 (15.0, 34.0)	24.0 (17.5, 32.0)		
Change to week 24	Mean (SD)	12.7 (14.16)	11.6 (14.89)	12.1 (14.45)	- 0.7 (-7.0, 5.6)	0.8330
	Median (Q1, Q3)	11.0 (4.0, 25.9)	13.0 (0.0, 23.0)	13.0 (0.0, 24.0)		
Left Ventricular End Diastolic Diameter, mm						
Baseline	Mean (SD)	62.7 (9.59)	62.8 (8.16)	62.7 (8.84)		
	Median (Q1, Q3)	62.0 (57.0, 69.7)	62.2 (56.0, 69.0)	62.0 (57.0, 69.7)		
Change to week 24	Mean (SD)	0.8 (9.42)	-1.1 (11.67)	-0.1 (10.60)	-1.9 (-6.4, 2.6)	0.3970
	Median (Q1, Q3)	0.0 (-5.0, 5.0)	-1.1 (-8.0, 1.0)	0.0 (-6.0, 3.5)		
Left Ventricular End Systolic Diameter, mm						
Baseline	Mean (SD)	56.3 (8.77)	55.4 (9.38)	55.8 (9.03)		
	Median (Q1, Q3)	55.5 (50.0, 62.3)	56.0 (46.0, 64.0)	56.0 (48.0, 63.0)		
Change to week 24	Mean (SD)	-4.6 (8.62)	-7.5 (10.24)	-6.0 (9.51)	-3.0 (-7.2, 1.3)	0.1684

	Median (Q1, Q3)	-5.0 (-10.5, 0.9)	-6.0 (-14.0, -1.0)	-6.0 (-13.0, 0.0)		
Tricuspid Annular Systolic Excursion, mm						
Baseline	Mean (SD)	20.7 (5.86)	21.1 (5.52)	20.9 (5.61)		
	Median (Q1, Q3)	19.0 (17.0, 24.0)	22.3 (18.0, 25.4)	20.7 (17.5, 25.0)		
Change to week 24	Mean (SD)	1.4 (8.30)	-0.6 (11.83)	0.3 (10.31)	-1.8 (-8.4, 4.8)	0.5847
	Median (Q1, Q3)	5.0 (0.0, 7.0)	0.0 (-0.4, 3.0)	0.0 (0.0, 6.5)		

Table 10.3 shows the biomarker levels and their change from baseline to follow up by treatment. The mean baseline NT- pro BNP was 3771.13 $\pm$ 2829.66 pmol/L dropping down to 1328.47 $\pm$ 1369.19 pmol/L by week 24. The mean change in NT Pro BNP from baseline to week 24 was - 2258.83 $\pm$ 2487.88 with no difference between HYIS and placebo ($p = 0.6425$). For galectin-3, the mean at baseline was 8.26 $\pm$ 7.68 ng/mL and came down to 6.18 $\pm$ 6.03 by week 24 of follow up. The mean change in galectin-3 level was -0.72 $\pm$ 7.13, also with no difference between HYIS and placebo ($p= 0.6997$).

Table 10.3 Changes in biomarkers from baseline to follow up by treatment - full analysis (restricted to biomarker sub set)

Measure	Statistic	Placebo (n=41)	HYIS (n=42)	Overall (n=83)	Model-adjusted treatment difference (95% CI)	P-value
NT Pro BNP pmol/L						
Baseline	N	39	41	80		
	Mean (SD)	4318.41 (2926.860)	3250.55 (2665.675)	3771.13 (2829.664)		
	Median	3476.00	2158.50	2882.25		
	Q1, Q3	2149.00, 6052.00	1246.00, 4461.00	1621.75, 4822.50		
	Min, Max	358.5, 9600.0	430.5, 9600.0	358.5, 9600.0		
	Geom. Mean	3332.18	2303.24	2757.58		
	95% CI of GM	2579.71, 4304.14	1742.88, 3043.76	2280.28, 3334.79		
	n (%) < LOD (171 pmol/L) [1]	0 (0%)	0 (0%)	0 (0%)		
	n (%) > ULOQ (6400 pmol/L) [1]	7 (17.9%)	4 (9.8%)	11 (13.8%)		
Follow up	N	32	34	66		
	Mean (SD)	1502.28 (1591.879)	1164.88 (1120.362)	1328.47 (1369.194)		
	Median	744.75	753.00	744.75		
	Q1, Q3	461.75, 1861.50	397.50, 1815.50	433.50, 1815.50		
	Min, Max	211.5, 6314.5	85.5, 4599.5	85.5, 6314.5		
	Geom. Mean	962.06	775.54	860.96		
	95% CI of GM	686.38, 1348.47	560.14, 1073.76	684.41, 1083.06		
	n (%) < LOD (171 pmol/L) [1]	0 (0%)	1 (2.9%)	1 (1.5%)		
	n (%) > ULOQ (6400 pmol/L) [1]	0 (0%)	0 (0%)	0 (0%)		
Change to week 24	N	30	33	63	1.10 (0.73, 1.66)	0.6425
	Mean (SD)	-2697.75 (2476.963)	-1859.82 (2467.246)	-2258.83 (2487.881)		
	Median	-2127.50	-983.00	-1472.00		

	Q1, Q3	-3615.00, -1097.00	-2450.00, -286.50	-3144.00, -513.50		
	Min, Max	-9009.0, 717.5	-8712.0, 287.5	-9009.0, 717.5		
	Geom. Mean	0.28	0.37	0.33		
	95% CI of GM	0.21, 0.39	0.28, 0.49	0.26, 0.40		
Galactin 3 ng/mL						
Baseline	N	39	41	80		
	Mean (SD)	7.42 (4.628)	9.06 (9.737)	8.26 (7.680)		
	Median	5.88	5.72	5.80		
	Q1, Q3	3.94, 10.20	3.70, 9.07	3.71, 9.65		
	Min, Max	1.8, 24.1	1.9, 45.0	1.8, 45.0		
	Geom. Mean	6.23	6.47	6.35		
	95% CI of GM	5.12, 7.58	5.09, 8.22	5.45, 7.40		
	n (%) < LOD (0.29 ng/mL) [1]	0 (0%)	0 (0%)	0 (0%)		
	n (%) > ULOQ (30 ng/mL) [1]	0 (0%)	2 (4.9%)	2 (2.5%)		
Follow Up	N	32	33	65		
	Mean (SD)	6.50 (7.910)	5.88 (3.449)	6.18 (6.030)		
	Median	4.34	4.82	4.66		
	Q1, Q3	3.06, 6.95	3.62, 6.64	3.40, 6.77		
	Min, Max	2.1, 45.0	2.4, 17.9	2.1, 45.0		
	Geom. Mean	4.84	5.18	5.01		
	95% CI of GM	3.82, 6.14	4.37, 6.15	4.35, 5.78		
	n (%) < LOD (0.29 ng/mL) [1]	0 (0%)	0 (0%)	0 (0%)		
	n (%) > ULOQ (30 ng/mL) [1]	1 (3.1%)	0 (0%)	1 (1.5%)		
Change to week 24	N	30	32	62	1.05 (0.81, 1.36)	0.6997
	Mean (SD)	0.20 (6.696)	-1.59 (7.505)	-0.72 (7.125)		
	Median	-0.36	-0.28	-0.28		
	Q1, Q3	-3.06, 0.99	-1.60, 1.17	-2.78, 0.99		
	Min, Max	-12.0, 26.1	-39.0, 9.4	-39.0, 26.1		
	Geom. Mean	0.91	0.93	0.92		
	95% CI of GM	0.72, 1.16	0.76, 1.15	0.79, 1.08		

The total number of CV death or HF hospitalization through 24 weeks was 9/80 (11.6%) while CV deaths through week 24 was 5/80 (6.8%). Using fitting Cox proportional hazards models, the associations of baseline biomarker values and changes at week 24 with cardiovascular death or hospitalization for heart failure and with cardiovascular death are shown on Table 10.4. Both NT- pro BNP and galectin 3 at baseline predicted combined CV death or HF hospitalization through week 24 (p values = 0.0328 and 0.0001 respectively) but only galectin 3 at baseline predicted CV death through week 24 (P = 0.0042). Gal3 at baseline also strongly predicted Dyspnea VAS change week 24 to baseline using linear regression models.

Table 10.4 Associations of biomarker baseline values and changes at week 24 with primary end points

Outcome [1]	Covariate	Effect size for a change of	Effect size (95% CI)	P-value	No. events (KM rate)
CV death or HF hospitalization through week 24	NT Pro BNP at baseline	Doubling	2.12 (1.06, 4.22)	0.0328	9/80 (11.6%)
	Galectin-3 at baseline	Doubling	2.81 (1.65, 4.79)	0.0001	9/80 (11.6%)
CV death through week 24	NT Pro BNP at baseline	Doubling	2.21 (0.85, 5.71)	0.1027	5/80 (6.8%)
	Galectin-3 at baseline	Doubling	2.84 (1.39, 5.79)	0.0042	5/80 (6.8%)
6MWT change week 24 to baseline (imputed)	NT Pro BNP at baseline	Doubling	10.78 (-11.86, 33.43)	0.3538	
	NT Pro BNP ratio week 24 to baseline	Doubling	-14.91 (-34.60, 4.77)	0.1431	
	Galectin-3 at baseline	Doubling	-26.01 (-54.27, 2.25)	0.0754	
	Galectin-3 ratio week 24 to baseline	Doubling	-16.34 (-43.50, 10.82)	0.2433	
Dyspnea VAS change week 24 to baseline (imputed)	NT Pro BNP at baseline	Doubling	-2.27 (-7.65, 3.12)	0.4119	
	NT Pro BNP ratio week 24 to baseline	Doubling	-3.42 (-6.01, -0.82)	0.0122	
	Galectin-3 at baseline	Doubling	-14.01 (-19.94, -8.08)	<.0001	
	Galectin-3 ratio week 24 to baseline	Doubling	0.36 (-3.53, 4.24)	0.8583	

[1] Effect sizes shown are hazard ratios for time-to-event outcomes and mean differences for continuous outcomes. In case of continuous outcomes, estimates have been adjusted for the respective baseline value.

For LVEF, LVEDD, LVESD, and TAPSE, linear regression models were applied to evaluate the association with baseline values as well as with change at week 24 for the two biomarkers (Table 10.5). Models evaluating the association with change from baseline have been adjusted for the baseline values of the respective biomarker. While NT Pro BNP at baseline only predicted change (week 24 to baseline) in LVEDD, Gal3 at baseline predicted changes (week 24 to baseline) in all the tested markers of LV remodeling (LVEF, LVEDD, LVESD) and RV remodeling (TAPSE).

Table 10.5 Association of biomarker baseline values and changes at week 24 with echocardiographic parameters

Outcome [1]	Covariate	Effect size for a change of	Effect size (95% CI)	P-value
LVEF change week 24 to baseline (imputed)	BNP at baseline	Doubling	-2.58 (-5.22, 0.06)	0.0589
	BNP ratio week 24 to baseline	Doubling	-1.34 (-3.76, 1.08)	0.2811
	Galectin-3 at baseline	Doubling	-5.15 (-8.19, -2.10)	0.0014
	Galectin-3 ratio week 24 to baseline	Doubling	0.04 (-3.48, 3.57)	0.9807
LVEDD change week 24 to baseline (imputed)	BNP at baseline	Doubling	2.74 (0.94, 4.53)	0.0038
	BNP ratio week 24 to baseline	Doubling	0.07 (-1.70, 1.85)	0.9359
	Galectin-3 at baseline	Doubling	4.95 (2.88, 7.02)	<.0001
	Galectin-3 ratio week 24 to baseline	Doubling	0.21 (-2.30, 2.71)	0.8719
LVESD change week 24 to baseline (imputed)	BNP at baseline	Doubling	1.62 (-0.17, 3.41)	0.0795
	BNP ratio week 24 to baseline	Doubling	-0.57 (-2.33, 1.18)	0.5251
	Galectin-3 at baseline	Doubling	3.51 (1.41, 5.61)	0.0016
	Galectin-3 ratio week 24 to baseline	Doubling	-1.11 (-3.49, 1.27)	0.3633
TAPSE change week 24 to baseline (imputed)	BNP at baseline	Doubling	-0.95 (-3.73, 1.82)	0.5049
	BNP ratio week 24 to baseline	Doubling	-0.54 (-2.23, 1.15)	0.5365
	Galectin-3 at baseline	Doubling	-5.00 (-7.63, -2.38)	0.0007
	Galectin-3 ratio week 24 to baseline	Doubling	-0.61 (-2.75, 1.53)	0.5802

[1] Effect sizes shown are mean differences for continuous outcomes. Estimates have been adjust ed for the respective baseline value

10.4 Discussion

The BAHEF study showed that in sub-Saharan Africa, HF affects men and women who are relatively young (mid fifties) and is mostly caused by hypertension and not ischaemic heart disease, as is seen in Western countries. [83] Similar findings were recently reported in the sub-Saharan Africa Survey of Heart Failure (THESUS-HF) registry. [36] Both studies showed that these patients had predominantly systolic dysfunction and low incidence of atrial fibrillation.

Overall, the BAHEF study did not achieve its primary end point mainly due to poor recruitment rate; only 21.5% of screened patients were eligible for entry into the study, which reflects the difficulty of recruiting patients for AHF trials in general. The various reasons for the poor recruitment into this study have already been enumerated and were mostly due to renal and hepatic dysfunction, low blood pressure and procedural difficulties. [466]

The African-American Heart Failure Trial (A-HeFT) [465] was similar to BAHEF study but focused on chronic HF instead of AHF. Despite the difference in the study population, the mean ages of the patients were similar, both for the overall BAHEF patients and for the restricted biomarker sub set group. They both had similar mean LVEF of 24% and had most of the patients in NYHA functional class III and IV. The mean LVEDD at recruitment was 62.7 $\pm$ 8.8 mm, similar to 65 $\pm$ 9mm in A-HeFT trial. However, the A-HeFT patients had less hypertension, higher incidence of DM and IHD as compared to BA-HEF.

We studied the relationship between NT pro BNP and galectin 3 and outcomes in this

cohort. We are not aware of similar study from sub Saharan Africa. We found both NT pro BNP and galectin 3 at baseline to predict the combined outcome of CV death or HF hospitalization through week 24, with galectin-3 more predictive than NT-Pro BNP (p values = 0.0001 and 0.0328 respectively). When the outcome of CV death alone was assessed, only galectin 3 at baseline predicted it through week 24 (P = 0.0042). This is similar to the findings in the PRIDE study. [442] They have shown that serum galectin-3 levels were elevated in patients with acute HF, and are prognostic of adverse outcomes over a 60-day period after presentation. Similar to our study, they also showed that galectin-3 was able to identify those HF patients at risk for short-term death or the combination of death or readmission within 60 days better than NT-pro BNP. [442] In a meta-analysis of three studies and 893 patients, mentioned in chapter 1 (under diagnosis of AHF), DeBoer[446] reported that patients with elevated galectin-3 above 17.8 ng/ml were nearly three times as likely to suffer short-term re-hospitalization (odds ratio 2.80, 95% CI 1.41–5.57, and 3.01, 95% CI 1.79–5.05, for 30- and 90-day readmissions, respectively). Also, baseline Gal3 was a predictor of re-hospitalization even after adjustment for age, gender, estimated glomerular filtration rates, NYHA functional class, LVEF and NT-pro BNP levels. The authors of this meta-analysis concluded that in acute HF, an elevated galectin-3 during an emergency department (ED) visits, hospital admission, or at hospital discharge is independently associated with early HF readmission. These findings are of clinical significance because the results of these studies suggest that galectin-3 may identify AHF patients with elevated risk for death and re-hospitalization independent of the severity of signs and symptoms at presentation.

Identification of those AHF patients at highest risk by combined assessment of serum

markers may help to tailor the most appropriate treatment strategy on a more individualized basis.

Gal3 at baseline also strongly predicted dyspnea VAS change week 24 to baseline using linear regression models in this study. In a study of 115 consecutive patients with acute dyspnoea, Shah and colleagues[443] found that dyspnoeic patients with HF and Gal3 concentrations higher than the median value of 15.0 (11.1—19.7) had a 63% 4-year mortality rate; compared to patients with concentrations lower than 11.0(9.1—14.4) who had a 37% mortality rate ($P = 0.003$).

Gal3 has been shown that cardiac macrophages are activated at an early stage in failure-prone, hypertrophied hearts and that these macrophages express Gal3. [440] It has been recently identified to be involved in the pathophysiology of HF through mediation of myocardial fibrosis and inflammation, contributing to myocardial remodeling. [533] Given mechanistic data in animal models implicating galectin-3 in cardiac remodelling and LV dysfunction, identifying associations between galectin-3 levels and cardiac structure and function is critically important. Because, measurement of galectin -3 is readily feasible and reliable in stored plasma, and its value in diagnosis and prognostication of AHF patients, it becomes an important biomarker in the management of AHF patients.

In this study we examined the associations between biomarker levels and cardiac structure and function through markers of LV and RV remodeling. While NT Pro BNP at baseline only predicted change (week 24 to baseline) in LVEDD, Galactin-3 at baseline predicted changes (week 24 to baseline) in all the tested markers of LV remodeling (LVEF, LVEDD, LVESD) and RV remodeling (TAPSE). In a study of hypertensive

African subjects, Ojji and colleagues showed that NT-pro BNP was significantly associated with LVEF ($p = 0.01$) but not with TAPSE.[535]

They also found that NT-pro BNP concentrations were not associated with LV mass index, interventricular septal wall thickness or posterior wall thickness in diastole, which is similar to findings of other workers. [536]

In the PRIDE study sub analysis, [443] to determine relationships between galectin-3 levels and cardiac structure, the authors showed that galectin-3 levels were significantly associated with echocardiographic markers of LV filling and diastolic function and valvular regurgitation. Similar to our study, they also observed significant association between Gal3 and poor RV systolic function (as reflected in fractional area change). In this study we used TAPSE to assess RV systolic dysfunction. Poor RV systolic function in AHF may reflect elevated LV filling pressures; thus, the association between galectin-3 levels and markers of poor RV performance reflect similar associations between galectin-3 and elevated left sided pressures. It is also possible that similar processes occurring in the LV (remodeling, fibrosis, and hypertrophy) may be occurring in the RV. Indeed the role of RV structure and function in short and longer term outcomes as well as remodeling in AHF is underappreciated, and our findings underscores the need for further research to determine the importance of the RV in AHF.

We suggest that our results provide bases for confirmation through a much bigger study on the role of these biomarkers in sub Saharan African patients with AHF. Development of bedside kits for NT Pro BNP and galectin -3 for risk stratification and referral to appropriate facility for immediate care will go along way in improving morbidity and mortality in this patients, especially in Africa where resources are scarce.

This sub study shares the same limitations with the overall BA-HEF study. [466] In addition and specific to biomarker analysis, the relatively small number of patients, with relatively limited numbers of events, may be a limitation, as a larger cohort would allow for increased scrutiny of short term outcomes. Because lack of complete data we were unable to assess the relationship of these biomarkers with LV diastolic function. Finally, patients were enrolled based on admission diagnosis and treatment for AHF. While this is highly representative of clinical practice, bias may have been introduced in those patients where AHF was incorrectly diagnosed, as galectin-3 is known to be elevated in other causes of acute dyspnoea.[537]

10.5 Conclusions

In conclusion, we have shown that in sub Saharan African patients with AHF, both NT pro BNP and Gal3 at baseline predicted combined CV death or HF hospitalization.. For cardiac remodeling, galectin-3 at baseline predicted changes (week 24 to baseline) in all the tested markers of LV remodeling and RV remodeling, whereas NT-Pro BNP at baseline which only predicted change (week 24 to baseline) in LVEDD. Galectin-3 provided important and significant prognostic value in identifying patients with AHF at elevated risk for subsequent HF morbidity and mortality.

11 Chapter 11: Conclusions and Future Perspective

11.1 Introduction

There is limited reliable information regarding causes, progression, treatment options and outcomes for patients with AHF in SSA. Because the various disease conditions that cause heart failure are prevalent in the region, knowledge of the profile of patients and distribution of the various aetiologies and outcomes of AHF patients in this part of the world is urgently needed. In addition, not much is known about the role of the conventional and novel biomarkers in the prognostication of these patients in SSA.

For SSA with limited available manpower and resources, one of the best ways to address the gap in knowledge on AHF was to have well-designed and managed clinical registry. Clinical registries provide reliable data about cohorts of patients who are likely to be a subset of a larger population with similar disease patterns as well as opportunities for physicians and scientists at large to generate knowledge about the current epidemiology, actual course and therapies of diseases in the context of their local health care system. This information is crucial for an objective estimation of the future health care needs and expenditures. [538] They also form the basis of hypothesis formulation for further investigation by clinical trials. For all these reasons, a clinical registry of AHF in SSA, the THESUS-HF registry was established. The results of THESUS-HF revealed among other things that despite the encouraging results of A-HeFT trial, [465] the patients in SSA are rarely treated with a combination of hydralazine and nitrates. This information formed the bases for the RCT (BAHEF) [466] which investigated the combination treatment of hydralazine and nitrates (HYIS) vs. placebo in sub Saharan Africans admitted with AHF.

In this doctoral work, we sought to address the several gaps in the knowledge about AHF in SSA using a clinical registry (THESUS-HF) and an RCT (BAHEF). The main findings of our investigations are summarized in the following sections below. We also speculate future research directions based on our findings.

11.2 The demographic and clinical characteristics of patients with AHF.

Results from both the THESUS registry and BAHEF study (chapter 4) have demonstrated that AHF in SSA affects young men and women in their early fifties, predominantly of black race. The aetiologies are mainly hypertension, idiopathic dilated cardiomyopathy and rheumatic valvular heart disease. HIV infection is as yet not a significant cause of AHF in SSA, despite high prevalence of the disease in the continent. Unlike the western population, ischemic heart disease was responsible for only a small percentage of AHF.

Most of the patients present late in NYHA functional class III or IV had significant co-morbidities, high readmission rates and mortality. In addition the data from THESUS – HF showed a high incidence of the use of aspirin in patients with non-ischemic HF, low rates of use of beta-blockers and combination of hydralazine and nitrates.

The findings in THESUS-HF tally with the results of previous smaller studies conducted in individual SSA countries. The difference however is that this is a much larger, wider study and this therefore makes the findings more credible than the previous smaller studies. In view of the credibility of the results of this study, it should be able to spur participating and non-participating countries to take appropriate action to prevent the emergence of some of the cardiovascular diseases in their countries as their economies improve. For example, measures to reduce cigarette smoking, obesity, sedentary habits and hyperlipidaemias should be incorporated into the health prevention strategies of all

SSA countries. The same goes with the establishment of national programmes to control hypertension and diabetes mellitus, two diseases that are able to increase the prevalence of ischaemic heart disease in the countries.

While the experience from THESUS -HF highlights the potential of generating accurate and reliable data on AHF and its aetiologies in SSA, the BAHEF study experience revealed the challenges of carrying an RCT in SSA. As outlined in chapter 3, this thesis is only concerned with the demography and clinical characteristics as well as the biomarker aspects of the BAHEF study. The details of the BAHEF study are not part of this work.

The findings from these 2 studies are needed to assist policy makers to plan health care priorities in the region.

Future perspective in terms of research on the epidemiology and treatment of AHF in SSA should study larger samples of AHF and focus more research on the emerging causes of AHF (hypertension and ischaemic heart disease) as well as HIV because of its importance in the region.

i. Hypertensive heart failure: There is currently an unmet critical need in HHF to design and conduct an African, hospital-based registries to better understand this heterogeneous patient population, inform public policy decisions, and guide basic, translational, and clinical research. [539] This kind of registry should capture comprehensive and longitudinal data including hospital course and post-discharge outcomes over long period of time. Future studies should also incorporate quality improvement initiatives focusing on continuity of care from initial presentation to the early post-discharge vulnerable period. In addition to traditional endpoints (i.e., hospitalization and mortality), patient-centered

outcomes should be designed that comprehensively and longitudinally capture the burden of worsening HF (i.e., quality of life impairments and functional limitations). [539] In addition, most AHF patients present to the ED. Conduct of such studies requires the ED has an appropriate infrastructure and of teams of qualified investigators and research coordinators capable of screening and randomizing patients in early AHFS stages, similar to models of thrombolytic therapy trials for acute MI. [71] There is need for extensive investment in research facilities in most African countries to allow conduct of RCTs on NCDs, including AHF.[466]

Results from epidemiological studies and animal research suggest that it may be possible to prevent or significantly delay many of the morbid events associated with hypertension (including HF) if susceptible individuals can be identified early enough in life. [540] In a recent doctoral thesis conducted at the University of Cape Town, D.B Ojji, [541] showed that the novel serum biomarker soluble ST2 differentiates hypertensives without LVH from those with LVH and hypertensives with LVH from hypertensive HF. This suggests that serum soluble ST2 may have the potential of predicting who develops HF among hypertensive patients. It is therefore important to note that although markers for early detection remain a challenge, efforts should be made to explore combinations of genotypic, biochemical, and physiological approaches to define and stratify the population at risk. [540] In addition, understanding prehypertension and its early markers that establish a biological risk of developing hypertension and target organ damage is an important research area.

ii. Ischaemic heart disease: As discussed in chapter 1, studies from many urban areas in sub-Saharan Africa suggest a pattern of adverse lifestyle choices and health behaviours

that are now leading to a rising prevalence of the major coronary risk factors. [277] There is also increase in urbanization leading to concomitant rise in the prevalence of hypertension, diabetes and dyslipidaemia, which are important risk factors of ischaemic heart disease. [278] At the same time many studies from SSA suggest that the unadjusted rates of myocardial infarction and heart failure related to ischemic heart disease remain low, particularly among the black African majority population on the continent. In most of the reports on IHD from SSA coronary angiographies were not done. It is of paramount importance to establish the true prevalence of, as well as the patients' characteristics and outcomes in IHD using appropriate methods that will include coronary angiography or highly sensitive biomarkers. Equally important, the current epidemiology of IHD in SSA provides an opportunity to conduct public health research on primary and secondary prevention policies as well as cost effective treatments on IHD. [288] This should be spearheaded by pan African organisations.

As their economies grow the countries need not go the way of Europe and America health wise. This is the one of core messages from these studies to all the health planners and health executors in all the SSA countries. Ischaemic heart disease must be prevented from becoming an epidemic in all the SSA countries as it presently is in developed countries for the simple reason that most SSA countries lack the resources and personnel required to handle the disease effectively should its prevalence continue to increase. It is therefore imperative that the prevalence of the disease is kept as low as possible in all African countries.

iii. All the three major cardiac manifestations of HIV, namely; HIVAC, pericardial disease and PH can cause heart failure. HIVAC portends a particularly poor prognosis. [253]

in addition, a growing prevalence of asymptomatic ventricular dysfunction, abnormal strain patterns, and a higher incidence of diastolic dysfunction is now seen in up to 64%of asymptomatic HIV-infected patients on ART. [542] There are significant knowledge gaps in HIV related heart disease in Africa. First, more research is needed to understand best practices in diagnosis and treating HIVAC in SSA. Second, while an inverse correlation between BNP levels and left ventricular function in HIV-infected patients has been seen in small case studies, [543] the specificity of BNP for cardiac disease in HIV-infected individuals is unclear. [544] There is need to investigate whether this cost-effective and simple test may be a useful screening tool for identifying HIVAC. Although soluble ST2 and GDF-15 have recently been associated with cardiac dysfunction and all-cause mortality in a controlled study of HIV infected patients, [545] it will be interesting to assess their role in diagnosis and prognostication of HIVAC in SSA. Similarly, it would be relevant to explore the combined diagnostic utility of all non-invasive tests including ECG, biomarkers and echocardiography to correctly identify or exclude HIV related PH. Considering the epidemiological significance of cardiac abnormalities in HIV infected individuals and the lack of definitive data on treatment for these patients, further research on this is also urgently needed, particularly in SSA.

11.3 Predictors of outcomes of AHF

We have enumerated in chapter 1 that AHF is a complex disease and its pathophysiology poorly understood. This, together with the lack of understanding of the predictors of outcome in AHF are responsible for the lack of progress in its treatment with available therapies (diuretics and nitrates), such that outcomes have been largely unchanged over the last 30–40 years. [546] To address this question, we investigated the predictors of short-

term outcomes in patients with AHF from the multicentre THESUS – HF registry. Interestingly, we found that despite the differences in age and disease characteristics, the main predictors for 6 months mortality and combined 60 days re-admission and death are largely similar in sub-Saharan Africa as in the rest of the world, with some exceptions such as the association of the HIV status with mortality (chapter 5). We also found simple assessments including edema, rales, oxygen saturation, and respiratory rate and asking the patient about general well-being are a valuable tools in predicting outcome (chapter 6). When we looked at the echocardiographic predictors of outcome (chapter 7), we found left atrial size and heart rate to predict 60 day readmission or death while heart rate, left ventricular posterior wall thickness (PWTd), and presence of aortic stenosis were associated with the risk of death at 6 months.

In this study we also found renal dysfunction is present in one-third of younger non-ischaemic AHF patients in Africa (chapter 8) but worsening renal function (WRF), is less prevalent and has different predictors compared with Western cohorts. Nevertheless, we still found WRF to be a strong and independent predictor of death or readmission over 60 days and all-cause death over 180 days.

The THESUS-HF registry showed the predictive utility of ECG abnormalities among Africans, ECG abnormalities, though non-specific were almost universal, some with prognostic value for mortality. [547] In a sub analysis looking specifically at AF (chapter 9), it was found to be present in one fifth of AHF patients, and 44% of them had rheumatic valvular heart disease, with valvular AF predicting death through day 180. Anticoagulation prescription rates were low and decreased progressively over time; only 22% of patients with AF were on oral anticoagulant at 6 months.

In addition to the above areas of concern, the measurement of medication adherence is still rare in routine clinical practice and has not been well studied among HF patients in SSA. Poor medication adherence leads to increased rates of exacerbation causing hospitalizations and increased morbidity. [548] For this reason, medication adherence has been called the "next frontier in quality improvement" and is an important part of cardiovascular outcomes research. [549] Among heart failure patients, studies of medication adherence have also found widely differing rates of non-adherence for the different drugs used in HF. [548] It will be very important to develop simple methods to measure the plasma levels drugs like ACEI and beta-blocker or use dried blood spot testing (DBS) to assess adherence to medications. This is an endeavor that we have already embarked upon with a pilot study planned using the BAHEF samples.

Other potential future areas of research in this area include, investigating whether hand-held echocardiography, which is available and less expensive, could be used to complement other diagnostic and prognostic tools like biomarkers and conventional TTE in AHF. The diagnostic capability of hand held echocardiography should be tested against conventional TTE in AHF in low resource settings like SSA.

Several studies have shown that AF in general and valvular AF in particular is associated with an increased risk of stroke or systemic embolism. [550] The finding of high prevalence of valvular AF and low rates of anticoagulation suggest that many AHF patients in SSA could be at risk of stroke and systemic embolism. In the future, 2 important questions need to be addressed; first the role of anticoagulation in the prevention of death, stroke and systemic embolism, as well as the problem associated with anticoagulation in SSA. Second, because of issues associated with monitoring of warfarin therapy in SSA, [551]

there is need for an RCT of warfarin versus the new oral anticoagulants (NOACs) in valvular AF in the region.

11.4 NT Pro BNP and Galectin – 3 and Outcomes

NT-Pro BNP and Gal3 have been well shown to predict adverse outcomes in patients with AHF and to also serve as a guide to therapy. [442,552] In a pre-specified secondary analyses of the BA-HEF data, we investigated the association between plasma levels of NT Pro BPN and galectin 3 and cardiovascular death or heart failure hospitalization as well as markers of LV and RV remodeling. We found that both the two biomarker levels at baseline predicted combined CV death or HF hospitalization through week 24 and the novel biomarker Gal3 is valuable in predicting changes (week 24 to baseline) in markers of LV and RV remodeling in African AHF patients. Indeed the role of RV structure and function in short and longer term outcomes as well as remodeling in AHF is underappreciated, and our findings underscores the need for further research to determine the importance of the RV in AHF. We also believe that our results provide bases for confirmation through a much bigger study on the role of these biomarkers in SSA patients with AHF. This may lead to the development of combined bedside kits for NT Pro BNP and Gal3 for risk stratification and referral to appropriate facility for immediate care. This will go a long way in improving morbidity and mortality in these patients, especially in Africa where resources are scarce.

In conclusion, several gaps exist in the contemporary knowledge of AHF globally, more so in SSA where the disease is prevalent. This work has provided greater insight into clinical characteristics of AHF, its aetiologies, outcome predictors and prognostic significance of conventional biomarker NT Pro BNP and novel biomarker Gal3 in AHF.

It has also raised some future research questions (Figure 11.1), which we hope to address in collaboration with colleagues from across the continent.

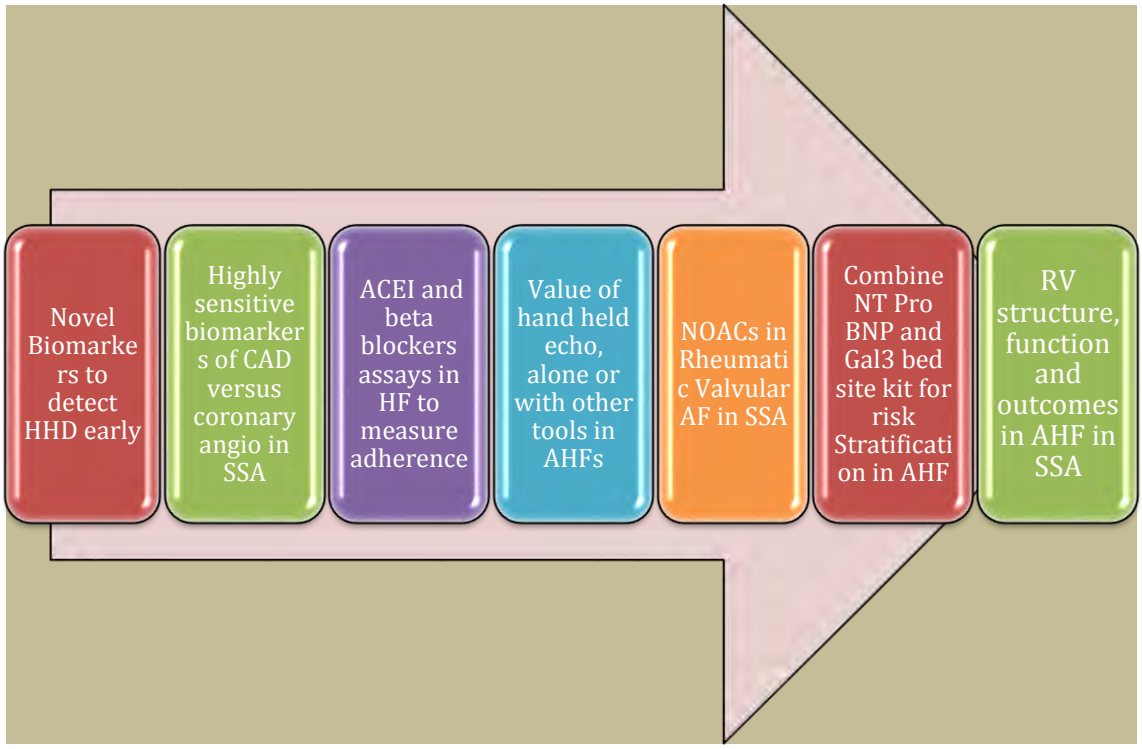


Figure 11.1 Potential areas of future research on acute heart failure in sub Saharan Africa

Publications and Presentations

Publications related to the Thesis and previous publications on heart failure.

1. Renal dysfunction in African patients with acute heart failure. **Sani MU**, Davison BA, Cotter G, Sliwa K, Edwards C, Liu L, Damasceno A, Mayosi BM, Ogah OS , Mondo C, Dzudie A, Ojji DB , Voors AA . Eur J Heart Fail. 2014 Jul; 16(7): 718-28.
2. Echocardiographic predictors of outcome in Acute Heart failure patients in Sub-Saharan Africa: Insights from THESUS-HF. **Sani MU**, Davison BA, Cotter G, Damasceno A, Mayosi BM, Ogah OS, Mondo C, Dzudie A, Ojji DB , Kouam Kouam C, Suliman A, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Sliwa K. *Accepted Cardiovascular Journal of Africa June 2016*
3. Bi treatment with hydralazine/nitrates vs. placebo in Africans admitted with acute HEart Failure (BA-HEF). Sliwa K, Damasceno A, Davison BA, Mayosi BM, **Sani MU**, Ogah O, Mondo C, Ojji D, Dzudie A, Kouam CK, Yonga G, Ba SA, Ogola E, Edwards C, Milo O, Cotter G. Eur J Heart Fail. 2016 May 20. doi: 10.1002/ejhf.581
4. Symptoms and Signs of heart failure at admission and discharge and Outcomes in the Sub Saharan Acute Heart Failure (THESUS HF) Registry. **Sani MU**, Cotter G, Davison BA, Mayosi BM, Damasceno A, Edwards C, Ogah OS, Mondo C, Dzudie A, Ojji DB, Kouam Kouam C, Suliman A, Yonga G, Ba SA, Maru F, Alemayehu B, Sliwa K. *Accepted Journal of Cardiac failure October 2016*
5. Prevalence, clinical characteristics and outcomes of valvular atrial fibrillation in a cohort of African patients with acute heat failure: Insights from THESUS-HF Registry. **Sani MU**, Davison BA, Cotter G, Mayosi BM, Edwards C, Ogah OS, Damasceno A, Ojji DB, Dzudie A, Mondo C, Kouam Kouam C, Suliman A, Yonga G, Ba SA, Maru F, Alemayehu B, Sliwa K. *Accepted Cardiovascular Journal of Africa November 2016*
6. NT - Pro BNP and Galectin-3 are prognostic biomarkers in Acute Heart failure in sub Saharan Africa: Lessons from the BAHEF Trial. **Sani MU**, Damasceno A, Davison BA, Cotter G, Mayosi BM, Edwards C, Azibani F, Adam T, Arif G, Jessen N, Sliwa K. *Submitted JACC-HF September 2016*

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10. Gender differences in clinical characteristics and outcome of acute heart failure in sub-Saharan Africa: results of the THESUS-HF study. Ogah OS, Davison BA, Sliwa K, Mayosi BM, Damasceno A, **Sani MU**, Mondo C, Dzudie A, Ojji DB, Kouam C, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Cotter G. Clin Res Cardiol. 2015 Jun; 104(6):481-90.
11. Echocardiographic Features Of Heart Failure With Preserved And Reduced Ejection Fraction In Kano Nigeria. K M Karaye, **Sani MU,** M S Mijinyawa, M M Borodo. Aetiology And - Nigerian Journal of Basic and Clinical Sciences 2007; 4 : 11- 17
12. Electrocardiographic abnormalities in patients with heart failure. Karaye KM, **Sani MU**. Cardiovascular Journal South Africa. 2008 ;19(1):22-5.
13. Factors associated with poor prognosis among patients admitted with heart failure in a Nigerian tertiary medical centre: a cross-sectional study. Karaye KM, **Sani MU**. BMC Cardiovascular Disorders 2008;8:16
14. Demographic and Clinical Characteristics of Heart Failure Patients in a Nigerian Tertiary Health Centre. Karaye KM, **Sani MU.** - Nigerian Journal of Basic and Clinical Sciences 2009; 6 (1): 26-35

Abstract Presentations

1. Echocardiographic Pattern of Acute Heart Failure in Aminu Kano Teaching Hospital, Kano, Nigeria. World Congress of Cardiology Dubai, UAE - April 2012
2. Renal Dysfunction in Patients Acute Heart Failure. South African Heart Association (SAHeart) Congress. Durban, South Africa – August 2014
3. Valvular Atrial Fibrillation is a common form of AF among Acute Heart failure patients in Sub-Saharan Africa: Insights from THESUS-HF. South African Heart Association. Sun City, South Africa – October 2015
4. Symptoms and Signs of heart failure at admission and discharge and Outcomes in the Sub Saharan Acute Heart Failure (THESUS HF) Registry. South African Heart Association. Sun City, South Africa – October 2015
5. Echocardiographic predictors of outcome in Acute Heart failure patients in Sub-Saharan Africa: Insights from THESUS-HF. Pan African Society of Cardiology (PASCAR) Congress. Port Louis, Mauritius – October 2015
6. Prevalence, characteristics and outcomes of atrial fibrillation in the sub Saharan acute heart failure (THESUS) registry. World Congress of Cardiology (WCC). Mexico City June 2016

Trainings and Workshops relevant to PhD

1. Essentials of Good Clinical Practice (GCP) for Health Professionals by Bristol-Myers Squibb Foundation. Cape Town South Africa March 2014
2. Cochrane Protocol development and meta-analysis Workshop in collaboration with College of Health Sciences
3. South African Heart Association / Mayo Clinic Group Workshop on Echocardiography Durban, South Africa. August 2016
4. Workshop on Systematic Review and Meta-analysis, organized by College of Health Sciences Bayero University Kano. Kano, Nigeria. February 2016

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Appendices

List of contributors to the THESUS-HF Study

List of contributors to the BAHEF Study

Statement of originality documents of publications

Ethical Approvals for the Study

Case Report Forms for the THESUS-HF Study

Case Report Forms for the BAHEF Study

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Statement of originality document: The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. (Arch Intern Med 2012; 172:1386-1394)

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Gad Cotter , Momentum Research Inc.	Conceived and designed the research, analysed and interpreted the data, drafted the manuscript, handled funding and supervision
Karen Sliwa, Hatter Institute, University of Cape Town	Conceived and designed the research, analysed and interpreted the data, drafted the manuscript, handled supervision
Candidate: I hereby declare that this work is wholly my own except where acknowledged as being the work of others (as listed above). I also acknowledge the contribution of others (as listed above) to this work in this Statement of Originality. Dr Mahmoud Sani 2016	Principal Supervisor: I hereby certify that all coauthors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality Prof Karen Sliwa 2016

Statement of originality document: Bi treatment with hydralazine/nitrates vs. placebo in Africans admitted with acute HEart Failure (BA-HEF). Eur J Heart Fail. 2016 May 20.

Name	**Responsibility**
Karen Sliwa, Hatter Institute, University of Cape Town	Conceived and designed the research, analysed and interpreted the data, drafted the manuscript, handled supervision
Albertino Damasceno, Mondlane Univesity	Conceived and designed the research, acquired the data, analysed and interpreted the data, handled supervision drafted the manuscript
Beth Davison, Momentum Research Inc.	Conceived and designed the research, performed statistical analysis, analysed and interpreted the data, drafted the manuscript
Bongani Mayosi , University of Cape Town	Conceived and designed the research, acquired the data, analysed and interpreted the data, drafted the manuscript
Mahmoud Sani, Bayero University Kano	Conceived and designed the research, acquired the data, analysed and interpreted the data, drafted the manuscript
Okechukwu Ogah, University College Hospital	Conceived and designed the research, acquired the data, analysed and interpreted the data, drafted the manuscript
Charles Mondo, Uganda Heart institute	Acquired the data, analysed and interpreted the data
Dike Ojji, University of Abuja	Acquired the data, analysed and interpreted the data,
Anastase Dzudie, Douala General Hospital	Acquired the data, analysed and interpreted the data
Charles Kouam Kouam, Douala General Hospital	Acquired the data
Gerald Yonga , Aga Khan University	Acquired the data
Serigne Abdou Ba, University of Dakar	Acquired the data
Elijah Ogola, University of Nairobi	Acquired the data, analysed and interpreted the data
Christopher Edwards, Momentum Research Inc.	Performed statistical analysis, analysed and interpreted the data
Gad Cotter, Momentum Research Inc.	Conceived and designed the research, analysed and interpreted the data, drafted the manuscript, handled funding and supervision
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Statement of originality document: Readmission and Death after an acute heart failure event: predictors and outcomes in sub-Saharan Africa: results from the THESUS- HF registry. Eur Heart J. 2013 Oct; 34(40):3151-3159.

Name	**Responsibility**
Karen Sliwa, Hatter Institute, University of Cape Town	Conceived and designed the research, analysed and interpreted the data, drafted the manuscript, handled supervision
Beth Davison, Momentum Research Inc.	Conceived and designed the research, performed statistical analysis, analysed and interpreted the data, drafted the manuscript
Bongani Mayosi , University of Cape Town	Conceived and designed the research, acquired the data, analysed and interpreted the data, drafted the manuscript
Albertino Damasceno, Mondlane Univesity	Conceived and designed the research, acquired the data, analysed and interpreted the data, handled supervision drafted the manuscript
Mahmoud Sani, Bayero University Kano	Conceived and designed the research, acquired the data, analysed and interpreted the data, drafted the manuscript
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Charles Mondo, Uganda Heart institute	Acquired the data, analysed and interpreted the data
Dike Ojji, University of Abuja	Acquired the data, analysed and interpreted the data,
Anastase Dzudie, Douala General Hospital	Acquired the data, analysed and interpreted the data
Charles Kouam Kouam, Douala General Hospital	Acquired the data
Ahmed Suliman, University of Khartoum	Acquired the data
Neshaad Schrueder, University of Cape Town	Acquired the data
Gerald Yonga , Aga Khan University	Acquired the data
Serigne Abdou Ba, University of Dakar	Acquired the data
Christopher Edwards, Momentum Research Inc.	Performed statistical analysis, analysed and interpreted the data
Gad Cotter , Momentum Research Inc.	Conceived and designed the research, analysed and interpreted the data, drafted the manuscript, handled funding and supervision
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Statement of originality document: Renal dysfunction in African patients with acute heart failure. Eur J Heart Fail. 2014 Jul;16(7):718-28.

Name	**Responsibility**
Mahmoud Sani, Bayero University Kano	Conceived and designed the research, acquired the data, analysed and interpreted the data, drafted the manuscript
Beth Davison, Momentum Research Inc.	Conceived and designed the research, performed statistical analysis, analysed and interpreted the data, drafted the manuscript
Gad Cotter , Momentum Research Inc.	Conceived and designed the research, analysed and interpreted the data, drafted the manuscript, handled funding and supervision
Karen Sliwa, Hatter Institute, University of Cape Town	Conceived and designed the research, analysed and interpreted the data, drafted the manuscript, handled supervision
Christopher Edwards, Momentum Research Inc.	Performed statistical analysis, analysed and interpreted the data
Licette Liu, University of Groningen	Conceived and designed the research, analysed and interpreted the data, drafted the manuscript
Albertino Damasceno, Mondlane Univesity	Conceived and designed the research, acquired the data, analysed and interpreted the data, handled supervision drafted the manuscript
Bongani Mayosi , University of Cape Town	Conceived and designed the research, acquired the data, analysed and interpreted the data, drafted the manuscript
Okechukwu Ogah, University College Hospital	Conceived and designed the research, acquired the data, analysed and interpreted the data, drafted the manuscript
Charles Mondo, Uganda Heart institute	Acquired the data, analysed and interpreted the data
Anastase Dzudie, Douala General Hospital	Acquired the data, analysed and interpreted the data
Dike Ojji, University of Abuja	Acquired the data, analysed and interpreted the data,
Adrian Voors, University of Groningen	Conceived and designed the research, analysed and interpreted the data, drafted the manuscript
Candidate: I hereby declare that this work is wholly my own except where acknowledged as being the work of others (as listed above). I also acknowledge the contribution of others (as listed above) to this work in this Statement of Originality. Dr Mahmoud Sani 2016	Principal Supervisor: I hereby certify that all coauthors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality. Prof Karen Sliwa 2016

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

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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

30 June 2014

HREC/REF: 417/2014

Prof K Sliwa
Hatter Institute Cardiovascular Research in Africa
4th Floor
Chris Barnard Building
FHS

Dear Prof Sliwa

Project Title: CHARACTERISTICS AND OUTCOMES OF ACUTE HEART FAILURE IN SUB-SAHARAN AFRICA-(PhD-candidate-Dr M Sani)-sub-study 037/2012

Thank you 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 30 June 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 supply the HREC approval renewal for the THESUS study.
Please update the Helsinki Declaration to 2013.

We acknowledge that the following student:- Dr Mahmoud Sani is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

AMINU KANO TEACHING HOSPITAL

P. M. B. 3452, ZARIA ROAD, KANO.

(☎: 07068297399, 08057203511, 064 - 377085 - 8) www.akth.org, E-mail: enquiries@akth.org, email: (akthkano@yahoo.com)

CHIEF MEDICAL DIRECTOR
DR. AMINU ZAKARI MOHAMMED, MBBS, FMCPath

CHAIRMAN M. A. C.
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DIRECTOR OF ADMINISTRATION
ALH. MUHD. SULAIMAN, B. Ed, CHPM, ADAN

NHREC/21/08/2008/AKTH/EC/881

AKTH/MAC/SUB/12A/P-3/V1/981

16th March, 2012

Dr. Mahmoud U. Sani
Department of Internal Medicine
AKTH, Kano

signature removed

Ufs:

The Head of Department
Internal Medicine
AKTH, Kano

signature removed

RE: ETHICAL APPROVAL

Further to your application in respect of your research proposal titled "Bi Treatment with Hydralazine/Nitrates Versus Placebo in Africans admitted with Acute Heart-Failure (B-A-HEF) trail". The Committee has reviewed the proposal and noted same as a prospective study.

In view of the above, Ethical approval is hereby granted to conduct the research.

However, the approval is subject to periodic reporting of the progress of the study and its completion to the Ethical Committee. Furthermore, you are to forward the dissemination plan of the report to the committee, please.

Regards

signature removed

Abdul Lawan
Ag. Secretary Ethical Committee
For: Chairman

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

10 April 2012

HREC REF: 037/2012

Prof K Sliwa-Haehnle
Hatter Institute for
Cardiovascular Research in Africa
4th Floor Chris Barnard Building

Dear Prof Sliwa-Haehnle

PROTOCOL NUMBER: B-AHEF
PROJECT TITLE: A PROSPECTIVE, PLACEBO CONTROLLED, DOUBLE-BLIND, RANDOMIZED STUDY TO COMPARE TREATMENT WITH HYDRALAZINE-ISOSORBIDE-DINITRATE (HYIS) VERSUS PLACEBO ON TOP OF STANDARD CARE IN AFRICAN PATIENTS ADMITTED WITH ACUTE HEART FAILURE (AHF) AND LEFT VENTRICULAR DYSFUNCTION.

Thank you for responding to the issues raised by the Faculty of Health Sciences Human Research Ethics Committee in your letter dated 27th March 2012.

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

Approval is granted for one year till the 30th April 2013.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

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.

Yours sincerely

signature removed

pp **PROFESSOR M BLOCKMAN**
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone (021) 406 6338 • Facsimile (021) 406 6411
e-mail:shantel.lakay@uct.ac.za

03 March 2008

REC REF: 068/2008

Prof BM Mayosi
Department of Medicine

Dear Prof Mayosi

PROJECT TITLE: THE SUB-SAHARAN AFRICA SURVEY OF HEART FAILURE (THESUS-HF)

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the establishment of the above mentioned registry.

Approval is for one year and we will require an annual progress report before the expiry date (29 February 2009).

Federal World Wide Assurance Number: FWA00001637
Institutional Review Board: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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

Please quote the REC. REF in all your correspondence.

Yours sincerely

signature removed

PROFESSOR M. BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

sh/kay

THESUS-HF

Baseline

Patient Number: ___ ___ - ___ ___ ___ Patient's Initials: ___ ___ ___

Demographics

1 Date of admission: ___ ___ / ___ ___ ___ / 200 ___ (day / month / year) **Time:** ___ ___ : ___ ___ (00:00 to 23:59)

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

3 Sex: ☐ 1 Male ☐ 1 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:** ___ ___ / ___ ___ ___ / 200 ___ (day / month / year) **OR** ☐ 96 NA

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

ECG (Electrocardiogram)

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

Baseline Labs First obtained at Admission

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

Baseline

Patient Number: ___ ___ - ___ ___ ___ Patient's Initials: ___ ___ ___

Baseline Characteristics at Time of Admission

1 Diabetes ..... ☐$_0$ No ☐$_1$ Yes → **If Yes: Check all that apply:** ☐ Diet ☐ Oral ☐ 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 ☐$_{99}$ 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's Initials: ___ ___ ___

Hospital Data See opposite page for instructions

Date →		___/___/200__ day month year	___/___/200__ day month year	___/___/200__ day month year	___/___/200__ day month year	___/___/200__ day month year	___/___/200__ day month year
1 Symptom	**Scale**	**1 Month Pre**	**Admission**	**Day 1**	**Day 2**	**Discharge or Day 7**	**Follow Up**
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	_____ ☐ NA
2 Signs	**Scale**	**1 Month Pre**	**Admission**	**Day 1**	**Day 2**	**Discharge or Day 7**	**Follow Up**
Blood pressure	systolic/diastolic	___/___	___/___	___/___	___/___	___/___	___/___
Heart rate	beats/minute	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___
Respiration	breaths/minute	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___
O_2 saturation	%	___ ___ . ___	___ ___ . ___	___ ___ . ___	___ ___ . ___	___ ___ . ___	___ ___ . ___
Temperature	°C	___ ___ . ___	___ ___ . ___	___ ___ . ___	___ ___ . ___	___ ___ . ___	___ ___ . ___
Peripheral edema	0 to 3+	_____	_____	_____	_____	_____	_____
Rales	0 to 3	_____	_____	_____	_____	_____	_____
JVP *(Jugular venous pressure)*	1 to 3 OR NA *(not evaluable)*	_____ ☐ NA	_____ ☐ NA	_____ ☐ NA	_____ ☐ NA	_____ ☐ NA	_____ ☐ NA
Weight	kg	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___
3 Labs	**Unit**	**1 Month Pre**	**Admission***	**Day 1**	**Day 2**	**Discharge or Day 7**	**Follow Up**
Creatinine	☐ mg/dL ☐ µmol/L	_____	NA*	_____	_____	_____	_____
BUN/urea	☐ mg/dL ☐ mmol/L	_____	NA*	_____	_____	_____	_____
Sodium	☐ mmol/L ☐ mEq/L	_____	NA*	_____	_____	_____	_____
BNP	pg/mL	_____	NA*	_____	_____	_____	_____
NT Pro BNP	pg/mL	_____	NA*	_____	_____	_____	_____

*Record admission lab values on CRF page 1.

Patient Number: ___ ___ - ___ ___ ___ Patient's Initials: ___ ___ ___

Hospital Data See opposite page for instructions (continued)

4 IV Drugs	1 Month Pre	Admission	Day 1	Day 2	Discharge or Day 7	Follow Up
Nitrates	☐0 No ☐1 Yes	☐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	☐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	☐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	☐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	☐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	☐0 No ☐1 Yes
5 PO Drugs	**1 Month Pre**	**Admission**	**Day 1**	**Day 2**	**Discharge or Day 7**	**Follow Up**
ACE inhibitors/ angiotensin antagonists	☐0 No ☐1 Yes	☐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	☐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	☐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	☐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	☐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	☐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	☐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	☐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	☐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	☐0 No ☐1 Yes

Outcomes

Patient Number: ___ ___ - ___ ___ ___ Patient's Initials: ___ ___ ___

Outcome

Hospital discharge date: ___ ___ / ___ ___ ___ / 200 ___
day month year

Rehospitalization Within 6 Months

	Rehospitalization #1	Rehospitalization #2	Rehospitalization #3
Admission Date →	___ ___ / ___ ___ ___ / 200 ___ (day / month / year)	___ ___ / ___ ___ ___ / 200 ___ (day / month / year)	___ ___ / ___ ___ ___ / 200 ___ (day / month / year)
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 Date of death: ___ ___ / ___ ___ ___ / 200 ___ (day / month / year)

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

3 Sudden death? ..... ☐0 No ☐1 Yes

4 During acute heart failure? ..... ☐0 No ☐1 Yes

5 During acute ischemia? ..... ☐0 No ☐1 Yes

6 Associated with arrhythmia? ..... ☐0 No ☐1 Yes

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

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

Echocardiographic Evaluation

Patient Number: ___ ___ - ___ ___ ___ Patient's Initials: ___ ___ ___

Echocardiographic Evaluation

Date of echocardiogram	___ ___ / ___ ___ ___ / 200 ___ (day / month / year)
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 A-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
19 Other	☐0 None ☐1 Mild ☐2 Moderate ☐3 Severe	☐0 No ☐1 Yes ☐ NA
Pericardial Effusion	**Severity**	**Tuberculosis?**
20 Pericardial effusion	☐0 None ☐1 Mild ☐2 Moderate ☐3 Severe	☐0 No ☐1 Yes ☐ NA
21 Other conditions	☐0 No ☐1 Yes → **If Yes: Specify:**	
22 Other conditions	☐0 No ☐1 Yes → **If Yes: Specify:**	

Diagnosis

Patient Number: ___ ___ - ___ ___ ___ Patient's 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 → **If Yes: Specify:** _____
12	**Other factors**	☐$_0$ No ☐$_1$ Yes → **If Yes: Specify:** _____

Contact Information Log

Patient Number	Full Name	Phone Number	Address	ID Number

Retain at Site

B-A-HEF

Visit 1: Screening

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Presentation

1. Date and time of hospital admission: __ __/__ __ __/__ __ __ __ (dd mmm yyyy) __ __ : __ __ (24 hr clock)
2. Date and time of start of screening: __ __/__ __ __/__ __ __ __ (dd mmm yyyy) __ __ : __ __ (24 hr clock)
3. Date and time informed consent signed: __ __/__ __ __/__ __ __ __ (dd mmm yyyy) __ __ : __ __ (24 hr clock)

Demographics

1. Age at screening: _____ years
2. Gender *(check only one)*: ☐ 1 Male ☐ 2 Female
3. Country of Birth: _____
4. Language of the subject's mother tongue *(check only one)*:

☐ 1 Afrikaans	☐ 7 Igbo	☐ 13 Shona	☐ 19 Tswana	☐ 99 Other: _____
☐ 2 Amharic	☐ 8 Ndebele	☐ 14 Sotho	☐ 20 Venda	
☐ 3 Arabic	☐ 9 Northern Sotho	☐ 15 Spanish	☐ 21 Wolof	
☐ 4 English	☐ 10 Oromo	☐ 16 Swahili	☐ 22 Xhosa	
☐ 5 French	☐ 11 Pedi	☐ 17 Swazi	☐ 23 Yoruba	
☐ 6 Hausa	☐ 12 Portuguese	☐ 18 Tsonga	☐ 24 Zulu	

5. Race *(check only one)*: ☐ 1 African or black ☐ 4 Arab ☐ 2 Colored or mixed race ☐ 5 Caucasian or white ☐ 3 Indian or Asian ☐ 99 Other: _____
6. Highest education level completed *(check only one)*: ☐ 1 None ☐ 3 Primary ☐ 5 College ☐ 2 Never in school ☐ 4 Secondary ☐ 6 University
7. Occupation (nurse, farmer, etc.): _____
8. Occupation type *(check only one)*: ☐ 1 None ☐ 6 Employed full time ☐ 2 Unemployed ☐ 7 Self employed ☐ 3 Student ☐ 8 Homemaker or housewife ☐ 4 Employed casual ☐ 9 Government grants or pension ☐ 5 Employed part time ☐ 99 Other: _____
9. Monthly per capita income: *If no personal income, income of household breadwinner.* ☐ 1 None ☐ 2 Below 30 USD ☐ 3 30 to 99 USD ☐ 4 100 to 999 USD ☐ 5 1000 to 1999 USD ☐ 6 2000 to 4999 USD ☐ 7 more than 5000 USD
10. Accommodation type *(check only one)*: ☐ 1 House or permanent building ☐ 2 Shack on serviced site with sanitation ☐ 3 Shack without sanitation ☐ 4 Traditional housing or hut ☐ 99 Other: _____

Visit 1: Screening

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Hospitalization for Heart Failure in the Past Year

Has the subject been hospitalized (i.e., kept overnight) for heart failure in the past year:

☐ 0 No

☐ 1 Yes ***If Yes:*** ***Number of hospitalizations:*** _____

Date of discharge of last hospitalization: __ __/__ __ __/__ __ __ __
(not including this hospitalization) dd mmm yyyy

Vital Signs / Physical Assessment

1. Blood pressures between admission and randomization:

Blood pressure #1:	__ __ __/__ __ __ mmHg (systolic / diastolic)	__ __/__ __ __/__ __ __ __ (dd / mmm / yyyy)	__ __ : __ __ (24 hr clock)
Blood pressure #2:	__ __ __/__ __ __ mmHg (systolic / diastolic)	__ __/__ __ __/__ __ __ __ (dd / mmm / yyyy)	__ __ : __ __ (24 hr clock)
Blood pressure #3:	__ __ __/__ __ __ mmHg (systolic / diastolic)	__ __/__ __ __/__ __ __ __ (dd / mmm / yyyy)	__ __ : __ __ (24 hr clock)

2. Heart Rate at screening: __ __ __ bpm
3. Respiration at screening: __ __ breaths/min
4. Body temp. at screening: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight at screening: __ __ __ . __ kg or __ __ __ . __ lbs
6. Height: __ __ __ . __ cm or __ __ __ . __ in
7. Body Mass Index (BMI): __ __ . __

Atrial Fibrillation at Screening

Was the subject in atrial fibrillation/flutter during screening?

☐ 0 No ☐ 1 Yes ☐ 88 Not performed, *provide reason*: _____

Chest X-Ray

Was a chest x-ray performed? ☐ 0 No ☐ 1 Yes

If Yes, was pulmonary congestion present? ☐ 0 No ☐ 1 Yes

Comments: _____

_____

_____

Visit 1: Screening

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Local Laboratory Results

Glucose	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____	**Uric Acid**	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____
Sodium	_____	☐ 3 mmol/L ☐ 4 mEq/L ☐ 99 _____	**Creatinine**	_____	☐ 1 mg/dL ☐ 2 µmol/L ☐ 99 _____
Potassium	_____	☐ 3 mmol/L ☐ 4 mEq/L ☐ 99 _____	**Bilirubin**	_____	☐ 1 mg/dL ☐ 2 µmol/L ☐ 99 _____
BUN	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____	**Albumin**	_____	☐ 5 g/L ☐ 6 g/dL ☐ 99 _____
AST	_____	☐ 10 IU/L ☐ 99 _____	**Hemoglobin**	_____	☐ 3 mmol/L ☐ 5 g/L ☐ 6 g/dL ☐ 99 _____
ALT	_____	☐ 10 IU/L ☐ 99 _____	**Total WBC**	_____	☐ 7 $x10^9$/L ☐ 8 /mm^3 ☐ 99 _____
Alkaline Phosphatase	_____	☐ 10 IU/L ☐ 99 _____	**Lymphocytes**	_____	☐ 9 % ☐ 99 _____

Local Laboratory Values

Was NT-pro-BNP measured? ☐ 0 No ☐ 1 Yes ***If Yes, provide value:*** _____ ☐ 3 mmol/L ☐ 15 pg/mL ☐ 99 _____

Was Troponin measured? ☐ 0 No ☐ 1 Yes

If Yes, provide value: Troponin I: _____ ng/mL

Troponin T: _____ ng/mL

Concomitant Medication Log – Visit 1: Screening

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: Record medications subject was taking 30 days prior to screening				
Medication		Route	Dose	Frequency
ACE Inhibitors	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
ARBs	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Beta Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Loop Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Inotropes	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Nitrates	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Aldosterone Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Digoxin	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________

Visit 1: Screening

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Medical History At Time of Admission

Does the subject have a known current or past history of any of the following disorders/conditions:

1. Family history of cardiovascular disease..... ☐ 0 No ☐ 1 Yes
2. Diabetes mellitus..... ☐ 0 No ☐ 1 Yes
   If Yes, controlled by: *(check all that apply)* ☐ 1 Insulin ☐ 1 Oral antidiabetic agents ☐ 1 Diet Only
3. Hypertension..... ☐ 0 No ☐ 1 Yes
4. Hyperlipidemia..... ☐ 0 No ☐ 1 Yes
5. Stroke or other cerebrovascular event..... ☐ 0 No ☐ 1 Yes
6. Cigarette smoking..... ☐ 0 No ☐ 1 Yes
7. Depression..... ☐ 0 No ☐ 1 Yes
8. HIV test positive..... ☐ 77 Unknown ☐ 0 No ☐ 1 Yes
   If Yes, Antiretroviral therapy? ☐ 0 No ☐ 1 Yes
9. Peripheral vascular disease (PVD)..... ☐ 0 No ☐ 1 Yes
10. Malignancy..... ☐ 0 No ☐ 1 Yes
11. Pacemaker (other than biventricular)..... ☐ 0 No ☐ 1 Yes
12. Biventricular pacing..... ☐ 0 No ☐ 1 Yes
13. Automatic internal cardiac defibrillator (AICD)..... ☐ 0 No ☐ 1 Yes
14. Asthma, bronchitis, chronic obstructive pulmonary disease (COPD)..... ☐ 0 No ☐ 1 Yes
15. Dementia..... ☐ 0 No ☐ 1 Yes
16. Pericardial disease..... ☐ 0 No ☐ 1 Yes
17. Cardiomyopathy..... ☐ 0 No ☐ 1 Yes
18. Dilated idiopathic cardiomyopathy..... ☐ 0 No ☐ 1 Yes
19. Peripartum cardiomyopathy..... ☐ 0 No ☐ 1 Yes
20. HIV cardiomyopathy..... ☐ 0 No ☐ 1 Yes
21. Hypertrophic cardiomyopathy..... ☐ 0 No ☐ 1 Yes
22. Endomyocardial fibroelastosis..... ☐ 0 No ☐ 1 Yes
23. Pericardial effusion/tamponade..... ☐ 0 No ☐ 1 Yes
24. Cor pulmonale..... ☐ 0 No ☐ 1 Yes
25. Tuberculosis..... ☐ 0 No ☐ 1 Yes
26. Beta-thalassemia..... ☐ 0 No ☐ 1 Yes
27. Sickle-cell anemia..... ☐ 0 No ☐ 1 Yes
28. Chronic liver disease..... ☐ 0 No ☐ 1 Yes

Medical History At Time of Admission (continued)

29. Rheumatic heart disease…….……..…….. ☐ 0 No ☐ 1 Yes

30. Rheumatic disease……..…….……..…….. ☐ 0 No ☐ 1 Yes

If Yes, answer the following:

30.1. Scleroderma (systemic sclerosis)…… ☐ 0 No ☐ 1 Yes

30.2. Mixed connective tissue disease..…..…... ☐ 0 No ☐ 1 Yes

30.3. Systemic lupus erythematosus.....…… ☐ 0 No ☐ 1 Yes

30.4. Rheumatoid arthritis……..…….. ☐ 0 No ☐ 1 Yes

30.5. Systemic necrotizing vasculitis…..…..…... ☐ 0 No ☐ 1 Yes

30.6. Idiopathic inflammatory myositis...…..…... ☐ 0 No ☐ 1 Yes

30.7. Other (specify):_____ ☐ 0 No ☐ 1 Yes

31. Valvular disease……...……..……..…… ☐ 0 No ☐ 1 Yes

If Yes, answer the following:

31.1. Mitral stenosis……..…… ☐ 0 No ☐ 1 Yes

31.2. Mitral regurgitation……..….. ☐ 0 No ☐ 1 Yes

31.3. Aortic stenosis……....……. ☐ 0 No ☐ 1 Yes

31.4. Aortic regurgitation……..….. ☐ 0 No ☐ 1 Yes

31.5. Other (specify):_____ ☐ 0 No ☐ 1 Yes

32. Ischemic heart disease……..……..……..…… ☐ 0 No ☐ 1 Yes

If Yes, answer the following:

32.1. Myocardial infarction (MI)…...…… ☐ 0 No ☐ 1 Yes

32.2. Coronary artery bypass graft (CABG)….. ☐ 0 No ☐ 1 Yes

32.3. Percutaneous intervention (PCI)...…… ☐ 0 No ☐ 1 Yes

33. Atrial fibrillation/flutter..……..……..…… ☐ 0 No ☐ 1 Yes

If Yes, provide type (check only one): ☐ 1 Chronic ☐ 2 Paroxysmal ☐ 3 Persistent

34. Most recent Ejection Fraction (EF) (if known) _____% Date of assessment: __ __/__ __ __/__ __ __ __
(including this hospitalization) dd mmm yyyy

35. Congestive heart failure (CHF)... ☐ 0 No ☐ 1 Yes **New York Heart Association classification:**
(1 month prior to admission) *(check only one)* ☐ 1 I ☐ 2 II ☐ 3 III ☐ 4 IV

36. Angina..……..... ☐ 0 No ☐ 1 Yes **Canadian Cardiovascular Society classification:**
(check only one) ☐ 1 I ☐ 2 II ☐ 3 III ☐ 4 IV

Visit 1: Screening

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Echocardiographic Evaluation

Date and time of echocardiogram: __ __/__ __ __/__ __ __ __ (dd / mmm / yyyy) __ __ : __ __ (24 hr clock)

1. Heart Rate: __ __ __ bpm ☐ 1 Normal sinus rhythm ☐ 2 Atrial Fibrillation ☐ 99 Other: _____

Left Heart Dimensions and LV Function

2. Left ventricular size systole: _____ ☐ 1 mm ☐ 99 other: _____
3. Left ventricular size diastole: _____ ☐ 1 mm ☐ 99 other: _____
4. Ejection Fraction: __ __ %
5. Intra ventricular septum *(diastole)*: _____ ☐ 1 mm ☐ 99 other: _____
6. Posterior wall *(diastole)*: _____ ☐ 1 mm ☐ 99 other: _____
7. Left atrial size, antero-posterior: _____ ☐ 1 mm ☐ 99 other: _____
8. Left atrial size, planimetry: _____ ☐ 1 mm^2 ☐ 99 other: _____

Diastolic Function

9. Mitral E-wave velocity: _____ ☐ 1 mm/sec ☐ 99 other: _____
10. E-wave deceleration time: _____ ☐ 1 msec ☐ 99 other: _____
11. Mitral A-wave velocity: _____ ☐ 1 mm/sec ☐ 99 other: _____ ☐ 88 NA
12. Mitral A-wave (duration): _____ ☐ 1 msec ☐ 99 other: _____ ☐ 88 NA

Right Heart Dimensions and Function — Severity

13. Dilatation right ventricle: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe
14. Dilatation right atrium: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe
15. Tricuspid regurgitation (TR) velocity: _____ ☐ 1 cm/sec ☐ 99 other: _____
16. Right ventricular systolic pressure (RVSP): _____ mmHg
17. Tricuspid annular plane systolic excursion (TAPSE): _____ ☐ 1 mm ☐ 99 other: _____

Valvular — Severity — Rheumatic?

18. Aortic Stenosis:	☐ 0 None	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
19. Aortic Regurgitation:	☐ 0 None/trace	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
20. Mitral Stenosis:	☐ 0 None	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
21. Mitral Regurgitation:	☐ 0 None/trace	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
22. Tricuspid Regurgitation:	☐ 0 None/trace	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
23. Other:	☐ 0 None	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA

Pericardial Effusion — Severity

24. Pericardial effusion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe

25. Other Conditions: ☐ 0 No ☐ 1 Yes ➔ **Specify:** _____
26. Other Conditions: ☐ 0 No ☐ 1 Yes ➔ **Specify:** _____

Visit 2: Randomization

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Eligibility

Did the subject meet all screening eligibility criteria?

☐ 1 Yes

☐ 0 No, **If No, specify criteria not met:**

Inclusion criteria number(s): _____, _____, _____, _____, ____

Exclusion criteria number(s): _____, _____, _____, _____, ____

Biomarker Samples

Were samples for biomarker assays drawn? ☐ 0 No ☐ 1 Yes, ***Date:*** __ __/__ __ __/__ __ __ __
dd mmm yyyy

Vital Signs / Physical Assessment

1. Blood pressure: __ __ __/__ __ __ mmHg
systolic diastolic
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Body temp.: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight: __ __ __ . __ kg or __ __ __ . __ lbs

6 Minute Walk Test and Subject Self-Report of Symptoms

1. 6MWT Distance: __ __ __ __ m
2. Dyspnea VAS: __ __ __ mm
3. General Well-Being VAS: __ __ __ mm

Physician Assessment (Check only one answer per question)

1. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
2. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
3. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
4. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
5. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Randomization (Visit 2) Date

Date study drug first dispensed: __ __/__ __ __/__ __ __ __
dd mmm yyyy

Study Drug Administration

1. Was study drug accountability performed? ☐ 0 No ☐ 1 Yes ***If Yes, complete the Study Drug Accountability Log***
2. Dose level assigned:
   HYD or placebo: ☐ 0 None ☐ 1 One tablet 3x daily ☐ 2 Two tablets 3x daily
   ISDN or placebo: ☐ 0 None ☐ 1 One tablet 3x daily ☐ 2 Two tablets 3x daily
3. Reason for dose change: ☐ 1 As per protocol ☐ 88 Not Applicable ☐ 2 Adverse Event ☐ 99 Other *(specify)*: _____

B-A-HEF

Concomitant Medication Log – Visit 2: Randomization

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: Record medications subject taking at Visit 2				
Medication		Route	Dose	Frequency
ACE Inhibitors	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
ARBs	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Beta Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Loop Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Inotropes	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Nitrates	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Aldosterone Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Digoxin	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________

Visit 3: Discharge or Day 7

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

1. Provide the type of assessment performed: ☐ 1 Discharge ☐ 2 Day 7

2. Did the subject attend the scheduled visit? ☐ 0 No ☐ 1 Yes

If No, provide source of information for this report:

☐ 0 None
☐ 1 Telephone contact
☐ 2 Spouse/relative
☐ 3 Subject's neighbor/friend
☐ 4 Health care provider
☐ 5 Public death registry
☐ 6 Other physician
☐ 7 Other *(specify)*: _____

If indirect contact, provide the subject status:
☐ 1 Alive
☐ 2 Dead ***Complete Death page***
☐ 77 Unknown

3. Date of assessment: __ __/__ __ __/__ __ __ __
dd mmm yyyy

Vital Signs / Physical Assessment

1. Blood pressure: __ __ __/__ __ __ mmHg
systolic diastolic
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Body temp.: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight: __ __ __ . __ kg or __ __ __ . __ lbs

6 Minute Walk Test and Subject Self-Report of Symptoms

1. 6MWT Distance: __ __ __ __ m
2. Dyspnea VAS: __ __ __ mm
3. General Well-Being VAS: __ __ __ mm

Physician Assessment (Check only one answer per question)

1. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
2. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
3. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
4. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
5. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Discharge from Index Hospitalization

Was the subject discharged prior to Week 24?

☐ 0 No
☐ 1 Yes, Due to Death, ***Complete Death Page***
☐ 2 Yes, Discharge date: __ __/__ __ __/__ __ __ __
dd mmm yyyy

B-A-HEF

Concomitant Medication Log – Visit 3: Discharge or Day 7

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: Record medications subject taking at Visit 3				
Medication		**Route**	**Dose**	**Frequency**
ACE Inhibitors	________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
ARBs	________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Beta Blockers	________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Loop Diuretics	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other Diuretics	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Inotropes	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Nitrates	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Aldosterone Blockers	________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Digoxin	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________

Visit 4: Week 2

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

1. Did the subject attend the scheduled visit? ☐ 0 No ☐ 1 Yes

If No, provide source of information for this report:

☐ 0 None
☐ 1 Telephone contact
☐ 2 Spouse/relative
☐ 3 Subject's neighbor/friend
☐ 4 Health care provider
☐ 5 Public death registry
☐ 6 Other physician
☐ 7 Other *(specify)*: _____

If indirect contact, provide the subject status:
☐ 1 **Alive**
☐ 2 **Dead *Complete Death page***
☐ 77 **Unknown**

2. Date of assessment: __ __/__ __ __/__ __ __ __
dd mmm yyyy

Rehospitalization Details

Has the subject been rehospitalized since the last assessment?

☐ 0 No
☐ 1 Yes ***Complete Rehospitalization Page***
☐ 88 NA, subject still hospitalized

Study Drug Administration

1. Was study drug accountability performed? ☐ 0 No ☐ 1 Yes ***If Yes, complete the Study Drug Accountability Log***

2. Dose level assigned:

HYD or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

ISDN or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

3. Reason for dose change:
☐ 1 As per protocol
☐ 2 Adverse Event
☐ 88 Not Applicable
☐ 99 Other *(specify)*: _____

Vital Signs / Physical Assessment

1. Blood pressure: __ __ __/__ __ __ mmHg
systolic diastolic
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Body temp.: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight: __ __ __ . __ kg or __ __ __ . __ lbs

Physician Assessment (Check only one answer per question)

1. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
2. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
3. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
4. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
5. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Adverse Events

Were there any Adverse Events since the last assessment? ☐ 0 No ☐ 1 Yes

If Yes, complete the Non-Serious Adverse Events CRF page or the Serious Adverse Event Form, as applicable.

Record all medications on Concomitant Medication Log

B-A-HEF

Concomitant Medication Log – Visit 4: Week 2

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: Record medications subject taking at Visit 4				
Medication		**Route**	**Dose**	**Frequency**
ACE Inhibitors	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
ARBs	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Beta Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Loop Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Inotropes	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Nitrates	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Aldosterone Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Digoxin	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________

Visit 5: Week 4

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

1. Did the subject attend the scheduled visit? ☐ 0 No ☐ 1 Yes

If No, provide source of information for this report:

☐ 0 None
☐ 1 Telephone contact
☐ 2 Spouse/relative
☐ 3 Subject's neighbor/friend
☐ 4 Health care provider
☐ 5 Public death registry
☐ 6 Other physician
☐ 7 Other *(specify)*: _____

If indirect contact, provide the subject status:
☐ 1 **Alive**
☐ 2 **Dead *Complete Death page***
☐ 77 **Unknown**

2. Date of assessment: __ __/__ __ __/__ __ __ __
dd mmm yyyy

Rehospitalization Details

Has the subject been rehospitalized since the last assessment?

☐ 0 No
☐ 1 Yes ***Complete Rehospitalization Page***
☐ 88 NA, subject still hospitalized

Study Drug Administration

1. Was study drug accountability performed? ☐ 0 No ☐ 1 Yes ***If Yes, complete the Study Drug Accountability Log***

2. Dose level assigned:

HYD or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

ISDN or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

3. Reason for dose change:
☐ 1 As per protocol
☐ 2 Adverse Event
☐ 88 Not Applicable
☐ 99 Other *(specify)*: _____

Vital Signs / Physical Assessment

1. Blood pressure: __ __ __/__ __ __ mmHg
systolic diastolic
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Body temp.: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight: __ __ __ . __ kg or __ __ __ . __ lbs

Physician Assessment (Check only one answer per question)

1. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
2. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
3. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
4. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
5. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Adverse Events

Were there any Adverse Events since the last assessment? ☐ 0 No ☐ 1 Yes

If Yes, complete the Non-Serious Adverse Events CRF page or the Serious Adverse Event Form, as applicable.

Record all medications on Concomitant Medication Log

B-A-HEF

Concomitant Medication Log – Visit 5: Week 4

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: **Record medications subject taking at Visit 5**				
Medication		**Route**	**Dose**	**Frequency**
ACE Inhibitors	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
ARBs	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Beta Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Loop Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Inotropes	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Nitrates	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Aldosterone Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Digoxin	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________

Visit 6: Week 8

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

1. Did the subject attend the scheduled visit? ☐ 0 No ☐ 1 Yes

If No, provide source of information for this report:

☐ 0 None
☐ 1 Telephone contact
☐ 2 Spouse/relative
☐ 3 Subject's neighbor/friend
☐ 4 Health care provider
☐ 5 Public death registry
☐ 6 Other physician
☐ 7 Other *(specify)*: _____

If indirect contact, provide the subject status:

☐ 1 **Alive**
☐ 2 **Dead *Complete Death page***
☐ 77 **Unknown**

2. Date of assessment: __ __/__ __ __/__ __ __ __
dd mmm yyyy

Rehospitalization Details

Has the subject been rehospitalized since the last assessment?

☐ 0 No
☐ 1 Yes ***Complete Rehospitalization Page***
☐ 88 NA, subject still hospitalized

Study Drug Administration

1. Was study drug accountability performed? ☐ 0 No ☐ 1 Yes ***If Yes, complete the Study Drug Accountability Log***

2. Dose level assigned:

HYD or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

ISDN or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

3. Reason for dose change:
☐ 1 As per protocol
☐ 2 Adverse Event
☐ 88 Not Applicable
☐ 99 Other *(specify)*: _____

Vital Signs / Physical Assessment

1. Blood pressure: __ __ __/__ __ __ mmHg
systolic diastolic
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Body temp.: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight: __ __ __ . __ kg or __ __ __ . __ lbs

Physician Assessment (Check only one answer per question)

1. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
2. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
3. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
4. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
5. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Adverse Events

Were there any Adverse Events since the last assessment? ☐ 0 No ☐ 1 Yes

If Yes, complete the Non-Serious Adverse Events CRF page or the Serious Adverse Event Form, as applicable.

Record all medications on Concomitant Medication Log

Visit 6: Week 8

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

6 Minute Walk Test and Subject Self-Report of Symptoms

1. 6MWT Distance: __ __ __ __ m
2. Dyspnea VAS: __ __ __ mm
3. General Well-Being VAS: __ __ __ mm

Local Laboratory Results

Glucose	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____	**Uric Acid**	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____
Sodium	_____	☐ 3 mmol/L ☐ 4 mEq/L ☐ 99 _____	**Creatinine**	_____	☐ 1 mg/dL ☐ 2 µmol/L ☐ 99 _____
Potassium	_____	☐ 3 mmol/L ☐ 4 mEq/L ☐ 99 _____	**Bilirubin**	_____	☐ 1 mg/dL ☐ 2 µmol/L ☐ 99 _____
BUN	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____	**Albumin**	_____	☐ 5 g/L ☐ 6 g/dL ☐ 99 _____
AST	_____	☐ 10 IU/L ☐ 99 _____	**Hemoglobin**	_____	☐ 3 mmol/L ☐ 5 g/L ☐ 6 g/dL ☐ 99 _____
ALT	_____	☐ 10 IU/L ☐ 99 _____	**Total WBC**	_____	☐ 7 x10^9/L ☐ 8 /mm^3 ☐ 99 _____
Alkaline Phosphatase	_____	☐ 10 IU/L ☐ 99 _____	**Lymphocytes**	_____	☐ 9 % ☐ 99 _____

Biomarker Samples

Were samples for biomarker assays drawn? ☐ 0 No ☐ 1 Yes, ***Date:*** __ __/__ __ __/__ __ __ __
dd mmm yyyy

B-A-HEF

Concomitant Medication Log – Visit 6: Week 8

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: Record medications subject taking at Visit 6				
Medication		**Route**	**Dose**	**Frequency**
ACE Inhibitors	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
ARBs	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Beta Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Loop Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Inotropes	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Nitrates	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Aldosterone Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Digoxin	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________

Visit 7: Week 12

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

1. Did the subject attend the scheduled visit? ☐ 0 No ☐ 1 Yes

If No, provide source of information for this report:

☐ 0 None
☐ 1 Telephone contact
☐ 2 Spouse/relative
☐ 3 Subject's neighbor/friend
☐ 4 Health care provider
☐ 5 Public death registry
☐ 6 Other physician
☐ 7 Other *(specify)*: _____

If indirect contact, provide the subject status:
☐ 1 **Alive**
☐ 2 **Dead *Complete Death page***
☐ 77 **Unknown**

2. Date of assessment: __ __/__ __ __/__ __ __ __
dd mmm yyyy

Rehospitalization Details

Has the subject been rehospitalized since the last assessment?

☐ 0 No
☐ 1 Yes ***Complete Rehospitalization Page***
☐ 88 NA, subject still hospitalized

Study Drug Administration

1. Was study drug accountability performed? ☐ 0 No ☐ 1 Yes ***If Yes, complete the Study Drug Accountability Log***

2. Dose level assigned:

HYD or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

ISDN or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

3. Reason for dose change:
☐ 1 As per protocol
☐ 2 Adverse Event
☐ 88 Not Applicable
☐ 99 Other *(specify)*: _____

Vital Signs / Physical Assessment

1. Blood pressure: __ __ __/__ __ __ mmHg
systolic diastolic
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Body temp.: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight: __ __ __ . __ kg or __ __ __ . __ lbs

Physician Assessment (Check only one answer per question)

1. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
2. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
3. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
4. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
5. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Adverse Events

Were there any Adverse Events since the last assessment? ☐ 0 No ☐ 1 Yes

If Yes, complete the Non-Serious Adverse Events CRF page or the Serious Adverse Event Form, as applicable.

Record all medications on Concomitant Medication Log

Concomitant Medication Log – Visit 7: Week 12

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: Record medications subject taking at Visit 7				
Medication		Route	Dose	Frequency
ACE Inhibitors	________________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
ARBs	________________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Beta Blockers	________________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Loop Diuretics	________________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other Diuretics	________________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Inotropes	________________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Nitrates	________________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Aldosterone Blockers	________________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Digoxin	________________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	________________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	________________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	________________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________

Visit 8: Week 16

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

1. Did the subject attend the scheduled visit? ☐ 0 No ☐ 1 Yes

If No, provide source of information for this report:

☐ 0 None
☐ 1 Telephone contact
☐ 2 Spouse/relative
☐ 3 Subject's neighbor/friend
☐ 4 Health care provider
☐ 5 Public death registry
☐ 6 Other physician
☐ 7 Other *(specify)*: _____

If indirect contact, provide the subject status:
☐ 1 **Alive**
☐ 2 **Dead *Complete Death page***
☐ 77 **Unknown**

2. Date of assessment: __ __/__ __ __/__ __ __ __
dd mmm yyyy

Rehospitalization Details

Has the subject been rehospitalized since the last assessment?

☐ 0 No
☐ 1 Yes ***Complete Rehospitalization Page***
☐ 88 NA, subject still hospitalized

Study Drug Administration

1. Was study drug accountability performed? ☐ 0 No ☐ 1 Yes ***If Yes, complete the Study Drug Accountability Log***

2. Dose level assigned:

HYD or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

ISDN or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

3. Reason for dose change:
☐ 1 As per protocol
☐ 2 Adverse Event
☐ 88 Not Applicable
☐ 99 Other *(specify)*: _____

Vital Signs / Physical Assessment

1. Blood pressure: __ __ __/__ __ __ mmHg
systolic diastolic
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Body temp.: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight: __ __ __ . __ kg or __ __ __ . __ lbs

Physician Assessment (Check only one answer per question)

1. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
2. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
3. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
4. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
5. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Adverse Events

Were there any Adverse Events since the last assessment? ☐ 0 No ☐ 1 Yes

If Yes, complete the Non-Serious Adverse Events CRF page or the Serious Adverse Event Form, as applicable.

Record all medications on Concomitant Medication Log

B-A-HEF

Concomitant Medication Log – Visit 8: Week 16

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: Record medications subject taking at Visit 8				
Medication		Route	Dose	Frequency
ACE Inhibitors	___	☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
ARBs	___	☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
Beta Blockers	___	☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
Loop Diuretics	___	☐ 1 IV ☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
Other Diuretics	___	☐ 1 IV ☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
Inotropes	___	☐ 1 IV ☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
Nitrates	___	☐ 1 IV ☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
Aldosterone Blockers	___	☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
Digoxin	___	☐ 1 IV ☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
Other	___	☐ 1 IV ☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
Other	___	☐ 1 IV ☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___
Other	___	☐ 1 IV ☐ 2 PO ☐ 99 Other: ___	___ ☐ 1 mg ☐ 99 other ___	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ___

Visit 9: Week 20

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

1. Did the subject attend the scheduled visit? ☐ 0 No ☐ 1 Yes

If No, provide source of information for this report:

☐ 0 None
☐ 1 Telephone contact
☐ 2 Spouse/relative
☐ 3 Subject's neighbor/friend
☐ 4 Health care provider
☐ 5 Public death registry
☐ 6 Other physician
☐ 7 Other *(specify)*: _____

If indirect contact, provide the subject status:
☐ 1 **Alive**
☐ 2 **Dead *Complete Death page***
☐ 77 **Unknown**

2. Date of assessment: __ __/__ __ __/__ __ __ __
dd mmm yyyy

Rehospitalization Details

Has the subject been rehospitalized since the last assessment?

☐ 0 No
☐ 1 Yes ***Complete Rehospitalization Page***
☐ 88 NA, subject still hospitalized

Study Drug Administration

1. Was study drug accountability performed? ☐ 0 No ☐ 1 Yes ***If Yes, complete the Study Drug Accountability Log***

2. Dose level assigned:

HYD or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

ISDN or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

3. Reason for dose change:
☐ 1 As per protocol
☐ 2 Adverse Event
☐ 88 Not Applicable
☐ 99 Other *(specify)*: _____

Vital Signs / Physical Assessment

1. Blood pressure: __ __ __/__ __ __ mmHg
systolic diastolic
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Body temp.: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight: __ __ __ . __ kg or __ __ __ . __ lbs

Physician Assessment (Check only one answer per question)

1. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
2. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
3. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
4. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
5. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Adverse Events

Were there any Adverse Events since the last assessment? ☐ 0 No ☐ 1 Yes

If Yes, complete the Non-Serious Adverse Events CRF page or the Serious Adverse Event Form, as applicable.

Record all medications on Concomitant Medication Log

Concomitant Medication Log – Visit 9: Week 20

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: Record medications subject taking at Visit 9				
Medication		**Route**	**Dose**	**Frequency**
ACE Inhibitors	________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
ARBs	________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Beta Blockers	________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Loop Diuretics	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other Diuretics	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Inotropes	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Nitrates	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Aldosterone Blockers	________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Digoxin	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________

Visit 10: Week 24

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

1. Did the subject attend the scheduled visit? ☐ 0 No ☐ 1 Yes

If No, provide source of information for this report:

☐ 0 None
☐ 1 Telephone contact
☐ 2 Spouse/relative
☐ 3 Subject's neighbor/friend
☐ 4 Health care provider
☐ 5 Public death registry
☐ 6 Other physician
☐ 7 Other *(specify)*: _____

If indirect contact, provide the subject status:

☐ 1 **Alive**
☐ 2 **Dead *Complete Death page***
☐ 77 **Unknown**

2. Date of assessment: __ __/__ __ __/__ __ __ __
dd mmm yyyy

Rehospitalization Details

Has the subject been rehospitalized since the last assessment?

☐ 0 No
☐ 1 Yes ***Complete Rehospitalization Page***
☐ 88 NA, subject still hospitalized

Study Drug Administration

1. Was study drug accountability performed? ☐ 0 No ☐ 1 Yes ***If Yes, complete the Study Drug Accountability Log***

2. Dose level assigned:

HYD or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

ISDN or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

3. Reason for dose change:
☐ 1 As per protocol
☐ 2 Adverse Event
☐ 88 Not Applicable
☐ 99 Other *(specify)*: _____

Vital Signs / Physical Assessment

1. Blood pressure: __ __ __/__ __ __ mmHg
systolic diastolic
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Body temp.: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight: __ __ __ . __ kg or __ __ __ . __ lbs

Physician Assessment (Check only one answer per question)

1. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
2. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
3. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
4. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
5. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Adverse Events

Were there any Adverse Events since the last assessment? ☐ 0 No ☐ 1 Yes

If Yes, complete the Non-Serious Adverse Events CRF page or the Serious Adverse Event Form, as applicable.

Record all medications on Concomitant Medication Log

Visit 10: Week 24

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

6 Minute Walk Test and Subject Self-Report of Symptoms

1. 6MWT Distance: __ __ __ __ m
2. Dyspnea VAS: __ __ __ mm
3. General Well-Being VAS: __ __ __ mm

Local Laboratory Results

Glucose	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____	**Uric Acid**	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____
Sodium	_____	☐ 3 mmol/L ☐ 4 mEq/L ☐ 99 _____	**Creatinine**	_____	☐ 1 mg/dL ☐ 2 µmol/L ☐ 99 _____
Potassium	_____	☐ 3 mmol/L ☐ 4 mEq/L ☐ 99 _____	**Bilirubin**	_____	☐ 1 mg/dL ☐ 2 µmol/L ☐ 99 _____
BUN	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____	**Albumin**	_____	☐ 5 g/L ☐ 6 g/dL ☐ 99 _____
AST	_____	☐ 10 IU/L ☐ 99 _____	**Hemoglobin**	_____	☐ 3 mmol/L ☐ 5 g/L ☐ 6 g/dL ☐ 99 _____
ALT	_____	☐ 10 IU/L ☐ 99 _____	**Total WBC**	_____	☐ 7 $x10^9$/L ☐ 8 /mm^3 ☐ 99 _____
Alkaline Phosphatase	_____	☐ 10 IU/L ☐ 99 _____	**Lymphocytes**	_____	☐ 9 % ☐ 99 _____

Biomarker Samples

Were samples for biomarker assays drawn? ☐ 0 No ☐ 1 Yes, ***Date:*** __ __/__ __ __/__ __ __ __
dd mmm yyyy

Echocardiographic Evaluation

Date and time of echocardiogram: __ __/__ __ __/__ __ __ __ (dd / mmm / yyyy) __ __ : __ __ (24 hr clock)

1. Heart Rate: __ __ __ bpm ☐ 1 Normal sinus rhythm ☐ 2 Atrial Fibrillation ☐ 99 Other: _____

Left Heart Dimensions and LV Function

2. Left ventricular size systole: _____ ☐ 1 mm ☐ 99 other: _____
3. Left ventricular size diastole: _____ ☐ 1 mm ☐ 99 other: _____
4. Ejection Fraction: __ __ %
5. Intra ventricular septum *(diastole)*: _____ ☐ 1 mm ☐ 99 other: _____
6. Posterior wall *(diastole)*: _____ ☐ 1 mm ☐ 99 other: _____
7. Left atrial size, antero-posterior: _____ ☐ 1 mm ☐ 99 other: _____
8. Left atrial size, planimetry: _____ ☐ 1 mm^2 ☐ 99 other: _____

Diastolic Function

9. Mitral E-wave velocity: _____ ☐ 1 mm/sec ☐ 99 other: _____
10. E-wave deceleration time: _____ ☐ 1 msec ☐ 99 other: _____
11. Mitral A-wave velocity: _____ ☐ 1 mm/sec ☐ 99 other: _____ ☐ 88 NA
12. Mitral A-wave (duration): _____ ☐ 1 msec ☐ 99 other: _____ ☐ 88 NA

Right Heart Dimensions and Function — Severity

13. Dilatation right ventricle: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe
14. Dilatation right atrium: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe
15. Tricuspid regurgitation (TR) velocity: _____ ☐ 1 cm/sec ☐ 99 other: _____
16. Right ventricular systolic pressure (RVSP): _____ mmHg
17. Tricuspid annular plane systolic excursion (TAPSE): _____ ☐ 1 mm ☐ 99 other: _____

Valvular — Severity — Rheumatic?

18. Aortic Stenosis:	☐ 0 None	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
19. Aortic Regurgitation:	☐ 0 None/trace	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
20. Mitral Stenosis:	☐ 0 None	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
21. Mitral Regurgitation:	☐ 0 None/trace	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
22. Tricuspid Regurgitation:	☐ 0 None/trace	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
23. Other:	☐ 0 None	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA

Pericardial Effusion — Severity

24. Pericardial effusion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe

25. Other Conditions: ☐ 0 No ☐ 1 Yes ➔ **Specify:** _____
26. Other Conditions: ☐ 0 No ☐ 1 Yes ➔ **Specify:** _____

Concomitant Medication Log – Visit 10: Week 24

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: Record medications subject taking at Visit 10				
Medication		**Route**	**Dose**	**Frequency**
ACE Inhibitors	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
ARBs	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Beta Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Loop Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Inotropes	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Nitrates	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Aldosterone Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Digoxin	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________

B-A-HEF

Study Drug Accountability Log

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Study Drug Accountability

Study Drug Status		Date Returned	Number of tablets returned	Date Dispensed	Number of tablets dispensed	Study Drug Kit Label(s)	
Visit 2: Randomization	**Was study drug dispensed?** ☐ 0 No, ***specify:*** ☐ 1 Subject withdrew consent ☐ 2 Death ☐ 3 Study drug intolerability ☐ 99 Other *(specify)*: _____ ☐ 1 Yes, ***provide details*** →			__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	*Affix study drug kit label(s) here*	*Affix study drug kit label(s) here*
Visit 4: Week 2	**Was study drug dispensed?** ☐ 0 No, ***specify:*** ☐ 1 Subject withdrew consent ☐ 2 Death ☐ 3 Study drug intolerability ☐ 99 Other *(specify)*: _____ ☐ 1 Yes, ***provide details*** →	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	*Affix study drug kit label(s) here*	*Affix study drug kit label(s) here*
Visit 5: Week 4	**Was study drug dispensed?** ☐ 0 No, ***specify:*** ☐ 1 Subject withdrew consent ☐ 2 Death ☐ 3 Study drug intolerability ☐ 99 Other *(specify)*: _____ ☐ 1 Yes, ***provide details*** →	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	*Affix study drug kit label(s) here*	*Affix study drug kit label(s) here*

Study Drug Accountability Log

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Study Drug Accountability

Study Drug Status		Date Returned	Number of tablets returned	Date Dispensed	Number of tablets dispensed	Study Drug Kit Label(s)	
Visit 6: Week 8	**Was study drug dispensed?** ☐ 0 No, ***specify:*** ☐ 1 Subject withdrew consent ☐ 2 Death ☐ 3 Study drug intolerability ☐ 99 Other *(specify)*: _____ ☐ 1 Yes, ***provide details*** →	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	*Affix study drug kit label(s) here*	*Affix study drug kit label(s) here*
Visit 7: Week 12	**Was study drug dispensed?** ☐ 0 No, ***specify:*** ☐ 1 Subject withdrew consent ☐ 2 Death ☐ 3 Study drug intolerability ☐ 99 Other *(specify)*: _____ ☐ 1 Yes, ***provide details*** →	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	*Affix study drug kit label(s) here*	*Affix study drug kit label(s) here*
Visit 8: Week 16	**Was study drug dispensed?** ☐ 0 No, ***specify:*** ☐ 1 Subject withdrew consent ☐ 2 Death ☐ 3 Study drug intolerability ☐ 99 Other *(specify)*: _____ ☐ 1 Yes, ***provide details*** →	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	*Affix study drug kit label(s) here*	*Affix study drug kit label(s) here*

Study Drug Accountability Log

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Study Drug Accountability

Study Drug Status		Date Returned	Number of tablets returned	Date Dispensed	Number of tablets dispensed	Study Drug Kit Label(s)	
Visit 9: Week 20	**Was study drug dispensed?** ☐ 0 No, ***specify:*** ☐ 1 Subject withdrew consent ☐ 2 Death ☐ 3 Study drug intolerability ☐ 99 Other *(specify)*: _____ ☐ 1 Yes, ***provide details*** →	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____	*Affix study drug kit label(s) here*	*Affix study drug kit label(s) here*
Visit 10: Week 24		__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____				
Early Study Drug Termination		__ __/__ __ __/__ __ __ __ dd mmm yyyy Initials: _____	HYD or placebo _____ ISDN or placebo _____				

Non-Serious Adverse Events

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Non-Serious Adverse Events

Did the subject experience any non-serious adverse event(s) that started between study drug start through 30 days post study drug discontinuation?

☐ 0 No ☐ 1 Yes*, If Yes. Provide details below:*

Adverse event	Start date	Maximum intensity	Action taken with study drug	Outcome	Causal relationship to study drug: HYD or HYD placebo	Causal relationship to study drug: ISDN or ISDN placebo	Was this event serious?	Stop date or ongoing at final exam
	__ __/__ __ __/__ __ __ __ dd mmm yyyy	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 None ☐ 4 Dose decreased ☐ 5 Temporarily interrupted ☐ 6 Discontinued	☐ 1 Resolved ☐ 2 Resolved with sequelae ☐ 3 Unresolved ☐ 4 Death	☐ 1 Suspected ☐ 2 Not suspected	☐ 1 Suspected ☐ 2 Not suspected	☒ 0 No*	__ __/__ __ __/__ __ __ __ dd mmm yyyy OR ☐ 1 Ongoing at final exam
	__ __/__ __ __/__ __ __ __ dd mmm yyyy	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 None ☐ 4 Dose decreased ☐ 5 Temporarily interrupted ☐ 6 Discontinued	☐ 1 Resolved ☐ 2 Resolved with sequelae ☐ 3 Unresolved ☐ 4 Death	☐ 1 Suspected ☐ 2 Not suspected	☐ 1 Suspected ☐ 2 Not suspected	☒ 0 No*	__ __/__ __ __/__ __ __ __ dd mmm yyyy OR ☐ 1 Ongoing at final exam
	__ __/__ __ __/__ __ __ __ dd mmm yyyy	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 None ☐ 4 Dose decreased ☐ 5 Temporarily interrupted ☐ 6 Discontinued	☐ 1 Resolved ☐ 2 Resolved with sequelae ☐ 3 Unresolved ☐ 4 Death	☐ 1 Suspected ☐ 2 Not suspected	☐ 1 Suspected ☐ 2 Not suspected	☒ 0 No*	__ __/__ __ __/__ __ __ __ dd mmm yyyy OR ☐ 1 Ongoing at final exam
	__ __/__ __ __/__ __ __ __ dd mmm yyyy	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 None ☐ 4 Dose decreased ☐ 5 Temporarily interrupted ☐ 6 Discontinued	☐ 1 Resolved ☐ 2 Resolved with sequelae ☐ 3 Unresolved ☐ 4 Death	☐ 1 Suspected ☐ 2 Not suspected	☐ 1 Suspected ☐ 2 Not suspected	☒ 0 No*	__ __/__ __ __/__ __ __ __ dd mmm yyyy OR ☐ 1 Ongoing at final exam

Please record all Serious Adverse Events on the Serious Adverse Event Form.

Non-Serious Adverse Events

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Non-Serious Adverse Events

Did the subject experience any non-serious adverse event(s) that started between study drug start through 30 days post study drug discontinuation?

☐ 0 No ☐ 1 Yes***, If Yes. Provide details below:***

Adverse event	Start date	Maximum intensity	Action taken with study drug	Outcome	Causal relationship to study drug: HYD or HYD placebo	Causal relationship to study drug: ISDN or ISDN placebo	Was this event serious?	Stop date or ongoing at final exam
	__ __/__ __ __/__ __ __ __ dd mmm yyyy	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 None ☐ 4 Dose decreased ☐ 5 Temporarily interrupted ☐ 6 Discontinued	☐ 1 Resolved ☐ 2 Resolved with sequelae ☐ 3 Unresolved ☐ 4 Death	☐ 1 Suspected ☐ 2 Not suspected	☐ 1 Suspected ☐ 2 Not suspected	X 0 No*	__ __/__ __ __/__ __ __ __ dd mmm yyyy OR ☐ 1 Ongoing at final exam
	__ __/__ __ __/__ __ __ __ dd mmm yyyy	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 None ☐ 4 Dose decreased ☐ 5 Temporarily interrupted ☐ 6 Discontinued	☐ 1 Resolved ☐ 2 Resolved with sequelae ☐ 3 Unresolved ☐ 4 Death	☐ 1 Suspected ☐ 2 Not suspected	☐ 1 Suspected ☐ 2 Not suspected	X 0 No*	__ __/__ __ __/__ __ __ __ dd mmm yyyy OR ☐ 1 Ongoing at final exam
	__ __/__ __ __/__ __ __ __ dd mmm yyyy	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 None ☐ 4 Dose decreased ☐ 5 Temporarily interrupted ☐ 6 Discontinued	☐ 1 Resolved ☐ 2 Resolved with sequelae ☐ 3 Unresolved ☐ 4 Death	☐ 1 Suspected ☐ 2 Not suspected	☐ 1 Suspected ☐ 2 Not suspected	X 0 No*	__ __/__ __ __/__ __ __ __ dd mmm yyyy OR ☐ 1 Ongoing at final exam
	__ __/__ __ __/__ __ __ __ dd mmm yyyy	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	☐ 0 None ☐ 4 Dose decreased ☐ 5 Temporarily interrupted ☐ 6 Discontinued	☐ 1 Resolved ☐ 2 Resolved with sequelae ☐ 3 Unresolved ☐ 4 Death	☐ 1 Suspected ☐ 2 Not suspected	☐ 1 Suspected ☐ 2 Not suspected	X 0 No*	__ __/__ __ __/__ __ __ __ dd mmm yyyy OR ☐ 1 Ongoing at final exam

Please record all Serious Adverse Events on the Serious Adverse Event Form.

B-A-HEF

Rehospitalization Form

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Rehospitalization Details

1. Date of hospital admission: __ __/__ __ __/__ __ __ __ (dd / mmm / yyyy)

2. Provide primary cause of hospitalization:
   - ☐ 1 Heart Failure
   - ☐ 2 Myocardial Infarction
   - ☐ 3 Unstable angina
   - ☐ 4 Chest Pain
   - ☐ 5 Acute renal failure
   - ☐ 6 Pneumonia
   - ☐ 7 COPD
   - ☐ 99 Other: _____

3. Was the subject discharged?
   - ☐ 0 No, due to death ***Complete Death Page***
   - ☐ 1 Yes ***If Yes, record discharge date:*** __ __/__ __ __/__ __ __ __ (dd / mmm / yyyy)

4. Provide the type of rehospitalization:
   - ☐ 1 Planned
   - ☐ 2 Unplanned, ***Please report event on SAE Form***

5. Did heart failure contribute to rehospitalization? ☐ 0 No ☐ 1 Yes

6. Did renal impairment contribute to rehospitalization? ☐ 0 No ☐ 1 Yes

7. Describe the hospital course: _____

_____

_____

Physical Examination on Presentation

1. Blood pressure: __ __ __/__ __ __ mmHg (systolic / diastolic)
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
5. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
6. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
7. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
8. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Diagnostic Findings

ECG: ☐ 1 Normal ☐ 2 Abnormal _____

_____

Chest x-ray: ☐ 1 Normal ☐ 2 Abnormal _____

_____

Echo: ☐ 1 Normal ☐ 2 Abnormal _____

_____

Other: _____

B-A-HEF

Rehospitalization Form

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Medication Details

1. Were there any changes or additions to oral medications? ☐ 0 No ☐ 1 Yes, *provide details*:

_____

_____

_____

_____

_____

_____

_____

_____

_____

2. Were there any IV medications given? ☐ 0 No ☐ 1 Yes, *provide details*:

_____

_____

_____

_____

_____

_____

_____

_____

_____

Rehospitalization Form

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Rehospitalization Details

1. Date of hospital admission: __ __/__ __ __/__ __ __ __ (dd / mmm / yyyy)

2. Provide primary cause of hospitalization:
   - ☐ 1 Heart Failure
   - ☐ 2 Myocardial Infarction
   - ☐ 3 Unstable angina
   - ☐ 4 Chest Pain
   - ☐ 5 Acute renal failure
   - ☐ 6 Pneumonia
   - ☐ 7 COPD
   - ☐ 99 Other: _____

3. Was the subject discharged?
   - ☐ 0 No, due to death ***Complete Death Page***
   - ☐ 1 Yes ***If Yes, record discharge date:*** __ __/__ __ __/__ __ __ __ (dd / mmm / yyyy)

4. Provide the type of rehospitalization:
   - ☐ 1 Planned
   - ☐ 2 Unplanned, ***Please report event on SAE Form***

5. Did heart failure contribute to rehospitalization? ☐ 0 No ☐ 1 Yes

6. Did renal impairment contribute to rehospitalization? ☐ 0 No ☐ 1 Yes

7. Describe the hospital course: _____

_____

_____

Physical Examination on Presentation

1. Blood pressure: __ __ __/__ __ __ mmHg (systolic / diastolic)
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
5. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
6. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
7. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
8. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Diagnostic Findings

ECG: ☐ 1 Normal ☐ 2 Abnormal _____

_____

Chest x-ray: ☐ 1 Normal ☐ 2 Abnormal _____

_____

Echo: ☐ 1 Normal ☐ 2 Abnormal _____

_____

Other: _____

Rehospitalization Form

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Medication Details

1. Were there any changes or additions to oral medications? ☐ 0 No ☐ 1 Yes, *provide details*:

_____

_____

_____

_____

_____

_____

_____

_____

_____

2. Were there any IV medications given? ☐ 0 No ☐ 1 Yes, *provide details*:

_____

_____

_____

_____

_____

_____

_____

_____

_____

Death

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Death

Did the subject die between signing informed consent and completing the study?

- ☐ 0 No
- ☐ 1 Yes, ***Complete the following section and report event on SAE Form.***
- ☐ 77 Unknown, subject lost to follow up or withdrew consent from review of records

Death Details

1. Date of death: __ __/__ __ __/__ __ __ __
   dd mmm yyyy
2. Provide primary cause of death:
   - ☐ 1 Heart failure/pump failure
   - ☐ 2 Sudden death
   - ☐ 3 Cerebral vascular accident (CVA)/stroke
   - ☐ 4 Sepsis
   - ☐ 77 Unknown
   - ☐ 99 Other: _____
3. Did the death occur in hospital?
   - ☐ 0 No
   - ☐ 1 Yes ***Complete Rehospitalization Form***
4. Describe the events leading up to the subject's death: _____
   _____
   _____
   _____
   _____
   _____
   _____
   _____
   _____
5. Describe the pertinent clinical history as is relates to the cause of death: _____
   _____
   _____
   _____
   _____
   _____
   _____
   _____
   _____

B-A-HEF

Withdrawal of Consent

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

Did the subject withdraw consent from participating in any aspects of the study?

☐ 0 No

☐ 1 Yes, ***Please enter date of withdrawal of consent***

Withdrawal of Consent Details

1. Withdrawal of consent date: __ __/__ __ __/__ __ __ __
   dd mmm yyyy

2. Level of withdrawal of consent *(check all that apply)*:

   ☐ 1 Not willing to receive any additional study drug

   ☐ 1 Not willing to provide any additional laboratory samples (blood draws and urine samples)

   ☐ 1 Not willing to provide detailed information about symptoms or be examined for study purposes.

   ☐ 1 Not willing to be contacted to check on progress.

   ☐ 1 Not willing to allow use of information from hospital records or health registration system to check on progress.

3. Did the subject re-consent to any of the levels above?

   ☐ 0 No

   ☐ 1 Yes, ***Please provide the level(s) the subject is now willing to participate*** *(check all that apply)*:

      ☐ 1 Now willing to receive any additional study drug

      ☐ 1 Now willing to provide any additional laboratory samples (blood draws and urine samples)

      ☐ 1 Now willing to provide detailed information about symptoms or be examined for study purposes.

      ☐ 1 Now willing to be contacted to check on progress.

      ☐ 1 Now willing to allow use of information from hospital records or health registration system to check on progress.

End of Study

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

1. Did the subject complete the double blind phase of the study?
   - ☐ 1 Yes, completed Week 24 Visit
   - ☐ 0 No

   If No, choose primary reason *(check only one)*
   - ☐ 1 Subject withdrew consent from follow-up, ***enter date subject withdrew below and fill out Withdrawal of Consent Page***
   - ☐ 2 Death, ***enter date subject died below and fill out Death Page***
   - ☐ 3 Subject was lost to follow-up, ***enter date last known alive below***

2. End of study date: __ __/__ __ __/__ __ __ __
   dd mmm yyyy

3. Will the subject continue in the open-label active treatment extension?
   - ☐ 1 Yes
   - ☐ 0 No

Investigator's signature

I have reviewed and found all the case report form data pertaining to this subject to be complete and accurate.

Investigator: _____ Date: __ __/__ __ __/__ __ __ __
Signature of Investigator
dd mmm yyyy

B-A-HEF

Unscheduled Visit: Early Termination of Study Drug

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Subject Status

1. Did the subject attend the scheduled visit? ☐ 0 No ☐ 1 Yes

If No, provide source of information for this report:

☐ 0 None
☐ 1 Telephone contact
☐ 2 Spouse/relative
☐ 3 Subject's neighbor/friend
☐ 4 Health care provider
☐ 5 Public death registry
☐ 6 Other physician
☐ 7 Other *(specify)*: _____

If indirect contact, provide the subject status:
☐ 1 **Alive**
☐ 2 **Dead *Complete Death page***
☐ 77 **Unknown**

2. Date of assessment: __ __/__ __ __/__ __ __ __
dd mmm yyyy

Rehospitalization Details

Has the subject been rehospitalized since the last assessment?

☐ 0 No
☐ 1 Yes ***Complete Rehospitalization Page***
☐ 88 NA, subject still hospitalized

Study Drug Administration

1. Was study drug accountability performed? ☐ 0 No ☐ 1 Yes ***If Yes, complete the Study Drug Accountability Log***

2. Dose level assigned:

HYD or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

ISDN or placebo:
☐ 0 None
☐ 1 One tablet 3x daily
☐ 2 Two tablets 3x daily

3. Reason for dose change:
☐ 1 As per protocol
☐ 2 Adverse Event
☐ 88 Not Applicable
☐ 99 Other *(specify)*: _____

Vital Signs / Physical Assessment

1. Blood pressure: __ __ __/__ __ __ mmHg
systolic diastolic
2. Heart Rate: __ __ __ bpm
3. Respiration: __ __ breaths/min
4. Body temp.: __ __ __ . __ °C or __ __ __ . __ °F
5. Weight: __ __ __ . __ kg or __ __ __ . __ lbs

Physician Assessment (Check only one answer per question)

1. Dyspnea on exertion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe (including dyspnea at rest)
2. Orthopnea: ☐ 0 None ☐ 1 1 pillow (10 cm) ☐ 2 2 pillows (20 cm) ☐ 3 > 30 degrees
3. Edema: ☐ 0 0 ☐ 1 1 + ☐ 2 2+ ☐ 3 3+
4. Rales: ☐ 0 No rales ☐ 1 Rales < 1/3 ☐ 2 Rales 1/3-2/3 ☐ 3 Rales > 2/3
5. Jugular venous pulse (JVP): ☐ 0 < 6 cm ☐ 1 6-10 cm ☐ 2 > 10 cm ☐ 88 Not Evaluable

Adverse Events

Were there any Adverse Events since the last assessment? ☐ 0 No ☐ 1 Yes

If Yes, complete the Non-Serious Adverse Events CRF page or the Serious Adverse Event Form, as applicable.

Record all medications on Concomitant Medication Log

Unscheduled Visit: Early Termination of Study Drug

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

6 Minute Walk Test and Subject Self-Report of Symptoms

1. 6MWT Distance: __ __ __ __ m
2. Dyspnea VAS: __ __ __ mm
3. General Well-Being VAS: __ __ __ mm

Local Laboratory Results

Glucose	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____	**Uric Acid**	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____
Sodium	_____	☐ 3 mmol/L ☐ 4 mEq/L ☐ 99 _____	**Creatinine**	_____	☐ 1 mg/dL ☐ 2 µmol/L ☐ 99 _____
Potassium	_____	☐ 3 mmol/L ☐ 4 mEq/L ☐ 99 _____	**Bilirubin**	_____	☐ 1 mg/dL ☐ 2 µmol/L ☐ 99 _____
BUN	_____	☐ 1 mg/dL ☐ 3 mmol/L ☐ 99 _____	**Albumin**	_____	☐ 5 g/L ☐ 6 g/dL ☐ 99 _____
AST	_____	☐ 10 IU/L ☐ 99 _____	**Hemoglobin**	_____	☐ 3 mmol/L ☐ 5 g/L ☐ 6 g/dL ☐ 99 _____
ALT	_____	☐ 10 IU/L ☐ 99 _____	**Total WBC**	_____	☐ 7 x10^9/L ☐ 8 /mm^3 ☐ 99 _____
Alkaline Phosphatase	_____	☐ 10 IU/L ☐ 99 _____	**Lymphocytes**	_____	☐ 9 % ☐ 99 _____

Biomarker Samples

Were samples for biomarker assays drawn? ☐ 0 No ☐ 1 Yes, ***Date:*** __ __/__ __ __/__ __ __ __
dd mmm yyyy

Unscheduled Visit: Early Termination of Study Drug

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Echocardiographic Evaluation

Date and time of echocardiogram: __ __/__ __ __/__ __ __ __ (dd / mmm / yyyy) __ __ : __ __ (24 hr clock)

1. Heart Rate: __ __ __ bpm ☐ 1 Normal sinus rhythm ☐ 2 Atrial Fibrillation ☐ 99 Other: _____

Left Heart Dimensions and LV Function

2. Left ventricular size systole: _____ ☐ 1 mm ☐ 99 other: _____
3. Left ventricular size diastole: _____ ☐ 1 mm ☐ 99 other: _____
4. Ejection Fraction: __ __ %
5. Intra ventricular septum *(diastole)*: _____ ☐ 1 mm ☐ 99 other: _____
6. Posterior wall *(diastole)*: _____ ☐ 1 mm ☐ 99 other: _____
7. Left atrial size, antero-posterior: _____ ☐ 1 mm ☐ 99 other: _____
8. Left atrial size, planimetry: _____ ☐ 1 mm^2 ☐ 99 other: _____

Diastolic Function

9. Mitral E-wave velocity: _____ ☐ 1 mm/sec ☐ 99 other: _____
10. E-wave deceleration time: _____ ☐ 1 msec ☐ 99 other: _____
11. Mitral A-wave velocity: _____ ☐ 1 mm/sec ☐ 99 other: _____ ☐ 88 NA
12. Mitral A-wave (duration): _____ ☐ 1 msec ☐ 99 other: _____ ☐ 88 NA

Right Heart Dimensions and Function — Severity

13. Dilatation right ventricle: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe
14. Dilatation right atrium: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe
15. Tricuspid regurgitation (TR) velocity: _____ ☐ 1 cm/sec ☐ 99 other: _____
16. Right ventricular systolic pressure (RVSP): _____ mmHg
17. Tricuspid annular plane systolic excursion (TAPSE): _____ ☐ 1 mm ☐ 99 other: _____

Valvular — Severity — Rheumatic?

18. Aortic Stenosis:	☐ 0 None	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
19. Aortic Regurgitation:	☐ 0 None/trace	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
20. Mitral Stenosis:	☐ 0 None	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
21. Mitral Regurgitation:	☐ 0 None/trace	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
22. Tricuspid Regurgitation:	☐ 0 None/trace	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA
23. Other:	☐ 0 None	☐ 1 Mild	☐ 2 Moderate	☐ 3 Severe	☐ 0 No	☐ 1 Yes	☐ 88 NA

Pericardial Effusion — Severity

24. Pericardial effusion: ☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe

25. Other Conditions: ☐ 0 No ☐ 1 Yes ➔ **Specify:** _____

26. Other Conditions: ☐ 0 No ☐ 1 Yes ➔ **Specify:** _____

B-A-HEF

Concomitant Medication Log – Early Termination of Study Drug

Site Number: __ __ __ __ Subject Number: __ __ __ Subject Initials: __ __ __

Concomitant Medication Log: Record medications subject taking at the Early Termination visit				
Medication		**Route**	**Dose**	**Frequency**
ACE Inhibitors	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
ARBs	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Beta Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Loop Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other Diuretics	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Inotropes	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Nitrates	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Aldosterone Blockers	____________	☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Digoxin	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________
Other	____________	☐ 1 IV ☐ 2 PO ☐ 99 Other: ________	________ ☐ 1 mg ☐ 99 other ________	☐ 1 QD ☐ 2 BID ☐ 3 TID ☐ 99 Other: ________