Title

A study of the contemporary profile, clinical outcomes and economic burden of acute heart failure in Abeokuta, Nigeria

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Thesis statement

A thesis submitted to the Faculty of Health Sciences, University of Witwatersrand,

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Candidate's declaration

I, Okechukwu Samuel Ogah declare that the thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

15th day of September , 2016

Dedication

This work is dedicated to my wife- **Fisayo,** and our images- **Chiamaka, Chidinma, Chidiebere** and **Chinelo** for their patience, care and understanding.

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First and foremost, I want to thank the ALMIGHTY GOD who has given me the Grace, Wisdom, Knowledge, Understanding and Patience to pursue this programme. Surely HE is “greater than the greatest, wiser than the wisest, better than the best and higher than the highest”. He is omniscient, the fountain of knowledge and the source of all blessings.

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TO GOD BE THE GLORY!

Publications and presentations arising from this work

A. Original Articles

1. **Ogah OS**, Stewart S, Falase AO, Akinyemi OJ, Adegbite GD, Alabi AA, Adesina JO, Durodola A, Sliwa K. Contemporary profile of acute heart failure in Southern Nigeria: Data from the Abeokuta Heart Failure Clinical Registry **(Published, JACC-Heart failure) JACC. Heart failure** 2014;**2**(3):250-9 .

2. **Ogah OS**, Stewart S, Falase AO, Akinyemi OJ, Adegbite GD, Alabi AA, Adesina JO, Durodola A, Sliwa K . Short-term outcome after hospital discharge in patients admitted with heart failure in Abeokuta, Nigeria: Data from the Abeokuta Heart Failure Registry **(Published, Cardiovascular Journal of Africa) Cardiovasc J Afr**. 2014 Sep 10;25:1-7. doi: 10.5830/CVJA-2014-040

3. **Ogah OS,** Stewart S, Falase AO, Akinyemi OJ, Adegbite GD, Alabi AA, Adesina JO, Durodola A, Sliwa K. Predictors of rehospitalisation in patients admitted with heart failure in Abeokuta, Nigeria: Data from the Abeokuta Heart failure Registry **(Published -Journal of Cardiac Failure) J Card Fail.** 2014 Nov; 20(11):833-40. doi: 10.1016/j.cardfail.2014.08.012.

4. **Ogah OS,** Stewart S**,** Falase AO, Onwujekwe OE, Olunuga TO, Adebayo SO, Sliwa K, The Healthcare cost of Heart Failure in Abeokuta, Nigeria: Insights from the Abeokuta Heart Failure Registry **(Published- Plos one) PLoS ONE 9(11): e113032. doi:10.1371/journal.pone.0113032**

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B. Review Articles

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10.Ogah OS, Falase AO, Stewart S, Sliwa S. Global Epidemiology of acute heart failure: A review **(Prepared for Cardiovascular Journal of Africa)**

C. Editorial

11. Cotter G, Cotter-Davison B, **Ogah OS**. The burden of heart failure in Africa. **European Journal of Heart Failure** 2013;**15**(8):829-31 doi: 10.1093/eurjhf/hft073[published Online First: Epub Date]|

Abstracts/ Presentations at international and local scientific conferences/meetings related to the PhD Project

1.Ogah OS, Preliminary result of a heart failure registry in Abeokuta, Nigeria : Data from the Abeokuta heart failure registry (Abstract.) **Cardiovasc J Afr.. 2009; 20(5):7.** Paper presented at the Pan African society of Cardiology conference and annual Nigerian Cardiac society congress held in Abuja Nigeria on 26-30 September, 2009

2. Ogah OS. The progression from hypertension to Heart failure. Paper presented at the Pan African society of Cardiology conference and annual Nigerian Cardiac society congress held in Abuja Nigeria on 26-30 September, 2009

3.Ogah OS. Heart Disease leading to heart failure in Nigeria. Paper presented at the South African Heart Congress. Sun City, South Africa 2009.

4.Ogah OS. Epidemiology of Heart Failure in Abeokuta Nigeria, Data from the Abeokuta Heart Failure Registry: Are there opportunities for the study of the molecular biology of Heart failure in Nigeria.

Paper presented at the International conference organized by the Alexander Von Humbodt Stiftung/Foundation Gemany in collaboration with the Ladoke Akintola University Osogbo, Nigeria titled 'Biotechnology: trends in advancement of life science research and development

in Nigeria' held at MicCom Golf Hotel and Resort , Obokun Road, Ada, Osun State, Nigeria on 9-12 August 2009

5.Ogah OS, Adegbite GD, Akinyemi RO, Falase AO, Carrington M, Stewart S, Sliwa K Epidemiology of Acute Heart Failure in Southern Nigeria: Data From The Abeokuta Heart Failure Registry(Abstract). ***Circulation*. 2010;122:e229**. Paper presented at the World Congress of Cardiology held in Beijing, China, 16-19 June 2010.

6.Ogah OS. Pulmonary Hypertension and Pulmonary Heart Disease in Nigeria: A Review (Abstract) ***PVRI Review*. 2010;2:95.** Paper presented at the 1st meeting of the Pulmonary Vascular Research Institute, Sub-Saharan Africa Region held in Cape Town, South Africa on 2010.

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8.Ogah OS, Falase AO, Carrington M, Stewart S, Sliwa K. Hypertensive heart failure in Nigerian Africans: Insights from the Abeokuta heart failure registry (Abstract) ***Circulation*. 2012; 125:e703.** Paper presented at the World Congress of Cardiology held in .Dubai, United Arab Emirate on 18-21 16-19 April 2012.

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11.Ogah OS, Stewart S, Onwujekwe OE, et al. Economic cost of Heart Failure in Abeokuta, Nigeria. Paper presented at the 43rd annual General Meeting and Scientific Conference of the Nigerian Cardiac Society, 18-19th September 2014 at Amazing Grace Event Centre, 25 Obio Imoh Street, Uyo, Akwa Ibom State, Nigeria.

12. **Ogah OS**, Stewart S, Falase AO, et al. Predictors of rehospitalisation in patients admitted with heart failure in Abeokuta, Nigeria. Journal of cardiac failure. Paper presented at the World Heart Failure Society Congress, 11-13 December 2014, AL AIN, United Arab Emirate.

13. **Ogah OS**, Stewart S, Falase AO, et al. Short-term outcomes after hospital discharge in patients admitted with heart failure in Abeokuta, Nigeria. Paper presented at the World Heart Failure Society Congress, 11-13 December 2014, AL AIN, United Arab Emirate

14. **Ogah OS**, Stewart S, Falase AO, et al. Contemporary profile of acute heart failure in Southern Nigeria: data from the Abeokuta Heart Failure Clinical Registry. Paper presented at the World Heart Failure Society Congress, 11-13 December 2014, AL AIN, United Arab Emirate

Other publications in the field of Heart Failure related to the work

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. **Archives of Internal Medicine. 2012;172:1386-1394**

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5.**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. Gender differences in clinical characteristics and outcome of acute heart failure in sub-saharan africa: Results of the THESUS-HF study. **Clinical research in cardiology, 2015 Jun;104(6):481-90**

Other recent publications in the other fields of Cardiovascular Medicine (Please see Appendix I)

Abstract

Background

Heart failure has become a global public health issue because of the rising global burden, high cost of care, frequent rehospitalisation and poor prognosis.

Compared to other regions of the world, there are limited data on contemporary clinical profile, outcome, and economic cost of heart failure in Sub-Saharan Africa in general and Nigeria (Africa's most populous country) in particular. We examined these in patients admitted with acute heart failure to a tertiary hospital in Nigeria.

Methods

This was a hospital based, prospective, observational study conducted at the Federal Medical Centre, Idi-Aba, Abeokuta, Nigeria. Detailed clinical documentation on cases of acute heart failure was carried out. The following data were obtained: demographic data, pre-admission history (previous heart failure related admissions). Others include NYHA functional class, symptoms, signs, self-reported cardiovascular risk factors, aetiology of heart failure, precipitating factors, co-morbidities, blood investigations, 12-lead ECG, echocardiography, medications and intra-hospital and 6-month outcomes.

The study cohort was prospectively followed up for 6 months post initial hospitalisation. The subjects were contacted through clinic visits or telephone calls at one and six months. Information obtained during follow-up included their wellbeing, prescribed pharmacotherapy, history of re-hospitalization and deaths (from next of kin if they died at home). In addition to patient or relation's telephone interviews, where necessary referring physicians were contacted for additional information.

The following health outcomes were documented - 1) length of initial hospital stay (LoS) in days, 2) survival status on discharge (dead or alive), 3) short-term case-fatality (30 days), 4) medium-term case-fatality (180 days), and 5) re-hospitalization status (180 days)

Heath economic data were extracted from the registry. Outpatient and inpatient costs were computed from the cohort of HF cases admitted in 2010 including personnel, diagnostic and treatment resources used for their management over a 12-month period. Indirect costs were also calculated. The annual cost per person was then calculated.

Results

The mean age of the subjects was 56.6±15.3 years (57.3±13.4 for men, 55.7±17.1 for women) and 204 (45.1%) were women. Overall, 415 (91.8%) subjects presented with de novo acute heart failure. The most common risk factor for HF was hypertension (pre-existing in 64.3% of cases). Type 2 diabetes mellitus was present in 41(10.0%). Hypertensive HF was the commonest aetiological cause of heart failure being responsible for 78.5% of cases. Dilated cardiomyopathy (7.5%), cor-pulmonale (4.4%), pericardial disease (3.3%), rheumatic heart disease (2.4%) and ischemic heart disease were less common (0.4%) causes. The majority (71.2%) of subjects presented with left ventricular dysfunction (mean left ventricular ejection fraction 43.9 ± 9.0%) and valvular dysfunction and abnormal left ventricular geometry were frequently documented. Mean duration of hospital stay was 11.4± 9.1 days and intra-hospital mortality was 3.8%.

Case fatality at 30-days was 4.2% (95%CI, 2.4-7.3%) for the cohort of newly presenting acute HF subjects that were followed up [3.9% (95%CI, 1.7-8.5%) in men and 4.5% (95%CI 2.1-9.3%) in women]. At 180-days, case-fatality was 7.3% (95%CI, 4.7-11.2%) [7.1% (95%CI, 3.8-12.7%) in men and 7.5% (95%CI 3.9-14.0%) for women] Patients with pericardial diseases had the highest early mortality. Mortality was related to some socio-demographic and clinical characteristics.

Thirty two denovo HF subjects (12.2%) were rehospitalised at least once. There were 21 men (65.6%) and 11(34.4%) women. Worsening heart failure was the commonest reason for readmission. Among others, factors associated with rehospitalization include presence of mitral regurgitation (OR, 2.37; 95%CI, 1.26-4.46), age greater than 60 years (OR, 2.04; 95%CI,

0.96-3.29), presence of tricuspid regurgitation (OR, 1.77; 95% CI, 0.86-3.61), and presence of atrial fibrillation (OR, 1.34; 95%CI, 0.59-3.03).

The total computed cost of care of HF in Abeokuta was 76, 288,845 Naira (US$508, 595) translating to 319,200 Naira (US$2,128 US Dollars) per patient per year. Inpatient and out-patient care contributed 46% and 54% of total cost respectively. The high cost of outpatient care was largely due to cost of transportation for monthly follow up visits. Payments were mostly made through out-of-pocket spending.

Conclusions

Compared to high income countries, individuals presenting with AHF in Abeokuta, Nigeria are relatively younger and still of a working age. It is also commoner in men and associated with severe symptoms because of late presentation.

Intra-hospital mortality is similar to other parts of the world. Rehospitalization after admission for HF is relatively common within 6-months.

The economic burden of heart failure in the study setting is high considering the minimum wage of 18,000 Naira (120 US dollars) per month in the country. This calls for financing reforms for the control of the disease, which may include a reduction or waiver of user fees in government hospitals, scaling up of financial risk protection pre-payment mechanisms such as health insurance and use of primary healthcare centres for follow-up visits for mild cases. The development and adequate funding of community HF care programmes in the country is also a possible panacea.

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Nomenclature

"A" wave	Late filling velocity of the ventricle in diastole
"E"	Early filling velocity of the ventricle in diastole
ACC	American College of Cardiology
ACEI	Angiotensin Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
ADHERE	Acute Decompensated Heart Failure National Registry
ADHF	Acute Decompensated Heart Failure
ADMA	Asymmetric dimethyl arginine
AF	Atrial fibrillation
AHA	American Heart Association
AHEAD	Acute Heart Failure Database
AIDS	Acquired immune deficiency syndrome
AIRE	Acute Infarction Ramipril Efficacy
AJOL	African Journals On-Line
AMVL	Anterior mitral valve leaflet
AO	Aortic root diameter
AR	Aortic Regurgitation
ARB	Angiotensin Receptor Blocker
ARVC	Arrhythmogenic right ventricular dysplasia
ASE	American Society of Echocardiography
ASE	American Society of Echocardiography
ATTEND	Acute Decompensated Heart Failure Syndromes
BC	Before Christ
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body surface area
CAD	Coronary Artery Disease
CD4	Cluster of differentiation 4
CDC	Centre for Disease Control
CH	Concentric Hypertrophy
CHARM	Assessment of Reduction in mortality and morbidity in patients with LV dysfunction already taking ACE inhibitors
CIBIS II	Cardiac Insufficiency Bisoprolol Study II
CKD	Chronic Kidney Disease
CONSENSUS	Cooperative North Scandinavia ENalapril Survival Study
COPD	Chronic obstructive pulmonary disease
COPERNICUS	Cavedilol Prospective Randomized Cumulative Survival
CRFs	Case report forms
CRT	Cardiac Resynchronisation Therapy
CV	Cardiovascular
CVDs	Cardiovascular diseases
DALYs	Disability adjusted life years
DBP	Diastolic Blood Pressure
DCM	Dilated Cardiomyopathy

DHF	Diastolic Heart Failure
DM	Diabetes Mellitus
DT	Deceleration Time
E/A	Ratio of the "E" wave to the "A" wave
ECG	Electrocardiography
ECHO	Echocardiography
EDTA	Ethylenediaminetetraacetic acid
EF	Ejection Fraction
EF	Ejection Fraction
EFICA	Etude Franc¸aise de l'Insuffisance Cardiaque Aigue
EGFR	Estimated Glomerular Filtration Rate
EH	Eccentric Hypertrophy
EMF	Endomyocardial fibrosis
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPHESUS	Eplerenone Post-AMI Heart Failure Efficacy and Survival Study
ESC	European Society of Cardiology
FMC	Federal Medical Centre
FS	Fractional shortening
HAART	Highly active antiretroviral therapy
HD	Heart disease
HF	Heart Failure
HFNEF	Heart Failure with Normal Ejection Fraction
HFPEF	Heart Failure with preserved ejection fraction
HHF	Hypertensive heart failure
HIV/AIDS	Human Immunodeficiency virus
HT-HF	Hypertensive heart failure
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
IHD	Ischaemic heart disease
ILVNC	Isolated left ventricular non-compaction
IVRT	Isovolumic relaxation time
IVSTd	Interventricular septal wall thickness in diastole
JVP	Jugular venous pressure
LASUTH	Lagos State University Teaching Hospital
LBBB	Left bundle branch block
LCZ 696	Entresto(TM) (sacubitril/valsartan)
LGA	Local Government Area
LOS	Length of stay in hospital
LV	Left Ventricular
LVEF	Left ventricular ejection fraction
LVH	Left Ventricular Hypertrophy
LVIDd	Left ventricular internal diameter in diastole
LVIDs	Left ventricular internal diameter in systole
LVM	Left ventricular mass
LVMI	Left ventricular mass index
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction

MR	Mitral regurgitation
NCDs	Non-Communicable Diseases
NSAIDs	Non-steroidal anti-inflammatory drugs
NT-proBNP	NT-Pro Brain Natriuretic Peptide
NYHA	New York heart association
OPTIMIZE	Organized program to initiate lifesaving treatment in hospitalized patients with heart failure
OR	Odd ratio
PCV	Packed cell volume
PHC	Primary Health Care
PMVL	Posterior Mitral valve leaflet
PND	Paroxysmal nocturnal dyspnea
PPCM	Peripartum cardiomyopathy
PWTd	Left ventricular posterior wall thickness in diastole
PWTs	Left ventricular posterior wall thickness in systole
RALES	Randomized Aldosterone Evaluation study
RBBB	Right bundle branch block
RHD	Rheumatic heart disease
RHF	Right heart failure
RO-AHFS	Romanian Acute Heart Failure Survey
RR	Relative Risk
RV	Right ventricle
RWT	Relative Wall thickness
SAVE	Survival and Ventricular Enlargement
SBP	Systolic Blood Pressure
SENIORS	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS)
SHF	Systolic Heart Failure
SHIFT	Systolic Heart Failure treatment with HF inhibitor Ivabradine trial
SOLVD	Studies of Left Ventricular Dysfunction
SPSS	Statistical Package of Social Sciences
SSA	Sub-Saharan Africa
SV	Sample Volume
THESUS-HF	The Sub-Saharan Africa Survey of Failure
TNF	Tumor Necrosis Factor
TR	Tricuspid Regurgitation
TRACE	Trandolapril Cardiac Evaluation
UK	United Kingdom
UNDP	United Nations Development Programme
US	United States
USA	United States of America
VAL-HEFT	Valsartan Heart Failure trial
VALIANT	Valsartan in Acute Myocardial Infarction
VHDX	Valvular Heart Disease
V-HEFT-II	Vasodilator – Heart Failure trial II
WCC	White Cell Count
WHO	World Health Organisation

Chapter 1: Introduction

1.1 Introduction

In the last 20-25 years, heart failure (HF) has emerged a major global public health problem. Although recognized as a more significant health problem in high income countries,(Sidney et al., 2013, Mosterd and Hoes, 2007) the syndrome both in its acute(Mosterd and Hoes, 2007) and chronic(Mosterd and Hoes, 2007) forms has emerged as an issue of global importance. It has been established that the burden of HF doubles with each passing decade after the age of 40 years especially in industrialized countries of the world due to aging population and increasing burden of risk factors including; hypertension, diabetes mellitus, ischaemic heart disease and, more recently obesity .(Cowie et al., 1997)

HF affects over 26 million people worldwide.(Bui et al., 2011) It is a highly symptomatic syndrome that affects 2-3% of the population in high income countries especially in people above the age of 65 years.(Redfield et al., 2003, Mosterd et al., 1999) Approximately 15 million (out of 900 million) Europeans and 5.8 million (out of 300 million) Americans are affected by HF.(Wijeysundera et al., 2010, McMurray et al., 2012) In the United States of America (USA) alone, up to 2.4 million hospital admissions can be attributed to HF as primary or secondary diagnoses.(Roger et al., 2011) It is the primary reason for 12-15 million office visits and 6.5 million hospital-days each year.(Roger et al., 2011) About 670,000 new cases occur in the USA yearly.

Over 39 million dollars is spent annually in the USA for the care of HF patients. In Europe, over 60% of economic cost of HF is related to hospital admissions.(Stewart et al., 2001a) This is because HF is associated with high rates of hospital admissions, readmissions and frequent clinic visits. Data from developed countries show that half of HF patients are rehospitalised within 6-months of discharge(Butler and Kalogeropoulos, 2008) and 70% of these are due to worsening of previously diagnosed HF.(Gheorghiade et al., 2005) In a recent report, Jencks et al(Jencks et al., 2009) showed that HF is the number one reason for readmission in the USA. HF readmission is associated with higher mortality compared to the index admission.

HF related admission and re-admission has been projected to rise in the coming years due to aging of the world population. By 2050, 1 in 5 Americans will be elderly and 80% of patients hospitalized for HF in that country are usually above 65 years.(2005)

HF 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 diagnosis of HF. Annual mortality is 10% thereafter. Those with severe HF have an annual mortality of >50%.(Murray-Thomas and Cowie, 2003)

Although there have been many therapeutic gains in the management of chronic HF(Scott and Jackson, 2013) leading to improved overall survival rates(Scalvini and Giordano, 2013), there has been very little parallel success in respect to AHF. This is particularly important when one considers the high proportion of patients who still require hospitalization for acute HF and associated high levels of in-patient case-fatality and poor short-to-medium term health outcomes.

1.2 Definitions/Nomenclature

There is no generally accepted definition of HF. The current definition of HF by major international/national societies of HF is as follows:

The European Society of Cardiology (ESC) defined HF 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 only at the expense of increased filling pressures)"(Dickstein et al., 2008) or "clinically as "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".(McMurray et al., 2012)

The American Heart Association/ American College of Cardiology (AHA/ACC) defined the condition as "a complex clinical syndrome that results from any structural or functional

impairment of ventricular filling or ejection of blood"(Yancy et al., 2013) while the **Heart failure society of America** defined HF as a "syndrome caused by cardiac dysfunction, generally resulting from myocardial muscle dysfunction or loss and characterized by either LV dilation or hypertrophy or both."(Heart Failure Society of et al., 2010)

The earliest definition of HF may be probably that by Thomas Lewis in 1933. He defined HF as ***"a condition in which the heart fails to discharge its content adequately"***. (Lewis, 1933b)He opined that the very essence of cardiovascular practice is the early detection of HF.

At various times in history, several authorities have provided definitions such as Wood (1950)(Wood, 1950), Denolin et al (1983)(Denolin et al., 1983), Poole-Wilson (1985)(Poole-Wilson, 1985), Harris (1987)(Harris et al., 1987), Braunwald(1988)(Braunwald, 1988) and Cohn (1988).(Cohn, 1988) These definitions are shown are shown in **table 1.1.**

Table 1.1:Various definitions of HF failure by different individuals and authorities

SNO	Person/Authority	Year	Definition
1.	Lewis(Lewis, 1933a)	1933	"A condition in which the heart fails to discharge its contents adequately".
2.	Wood(Wood, 1950)	1950	"A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure".
3.	Denolin(Denolin et al., 1983)	1983	"Heart failure is the state of any heart disease in which, despite adequate ventricular filling, the heart's output is decreased or in which the heart is unable to pump blood at a rate adequate for satisfying the requirements of the tissues with function parameters remaining within normal limits".
4.	Harris(Harris et al., 1987)	1987	"A syndrome which arises when the heart is chronically unable to maintain an appropriate blood pressure without support".
5.	Braunwald(Braunwald, 1988)	1988	"A pathophysiological 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 metabolizing tissues".
6.	Cohn (Cohn, 1988)	1988	"A syndrome in which cardiac dysfunction is associated with reduced exercise tolerance a high incidence of ventricular arrhythmias and shortened life expectancy".
7.	Poole-Wilson(Poole-Wilson, 1996)	1996	"A clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of haemodynamic, renal, neural and hormonal responses".

1.3 Classification of HF

1.3.1 Acute and chronic HF

Acute HF: This is defined as "the sudden or gradual onset of the signs and symptoms of HF requiring unplanned office visits, emergency room visits, or hospitalization". "Irrespective of the precipitating factor, pulmonary and systemic congestion due to elevated right or left heart filling pressures is an almost universal feature of acute decompensated heart failure (ADHF). This may present in the form of acute pulmonary oedema due to LV failure, cardiogenic shock especially in the setting of acute myocardial infarction (usually characterized by hypotension, oliguria and peripheral vasoconstriction)

Chronic HF: This is a clinical syndrome resulting from chronic cardiac decompensation associated with left-sided or right-sided heart failure

1.3.2 Systolic and diastolic HF

Systolic HF: HF due to impaired LV systolic function (usually echocardiographically determined EF of <45%).

Diastolic HF: HF due to the need for higher filling pressures to obtain normal LV end diastolic volume. It is also called HF with normal or preserved ejection fraction (EF >45%). These terms are not mutually exclusive as most patients with systolic dysfunction have different forms of diastolic dysfunction. HF with normal EF (HFNEF) is more common in the elderly, women, diabetics, and individuals with long standing hypertension. It has a better prognosis than heart failure with LV systolic dysfunction although in the Canadian study there was no difference in outcome between these forms of HF.(Owan and Redfield, 2005, Rutten et al., 2003) There is still no consensus on the definition of HFNEF. Some workers even believe that it is over estimated. **Table 1.2** shows the differences between SHF and DHF).

1.3.3 Symptomatic and asymptomatic LV dysfunction.

It is now known that more than half of individuals with left ventricular systolic dysfunction (EF<35-40%) are asymptomatic. This is commoner in people with coronary artery disease (RR=12.5, 95%Cl = 4.5-33.3), hypertension (RR=3.5, 95%Cl = 1.4-8.5) and abnormal ECG (RR 7.1,

95%Cl 2.8-16.7). Asymptomatic LV systolic dysfunction is a precursor for the development of HF and CV events.(Wang et al., 2003) Since HF is characterized by symptoms and signs, asymptomatic LV dysfunction is not the same as HF.

Table 1.2. Differences between diastolic and systolic HF.

Characteristic	**Diastolic HF**	**Systolic HF**
Age	Frequently elderly	All ages, typically 50-70 years
Sex	Frequently female	More often males
LV ejection fraction	Preserved or normal, approximately 40% or higher	Depressed, approximately 40% or lower
LV cavity size	Usually normal, often with concentric LVH	Usually dilated
LVH on 12 lead ECG	Usually present	Sometimes present
Chest radiography	Congestion without cardiomegaly	Congestion and cardiomegaly
Heart sound	Fourth heart sound present	Third heart sound present
Co-existing conditions		
Hypertension	+++	++
Diabetes mellitus	+++	++
Previous myocardial infarction	+	+++
Obesity	+++	+
Chronic lung disease	++	0
Sleep apnoea	++	++
Long term dialysis	++	0
Atrial fibrillation	+ (usually paroxysmal)	+ (usually persistent)

(Table adapted from Aurigemma et al(31) and Meyer et al(32)

1.4 Historical perspective

The concept of HF has been known by man from time immemorial. History shows that there were descriptions of HF in ancient Egypt, Greece and India. The Romans were known to have used the Foxglove as a medicine in heart disease. It was not until the description of human circulation by William Harvey that the nature of the condition became clearer. Other major advances in medicine and science led to improvement in the understanding of the pathophysiology, and management of HF. These include the discovery of x-rays by Roentgen, electrocardiography by Einthoven, echocardiography by Inge Edler as well as cardiac catheterization and nuclear medicine.

Blood-letting and leeches were used in ancient times for the treatment of HF. In 1785, William Withering published the benefits of digitalis. Doctors used Southey tubes in the 19th and 20th centuries to let-out fluid from oedematous peripheries of HF patients. In 1985, thiazide diuretics were introduced. Prior to this mercurial agents were used as diuretics but these were associated with toxicity. In 1967 Christian Barnard performed the human heart transplantation for the treatment of end stage intractable HF in the Republic of South Africa.

The use of vasodilators in HF started with the discovery of angiotensin converting enzyme inhibitor in the 70s. The first co-operative West Scandinavian Enalapril Survival Study (CONSENSUS – 1) was the landmark study that demonstrated the unequivocal benefits of enalapril in patients with HF. **Table 1.3** shows the landmark events in the evolution of man's understanding of HF since 1628 when human circulation was described while **Table 1.4** shows landmarks in the advancement of HF treatment. According to Katz(Katz, 2008), since the 5th century BC, physicians and scientists have approached the syndrome of HF in at least nine different ways: 'A clinical syndrome' circulatory disorder, altered architecture of the heart, abnormal haemodynamics ,disordered fluid balance, biochemical abnormalities, maladaptive hypertrophy, genomics and epigenetics'

Table 1.3. Landmark events in the evolution of man's understanding of HF

Period	Landmark event
5th century BC (Ancient Greek & Romans)	Hippocrates corpus described "rales"
3rd century BC	Centre of medical science moved to Alexandria in Egypt. Human anatomy and physiology were studied by Herophilus and Erasistratus. Recognized that the human heart contracts and understood the role of semblance values. Held that arteries contain air and that blood flows from the right ventricle into veins
2nd century BC Galen, Greek physician	Viewed heart as source of heat. Failed to understand that the heart is a pump. Palpated the arterial pulse but believed it was transmitted along the arterial wall rather than by blood flow. Probably the first to describe atrial fibrillation. Galen's erroneous view that the main role of the heart is to distribute heat by ebb and flow dominated Western medical science for over 1500 years. Treatment for dyspnea and dropsy during this period was based on this humoral belief.
17th century	William Harvey describes human circulation in **1628.** In **1668,** Richard Lower noted that the ejection function of the heart was impaired in cardiac tamponade Raymond Vieussens described the physiological basis for the signs and symptoms in mitral stenosis
18th century	In **1745,** Giovanni Hancisi described eccentric LVH in aortic regurgitation and concentric LVH in aortic stenosis. Noted that LV dilatation weakens the heart. Nicholas Corvisat and John Bell documented that eccentric LVH carried worse prognosis than concentric pattern. Corvisat also described two mode of death in HF: Progressive HF or sudden death.
19th century	**1833**: Joseph Hyaathe Bertin reported that LV dilatation weakens the myocardium. Austin Flint demonstrated that concentric LVH was an adaptive mechanism in pressure overload William Osler documented the adverse consequences of concentric LVH

	1895: Roentgen discovered X-ray which allowed evaluation of cardiac size.
20th century	**1918:** Ernest H Starling describes that Starlings law of the heart. **1920:** Inorganic mercurial substance was first used by Saxi and Heiling to achieve diuresis but this was associated with toxicity **1920-30s:** The concept of energetic thermodynamics in the study of cardiovascular pathophysiology was introduced by workers such as Helmholtz, Hill, Starling, Visscher and Oslen. **1940:** AndreCour and Dickinson W Richard introduced cardiac catheterization which led to improvement in the understanding of cardiac haemodynamics **1950:** Felix Meerson confirmed the earlier observation by Osler that overload-induced hypertrophy is both beneficial and deleterious **1960:** Open heart surgery commenced **1985:** Janis Pfeiffer and his colleagues gave a clue to the mechanism of the survival benefit of ACEI;-slowing of cavity dilatation (remodeling) following myocardial infarction. **1987:** Eugene Braunwald and others introduced the field of molecular cardiology and genomics **2000:** Application of the field of epigenetics in the study of HF

Table 1.4. Landmark trials in the advancement of HF treatment

a. Inhibition of the renin-angiotensin-aldosterone system.	**The Cooperative North Scandinavia ENalapril Survival Study (CONSENSUS)** showed that Enalapril improved symptoms as well as life expectancy in HF compared to placebo, but had no impact on sudden cardiac death.(1987) **The vasodilator – Heart Failure trial II (V-HeFT – II).** Tested Enalapril or hydralazine/isosorbide dinitrate in class II and III HF. Sudden death and mortality was reduced by 14 and 12% respectively in the Enalapril group compared to 23% and 10% respectively in the hydralazine/isosorbide dinitrate.(Cohn et al., 1991) **The studies of Left Ventricular Dysfunction treatment (SOLVD – treatment)** demonstrated a reduction of total mortality in HF patients by 8% as well as fewer deaths and hospitalizations due to HF in patients on Enalapril compared to placebo.(1991, 1992a) **Others** The Survival and Ventricular Enlargement (SAVE) trial (Used Captopril)(Pfeffer et al., 1992), the Acute Infarction Ramipril Efficacy (AIRE) trial (used Ramipril)(1993) and the Trandolapril Cardiac Evaluation (TRACE) trial (Ref) (used Trandolapril)(Kober et al., 1995) All showed that ACE inhibition significantly improved survival and reduces morbidity and mortality associated with CV events in HF.
b. Inhibition of Angiotensin Receptors	These are used where ACE inhibitors are contraindicated. **Valsartan Heart Failure trial (VAL-HeFT)**: Mortality at 2 years was 18 vs. 25%, RRR 28%.(Cohn et al., 2001) **"Assessment of Reduction in mortality and morbidity in patients with LV dysfunction already taking ACE inhibitors "(CHARM – Added trial)**. The trial demonstrated that Candesartan significantly improved outcomes versus placebo in patients already taking ACE inhibitors or beta blockers.(Pfeffer et al., 2003) (McMurray et al., 2003) **The CHARM – Alternative trial**: in patients with LV dysfunction who do not tolerate ACE inhibitors, it was shown that Candesartan at 32mg/day significantly reduced CV related morbidity and hospitalization for HF in individuals who do not tolerate ACE inhibitors.(Granger et al., 2003) **Valsartan in Acute Myocardial Infarction (VALIANT trial)** The trial demonstrated that Valsartan (160mg) is as effective as Captopril (150mg) in the reduction of all-cause mortality in individuals with myocardial infarction complicated by HF. However combination of Captopril and Valsartan did not show additional benefit.(Pfeffer et al., 2000)

c. Aldosterone antagonists	**The Randomized Aldosterone Evaluation study (RALES).** In HF patients with systolic dysfunction (EF 25%) and who are in class III and IV NYHA class, aldactone compared to placebo was associated with a significant 30% reduction in relative risk of all-cause mortality.(Pitt et al., 1999) **The Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS).** Eplerenone showed reductions in all-cause mortality as well as combined endpoint of CV mortality and hospitalization for CV events.(Pitt et al., 2006) **Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF**). The study confirmed the previously observed findings with Eplerenone but in those with mild symptoms.(Zannad et al., 2011)
d. Blockage of sympathetic nervous system with beta-blockers.	**The US Carvedilol Heart Failure Program.** This was the first study to demonstrate the benefit of beta blockers in the management of HF. The trial showed that Carvedilol reduced HF associated overall mortality by 65% and combined risk of death or rehospitalization by 38% compared to placebo.(Packer et al., 1996) **The Cardiac Insufficiency Bisoprolol Study II (CIBIS II)** In NYHA class IV HF and EF≤35%, bisoprolol was associated with lower overall mortality compared to placebo. Bisoprolol use was also associated with fewer HF related deaths and all cause hospital admissions.(1999a) **The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS trial).** (Ref) The trial reported 27% reduction in the combined risk of death or hospitalization for a cardiovascular cause and 40% in the number of days in hospital for HF with carvedilol compared to placebo.(Packer et al., 2002) **The study of the effects of Nebivolol Intervention on Outcomes and Rehospitalization in seniors with Heart Failure (SENIORS).** The authors demonstrated that beta-blockage with Nebivolol is effective and safe in elderly patients with HF.(Flather et al., 2005)
e. Sinus node inhibition	**The systolic Heart Failure treatment with HF inhibitor Ivabradine trial (SHIFT).** The trial revealed a reduction in mortality from HF as well as HF related hospitalization.(Swedberg et al., 2010)
Paradigm – HF trial.	This is a randomized, double blind phase III study that demonstrated the efficiency and safety of angiotensin receptor Neprilysin inhibitor (LCZ696) in the treatment of HF. In patients with HF and reduced EF, LCZ969 was found to be superior to Enalapril. It reduced risk of death from CV causes by 20%, reduced HF hospitalization by 21% and all-cause mortality by 16%.(McMurray et al., 2014, McMurray et al., 2013)

Chapter 2: Literature review on acute heart failure

Introduction and definition*:* Acute heart failure (AHF) can be defined as a rapid onset of or change in symptoms and signs of HF.(Metra et al., 2014, Yancy et al., 2013, McMurray et al., 2012) The syndrome is often life threatening, often requiring immediate medical care in the form of hospital admission due to the deterioration of individuals with pre-existing HF but can also be the first presentation of HF (denovo AHF). It is often precipitated by one or more factors such as infection, ischemia, hypertensive crisis, dietary indiscretion and non-compliance to medication.

The presentation of AHF may vary and the syndrome is heterogeneous due to differences in economic development, genetic susceptibility, cultural practices and burden of CV risk factors. Worldwide, the hospitalization for AHF is common and a growing public health problem.

Data from the USA suggests that AHF first admission occurs in about 400 per 100,000 populations. It is also approaching 1,000 per 100,000 populations for second hospitalization. More than 5.7 million people in that country who are aged 20 years and above are living with HF (2.7% prevalence) (Roger et al., 2012a, Roger et al., 2012b) There were 670,000 new cases in people aged 45 years and above in 2008 in a population of about 304 million people. Incidence tripled between the year 1979 and 2004 and the prevalence is higher in men compared to women with heavy predominance with advancing age.(Roger et al., 2012a, Roger et al., 2012b) In Canada, approximately 500,000 persons are living with HF (1.5% prevalence). The annual incidence is approximately 50,000 new cases in a population of 32.7 million people in 2006.(Ross et al., 2006) **Table 2.1** shows the proportion of people living with HF in various countries. **Table 2.2** depicts the proportion of AHF patients to total admission in some countries. This ranges from 0.65 in South Africa to 3.73 in some European countries.

Registries of AHF have shown some characteristics and regional as well as continental differences in the mode of presentation, aetiology, burden and type of co-morbidities, precipitating factors, treatment and outcome of AHF syndrome. Some of the recent AHF registries include; the ADHERE(Fonarow, 2003),

OPTIMIZE(Fonarow et al., 2004), Euro HF survey I(Cleland et al., 2003) and II(Nieminen et al., 2006a), EFICA(Zannad et al., 2006), AHEAD(Spinar et al., 2011), ATTEND(Sato et al., 2010), THESUS-HF(Damasceno et al., 2012) etc.

Table 2.1. Proportion of population living with HF in some countries around the world.

Continent	**Country**	**Proportion of population with HF**
Africa(Damasceno et al., 2007)	None	No population based study
Asia(Hung et al., 2000) (Ng and Niti, 2003, Koseki et al., 2003)	China	1.3%
	Japan	1%
	Malaysia	6.7%
	Singapore	4.3%
Australasia(2011)	Australia	1.3%
Europe(2012c, Galinier et al., 2012, Nieminen et al., 2006a)	International	1-2%
	France	2.2%
	United Kingdom	1.3%
Middle East (Agarwal et al., 2001)	Oman	0.5%
North America(Ross et al., 2006, Roger et al., 2012a, Roger et al., 2012b, Heidenreich et al., 2013)	Canada	1.5%
	United State	2.7%
South America(Bocchi et al., 2013)	No data	No population based study

Table 2.2. shows the proportion of AHF patients to total admission in some countries

Continent/Region	Country	No. of HF admissions	HF admissions/Total admission
Africa(Stewart et al., 2008)	South Africa	NA	0.65
Asia(2014e, 2014f, 2014d)	Japan	174,957	1.24
	Korea	57,147	0.78
	Singapore	15,535	NA
Australasia(2014e, 2014f, 2014d)	Australia	53035	1.38
	New Zealand	9876	1.53
Europe(2014e, 2014f, 2014d)	International (22 countries)		0.32-3.73
	International(18 countries)	626185	NA
	France	159143	1.46
	Germany	306250	1.54
	Poland	229428	3.73
	United Kingdom	73790	0.88
Middle East(2014e, 2014f, 2014d)	Israel	19707	1.31
North America(2014e, 2014f, 2014d)	Canada	49829	1.76
	United states	1179151	3.04
	Brazil	235692	2.11
South America(2014e, 2014f, 2014d)	Chile	27607	1.70
	Mexico	90695	1.64

2.1 Methods

A Medline /Pubmed search was conducted from January 1, 2000 to December 31, 2014 to identify studies on acute HF worldwide. Manuscripts written in English language were reviewed. The search criteria were 'heart failure' or 'cardiac failure' AND 'registry' or 'survey'. The reference lists of identified papers were critically reviewed for additional information. Data extracted were summarized or grouped as follows: brief description of each registry/survey, socio-demographic profile, clinical profile including major symptoms and signs, laboratory profile (blood and non-blood based), aetiological risk factors, precipitating factors, co-morbidities, hospital management and intra-hospital outcome (length of stay and discharge status) and post-discharge outcomes. **Figure 2.1** is a flow diagram showing how the data were extracted. **Figure 2.2** presents these registries and surveys in different continents. **Tables 2.3-2.7** were used to summarise the information

A separate search was done specifically for HF in Sub-Saharan Africa (SSA) from 1 January 1950 to 31 December 2014.

The search criteria include: "heart disease", "cardiovascular disease", heart failure", "cardiac failure", "hypertension", "rheumatic heart disease"., "cardiomyopathy", "dilated cardiomyopathy" "endomyocardial fibrosis", "peripartum cardiomyopathy" "pericarditis/ pericardial effusion", "cor-pulmonale", "coronary artery disease" "ischaemic heart disease" and "sub-Saharan Africa". Literatures published in English language were retrieved. English abstracts of articles written in other languages were also retrieved. This was supplemented with search of other database such as African index medicus, African journals on-line (AJOL) World Bank database, WHO global infobase as well as the global cardiovascular infobase and global health library.

We also consulted additional papers as well as book chapters referenced through this search strategy. Articles that focused on epidemiology and aetiology of heart disease in SSA have been reviewed.

One thousand six hundred and twenty six (1,626) articles were initially retrieved. Thereafter, studies that were not relevant to the review were excluded such as case reports, studies on pathophysiology of heart disease and studies carried outside the sub-region. We conducted a review of the remaining 102 articles. These are categorized into the regions of SSA and presented as clinical studies **(Table 2.8)**

We identified a total of 71 studies involving 72,971 patients that described the pattern of heart disease in SSA during the period 1950 - 2014. Most studies on heart disease in the region were hospital based (n = 100) with few population based studies (n = 2). More were focused on urban centres. We retrieved 71 clinical studies (as summarized in **Table 2.8)** Ten (10) were from Southern Africa, 32 from West Africa, 11 from East Africa and 9 each from central and the horn of Africa)

2.2 Sociodemographic characteristics

2.2.1 Age at presentation

AHF syndrome is a disease of the elderly in high-income countries of Europe, North America and Japan. Mean age ranges from 70-75 years.(Adams et al., 2005a, Fonarow et al., 2007b, Sato et al., 2010, Nieminen et al., 2006a) Patients are younger in South America(Bocchi et al., 2013), South Asia and sub-Saharan Africa.(Damasceno et al., 2012) **Figure 2.3** shows the mean age of AHF in different reports across the world regions.

2.2.2 Gender distribution

The sex ratio varies from region to region. The proportion of men in the different registries ranges from 49% to 67%. (**Figure 2.3**) The rate is generally commoner in men except in the THESUS-HF and ADHERE registry. This may be due to selection bias.

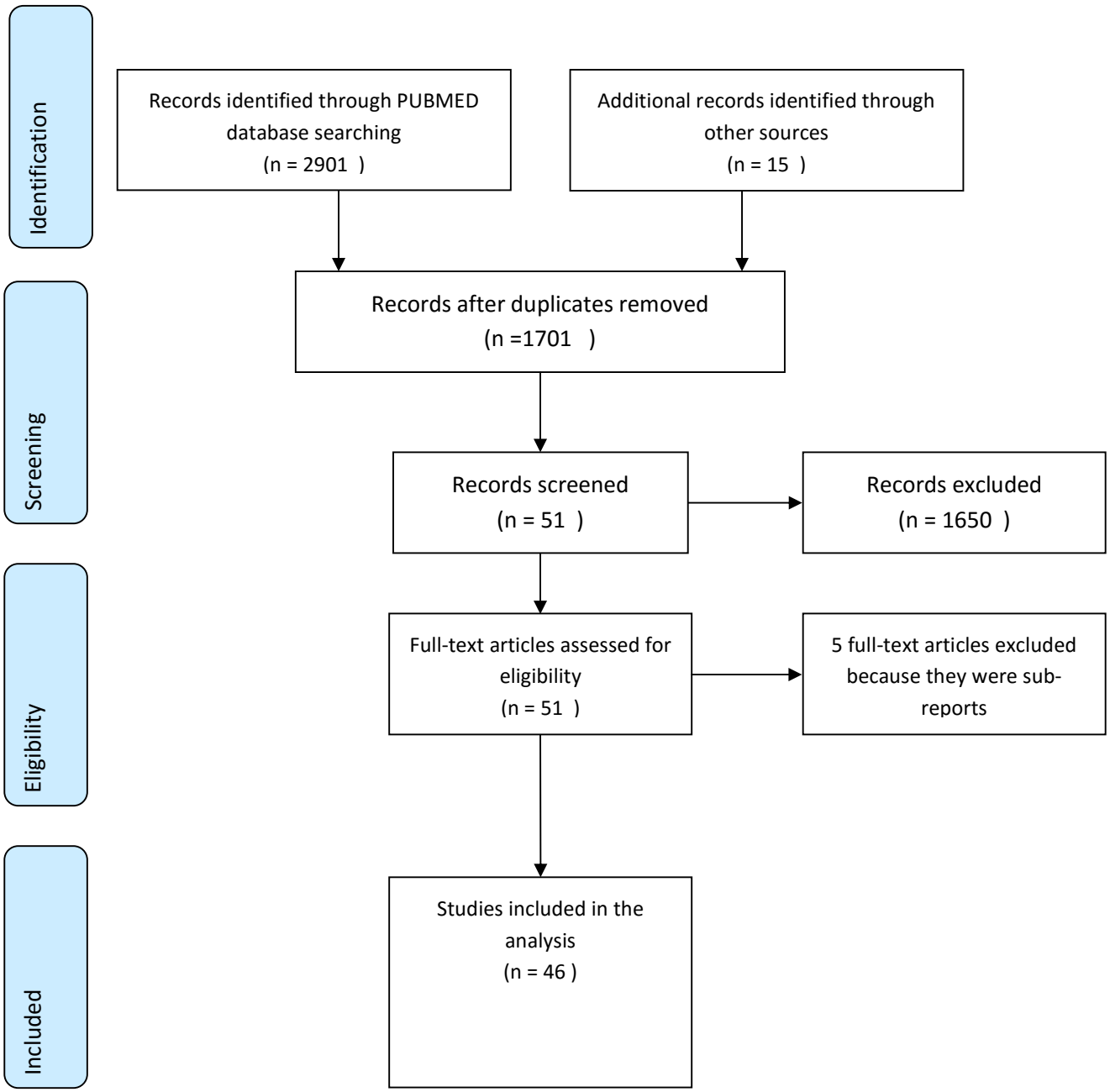


Figure 2.1: Flow chart showing how the literatures were extracted

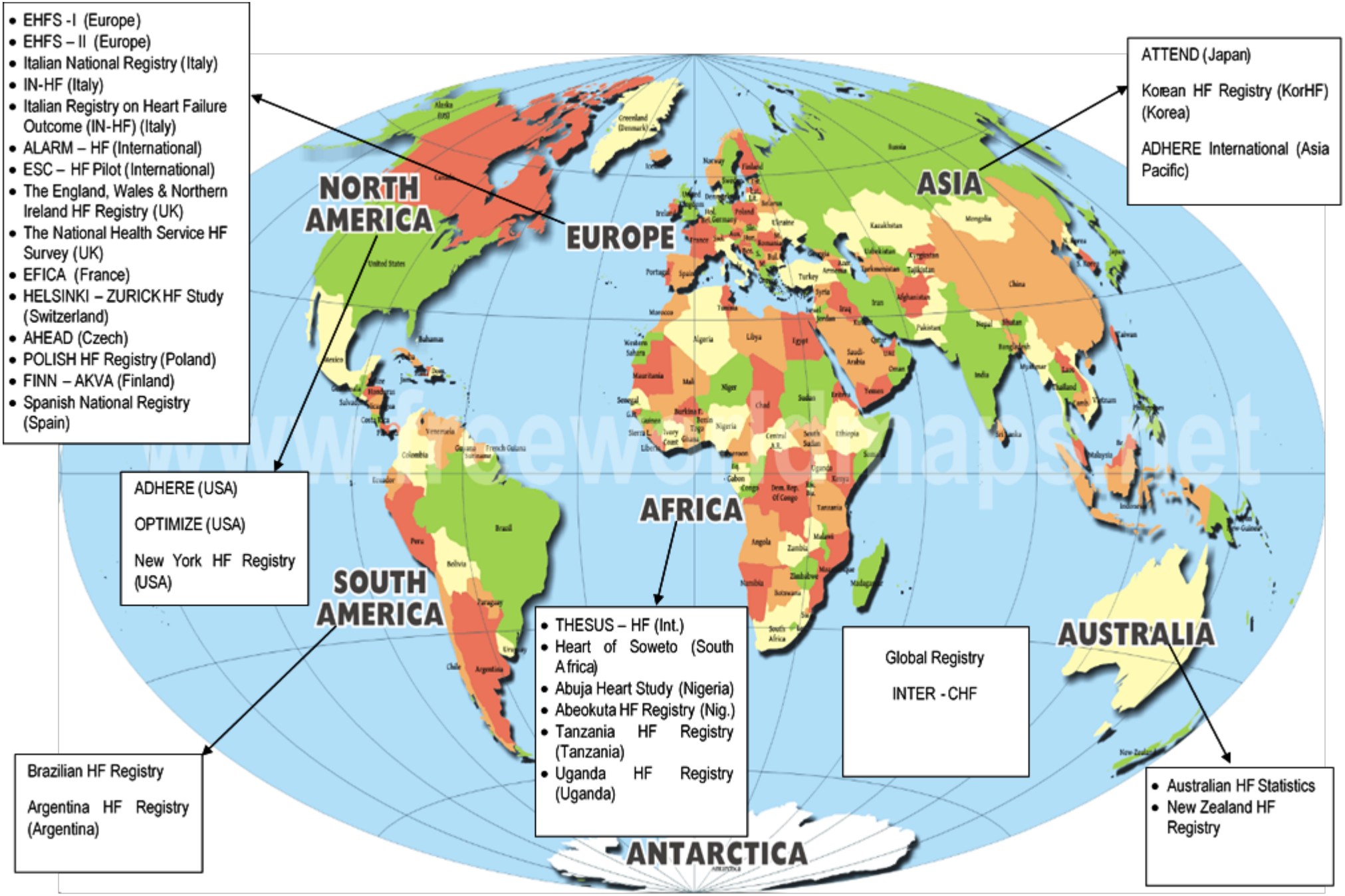


Figure 2.2. Acute HF registries /surveys in different parts of the world

Table 2.3 shows the characteristics of AHF patients in different regions of the world.

Characteristics	**ADHERE(Adams et al., 2005a)**	**EHFS-I(Cleland et al., 2003)**	**EHFS-II(Nieminen et al., 2006a)**	**Italian(Tavazzi et al., 2006)**	**E&W Survey(Nicol et al., 2008)**	**EFICA(Zannad et al., 2006)**	**ATTEND(Sato et al., 2010)**	**AHEAD(Spinar et al., 2011)**	**OPTIMIZE(Fonarow et al., 2004)**	**THESUS-HF(Damasceno et al., 2012)**	**KorAHF(Choi et al., 2011)**	**HIJC-HF(Kawashiro et al., 2008)**
Country/Region	US	Europe	Europe	Italy	UK	FRANCE	Japan	Europe	US	SSA	KOREA	JAPAN
No of patients	187,565	11,327	3580	2807		581	1110		48,612	1006	3,200	3,578
Mean age	72	71	69.9	73		73	73		73	52	67.6	69.8
Male (%)	49	53	61.3	60.5		59	59		48	49.4	50	59.3
Body mass index	NA		26.8	NA		NA	NA		NA	25.2	23.2	21.4
Obesity												
ESC Clinical class of HF												
Denovo	24		37.1	NA		22				16.3		
Decompensated	NA		65.4	NA								
Acute pulmonary oedema	NA		16.2	NA		65	63		13	NA	70.4	35.5
Cardiogenic shock	3	<1	3.9	7.7		29	NA		NA	NA	29.6	65.5
Hypertensive heart failure	NA		11.4			NA	NA		NA	NA	NA	NA
Right heart failure	NA		3.2	NA		NA	NA		NA	NA	NA	NA
New-onset AHF (%)	NA		37.1	NA		NA	NA		NA	45.4	36.7	11.5
Hospitalization for HF within last 12 months (%)	NA	65	44.5	NA		NA	NA		NA	NA	NA	NA
NYHA (III or IV)	47.2		NA	NA								
Clinical history/Co-morbidities												
Coronary artery disease (%)	5.7	68	53.6 (54)	NA		31	39.1		39.1	34.6	74	6.4

Previous MI (%)	31	39	NA	36.5		46	1.4		1.4	NA	NA	33.5
Previous revascularization (%)	NA	NA	NA	19.1		22	NA		NA	NA	NA	NA
Hypertension	74	53	62.5	65.6		33	NA		NA	NA	NA	NA
Diabetes mellitus	44	27	32.8	38.4		60	71		71	55.4	46.5	54.1
Atrial fibrillation/flutter	31	9	38.7	NA		27	34		42	11.4	30.5	31.4
Previous stroke or TIA	17	NA	13.3	9.2		25	40		31	18.3	NA	36.4
Renal failure	NA	17	16.8	24.7		1	12		16	NA	18.9	NA
Dyspnoea	32				40	NA						
Dyspnoea on exertion	44				35	NA						
Rales	68					34		77.6				
Oedema orthopnea	66				23	59		68				
HFpEF	46(40)				55(40)	34	27(45)	43.69(>40)				
HFrEF	75				65	56	66					
EF	34			40								
LVSD	63	53		50				53				
Valvular disease	NA	29	34.4	11.4		53	NA		NA	7.7	9.2	22.8
Anaemia	NA	NA	14.7	NA		NA	NA		NA	NA	NA	23.1
COPD	29(31)	32	19.3	29.7		NA	10		NA	15.2	NA	44.2
Dilated cardiomyopathy	NA	NA	19.3	NA		NA	9		28	NA	3.5	NA
Peripheral vascular disease (%)	NA	NA	NA	12		NA	NA		NA	NA	NA	20.8
Pacemaker implanted	4.7	NA	9.1	12.4		NA	NA		NA	NA	NA	NA
Implanted cardiac defibrillator (%)	NA	NA	NA	4.5		NA	4.7		4.7	NA	NA	NA
Active smoker (%)	NA	NA	NA	14.5		34	NA		NA	NA	NA	NA
HIV positive	NA	NA	NA	NA		NA	NA		NA	9.8	NA	NA

Etiologic profile			NA	NA		NA	NA		NA	NA	NA	NA
Ischaemic (%)	57		53.6	46		NA	NA		NA	NA	NA	NA
Hypertensive (%)	NA		11.4	14.9		NA	NA		NA	13	NA	NA
Valvular	NA		34.4	11.4		NA	NA		NA	NA	NA	NA
Dilated cardiomyopathy	NA		19.3	NA		61	33		46	7.7	52.3	33.5
Corpulmonale	NA		3.2	NA		15	18		23	45.4	36.7	11.5
Precipitating factors (on admission)												
ACS (%)	NA		30.2	NA		21	NA		NA	14.3	12.7	23.1
Arrhythmia (%)	NA		32.4	NA		15	NA		NA	18.8	26.5	20.8
Valvular cause (%)	NA		26.8	NA		NA	NA		NA	NA	NA	NA
Infection (%)	NA		17.6	NA		NA	NA		NA	NA	NA	NA
Non-compliance with therapy (%)	NA		22.2	NA		NA	NA		NA	NA	NA	NA
Inadequate diuretic therapy	NA	NA	NA	NA	NA	NA	NA		NA	NA	0.4	NA
Hypertensive crisis	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hypertension	37					NA	42	NA	NA	NA	NA	NA

Table 2.4. shows more data the characteristics of AHF patients in different regions of the world.

Characteristics	EFICA(Zannad et al., 2006)	ATTEND (Sato et al., 2010)	AHEAD(Spinar et al., 2011)	OPTIMIZE(Fonarow et al., 2007b)	THESUS-HF(Damasceno et al., 2012)	KORHF(Choi et al., 2011)	HIJC-HF(Kawashiro et al., 2008)	FINN-AKVA(Siirila-Waris et al., 2006)	POLISH (Venskutonyte et al., 2009)	ESC_PILOT(Maggioni et al., 2010)	ALARM(Follath et al., 2011)	RO_AHFS(Chioncel et al., 2011)	IN-HF(Oliva et al., 2012)	FINN-AKVA	POLISH
Country/Region	FRANCE	Europe	Europe	US	SSA	KOREA	JAPAN	FINLAND	POLAND	Europe	Europe	Romania	Italy	FINLAND	POLAND
Study period			2006-2009	2003-2004	2006-2009	2004-2009		2004		2009-2010	2006-2007	2008-2009			
Year of publication			2011	2006		2011		2006		2010		2011		620	270
No of patients	581	1110	4153	48,612	1006	3,200	3,578	620	270	1,892	4,953	3,224		75.1	68
Age	73	73	74	73	52	67.6	69.8	75.1	68	70		69		50.4	71
Male (%)	59	59	58	48	49.4	50	59.3	50.4	71	63	62	58			
Body mass index	NA	NA		NA	25.2	23.2	21.4	27.7	NA					27.7	NA
Obesity	22				16.3										
ESC clinical class of HF															
Denovo	65	63		13	NA	70.4	35.5	49	27		36.2			49	27
Decompensated	35	NA		NA	NA	29.6	65.5	51	73		63.8			51	73
Acute pulmonary oedema	NA	NA		NA	NA	NA	NA	NA	20		36.7			NA	20
Cardiogenic shock	NA	NA		NA	NA	NA	NA	NA	2		11.7			NA	2
Hypertensive heart failure	NA	NA		NA	45.4	36.7	11.5	NA	11		7.4			NA	11
Right heart failure	NA	NA		NA	NA	NA	NA	NA	11		4.5			NA	11
NYHA (III or IV)	31	39.1		39.1	34.6	74	6.4	NA	NA						
Clinical history/Co-morbidities														NA	NA
Hospitalization for HF within last 12 month (%)						29.6					36.4				
Coronary artery disease (%)	51	NA	51	1.4	NA	NA	33.5	55.2	54		30.7			55.2	54
Previous MI (%)	22	NA		NA	NA	NA	NA	27.7	37			17		27.7	37
Previous revascularization (%)	33	NA		NA	NA	NA	NA	NA	22					NA	22
Hyperlipidaemia				32								40		54.7	60
Hypertension	60	71		71	55.4	46.5	54.1	54.7	60	62	43.5	67	58	32.3	39
Diabetes mellitus	27	34		42	11.4	30.5	31.4	32.3	39	35	45	33	40	29.4	44
Atrial fibrillation/flutter	25	40	27	31	18.3	NA	36.4	29.4	44	44	24.4	44	38	17.4	13
Dyspnoea at rest			63	44									44		

Dyspnoea on exert															
Orthopnoea			53	27											
PND			53	15											
Rales			66	64											
Oedema			67	65											
Previous stroke or TIA	1	12		16	NA	18.9	NA	17.4	13						
Renal failure	53	NA		NA	7.7	9.2	22.8	9.4	39	26	21	33			
Valvular disease	NA	NA		NA	NA	NA	23.1	12.1	21		14.4				
Anaemia	NA	NA		NA	15.2	NA	44.2	NA	17		24.8	30		9.4	39
COPD	NA	9		28	NA	3.5	NA	12.6	NA		12.6			12.1	21
Dilated cardiomyopathy	NA	NA		NA	NA	NA	20.8	9.9	NA					NA	17
Peripheral vascular disease (%)	NA	NA		NA	NA	NA	NA	NA	NA					12.6	NA
Pacemaker implanted	NA	4.7		4.7	NA	NA	NA	NA	NA		5.5			9.9	NA
Implanted cardiac defibrillator (%)	NA	NA		NA	NA	NA	NA	NA	NA					NA	NA
Active smoker (%)	34	NA		NA	9.8	NA	NA	NA	NA					NA	NA
Cancer	NA	NA		NA	NA	NA	NA	NA	3					NA	NA
Thyroid disease	NA	NA		NA	NA	NA	NA	NA	12					NA	NA
HIV positive	NA	NA		NA	13	NA	NA	NA	NA					NA	3
Etiologic profile														NA	12
Ischaemic (%)	61	33		46	7.7	52.3	33.5	55.2	55	51	61	61		NA	NA
Hypertensive (%)	15	18		23	45.4	36.7	11.5	54.7	24		44	44		NA	NA
Valvular	21	NA		NA	14.3	12.7	23.1	12.1	21					55.2	55
Dilated cardiomyopathy	15	NA		NA	18.8	26.5	20.8	9.9						54.7	24
Corpulmonale	NA	NA		NA	NA	NA	NA	NA	NA					12.1	21
Toxic	NA	NA		NA	NA	NA	NA	NA	4					9.9	NA
myocarditis/infection	NA	NA		NA	NA	NA	NA	NA	8					NA	NA
Infiltrative	NA	NA		NA	NA	0.4	NA	NA	NA					NA	4
Precipitating factors (on admission)															NA
ACS (%)	42	NA		NA	NA	NA	NA	31.9	8		36.9			NA	NA
Arrhythmia (%)	25	NA		NA	NA	NA	NA	34	18		26.9			NA	NA

Valvular cause (%)	NA	NA		NA	NA	NA	NA	12.1	NA					31.9	8
Infection (%)	20	NA		NA	NA	NA	NA	23.5	9		16.3			34	18
Non-compliance with therapy (%)	7	NA		NA	NA	NA	NA	NA	NA		13.4			12.1	NA
Inadquate diuretic therapy	NA	NA		NA	NA	NA	NA	NA	43					23.5	9
Hypertensive crisis	8	NA		NA	NA	NA	NA	NA	NA					NA	NA

Table 2.5. Shows data on the outcome of HF in different parts of the world

Outcome	Indonesia(Siswanto et al., 2010)	ADHERE (Adams et al., 2005a)	ADHERE-AP (Atherton et al., 2012)	OPTIMIZE (Fonarow et al., 2007b)	ARGENTINA (Perna et al., 2006)	EHFS-I(Cleland et al., 2003)	EHFSII (Nieminen et al., 2006a)	Italian (Tavazzi et al., 2006)	EFICA (Zannad et al., 2006)	ATTEND (Sato et al., 2010)	Poland (Venskutonyte et al., 2009)	KorHF (Choi et al., 2011)	THESUS-HF(Damasceno et al., 2012)	AHEAD (Spinar et al., 2011)
Length of hospital stay (LOS)														
Median	7.1	4.2	6.0	NA		11	9	9	15.1	21	NA	NA	9.2	7.1
Mean				5.7	7-9.3		NA			31				
Intrahospital mortality (%)	9.0	4.0	4.8	3.8	4.6-12.1	6.9	6.7	7.3	27/43	7.7	8.5	6.4	4.2	12.7
Post-discharge outcome														
i. Rehospitalisation (%)														
30-day		22.1												
90-day				29.6		24.2	NA							
180-day								38.1					17.8	
1-year		65.8		NA										
5-year														
ii. Mortality														
30-day		10							27.4					
90-day				8.6		13	NA							
180-day								13				15	17.8	
1-year		36							46.5					
5-year														

Table 2.6. Shows more data on the outcome of HF in different parts of the world

Outcome	FINN-AKVA(Siirila-Waris et al., 2006) (FINLAND)	Bueno et al(Bueno et al., 2010) (USA)	Aranda et al(Aranda et al., 2009) (USA)	Cutis et al(Curtis et al., 2008) (USA)	Heidenreich et al(Heidenreich et al., 2010) (USA)	ESC-HF Pilot(Maggioni et al., 2013) (Europe)	INHF(Oliva et al., 2012) (Italy)	Tavazi(Tavazzi et al., 2006) (Italy)	EAHFE(Jacob Rodriguez et al., 2011) (Spain)	HIJC-HF(Kawashiro et al., 2008) (Japan)	Nicol et al(Nicol et al., 2008) (UK)	Rudiger et al(Rudiger et al., 2005) (Switzerland)	Klapholz et al(Klapholz et al., 2004) (USA)	Logeart(Logeart et al., 2013) (France)
Length of hospital stay (LOS)														
Median	7	6.3	5.5		6.2	NA	10				8	9	6	
Mean														10.6
Intrahospital mortality (%)	7.1	4.2	4.4		2.8	3.8	6.4				15	8	4.2	8
Post-discharge outcome														
i. Rehospitalisation (%)														
30-day		24.8/21.9	26.9	22.7	16.7						NA	NA	NA	
90-day											NA	NA	NA	
180-day			60					38.1			NA	NA	NA	
1-year				67		43.9	30.7		27.2					
5-year														
ii. Mortality														
30-day		10.9			5.0						NA		NA	
90-day	15										18		NA	
180-day											NA		NA	
1-year	20.0				24.3		24			11.4	NA			
5-year	60.3													

Table 2.7. shows more data on the outcome of HF in different parts of the world

	ALARM - HF(Follath et al., 2011)	**ATTEND (Sato et al., 2010) (Japan)**	**OFICA(Oliva et al., 2012) (France)**	**Dharmorajan et al(Dharmarajan et al., 2013) (USA)**	**Jencks et al(Jencks et al., 2009) (USA)**	**Rodriguez et al(Jacob Rodriguez et al., 2011) (Spain)**	**Pei et al (China)**	**Tseng et al (Taiwan)**	**Ng et al(Ng and Niti, 2003) (Singapore)**	**Tsutsui et al(Tsutsui et al., 2006a) (Japan)**	**Hamaguchi et al(Tsuchihashi-Makaya et al., 2009) (Japan)**	**Nicol et al(Nicol et al., 2008) (UK)**	**Lee et al(Lee et al., 2004)**	**Joffe(Joffe et al., 2013)**	**Ng et al(Ng et al., 2008)**	**IMPACT-HF(O'Connor et al., 2005)**
Length of hospital stay (LOS)																
Median	6	21	13												8.7	
Mean		31														6
Intrahospital mortality (%)	12	7.7	8.2			5.3			2.5	6.30	8.8	12	9.5	5.5	7.1	2.8
Post-discharge outcome																
i. Rehospitalisation (%)																
30-day				24.8	19.6	27.2							8.7			
90-day					34								14.1			
180-day																
1-year					56.1					40	33.1		23.8			
5-year																
ii. Mortality																
30-day						8.9	5.30	3.90					11.4-men 11.8-women			
90-day																
180-day																
1-year														34-men 32.3-women	37.3	
5-year															78.5	

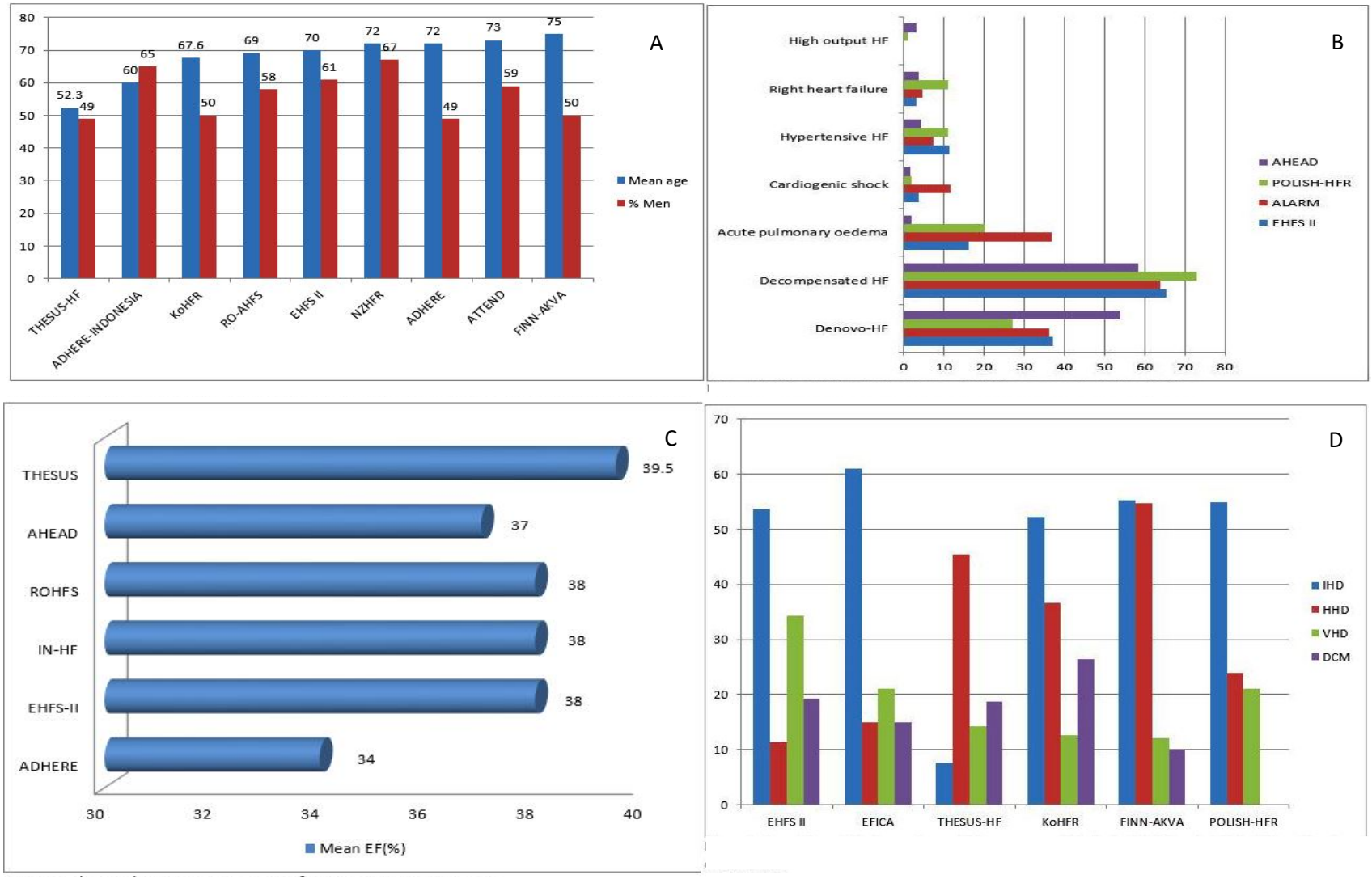


Figure 2.3. Shows mean age of AHF and proportion of men in different reports across the world regions (2A)(Damasceno et al., 2012, Siswanto et al., 2010, Choi et al., 2011, Chioncel et al., 2011, Nieminen et al., 2006a, Peraa et al., 2011, Adams et al., 2005a, Sato et al., 2010, Siirila-Waris et al., 2006, Fonarow et al., 2007b), spectrum of AHF syndrome (2B)(Spinar et al., 2011, Venskutonyte et al., 2009, Follath et al., 2011, Nieminen et al., 2006a), mean ejection fraction (EF) in some registries (2C)(Damasceno et al., 2012, Spinar et al., 2011, Chioncel et al., 2011, Oliva et al., 2012, Nieminen et al., 2006a, Adams et al., 2005a), pattern of heart disease in different regions of the world (2D)(Nieminen et al., 2006a, Zannad et al., 2006, Damasceno et al., 2012, Choi et al., 2011, Siirila-Waris et al., 2006, Atherton et al., 2012)

2.2.3 Ethnic/racial distribution

Large registries from the United States and Canada where different groups were represented afford the opportunity to examine the ethnic or racial differences in the characteristics, clinical presentation and outcome of AHF. In the US and Canada, ethnic minorities constitute 36.3% and 16.2% of the population respectively. Differences in risk factor burden as well as access to care, severity of disease influence the outcome among the different races.

Blacks constitute 12.6% and 2.5% of the population in USA and Canada respectively. Data from the ADHERE registry shows that black patients are younger than Caucasians (63.5 years vs. 72.5 years).(Adams et al., 2005a) They are less likely to have HF secondary to coronary heart disease (CHD) (30,0 vs. 56.1%), more likely to have left ventricular ejection fraction <40% (58.4 vs. 49.7%) and more likely to have diabetes mellitus (DM), hypertension, obesity and renal failure at presentation. They are also more likely to have higher initial blood pressure (BP) and a narrow QRS complex on ECG. Alternatively, they have lower rates of in-hospital mortality (2.8 vs. 4.5%) compared to whites.(Adams et al., 2005a)

Furthermore, compared to whites even after adjusting for major co-variates in the non-ischemic arm but not in the ischaemic group, African Americans have higher rates of readmission within 1-year of discharge (68.2 vs. 63.0%, $p<0.001$) but lower 30-day (6.3 vs. 10.7%, $p<0.001$) and 1-year mortality rates (31.5% vs.40.1%, $p<0.001$) compared to white patients.(Rathore et al., 2003)

The ARIC study which had a long-term follow up revealed that there was no difference in age-adjusted 30-day and 1-year case fatality. However at 5-years, African Americans demonstrated greater case fatality in both men and women compared to whites ($p=0.02$ and 0.03 respectively)(Loehr et al., 2008) African Americans also have the highest incidence of HF (3.0/1000 person years followed up) and are the youngest at presentation compared to other ethnic groups in America.(Rathore et al., 2003)

In Canada, the black population has the highest prevalence of 2 or more CV risk factors but paradoxically have lower prevalence of heart disease compared to other ethnic groups (3.4% vs. 5.0% for Caucasians 5.2% for South Asians and 3.2% for Chinese.(Chiu et al., 2010)

The Hispanics have the second highest incident rate of HF in the United States (3.5/1000 person years). The rate for white Americans and Chinese is 2.4 and 1.0 per 1000 person years respectively.(Bahrami et al., 2008) Hispanics have the highest rate of DM, dyslipidemia and renal dysfunction. Paradoxically Hispanic Americans have favorable mortality and quality of life compared to other groups.(Bahrami et al., 2008)

South Asians constitute 4% of the general population in Canada. IHD is particularly prevalent and occur at a younger age in this population compared to other races. They have higher rate of DM, central obesity and smoking in that country.(Joshi et al., 2007) In one study, South Asians were found to have more extensive disease, present almost one hour later and but show similar short and long term outcomes to that of Canadian whites.(Khan et al., 2010)

The Chinese HF patient in Canada are relatively older, have lower rates of CHD, multi-vessel disease and HF but they have higher rates of valvular heart disease compared to whites. They are also more likely to have HF with preserved ejection fraction (HFpEF) as well as limited insight on their disease status and CV risk factors.(Chow et al., 2008) The group makes up about 3.9% of the Canadian population.

CHD and HF is also becoming a major problem among the Aboriginal population in Canada. This is because of increasing rates of CV risk factors in the population over a period of 17 years.(Shah et al., 2000)

The group is particularly disadvantaged in the country. They are more likely to live in crowded homes as well as in houses that need major repairs. They also have 7.4 and 5.2 years shorter life expectancy in men and in women respectively compared to other ethnic groups.

2.3 Clinical profile

2.3.1 Symptoms and signs

Dyspnoea at rest was reported in 32-63% of patients while dyspnoea on exertion was documented in 35-44%. 27-53% had orthopnea while rales were reported in 34-77.6% of the subjects. Oedema was present in 23-68%. **(Table 2.3, Table 2.4)**

2.3.2 Clinical class of AHF

Acute presentation of decompensated chronic HF is the common form of AHF in high-income countries. In the THESUS-HF and Korean HF registry, denovo presentation of acute HF was commoner. It has been documented that 7-59% are admitted through the intensive care unit (ICU) but this depends on the inclusion criteria for the registry. The proportion who present in cardiogenic shock ranges from less than 1% to 32%. Acute pulmonary oedema, hypertensive heart failure, right heart failure and high output HF are present in 1.8-37%, 4.3-11.4%, 3.2-11% and 1.2-3.2% respectively. Previous history of HF has been documented in 51-75% while 20-45% has had at least one previous AHF admission. **(Table 2.3, Table 2.4)**

2.3.3 Aetiological risk factors

Figure 2.3-D shows the relative importance of the different aetiological risk factors for HF in different regions of the world. Ischaemic heart disease is by far the commonest risk factor for HF in high income countries of Europe and North America. In SSA, the prominent aetiological risk factors are non-ischaemic such as hypertension, dilated cardiomyopathy and rheumatic heart disease. Degenerative valve disease is also common in high income countries.

2.3.4 CV risk factors and co-morbidities

CV risk factors and co-morbidities (both cardiac and non-cardiac) are common in AHF patients. **(Table 2.3, Table 2.4)**

About 7.7% of AHF patients in SSA and 68% in Europe have coronary artery disease (CAD). The proportion with previous myocardial infarction (MI) ranges from 17-39%. History of hypertension is present in 43.5-76%. Diabetes mellitus (DM), atrial fibrillation (AF), chronic kidney disease (CKD) and anemia is present in 11.4-44%, 9-44%, 14.4-17% and 16.8-53% respectively. Apart from the impact on the pathophysiology of the condition, co-morbidities also affect the drug therapy, outcome as well as the cost of treatment of AHF patients. Furthermore some co-morbidity such as psychosomatic disorders may be under-reported.

2.3.5 Precipitating factors

Commonly reported precipitating factors include acute coronary syndromes (ACS), hypertensive crisis, valvular dysfunction and infections. Others include inadequate diuretic therapy, non-compliance with therapy and arrhythmias **(Table 2.3, Table 2.4)** (Zannad et al., 2006, Siirila-Waris et al., 2006, Follath et al., 2011, Venskutonyte et al., 2009) In the EFICA study(Zannad et al., 2006), ACS was responsible for 42%, arrhythmias (25%), infections (20%), non-compliance with therapy (7%) and hypertensive crisis (8%)

2.4 Laboratory findings

2.4.1 Blood investigations

Anaemia is present in about 50% of AHF patients, with about a quarter presenting with at least moderate degree of anaemia. One-fifth of patients have hyponatremia on admission (serum sodium of less than 135meq/L). The prevalence of hyponatremia is generally higher in individuals who were admitted into the intensive care or coronary care unit. Over 30% of AHF patients have an estimated

glomerular filtration rate of ≥90ml/min.1.73m^2. About 20% have severe chronic kidney disease (CKD) (eGFR<30ml/min/1.73m^2). Biomarker such as natriuretic peptide is not generally available in many studies.

2.4.2 Electrocardiography

The prevalence of atrial fibrillation (AF) ranges from 9 to 44%. About 20% of AHF patient present with new onset AF. Over a third will have prolonged QRS complex. In the Romanian acute HF registry (RO-AHFS) the following ECG abnormalities were observed at baseline: atrial fibrillation (44.3%)

, second or 3rd degree AV block (5.4%), right bundle branch block (RBBB) (10.6%), and left bundle branch block (LBBB)(16.7%) Others include pacemaker (3.8%), LVH (23.3%) and QRS complex >120ms (but no RBBB or LBBB) (4.3%)(Chioncel et al., 2011)

2.4.3 Echocardiography

Heart failure with preserved EF (HFPEF) in present in about half of patients. In the RO-AHFS registry(Chioncel et al., 2011), 23.8%, 19.8%, 7.1% and 1.1% had significant mitral valve disease, aortic valve disease, LV aneurysm and mechanical complications due to acute myocardial infarction respectively.

The mean LV end-diastolic diameter, LV end-systolic diameter and LV ejection fraction were 61.7cm, 47.1cm and 37.7% respectively.

2.5 In-hospital care

2.5.1 Drug Therapy

Diuretics are widely used in all the regions of the world for the management of AHF, although the route, dosage and duration of therapy have been less studied. There is also regional variation in the use of vasodilators. The use of inotropes is more in Europe compared to North American and much less so in regions where the aetiology of HF is predominantly non-ischemic. However use of aldosterone antagonists e.g. spironolactone is low in North America.

The dosage of medication, specific intolerance, contraindications to commencement or up-titration is not well documented. Comparison of use of these medications between specialized centres and primary/secondary centres is also less documented.

2.5.2 Procedural interventions

Data shows that less than 10% of patients with AHF in high income countries of Europe and America (where IHD is the predominant aetiology) undergo coronary angiography during index admission. Pulmonary artery catheters are not commonly placed during hospitalization.

Use of evidence based therapies for HF appears to be highest in high income countries of Western Europe, Japan and North America compared to developing economies of Asia, Eastern Europe, South America and Africa. The frequency use of device therapies such as ICD and CRT in AHF is not well documented.

2.6 Outcomes in AHF

2.6.1 Length of hospital stay (LOS)

This generally ranges from 4 and 21 days.(2012c, Maggioni et al., 2013, Bueno et al., 2010, Joffe et al., 2013, Aranda et al., 2009, Fonarow et al., 2007a, Abraham et al., 2008, Ng et al., 2008, Siirila-Waris et al., 2006, Nieminen et al., 2006a, Oliva et al., 2012, Logeart et al., 2013) **(Figure 2.4)** The longest LOS has been reported from Japan and Brazil.(Bocchi et al., 2013, Sato et al., 2010) This could be related to policy of care as well as differences in insurance in different countries.(Sato et al., 2010) LOS is longer in Europe compared to the USA. Longer LOS appears to be beneficial to patients as it affords time for is aboutstabilization and reduces the incidences of early rehospitalisation. (2012c, Maggioni et al., 2013, Bueno et al., 2010, Joffe et al., 2013, Aranda et al., 2009, Fonarow et al., 2007a, Abraham et al., 2008, Ng et al., 2008, Siirila-Waris et al., 2006, Nieminen et al., 2006a, Oliva et al., 2012, Logeart et al., 2013) LOS has fallen in Europe by 1-2 days(Stewart et al., 2001b) and from 5.6 to 5.3 days in the USA in the last decade.(Bueno et al., 2010) LOS appears to increase with age.(Bueno et al., 2010) In one study, LOS was 5.2 days for those aged 60-64 years compared to 7.2 days for patients aged 85 years and above.(2012c) **(Table 2.5, Table 2.6, Table 2.7)**

2.6.2 HF related mortality

Intrahospital mortality

This ranges from a rate of 2.5% in one US study(Ng et al., 2008) to 27% in the EFICA study by Zannad et al(Zannad et al., 2006). The latter were patients admitted in the intensive care unit with most in cardiogenic shock. **(Figure 2.5)**

Short- and medium-term mortality

The 30-, 90-, 180-day and 12-month mortality associated with the development of AHF is shown **figure 2.6.** Short- and medium-term outcomes have improved in the last few years.(Bueno et al., 2010, Chen

et al., 2011, Curtis et al., 2008, Blackledge et al., 2003b, Schaufelberger et al., 2004) In one USA report, intrahospital mortality rates fell from 8.5% in 1993 to 4.3% in 2006, while 30-day mortality rate fell from 12.8% to 10.7% during the same period. In another report intrahospital mortality fell from 5.1% to 4.2% between 2001 and 2005 although the 6-month and 12-month mortality rate remained fairly unchanged during same period.(Curtis et al., 2008) Chen et al(Chen et al., 2011) also analyzed Medicare

data of 55 million patients between 1999 and 2008 and clearly showed reduction of 1-year mortality from 31.7% to 29.6%.

Long-term mortality

Long-term outcome for acute HF has remained poor despite improvement in HF management. The reported 5-year mortality rate is in the range of 70 %.(2012c, Joffe et al., 2013, MacIntyre et al., 2000, Cowie et al., 2000, Roger et al., 2004, Jhund et al., 2009) **(figure**

2.7**)** However community based reports from Scotland and the USA showed some improvement in 5-year mortality rate.(Jhund et al., 2009, Roger et al., 2004, Joffe et al., 2013) The 5-year mortality rate in Scotland in 2004 was 65%.(Jhund et al., 2009) Between the period 1979-1984 and 1996 -2000, 5-year mortality fell according to one USA report.(Roger et al., 2004) In another report, 1-year and 5-year mortality rates fell from 57.4% and 80.3% to 45.3% and 70.5% respectively.(Joffe et al., 2013)

2.6.3 Predictors of mortality

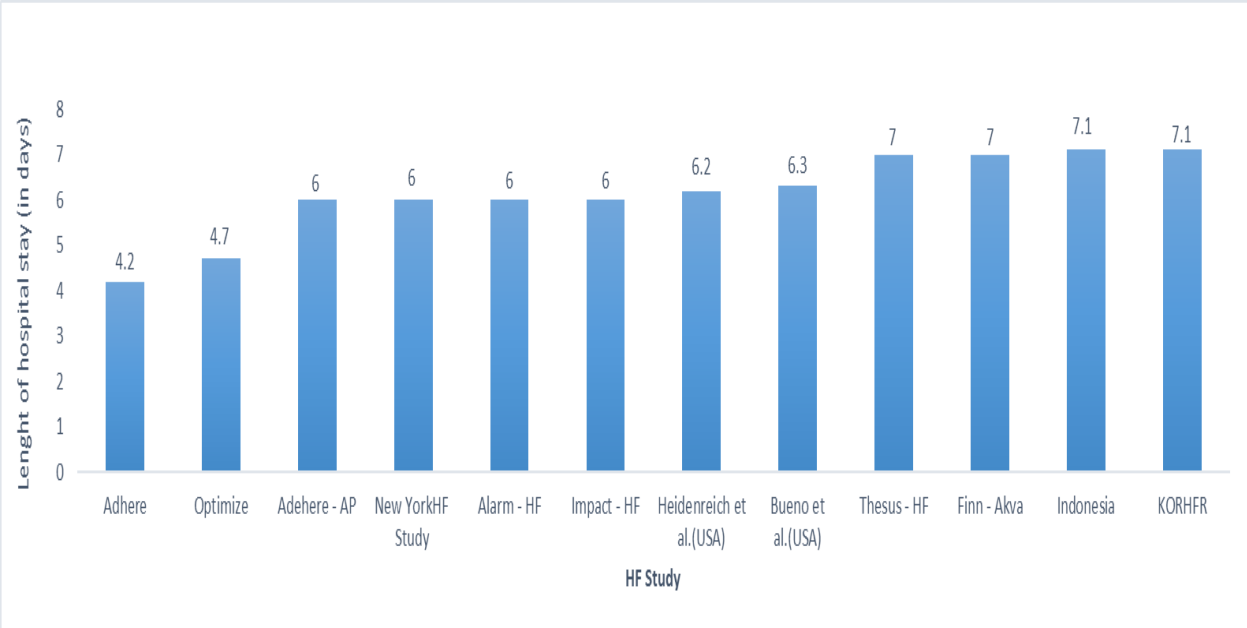
The well described independent predictors of morbidity and mortality in AHF include age(Joynt et al., 2013), co-morbidities (both cardiac and non-cardiac)(Kociol et al., 2010) heart rate(Kociol et al., 2010), blood pressure(Rodriguez and Marelli, 2014) renal function(Siirila-Waris et al., 2006), serum sodium(Ng et al., 2008), haemoglobin concentration(Abraham et al., 2008), natriuretic peptide concentration(Mosterd et al., 1999, McDonagh et al., 1997), troponin levels(McDonagh et al., 1997, Redfield et al., 2003), QRS duration(Nieminen et al., 2006a, McDonagh et al., 1997) and evidence based medications for AHF.(McMurray et al., 2012)

Both the ADHERE (Adams et al., 2005a) and OPTIMIZE-HF(Fonarow et al., 2007b) registries found systolic blood pressure and renal function as independent predictors of outcome. In the OPTIMIZE-HF registry, eight factors (such as age, body weight, systolic BP, serum sodium and creatinine as well as co-morbid conditions predicted the combined and point of death or readmission with a c-index of 0.72.(Fonarow et al., 2007b) In addition, combination of elevated B-type NP and positive troponin levels identified a subset of AHF patients who are at risk of short term mortality. These findings have been corroborated by many other studies globally.

It is now well established that; AHF patients have relatively low intra-hospital mortality but higher risk of early out-of-hospital readmission and mortality, and the risk of readmission and mortality can now be predicted using some clinical and/or laboratory based models. This is better so with mortality than readmission model. Furthermore, the absence of high risk features does not really identify populations who are at absolute low risk.

2.6.4 Hospital readmission

Readmission after an initial or index case of HF is common (Maggioni et al., 2013, Kociol et al., 2010, Cleland et al., 2003, Aranda et al., 2009, Tavazzi et al., 2013, Tavazzi et al., 2006, Jacob Rodriguez et al., 2011, Dharmarajan et al., 2013, Curtis et al., 2008, Jencks et al., 2009, Heidenreich et al., 2010) and CV reasons are responsible in about 30% of cases.(Maggioni et al., 2013, Nieminen et al., 2006a, Aranda et al., 2009, Dharmarajan et al., 2013, Jencks et al., 2009) It has been shown that 30-day readmission in the USA ranges from 20-25%.(Maggioni et al., 2013, Dharmarajan et al., 2013, Jencks et al., 2009) Higher rates of 60-67% have been reported following longer follow up.(Kociol et al., 2010, Aranda et al., 2009, Curtis et al., 2008) In Europe this ranges from 24% at 90-days to 44% at 1-year after discharge from the hospital.(Cleland et al., 2003, Nieminen et al., 2006a, Maggioni et al., 2013) It is now known that timely readmission for HF is associated with better patients' outcomes. This has been demonstrated by various HF programs in USA and Europe.(Rauh et al., 1999, Galvao et al., 2006)**(Figure 2.8)**



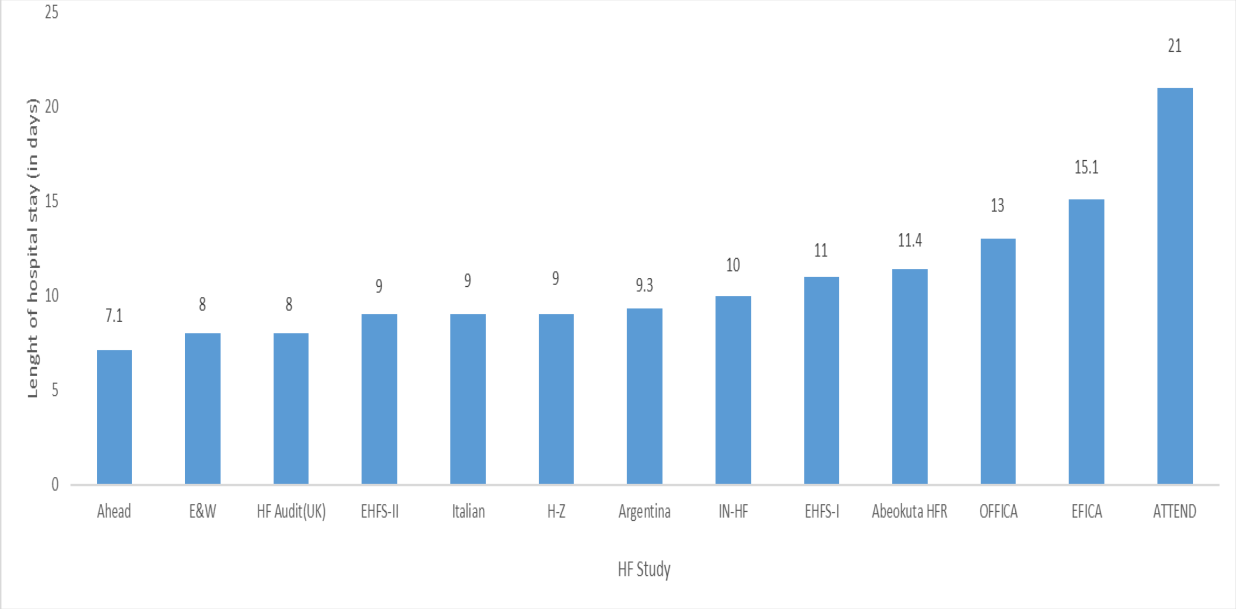


Figure 2.4. Length of hospital stay in various studies around the world

Ref**.** (Atherton et al., 2012, Adams et al., 2005a, Fonarow et al., 2007b, Klapholz et al., 2004, Follath et al., 2011, O'Connor et al., 2005, Heidenreich et al., 2010, Bueno et al., 2010, Damasceno et al., 2012, Siirila-Waris et al., 2006, Siswanto et al., 2010, Choi et al., 2011, Spinar et al., 2011, Nicol et al., 2008, 2012c, Nieminen et al., 2006a, Tavazzi et al., 2006, Rudiger et al., 2005, Perna et al., 2006, Oliva et al., 2012, Cleland et al., 2000, Logeart et al., 2013, Zannad et al., 2006, Sato et al., 2010)

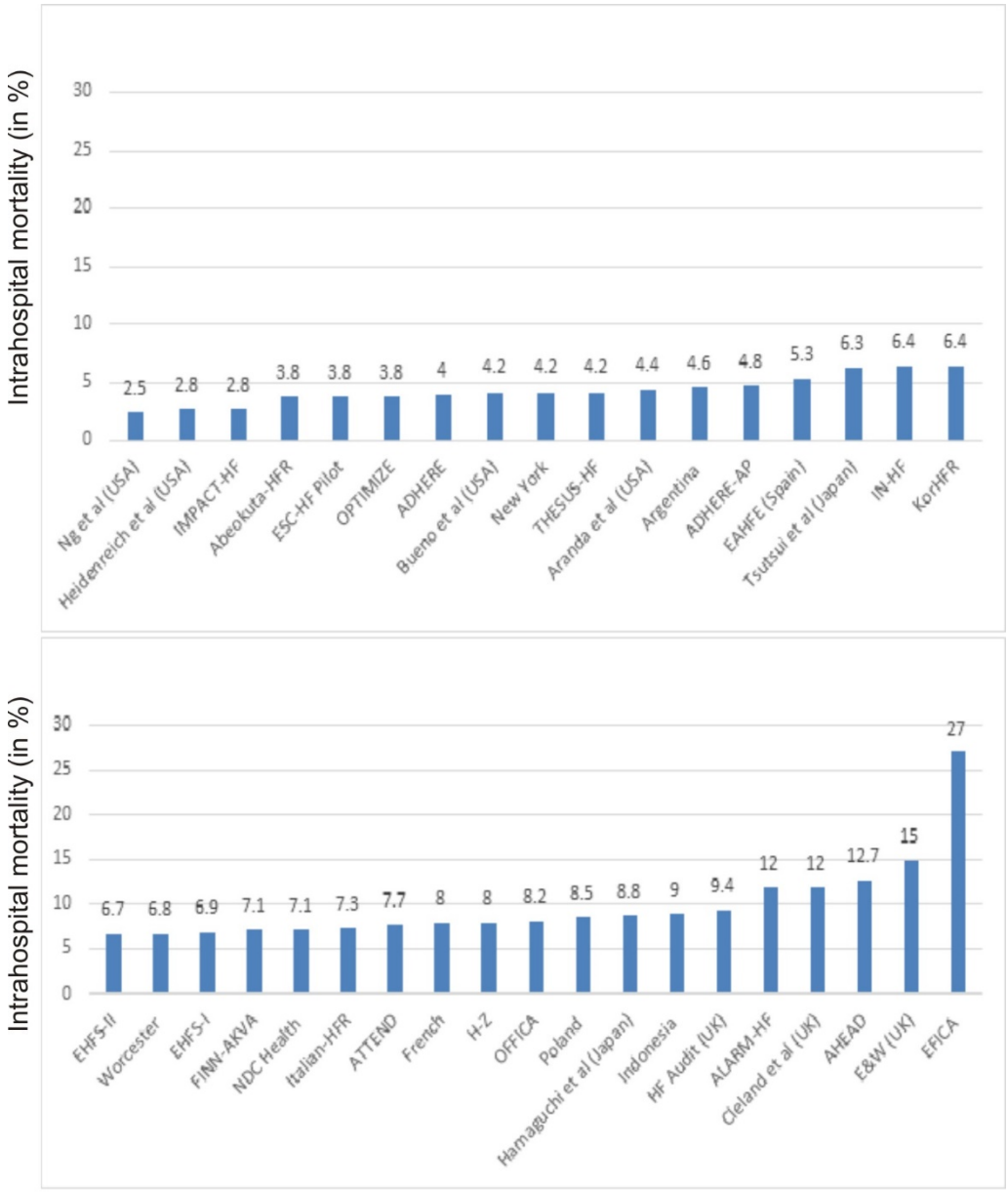
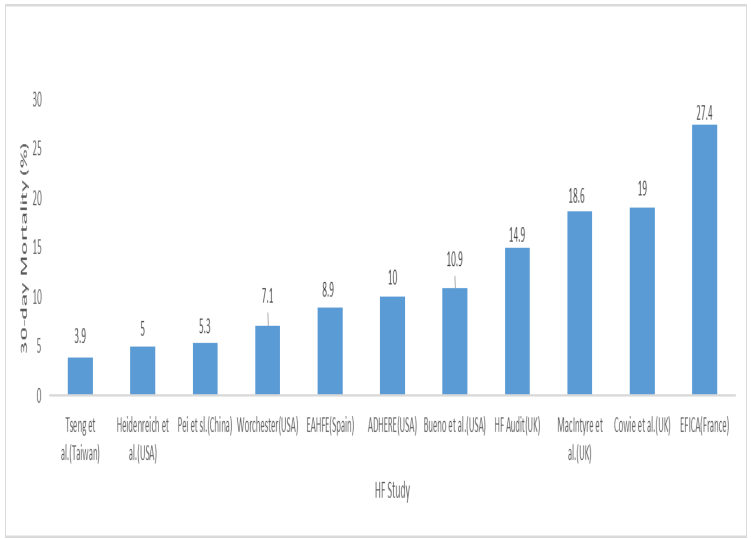
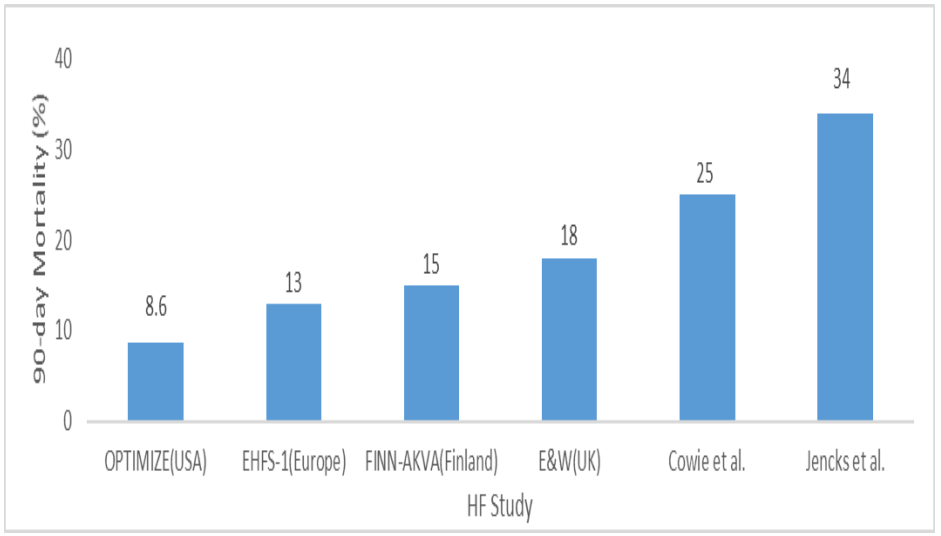
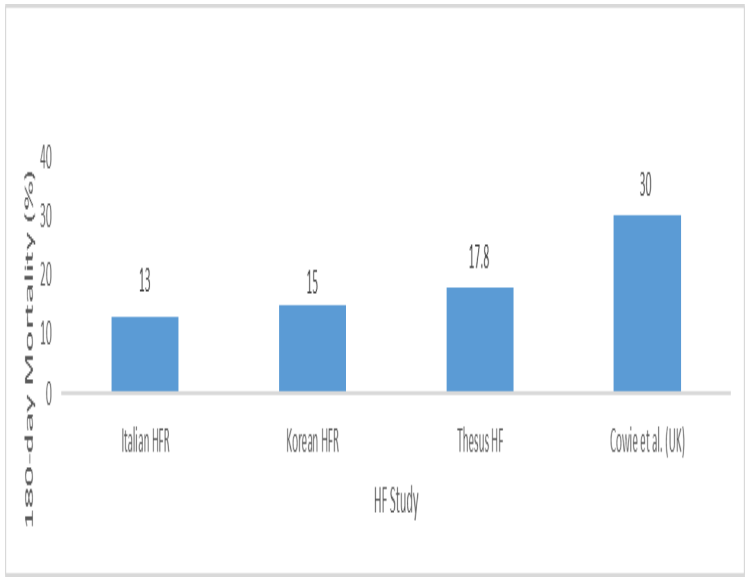


Figure 2.5. Intrahospital mortality rate following admission for acute HF in various studies around the world.

Ref(Ng et al., 2008, Heidenreich et al., 2010, O'Connor et al., 2005, Maggioni et al., 2013, Fonarow et al., 2007b, Adams et al., 2005a, Bueno et al., 2010, Klapholz et al., 2004, Damasceno et al., 2012, Aranda et al., 2009, Perna et al., 2006, Jacob Rodriguez et al., 2011, Atherton et al., 2012, Tsutsui et al., 2006a, Oliva et al., 2012, Choi et al., 2011, Nieminen et al., 2006a, Joffe et al., 2013, Cleland et al., 2000, Siirila-Waris et al., 2006, Tavazzi et al., 2006, Sato et al., 2010, Logeart et al., 2013, Rudiger et al., 2005, Venskutonyte et al., 2009, Hamaguchi et al., 2009, Siswanto et al., 2010, 2012c, Follath et al., 2011, Spinar et al., 2011, Nicol et al., 2008, Zannad et al., 2006)







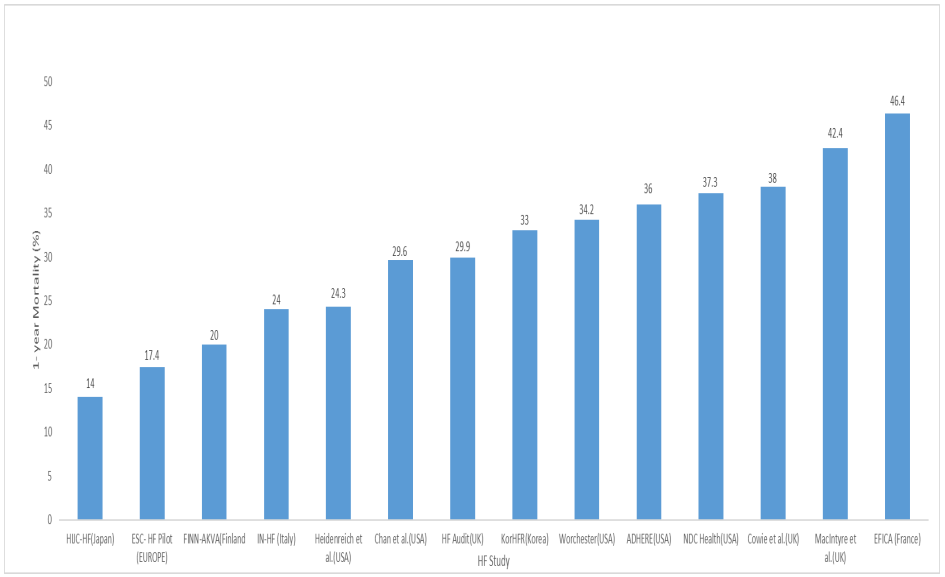
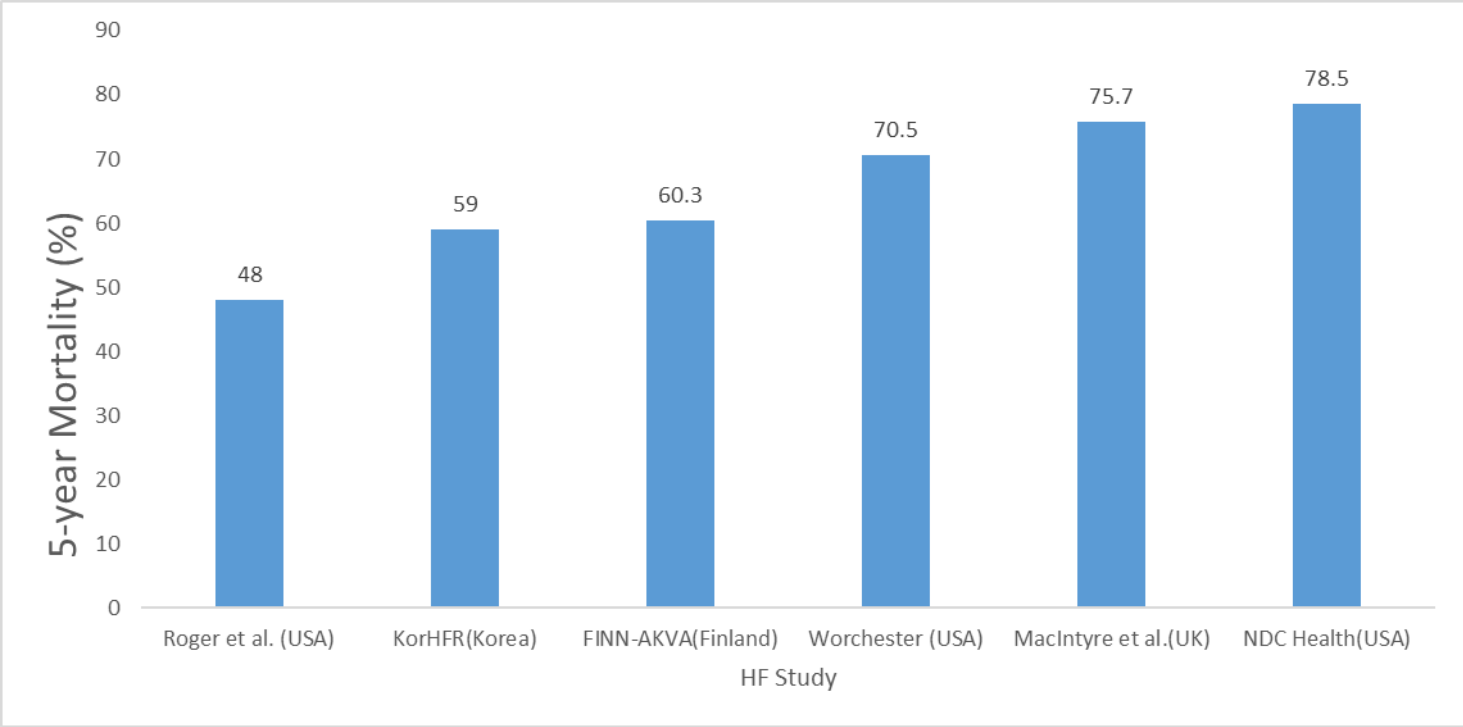


Figure 2.6. Mortality after admission for acute HF



2.7. Five-year mortality after onset of acute HF

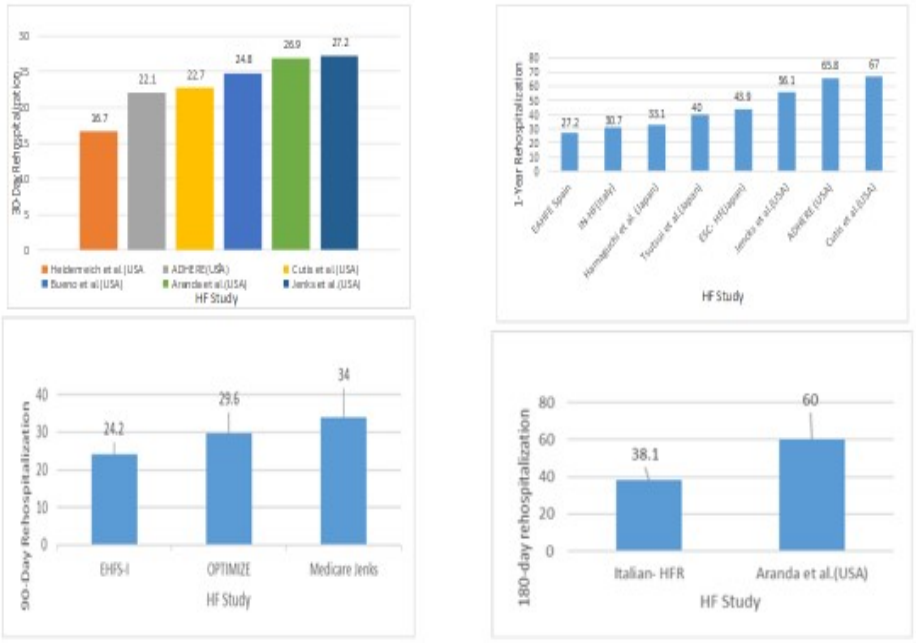


Figure 2.8. Rehospitalisation after admission for acute HF

2.7 The healthcare cost of HF

The economic cost of treatment of HF is huge due to high level of hospital care especially in high income countries. HF is responsible for 1-2% of direct healthcare expenditure in high income countries. For instance, direct cost of HF was estimated as 2.9 billion Euros in Germany (60% due to in-patient care).(Neumann et al., 2009) HF was estimated to cost about 39.2 billion Dollars in the USA in 2010 representing 2% of the budget allocated to health.(Roger et al., 2011) About 80% of direct cost for HF is due to hospital admissions.(Heidenreich et al., 2013) Joynt et al(Joynt et al., 2013) estimated hospital admission in 2010 to cost about 91.9 million Dollars (3.1% of the total expenditure) It has been projected that this cost will double in the next 20-years due to increasing number of people with the syndrome.(2012c, Heidenreich et al., 2013)

2.8 Psychosocial impact of HF

HF is associated with psychosocial dysfunction. Physical disability due to easy fatigability and shortness of breath affect activities like work, leisure and other social activities. Thus patients are often isolated. Psychological problems associated with HF include anxiety, fear and depression.(Jeon et al., 2010) Patients often experience guilt and frustration because of their dependence on others. Furthermore family members and caregivers also share in this psychosocial burden.(Stromberg, 2013, Brostrom et al., 2003)

2.9 Trend in hospitalization for acute HF

In most high income countries, it has been shown that hospitalizations for HF have increased in the last 10-years.(McMurray et al., 1993a, Stewart et al., 2001b) It rose by about 40% in Germany in a period of 7 years (2000-2007) while in the United Kingdom it rose by 57% since the year 2006.(Neumann et al., 2009, Stewart et al., 2001b, Stewart et al., 2003) On the other hand, the number of patients with primary diagnosis of HF is reported to be decreasing in the

USA (Chen et al., 2011), although the country's national hospital discharge survey shows no appreciable change in HF admissions between 2000 and 2010.(Hall et al., 2012)

In high income countries HF is a common cause of hospital admissions in those aged 65 years and above.(Rodriguez and Marelli, 2014) It is also responsible for 29% of emergency department visits in the USA (approximately 10.5 million visits) in those aged 40 years and above.(Hugli et al., 2005) About 5% of emergency admission in the UK is due to HF.(2012c) HF accounts for a large proportion of healthcare consumption and longer hospital stay.(Bueno et al., 2010)

There are some limitations in the available data on acute HF globally. Geographical representation in many major AHF registries is lacking. Most studies are from Europe and North America which is just 15% of the global population. Findings therefore cannot be extrapolated to other regions especially middle and low income countries.

Most AHF data have been collected in a non-consecutive form. This can result in differential enrolment and may also not be truly representative of the population.

Basic laboratory and clinical variables were captured in many registries such as haemoglobin, electrolyte and urea, bilirubin, ECG and echocardiography. Characteristics of medications in terms of routine dosage and duration have not been well documented. Quality improvement initiatives and process of care measures were also not included in many surveys.

2.10 Heart failure and heart disease in Sub-Saharan Africa

Sub-Saharan Africa (SSA) is the geographical term used to describe the region of the African continent that lie south of the Sahara desert. It covers a land area of 24.3 million square meters. In 2007, the population of the region was estimated to 800 million with a growth rate of 2.3% per annum. The United Nation has projected a population of 1.5 billion by 2050(2006c). SSA is comprised of the following regions: 1. West Africa, 2. Central Africa or Middle Africa 3. Eastern Africa 4. Horn of Africa and 5. Southern Africa (2009)The population of SSA is very diverse both physically and culturally and they have differing ethnic background. For instance the Negroes inhabit most of West Africa; the Tuaregs Nilohamites occupy the east horn of the continent, while the Bantus inhabit the Central and Southern Africa. There are also the Hottentots in rural Namibia and the pygmies of the Congo Basin.(2009)

2.10.1 Historical background

Cooke(Cooke, 1901) appears to be one of the earliest workers to have reported on the pattern of diseases in Africa. In 1901, he analysed 1,500 in-patients he saw at a hospital in Uganda. He observed that 3% of all hospital admissions and 6% of all medical admissions were due to heart disease. He wrote “Valvular diseases of the heart are common”, “Atheroma and aneurysms are very rare, although syphilitic endarteritis obliterans is probably common” and “high tension pulses are not often met with”.(Vaughan, 1977a)

Fifty years after, Sharper and his colleagues analysed 1957 medical admission seen at the Mulago hospital in Kampala and noted that cardiovascular disease was responsible for 8-10% of medical admissions. The main cardiac conditions reported were hypertension, rheumatic heart disease, endomyocardial fibrosis and syphilitic heart disease.(Shaper and Williams, 1960, Shaper and Shaper, 1958)

Similar work carried out in other countries in the 60s and 70s reported similar percentage that cardiovascular diseases are of all medical admissions. For example, 11.2% for Ibadan, Nigeria(Lauckner et al., 1961), 8.6% for Mombasa, Kenya(Turner, 1962a), 8.8% for Dar es Salaam, Tanzania(Nhonoli, 1968), 4.3% for Blantyre, Malawi(Brown and Willis, 1975) and 8.6% for Sekukhuneland, South Africa(Edginton et al., 1972) **(Table 2.8)**

Studies in late 70s, 80s and in the 90s also show the prominence of hypertensive heart disease, rheumatic heart disease and dilated cardiomyopathy as the main cause of heart disease in the region and decreasing incidence of syphilitic heart disease.

More recent studies have used echocardiography in the evaluation of heart diseases in the region. These have document peculiar characteristics of heart diseases in SSA(Oyoo and Ogola, 1999, Amoah and Kallen, 2000) (Kingue et al., 2005) (Ojji et al., 2009, Sliwa et al., 2008) (Stewart et al., 2008, Ojji et al., 2009, Ogah et al., 2014a, Makubi et al., 2014, Okello et al., 2014)

Table 2.8. Clinical Studies of Heart Failure in Africa

NO	Lead author	Country	Year	No	HHDX (%)	VHDX (%)	DCM (%)	EMF (%)	CP (%)	PDX (%)	SHDX (%)	IHD (%)	CHD (%)	Misc/Others (%)
Southern Africa														
1	Sliwa(Sliwa et al., 2008, Stewart et al., 2008)	SA	2008	844	33	8	35	-	27	-	-	9	-	-
2	Maharaj(Maharaj, 1991)	SA	1991	225	13.8	11.1	48.4	-	16.9	8.0	-	-	-	1.8
3	Powell(Powell and Wright, 1965)	SA	1965	270	14.0	17.0	34.0	-	10.0	6.0	10.0	-	-	9.0
4	Schrire(Schrire, 1964)	SA	1964	1952	34	19	5	-	2	12	2	1	5	20
5	Cosnett(Cosnett, 1962)	SA	1962	1000	20.2	20.5	13.8	-	16.2	2.5	8.8	0.6	0.6	17.0
6	Schwartz(Schwartz et al.,	SA	1958	275	19.6	23.6	37.5	-	10.9	4.0	1.1	0.4	1.1	-

	1958)													
7	Baldachin(Baldachin, 1963)	ZB	1963	564	22.2	38.3	7.3	-	5.1	2.8	11.3	-	7.1	5.9
8	Gelfand(Gelfand, 1957)	ZB	1957	189	14.8	27.0	15.4	-	3.7	6.9	10.5	-	8.9	12.8
9	Soliman(Soliman and Juma, 2008)	MA	2008	3908	24.2	33.6	18.6	0.08	-	14.2	0	0.08	4.4	1.5
10	Brown(Brown and Willis, 1975)	MA	1975	114	16	35	5	-	8	7	4.4	-	2.5	22.8
Western Africa														
1	Ojji(Ojji et al., 2009)	NG	2009	340	62.6	11.5*	17.0*	1.2	1.8	2.3	-	-	0.29	
2	Onwuchekwa(Onwuchekwa and Asekomeh, 2009)	NG	2009	423	56.3	4.26	7.3	0.2	2.13	-	-	0.24	0.24	
3	Karaye(Karaye and Sani, 2008)	NG	2008	79	57	12.7	24	-	2.5	12.7	-	7.6	-	-
4	Ansa(Ansa et al., 2008)	NG	2008	558	55.7	6.6	15.1	-	-	-	-	-	-	22.4

5	Familoni(Familoni et al., 2007)	NG	2007	82	43.4	9.8	28	2.2	3.7	1.5		8.5	-	3.5
6	Adewuya(Adewuya et al., 2006)	NG	2006	100	58	10	11	-	15	-	-	-	8.0	-
7	Antony(Antony, 1980)	NG	1980	315	11.7	13.7	47	-	6.3	-	-	-	-	21.2
8	Abengowe(Abengowe, 1979)	NG	1979	354	45.5	14.4	20.6	-	2.3	7.9	-	0.8	0.6	7.9
9	Haddock(Haddock, 1979)	NG	1979	41	43.9	24.4	31.3							
10	Ladipo(Ladipo et al., 1977)	NG	1978	360	35.8	11.9	35	-	8.1	-	0.6	-	0.3	-
11	Uzodike(Uzodike, 1975)	NG	1977	348	15.5	25.6	25.8	2.5	9.5	4.8	-	1	-	-
12	Ogunmekan(Ogunmekun, 1973)	NG	1973	131	41.2	2.3	44.3	4.6	2.3	-	-	-	-	7.6
13	Oviasu(Oviasu, 1973)	NG	1973	225	69.8	8.0	9.8	5.3	1.8	-	-	-	2.7	0.9
14	Carlisle(Carlisle and Ogunlesi,	NG	1972	267	28.5	18.1	13.9	12.1	6.8	6	-	1.5	5.3	8.3

	1972)													
15	Okuwobi(Okuwobi, 1967)	NG	1967	137	26	13	22	14	28	6		7		
16	Ikeme(Ikeme and Parry, 1966)	NG	1966	225	39.1	8.0	29.3	9.8	1.8				2.2	10.2
17	Lauckner(Lauckner et al., 1961)	NG	1961	155	18.7	18.7	30.3	14.2	0.6	0.6	-	1.3	5.2	5.2
18	Beet(Beet, 1956)	NG	1956	358	34	23	8	-	1.7	2.2	16	-	2.2	12.2
19	Nwokolo(Nwokolo, 1955)	NG	1955	40	15	7.5	2.5	10	2.5	12.5	7.5		5	25
20	Serme(Serme et al., 1991)	BF	1991	399	49.1	13.0	18.1	-	-	-	-	6.5	0.8	-
21	Bertrand(Bertrand E et al., 1991)	IC	1991	1960	39.3	14.5	7.2	1.9	-	-	-	6.5	12.4	-
22	Bertrand(Bertrand et al., 2006)	**	2006	665	52.3	11.1	20.6	-	-	-	-	6.1	-	9.9
23	Fofana(Fofana	GU	1988	574	37.5	14.0								

	et al., 1988)													
24	Amoah(Amoah and Kallen, 2000)	GH	2000	572	21.3	20.1	11.4	3.8				9.7	9.8	23.6
25	Owusu(Owusu, 2007)	GH	2007	167	42.5	21.6	17.4		2.4	4.2		3.5	2.4	
26	Ikeme(Ikeme et al., 1978)	GH	1977	559	89.3	2.4	7.8						1.6	
27	Payet(Payet et al., 1963)	SE	1963	100	25	20	26	5		6		2		16
28	Harling(Harling et al., 1965)	GB	1965	154	14.3	16.9	33.8		9.7	5.8	5.2			9.7
29	Rowland(Rowland, 1965)	SL	1965	224	32.1	8.9	23.2				11.2		9.4	
30	Sankale(Sankale et al., 1969, Sankale et al., 1958)	MALI	1958	250	17.2	20.8	29.2			4.4	14	1.6	3.6	9.2
31	Pole(Pole et al., 1979)	GH	1976	241	44.8	16.6	21.2					3.7	2.5	11.6

32	Cenac	NIGER	1985	162	25.9	37.0	5.5			6.8			4.9	19.8
Eastern Africa														
1	Oyoo(Oyoo and Ogola, 1999)	KE	1999	91	17.6	31.9	25.3	-	7.7	13.2	-	2.2	2.2	-
2	Parker(Parker, 1973)	KE	1973	523	6.9	46.1	8.4	0.8	-	1.3	0	1.3	18.2	17.2
3	Turner(Turner, 1962a)	KE	1962	168	39.9	20.2	1.8	11.9	6.0	6.5	4.2	2.4	-	4.8
4	D'Arbela(D'Arbela et al., 1966)	UG	1966	449	19.5	24.7	13.5	11.1	5.0	3.5	6.2	0.7	8.0	11.1
5	Shaper(Shaper and Williams, 1960)	UG	1960	712	37.4	14.7	-	13.6	0.28	3.5	13.6	1.3	1.3	14.6
6	Williams(Williams et al., 1952)	UG	1952	352	31.3	11.6	9.1	16.2	0	6.5	20.2	0	1.7	0.9
7	Vaughan(Vaughan, 1977b)	TZ	1977	20,572	22.4	10.6	-	-	-	-	-	7.4	-	59.6
8	Kanti	UG	1971	871	29.9	22.8	8.3	7.9	5.1	6.8	4.5	0.2	1.3	18.2
9	Obineche(Obineche, 1976)	ZB	1976	170	33.5	21.8	21.8		5.3	2.9			1.3	13.5

10	Nhonoli(Nhonoli, 1968)	TZ	1968	225	42.2	9.8	11.1	4.0	4.9	5.3	5.3	2.7	1.3	18.2
11	Bovet(Bovet, 1995)	SY	1995	667	18.8	2.4	9.8	-	-	-	-	21.0	-	42.5***
Central Africa														
1	Tambwe(Tambwe et al., 1995)	ZA	1995	317	40	4.0	15	-	-	4.0	-	3.0	-	0.5
2	Kingue(Kingue et al., 2005)	CAM	2005	167	54.4	24.6	26.3	-	-	-	-	-	2.4	-
3	Kingue(Kingue et al., 2000)	CAM	2000	312	38.5	25.6	22.5	0.6	-	-	-	0.9	-	-
4	Mboulley-Kofo(Mboulley-Koto and Bouelet, 2000)	CAM	2000	1959	38.6	13.9	17.8	-	-	-	-	1.5	-	-
5	Ikama+(Ikama et al., 2008)	CO	2008	225	34.5	9.4	7.6	-	11.2	-	-	25.6	-	3.6
6	Amendezo(Amendezo et al., 2008)	RW	2008	226	42.9	11.5	11.9	-	-	8.0	-	3.1	-	22.5
7	S'jongers(S'Jongers and	RW	1960	5307	22.7	30	-	-	4.0	-	10.0	23.3	8.0	2.0

	Enderle, 1960)													
8	Miller(Miller et al., 1962)	GAB	1962	416	19.3	32.7	7.5	12.8	1.5	1.0	8.5	4.7	10.0	2.0
9	Mets(Mets, 1993)	RW	1993	86	25.6								2.3	
Horn of Africa														
1	Maru(Maru, 1993)	ET	1993	474	38.1	40.2	4.7	-	-	4.5	2.1	6.0	2.1	2.3
2	Hodes(Hodes, 1988)	ET	1988	338	13.9	50.0	10.4	1.2	-	-	-	-	-	10.6
3	Gebrehiwot(Gebrehiwot, 1982)	ET	1982	NA	15.4	49.3	8.8	-	-	2.6	7.9	7.4	3.0	2.2
4	Lester(Lester and Tsega, 1976)	ET	1976	NA	32.7	37.6	11.6	-		-	-	7.2	2.4	-
5	Laivonic(Laivonic, 1970)	ET	1970	559	30.0	28.5	6.6	-	5.6	3.2	21.5	4.4	-	-
6	Parry(Parry and Gordon, 1968)	ET	1968	558	16.3	34.8	13.6	-	1.6	10.8	16.8	-	-	6.1
7	Vukotich(Vukot	ET	1968	435	13.6	23.5	22	-	6.5	4.4	22.7	4.4	1.6	0.5

	ich, 1968)													
8	Molineaux(Molineaux et al., 1965)	ET	1966	NA	13.3	32.6	-	-	-	1.7	17.4	?17.4	1.7	13.2
9	Halim(Halim and Jacques, 1961)	SU	1961	958	44.4	25.4	-	3.2	2.0	-	6.0	12.6	3.7	2.7

HHDX=Hypertensive heart disease, VHDX= valvular heart disease, DCM= Dilated Cardiomyopathy, EMF= Endomyocardial fibrosis, CP= Cor-pulmonale, PDX = Pericardial diseases, SHDX= Syphilitic heart disease, IHD= Ischaemic Heart Disease, CHDX= Congenital heart disease, Misc = MiscellaneousSA=South Africa, NG= Nigeria, GH=Ghana, CAM= Cameroun, KE=Kenya, SE= Senegal, GU= Guinea, GB= Gambia, GAB= Gabon, UG= Uganda, ET= Ethiopia, ZB=Zimbabwe, CO= Congo, SY=Seychelles, ZA= Zaire, TZ= Tanzania , RW= Rwanda** A multicentre study involving 7 Francophone countries., +Study was carried out in elderly subjects (>= 60 years), @ Community based study, ++ Includes 19.6% due to heart failure, 18.2% due to cerebrovascular disease and 9.7% classified as others. ∞Percents obtained from Maru et al

2.10.2 Sociodemographic characteristics

Age of Presentation

The mean age of presentation of heart disease in the region ranges from 40-55 years. This implies that the condition affects the productive age group with the associated longer disability adjusted life years. In the recent THESUS-HF study(Damasceno et al.), the median age was 55 years. Soliman et al (Soliman and Juma, 2008) reported a mean age of as low as 40 years in a study in Malawi. Several other studies in SSA have reported a mean age of 50-55 years (Sliwa et al., 2008, Stewart et al., 2008, Ogah et al., 2008, Laabes et al., 2008, Ojji et al., 2009, Kingue et al., 2005, Oyoo and Ogola, 1999, Habte et al.).The observation therefore suggests that HF affects SSA subjects at the prime of their life. This will definitely result in limitation in parenting, employment as well as the ability of individuals to be active in their community. Contrary to the situation in SSA, HF is essentially a problem of elderly people in high income countries (Nieminen et al., 2006a, Tsuchihashi-Makaya et al., 2009, Tsutsui et al., 2006a, Adams et al., 2005a, Fonarow et al., 2009) where the average age at presentation (72 years) is about two decades later than in SSA.

Gender distribution

Heart disease in SSA is generally more frequently reported in men than in women (42.6- 49.1% in women).(Ogah et al., 2008) (Ojji et al., 2009) (Onwuchekwa and Asekomeh, 2009) (Kingue et al., 2005) (Soliman and Juma, 2008) (Habte et al.) On the other hand, Heart disease rates were reported to be higher in women in the Heart of Soweto study (57%)(Stewart et al., 2008) in Jos (North central region of Nigeria)-68.6%(Laabes et al., 2008) in Kenya (51.6%)(Oyoo and Ogola, 1999)and Uganda (66.2%)(Kuule et al., 2009)

The gender differences reported from different region of SSA may be related to patient selection, sex differences in the burden of cardiovascular risk factors such as hypertension, diabetes mellitus, obesity and cigarette smoking. The pattern of heart diseases is also

important. In areas with predominance of rheumatic heart disease and cardiomyopathy (especially peripartum cardiomyopathy), HF rates tends to be commoner in women than in men. Healthcare seeking behavior may also play an important role. It is more likely to take the breadwinner in the home than the dependent.

Clinical presentation

HF subjects in SSA present with severe symptoms (NYHA classes III and IV). This was reported in 96.8% of cases by Kuule et al in Uganda and 93.1% by Laabes et al in Jos Nigeria (93.1%) but far less than the report by Stewart et al in the Heart of Soweto (34%) and Damasceno et al (34.6%). Oyoo et al (Kenya) also reported a lower figure (37.4%) while Tantchou (Cameroon) reported 51%. In the US ADHERE cohort, 74% of them were in NYHA III and IV (Adams et al., 2005a)

Laabes et al documented dyspnoea (100%), orthopnoea (92%), PND (97%), displaced apex beat (99%), hepatomegaly (95.1%), elevated JVP (67.6%) and hepatomegaly in 95.1%). In the Heart of Soweto study, dyspnoea was present in 89% of Blacks enrolled in the study. Similar observation was also made by Oyoo in a study in Nairobi, Kenya. In Indonesia(Siswanto et al., 2010), dyspnoea, orthopnoea, basal crackles and pedal oedema were present in 97%, 31.5%, 86.3% and 42%b respectively. In the US, these were documented in 89%, 32%, 60% and 62% respectively (Adams et al., 2005a).

Aetiological risk factor for HF in SSA

Hypertensive heart disease

Many years ago Donnison(Donnison, 1929) reported that hypertension was uncommon in Africa. This observation was later supported by the post-mortem studies by workers like Jex-Blake(Jex-Blake, 1934), Vint(Vint, 1937) as well as clinical study by William(Williams, 1941) in 1941. However, by 1946, workers started reporting on the impact of hypertension on the

cardiovascular health of the African. Davies(Davies, 1948) noted that hypertensive heart disease was the commonest cause of congestive heart failure in Kampala. Similar report was also noted in South Africa(Becker, 1946). Within same period, many other authors from different parts of Africa also documented that the disease is common in the continent, occasionally with prevalence similar to data from Europe and America.

It is known that in isolated and primitive areas of the continent the prevalence of hypertension is very low and in these populations, blood pressure remain within a narrow range throughout adult life(Akinkugbe et al., 1991). Blood pressure rises modestly with age in rural dwellers and much more in those who live in the cities.

More recent data from the continent suggest that hypertension is a major cause of cardiac morbidity and mortality (Opie, 2006, Akosa and Armah, 2005). High blood pressure is in fact regarded as the foundation of cardiovascular disease in Africa(Cooper et al., 2003). In a recent systematic review of hypertension survey in Africa, it was shown that hypertension increased from 54.6 million cases in 1990 to 130.2 million in 2010. The prevalence is projected to rise to 216.8 million cases by 2020, each with an age-adjusted prevalence of 19.1% (13.9, 25.5), 24.3% (23.3, 31.6) and 25.3% (24.3, 39.7) respectively.(Adeloye, 2014)

Hypertension is responsible to close to 60% of cases of HF when the clinical studies are pooled **(Table 2.8)**. In the Heart of Soweto study, among the 1196 persons with the diagnosis of secondary hypertension, 682 or 57% (mean age 60±14 years) had hypertensive HF.(Sliwa et al., 2008). In the INTERHEART study, hypertension was reported as a strong contributor to the hazards of CVD in black Africans, with an odd ratio of 7.0 versus 2.3 to 3.9 in other ethnic groups ($p < 0.0002$) (Steyn et al., 2005).

Hypertension in Africa is associated with body weight, lower intake of potassium and salt sensitivity(Seedat, 1990). The peak age group is 40 - 49 yrs. Men are affected more than women. The patterns of presentation of hypertensive HF vary. Some present with acute left

ventricular failure and severely elevated blood pressure. A sub-group present with HF and normal blood pressure which tend to rise as the HF is being treated. And yet a third group present with HF and normotension all through. The last group is usually difficult to differentiate from dilated cardiomyopathy in the absence of other signs of long standing hypertension(Araoye and Olowoyeye, 1984).

The mortality attributable to high blood pressure in most West African Countries ranges between 3 - 7% and cardiovascular mortality is in the range of 20 - 45%(Muna, 1993). Women may have added morbidity in Africa if the role of hypertension in pregnancy is factored in. Hypertension is largely asymptomatic until end-organ damage ensues and this is partly responsible for late diagnosis of the disease. Inadequate screening and sub-optimal health facility utilization are also implicated. Therefore, early diagnosis and appropriate therapy would lead to a significant reduction in the prevalence of hypertensive HF in Africa.

Rheumatic Heart Disease (RHD)

It is estimated that 12 million people live with the disease and it results in about 400,000 deaths each year. Two million people will require repeated hospital admission and over a million will need surgery to improve their quality of life. It is common in areas with poor housing condition and an indicator of their plight.

Like hypertension, this was initially thought to be uncommon in Africa(Donnison, 1929). But Cooke in 1901 reported that valvular diseases are common in the continent(Cooke, 1901). This was also supported by reports by other workers(Heinmann, 1929). Post-mortem studies have been inconsistent. This may be due to the attitude of Africans towards autopsy.

SSA has the highest prevalence of RHD which is in the range of 1-14/1000 children.(Marijon et al., 2007) (Carapetis et al., 2005) (Kimbally-Kaky et al., 2008)Echocardiographic based population studies report higher prevalence of 7.5-51.6 / 1000 children.(Beaton et al., 2012,

Kane et al., 2013) School surveys have given a prevalence of $2.7/10^3$ in Kenya(Anabwani and Bonhoeffer, 1996), $4.3/10^3$ in Ethiopia(Oli and Asmera, 2004), and $6.9/10^3$ in South Africa(McLaren et al., 1975) (amongst black children). Marijon et al reported a prevalence of $30/10^3$ from an echocardiography-based school survey.(Marijon et al., 2008)

RHD accounts for 12 - 32% of cardiovascular admissions in SSA. Recent reports suggest that that 6.6-34% of CV related hospital admissions or echocardiographic data in SSA is due to RHD and up to 2.3% of pregnant women have the disease.(Tantchou Tchoumi et al., 2011a, Tantchou Tchoumi and Butera, 2009, Soliman and Juma, 2008, Ike, 2008, Sani et al., 2007a).

There are peculiar features of rheumatic heart disease in Africa (similar to reports from other tropical environments). These are the young age at presentation, the severity of the lesions, as well as the high mortality associated with it. History of rheumatic fever can be obtained in only less than 50% of patients. Pure mitral incompetence and mixed mitral valve disease were the commonest valvular lesions that were demonstrated(Onwuchekwa and Ugwu, 1996). This is consistent with the findings of other workers in Africa (Jaiyesimi and Antia, 1981a, Jaiyesimi and Antia, 1981c, Fadahunsi et al., 1987, Sani et al., 2007a). A rheumatic carditis has been shown to run a more fulminant course in sub-Saharan Africa (like in other tropical countries) compared to the developed countries (1981, Essop and Nkomo, 2005, Nkomo, 2007, Nkomo et al., 2006). In earlier studies, 33% of 124 mitral valvotomies were in patients under the age of 16 years in one reported from Kenya.

The disease appears to be commoner in women. Events in women's life such as pregnancy frequently unmask the condition(Cole and Adeleye, 1982). Morbidity and mortality is said to be high especially in women and young people (Cole and Adeleye, 1982, Cole, 1976) . Mortality at 6-month mortality is estimated as 17.8%.(Gunther et al., 2006) In one report from Ethiopia,

the annual mortality from RHD is as high as 12.5% and 70% of such deaths were before the age of 26 years.(Oli and Asmera, 2004)

Sliwa et al (Sliwa et al.) reported on the characteristics of 344 adult rheumatic heart disease cases in the heart of Soweto study. The disease was commoner in black women (68%). The most common valvular lesion (n = 204, 59%) was mitral regurgitation (MR), with 48 (14%) and 43 (13%) cases, respectively, having combination lesions of aortic plus MR and mixed mitral VHD. Impaired systolic function was demonstrated in 28/204 cases (14%) of predominant MR and in 23/126 cases (18%) with predominant aortic regurgitation. The finding from the study makes a case **for** the first episode of RHD to be made a notifiable condition in high burden countries in order to ensure control of the disease through register-based secondary prophylaxis programmes.

In many countries in SSA, facilities for accurate diagnosis are unavailable. Treatments options such as valvotomy, valvuloplasty and prosthetic valve replacement are either unavailable or unaffordable to a vast majority of the population. Worse still secondary preventive measures are also either unavailable or unaffordable.

The lack of infrastructure, political, economic and social instability, malnutrition and poverty are all factors implicated in the high prevalence of rheumatic fever in Africa which is otherwise, largely preventable(Essop and Nkomo, 2005). This culminates in a great burden of rheumatic valvular heart disease and infective endocarditis.

The Cardiomyopathies

Dilated cardiomyopathy (DCM), endomyocardial fibrosis (EMF) and peripartum cardiomyopathy (PPCM) are common and endemic in SSA. Other forms of cardiomyopathy are less common.

Dilated Cardiomyopathy (DCM)

DCM is a major cause of heart failure in SSA. It has been plagued with diagnostic and therapeutic challenges due to lack of appropriate facilities, definitive diagnosis and interventions in resource poor African centres.

DCM contributes about 18% of cardiac related admissions in West and South African clinical studies. It also accounts for 10% of cardiac diseases at autopsy and 12% echo-based studies. It typically presents with progressive heart failure and is associated with high mortality. In one study, the 4-year mortality was found to be 34%.

There **are** marked regional differences in the pathogenesis of dilated cardiomyopathy in Africa. The causative factors that have been implicated in several studies across Africa include infection(Falase et al., 1982, Falase et al., 1977) and myocarditis(Basile et al., 1973, Falase, 1979), "burnt out" untreated hypertension(Falase, 1977), genetic factors, alcohol, nutritional deficiencies, autoimmune mechanisms ,iron overload and pregnancy(Mayosi, 2007)

The current concept is that 30% of the disease has genetic basis. Familial DCM is caused by a mutation in more than 25 chromosome loci. The genes affected are those encoding contractile, cytoskeleton and calcium regulatory proteins.

In 1975, Owor and Rwomushana reported the first case of familial DCM in Africa(Owor and Rwomushana, 1975). They described twin brothers who were affected by the condition in Uganda. Subsequently other workers have documented familial DCM in other parts of SSA especially from South Africa(Przybojewski et al., 1984). However, there are no systematic family studies of the condition in SSA.

Some gene association studies have however been done especially in South Africa. Some of the findings include:

1. An association with HLADR1 And DRW10 antigens suggesting possible genetically determined immune factors may be responsible for the disease(Maharaj and Hammond, 1990, Maharaj et al., 1987)
2. An association with mutation in troponin T-gene(Arg141Trp)(Mayosi et al., 1999) and mitochondrial T16185c polymorphism.

On the other hand there is no evidence of association with cardiac (ACTC1) and skeletal (ACTA1) alpha-actin gene, alpha-2c adrenoceptor (ADRB2c) gene, beta-1 adrenoceptor (ADRB1) gene and tumor necrosis factor-alpha (TNFA) gene.

Some data suggest the immune modulating agent pentoxifylline may be beneficial in the management of DCM in the region. In one trial, patients on this agent had improvement in effort tolerance, left ventricular function and trend towards lower mortality than those on standard treatment for heart failure(Sliwa et al., 2002).

In a 14-yer follow up of DCM patients in South Africa, a mortality of 10%/ year was recorded for both familial and idiopathic DCM. Heart transplantation was an independent predictor of survival while NYHA III and IV and use of digoxin were associated with poor outcome.

Endomyocardial fibrosis (EMF)

This is a form of restrictive cardiomyopathy in which there is a deposition of fibrous tissue in the mural endocardium resulting in impaired diastolic function as well valvular dysfunction resulting from entrapment of papillary muscles of the atrioventricular valve. It occurs mainly in the tropical and subtropical areas of Africa. It was first described by William in 1938. It is also called Davies disease because of the seminal work done by Davies on this disorder in Uganda(Davies and Ball, 1955, Davies, 1956, Davies, 1968). A comprehensive description of the clinical features have been documented by Hutt(Hutt et al., 1965) as well as other workers(Shaper, 1972, Parry and Abrahams, 1965).Recently Mocumbi et al have suggested a diagnostic criteria for diagnosis.(Mocumbi et al., 2008)

EMF has been reported in at least seventeen SSA countries: Congo, Cameroon, Egypt, Ethiopia, Gabon, Ghana, Kenya, Malawi, Mozambique, Nigeria, Senegal, South Africa, Sudan, Tanzania, Uganda, Zambia and Zimbabwe. It has also been reported in India and South America. It is rare in Northern and Southern Africa. Right sided EMF appears to be commoner. The peak age incidence is 11-15 year in both sexes. In a population based study in Mozambique, a prevalence of 8.9% was found.

EMF is a disease of childhood and early adolescence. It has also been reported in older adults and infants. A second peak of incidence has shown during the reproductive age of women. The preponderance of one gender over the other is inconsistently reported. In a large database from Mozambique, it was reported to be more prevalent in males.

The pathophysiology postulated is as follows: endocardial thickening of the ventricles lead to cardiac constriction or restriction and atrio-ventricular valvular incompetence resulting in regurgitation. The right ventricular cavity is usually obliterated from below by the advancing fibrosis of layered mural thrombi. In severe and late cases, the papillary muscles are buried in a layer of fibrous tissue leading **to** functionless tricuspid valve and aneurysmal right atrium. When the left ventricle is involved dense fibrous tissue are deposited at the apex, spreading around the cavity of the LV or may first appear around the papillary muscles of the posterior cusp of the mitral valve (leading to anchoring of the muscle and valvular regurgitation)(Davies and Ball, 1955, Parry and Abrahams, 1965)

Chronic pericardial effusion commonly complicates right sided EMF while pleural effusion is commoner with left or biventricular disease(Parry and Abrahams, 1965). The clinical features depend on the stage of the disease, the anatomical damage done on the affected valve as well as the resultant effect on heart function. An initial illness with fever, chills, night sweats, facial

swelling, and urticaria can occur and is reported in 30-50% of cases. This can be fatal within months but little is known about this phase of the disease(Parry and Abrahams, 1965).

In left sided EMF, the ventricle is not enlarged and there is almost always mitral incompetence and a loud pulmonary component of the second heart sound and progressive pulmonary hypertension. There is usually an early third heat sound. When the right ventricle is involved, the classical picture is that of a young patient with 'egg on stick' or 'orange on stick' appearance (massive ascites and minimal pedal oedema; often with delayed puberty , some exophthalmos and central cyanosis(Parry and Abrahams, 1965). The arterial pulse is usually of small volume or feeble. Atrial fibrillation is common. Massive pericardial effusion or a rotated heat (because of massive right atrium) could give an impalpable heart. An abrupt third heart sound is common but murmur may be absent.

The pathogenic process is explained by eosinophil and its constituents. The suggested sequelae is as follows(Parry and Abrahams, 1965):

1. A trigger to eosinophilia (helminthic or other infections and liberation of eosinophilic major basic proteins and cationic proteins which are toxic to the cardiac cells as well as other cells in the body
2. The damaged endocardium serves as a nidus for thrombus formation
3. Thrombus formation builds up due to release of platelet activating factors by the eosinophils
4. Further mural thrombi are laid down at the original and adjacent sites leading to the formation of fibrotic mass.

Although this explanation appears plausible, it does not offer reason why the disease is rare in some parts of the tropics, the reported ethnic differences(Shaper, 1970) and some familial cases of EMF(Adi, 1963).

Despite the fact that the aetiology of this condition has not been resolved by scientist since the first description, the volume of publication on it has dwindled in the last decade. The cause has remained a mystery despite several proposed aetiological factors(Bukhman et al., 2008). Some of the factors that have been implicated in the past include: 1. Infections/Infestations e.g cardiotropic viruses, mycoplasma pneumonia, malaria, schistosomiasis, 2. Autoimmunity, 3. Hypereosinophilia, 4. Genetics, and 5. Traditional medications.

Trend in the incidence and prevalence of EMF has not been well studied in SSA. Ellis et al showed that the prevalence has not changed in Uganda. On the other hand, EMF was shown to have declined from 10% in the 1960/70s to 0.02% from medical admissions and 0.04% for cardiac related admissions in the first decade of 21st century. This may not be unconnected with improvement in healthcare delivery as well as control of communicable diseases in that part of the country.

The prognosis of EMF is poor. The survival of patients after diagnosis is about 2-years.

Peripartum Cardiomyopathy (PPCM)

This is defined as heart muscle disease in which left ventricular systolic dysfunction and symptoms of heart failure occur between the last month of pregnancy and the first five months postpartum. In many parts of Africa, the prevalence is about 1/1,500 deliveries. However, the Northern part of Nigeria appears to be the hot spot for the condition where it affects 1/100 women after delivery. Recent echocardiographic based study from this part of Nigeria confirms similar prevalence(Isezuo and Abubakar, 2007). The epidemiology, pathophysiology and clinical features of this condition have been reviewed in detail elsewhere (Sliwa et al., 2006, Ntusi and Mayosi, 2009a, Abboud et al., 2007, Tibazarwa and Sliwa). Most

patients present within the first four months after delivery. Only about 10% present in the last month of pregnancy.

Symptoms and signs are similar to other forms of systolic dysfunction. In addition, they are prone to thromboembolic phenomenon(Isezuo et al., 2005).

Aetiological factors implicated include multiparty, advanced maternal age, multiple gestation, preeclampsia, gestational hypertension and Black race. Several plausible aetiological mechanisms have been advanced. These include genetic predisposition, myocarditis, cardiotropic viral infections, chimerism, apoptosis and inflammation. Others include abnormal haemodynamic response, immune complexes, cardiac nitric oxide synthase, immune dendritic cells, cardiac dystrophin etc. (Ntusi and Mayosi, 2009a, Ramaraj and Sorrell, 2009).

A novel molecular mechanism of PPCM has been documented. Such mechanisms include elevated pro-inflammatory markers such as sFas /Apo 1, interferon-gamma, interleukin-6 and C - reactive protein. These **point** to the pro-inflammatory mechanism in the initiation, progression and prognosis of the disease.

A pathophysiological circuit that involves unbalanced oxidative stress which leads to enhanced cleavage of prolactin into pro-apoptotic and angiogenic 16KDa sub-fragments has been described. This process results in endothelial damage and LV dysfunction. Presence of endothelial damage in PPCM is further supported by the presence of endothelial microparticles suggesting apoptosis with impaired microcirculation. Furthermore the angiogenic imbalance in this condition may also be contributed by soluble fms-like tyrosine kinase.(Sliwa et al., 2010b)

About 23-54% of PPCM patients have normalization of LV function at 6-months. Poor outcome is associated with increased LV systolic dimension, lower body mass index and low serum cholesterol at the time of presentation. On the other hand older age and smaller LV end-

systolic diameter is associated with higher chances of recovery of LV function.(Sliwa et al., 2010b)

The mortality associated with PPCM is 15% at 6 months, 28% at 2 years and 42% in over 25 years of follow up. Predictors of mortality include NYHA functional class at presentation, cardiothoracic ratio, electrocardiographic QRS duration and higher diastolic pressure (Adesanya et al., 1989, Ford et al., 1998) A proof-of-concept pilot study has provided some evidence of the benefit of bromocriptine in PPCM patients (Ref 62)

Other Cardiomyopathies

Hypertrophic cardiomyopathy

Earlier reports of this condition were mainly anecdotal and it was generally thought to be uncommon in Africa. The earliest report appears to be that of Lewis et al in 1973(Lewis et al., 1973). Thereafter other reports followed (Colyn and Kleynhans, 1990, Neutel and Myburgh, 1987, Myburgh et al., 1987, Przybojewski and Blake, 1984, Lewis et al., 1983). In 1240 consecutive echocardiography in Ethiopia, the prevalence of HCM was 4.3% (54 subjects) and accounted for 34.4% of cardiomyopathies(Abegaz, 1990). In a similar study in Tanzania, it accounted for 0.2% of 6680 echocardiograms(Posen et al., 1995). HCM is the third commonest cardiomyopathy in Ghana (Amoah and Kallen, 2000).

The genetic studies done on this condition have emanated only from South Africa where facilities are available (van der Merwe et al., 2008b, Heradien et al., 2007, Moolman-Smook et al., 2002, Blair et al., 2002, Andersen et al., 2001, Moolman-Smook et al., 2000, Moolman-Smook et al., 1999, Moolman-Smook et al., 1998, Moolman et al., 1995, Moolman et al., 1993). The disease-causing genetic mutation or loci has been documented. These include beta-myosin heavy chain (MYH7) gene, myosin binding protein c (MYBPC3) gene, and troponin T (TNNT2) gene. Carriers of T (TNNT2) R92W mutation develop cardiac hypertrophy after the age of 35

years. They also have abnormal response to exercise which may explain the high mortality associated with this mutation. (Revera et al., 2007b)

The physiological effects of genetic mutations that cause HCM have also been studied in the continent. TNNT R92W mutation is associated with a relative increase in LV systolic functional parameters. Reduced diastolic function has been demonstrated in MYH7 A797T mutation while MYH7 R403W mutation is associated with reduction in both systolic and diastolic function.(Revera et al., 2007a, Heradien et al., 2009)

Furthermore angiotensin II type 2 receptor (AGTR2) gene and angiotensin converting enzyme 2 (ACE2) gene have been identified as genetic risk factors (i.e. genetic polymorphism with evidence of association with HCM).(van der Merwe et al., 2008a, Carstens et al., 2010)

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

The first report of ARVC from the region was in the year 2000.(Munclinger et al., 2000) Kindred that are linked to ARVC type 6 locus have been documented.(Matolweni et al., 2006) The first multicentre registry of ARVC was reported from South Africa.(Watkins et al., 2009) Data from the registry shows that the disease occurs in all racial and ethnic groups in the country. Symptoms starts from the third decade of life and the most common symptoms are palpitation, dizziness, syncope and chest pain. Symptoms are more pronounces in males. The reported male to female ratio was 2:1. About 28% were professional endurance athletes at some point in their lives. About 30% of the participants have family members who are also affected and 25% had Plakophilin-2 gene defect.(Watkins et al., 2009, Hendricks et al., 2010)

Interestingly the rare 'allele-dose-defect' was demonstrated in one of the subjects while haplotype analysis also demonstrated the uncommon 'founder effect' in many of the subjects.(Watkins et al., 2009, Hendricks et al., 2010)

The annual mortality was 2.8% and 5-year cumulative mortality was 10%.(Watkins et al., 2009, Hendricks et al., 2010)

Isolated Left Ventricular Non-compaction (ILVNC)

Ker et al(Ker and Van Der Merwe, 2006) reported the first case of ILVNC in SSA in 2006. Since then there has been reports other centres in Djibouti(Massoure et al., 2011), South Africa(Peters et al., 2012a, Peters et al., 2012b) and Sudan(Ali, 2008). The disorder is a common cause of HF, disorders of cardiac rhythm and cardio-embolism and is as a result of failure of the myocardium to compact in-utero.

In a series comprising of 54-ILVNC patients, Peters et al (Peters et al., 2012a) in Johannesburg showed that the prevalence is 6.9% and the mean age of presentation is 45.4±13.1 years. Occurs commoner in males (55.6%) and majority (63.0%0 present in NYHA class II. HF with systolic dysfunction is the common mode of presentation (98.1%) The identified sites of non-compaction include apical (100%), mid-inferior (74.1%), and mid-lateral walls (64.8%). The disorder was also documented to be associated with pulmonary hypertension (83.3%), right ventricular (RV) dilation (74.1%), and impaired RV function (59.3%).

HIV associated cardiomyopathy

This is another cause of HF in Africa. Globally the prevalence was 2-40% in the pre-highly active anti-retroviral treatment (Pre-HAART) era.(Sani et al., 2005, Syed and Sani, 2013) However with the introduction of HAART, the prevalence has fallen in many parts of the world. But in some parts of SSA, due to poverty, ignorance, weak health system, malnutrition and low utility of HAART, the burden of HIV associated cardiomyopathy is prevalent. The effectiveness of HAART is also supported by data from Uganda that showed low prevalence of this condition in children on this treatment.(Tukei et al., 2012)

The true prevalence of HIV associated cardiomyopathy is unknown in the sub-region. Prevalence from reported literature ranges from 5% in Nigeria to 57% in Burkina faso.(Twagirumukiza et al., 2007, Niakara et al., 2002, Olusegun-Joseph et al., 2012) It is the commonest cardiac diagnosis in HIV infected people in the Heart of Soweto study and more common in those with high viral load and lower CD4 count.(Sliwa et al., 2012)

Pericardial Diseases

Pericarditis and pericardial effusion are common in SSA and are frequently a cause of heart failure in the region. In some areas over 15% of cardiovascular admission may be due to primary pericardial diseases. Tuberculosis is the leading cause of pericardial disease in Africa and this is often complicated by constrictive pericarditis. The burden of pericardial disease in SSA has escalated due to the impact of HIV/AIDS.

Next to tuberculosis is purulent pericarditis secondary to streptococcal or staphylococcal infection. Viruses may be responsible for most cases of benign pericarditis without demonstrable aetiology. Other causes include parasitic infections such as trypanosomiasis and malaria.

Congenital Heart Disease

Few publications have looked at cardiovascular disease in young Africans despite the fact that two-thirds of the population of SSA are made up of children and young adults. Congenital heart diseases constitute about 0.3% of heart diseases seen in northern Nigeria(Ladipo, 1978) to 12% in the series documented by Bertrand in Ivory Coast.(Bertrand E et al., 1991) The high value in the later may be because the centre at a time served a large referral centre for cardiac surgery in West Africa.

A prevalence of 13.1% was documented in Cameroon (mean age 10±9 years, range-2months to 41 years.(Tantchou Tchoumi et al., 2011b) About 35% of children with HF in Uganda have congenital heart disease.(Ellis et al., 2007)

To the best of our knowledge the only population based data on congenital heart disease is from Mozambique where the prevalence was reported as 2.3/1000 children.(Marijon et al., 2006)

The pattern of cardiac lesions appears not to be different from reports from other parts of the world in terms of the most frequent lesions. In the decreasing order of frequency, ventricular septal defect, atrial septal defect, Fallot's tetralogy and patent ductus arteriosus are the common congenital heart diseases that may lead to cardiac failure in Africa(Sani et al., 2007b, Marijon et al., 2006, Bassili et al., 2000, Bannerman and Mahalu, 1998, Kokou et al., 1996, Jaiyesimi and Antia, 1981b, McLaren et al., 1979, Antia, 1974, Levin and Kanarek, 1973, van der Horst, 1985, van der Horst and Wainwright, 1969, Wood et al., 1969, Gupta and Antia, 1967, Schrire, 1963, Caddell and Morton, 1967, Caddell and Connor, 1966). Recognition of cyanosis in the dark skin may pose a challenge coupled with the fact that anaemia is common in SSA population.

Lack of trained man-power, scarcity of diagnostic tools as well as poverty mitigates the care of patients with congenital heart disease in the region.

Coronary artery disease

It is generally believed that coronary artery disease is uncommon in SSA. However recent reports emanating from the region suggest that the disease is emerging and when it occurs, the clinical as well as the pathological features are similar to that seen in Caucasians(Williams, 1971). In early reports, Edington(Edington, 1954) in 1954 noted only three cases in about 3500 consecutive autopsies in present day Ghana. Sharper and Williams(Shaper and Williams, 1960)

documented 9 cases seen in Uganda over a three year period (1955-1957). Falase et al(Falase et al., 1974) reported 26 cases over a period spanning 1961-70 and calculated a prevalence rate of 1: 20,500 for Ibadan, Nigeria. In another study by same author, the prevalence has increased to 1: 10,000. Okuwobi (Okuwobi, 1968) saw seven cases over a period of three years. Bertrand(Bertrand, 1995) reported 75 cases over a 6-year period and this accounted for 0.83% of total cardiac related admission.

Recent reports still report low prevalence of this condition but the trend is that it is on the increase. In a study of heart failure in elderly subjects (60 years and above), Ikama and his colleagues reported a prevalence of 25.6% in this age group(Ikama et al., 2008).

Studies done in South Africa between 1992 and 2008 show remarkable increase in the prevalence of the disease. In 1994, the prevalence was 0.2%(1994) but the recent report from the Heart of Soweto study show a prevalence of about 10%. This is remarkable evidence of gradual shift in disease pattern (epidemiologic transition) in this population. The prevalence reported in earlier studies ranged from 0.4-1.0 percent (Cosnett, 1962, Schrire, 1971, Schwartz et al., 1958) **(Table 2.8)**

Pulmonary heart disease (Cor-pulmonale) and pulmonary hypertension

This is also emerging as a common cause of heart disease in SSA. In the Heart of Soweto study, right heart failure or cor-pulmonale was documented in 27% of individuals admitted for heart failure. The prevalence in other regions is as follows: 0.8-9.5% in West Africa and 0.3-7.7% in Eastern Africa.

At least four reports have looked at the aetiology of pulmonary heart disease in SSA (Sofowora, 1971, Turner, 1962b, Okuwobi, 1967, Toure et al., 2000). The common aetiological factors described include chronic obstructive pulmonary disease, bronchiectasis, tuberculosis,

bronchial asthma, pulmonary fibrosis of unknown origin, pulmonary embolism (acute cor-pulmonale) and thrombo-embolic obliterative pulmonary hypertension.

Tuberculosis and chronic obstructive pulmonary disease is the major culprit. The situation is worsened by the emergence of HIV/AIDS. Globally there has been an increase in the incidence of tuberculosis by 2.2 million from 1997 to 2005 and 95% of this is occurring in developing countries. In a recent autopsy report from South Africa, it was reported that 31% of cases had pulmonary hypertension as cause or part of their cardiac lesion.

HIV(Steenekamp et al., 1992) associated pulmonary hypertension is being increasingly reported in SSA. Hakim et al(Hakim et al., 1996) and Niakara et al(Niakara et al., 2002) recently reported a prevalence of 5%. Other causes of pulmonary hypertension in SSA include: sickle cell anemia(Aliyu et al., 2008), connective tissue disease, congenital heart disease(Diop et al., 1995), valvular heart disease(Sani et al., 2007a), schistosomiasis(Mpe, 2000, Turner, 1964), laryngeal papillomatosis(Grobbelaar et al., 2005), sarcoma(Govender and Pillay, 2001), herbal remedies(Heath et al., 1975), hypertensive disorders of pregnancy(Desai et al., 1996), vaso-occlusive disorders(McCulloch et al., 2003) and primary pulmonary hypertension(Bouldouyre et al., 2006).

Chapter 3: Justification

3.1 Justification

Most of the published data and current knowledge on HF epidemiology are based on studies in Europe and America. The information obtainable from previous studies in sub-Saharan Africa is limited. Many of the studies were based on clinical diagnosis alone without the use of such investigations as echocardiography. There is also paucity of information on mode of treatment, as well as outcome/ prognosis of HF in the sub-region. The cost of HF in Sub-Saharan Africa (SSA) is unknown.

3.2 Study Hypothesis

Given the epidemiologic transition occurring in developing countries, it is hypothesized that there will be increasing prevalence of heart failure. It is also hypothesized that outcome of contemporary treatment of HF will differ from data from advanced countries.

3.3 Objectives

The objectives of the study are:

3.3.1 Primary objective

The primary objective of this study is to determine the clinical characteristics, six month outcome as well as cost of HF in Abeokuta, Nigeria and to compare our findings with that of the Heart of Soweto in South Africa**.**

3.3.2 Secondary objectives

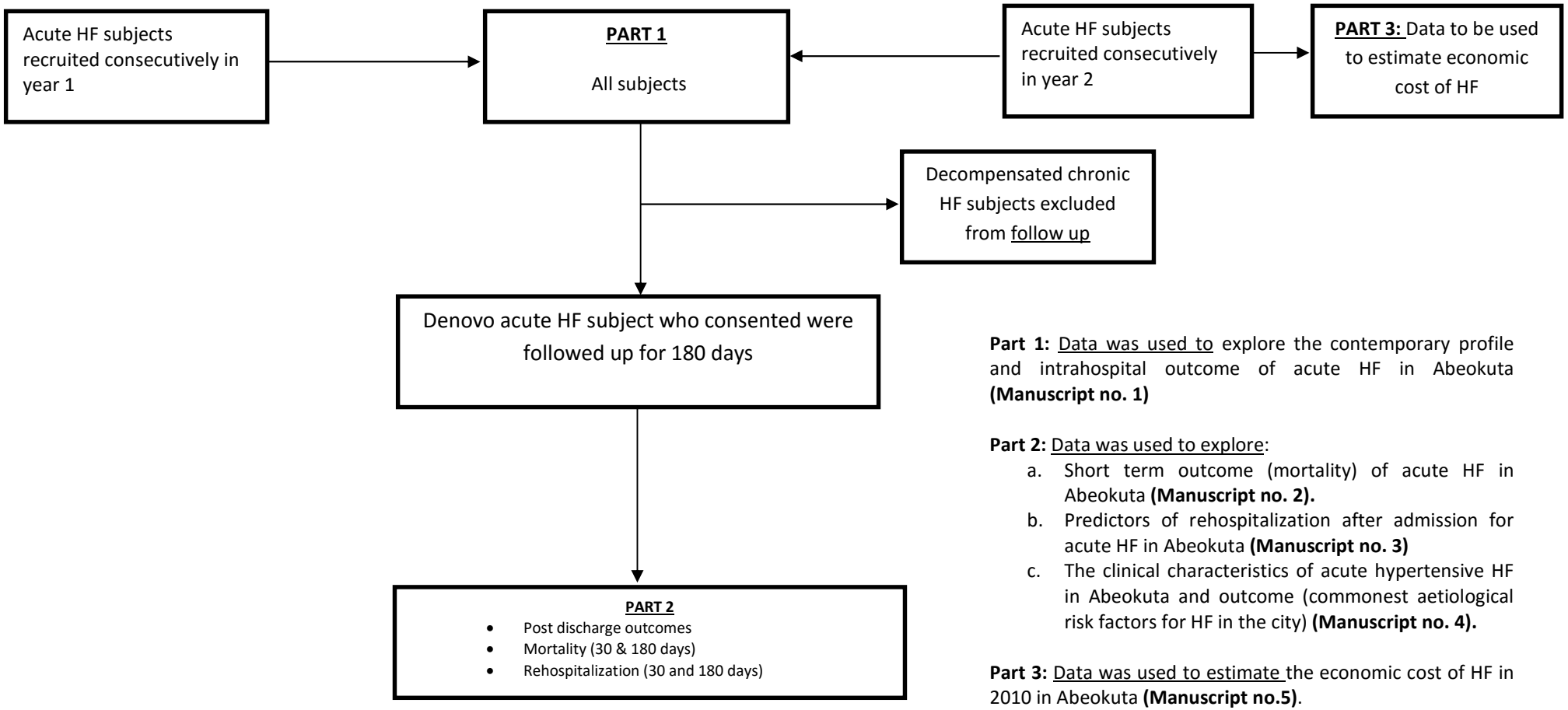
1. To describe the relative importance of the different aetiological factors for HF in Abeokuta, Nigeria
2. To describe the demography and clinical characteristics of patients admitted for HF in Abeokuta
3. To describe the short and medium term outcomes of HF in Abeokuta and to determine the predictors of outcome.
4. To calculate the cost of heart failure care in Abeokuta based on data generated from the study

3.4 End-points

1. HF related hospitalization and rehospitalisation in Abeokuta Nigeria
2. HF related and all-cause mortality
3. Comparison of HF in Abeokuta with data from the Heart of Soweto and other parts of the world.
4. Description of possible changes in the aetiology of HF in Abeokuta over time (comparison with similar study in the early 70s in Nigeria)
5. Identification of prognostic factors
6. Estimation of economic cost of Heart failure

3.5 Study plan

Figure 3.1 shows the study plan for the project.



Part 1: Data was used to explore the contemporary profile and intrahospital outcome of acute HF in Abeokuta **(Manuscript no. 1)**

Part 2: Data was used to explore:

a. Short term outcome (mortality) of acute HF in Abeokuta **(Manuscript no. 2).**
b. Predictors of rehospitalization after admission for acute HF in Abeokuta **(Manuscript no. 3)**
c. The clinical characteristics of acute hypertensive HF in Abeokuta and outcome (commonest aetiological risk factors for HF in the city) **(Manuscript no. 4).**

Part 3: Data was used to estimate the economic cost of HF in 2010 in Abeokuta **(Manuscript no.5)**.

Figure 3.1.The study plan for the project

Chapter 4: Materials and Methods (General)

4.1 Design and setting

This was a prospective, observational study conducted at the Federal Medical Centre (FMC), Abeokuta, Nigeria.

Nigeria is located in the West Coast of Africa. It shares land border with Niger Republic in the North, Chad and the Cameroon in the East and Republic of Benin in the West.

The southern border is the Gulf of Guinea in the Atlantic Ocean. The country has a land area of 923,768km^2 (356,667 sq. miles) and an estimated population of 174,507,539 inhabitants (2013 estimate) Worldwide the country is the 8th most populous country. It is the most populous black nation globally as well as Africa's most populous country.

It operates three tiers of Government (local, state and Federal Governments). The country is divided into 36 states and a Federal Capital Territory (Abuja). Politically it is structured into six geopolitical zones (North-West, North-Central, North-East, South-West, South-East and South-South)

It is classified as a low - middle income country with a Gini Index of 43.7 and income per capita of $1490. About 49% of the population is living in urban areas; the gross national income per capita is $2070. The literacy rate in the country is 69.1% according to the UNDP. In terms of poverty rate, it is estimated that 64.4% of the population live under 1.25 dollars /day while 83.9% live under 2 dollars /day.

Life expectancy at birth is 51 years for both sexes (53 for men and 54 for women). The mortality rate for under 5s is 138/1000 and the maternal mortality ratio is 840/10^5 live births. Non-communicable diseases contribute about 14% of the number of years of life lost. The number of doctors /10 000 population is about 4. 5.1% of men and 9.0% of women aged 20 years and above are obese; 11.9% of men and 1.0% of women aged 15 years and above smoke cigarettes. The prevalence of HIV (per 1000 adults aged 15-49 yrs) is 36 while the prevalence of tuberculosis (per 100 000 population) is 497.

The total expenditure on health per capita (international dollar) was 161 in 2012 while the total expenditure on health as percentage of the GDP was 6.1.

Abeokuta is the capital city of Ogun state, one of the 36 States that make up the Federal Republic of Nigeria (**Figure 4.1**,**Figure 4.2**). Ogun State has twenty Local Government areas (LGAs) and inhabited mainly by the Yoruba ethnic group of South-west Nigeria. The State has a land area of 16, 409, 26 km^2 and it is endowed with favourable climate and good vegetation all year round. According to the national census of 2006, Ogun State has a total population of 3,751,140 inhabitants comprising 1,864,907 and 1,886,233 males and females respectively. It has a population density of 220/km^2. It is located within the co-ordinates 7°00'N 3° 35' E. (2006a)

Abeokuta is the capital and largest city in the State and has two of the twenty LGAs (Abeokuta North and Abeokuta South LGAs) It is situated on the East Bank of the Ogun River, "near a group of rocky outcrops in a wooded Savanna". The name "Abeokuta" literally means "underneath of the rock" or indirectly "in refuge among rocks." It was founded in 1825 as a place of refuge from slave hunters who often invade from Ibadan and Dahomey. The city is about 78km (by rail) north of Lagos (the largest, former administrative capital and current commercial/economic capital of Nigeria). It is located within the geographic co-ordinates of 7° 9' 39'N 3° 20' 54' E and at about 66m above sea level.

As at the year 2012, the city was estimated to have a population of 888,924 and 1,117,000 for the city and metropolis respectively.

FMC Abeokuta is a 250 bedded tertiary health centre that was established in 1993 by the Federal Government of Nigeria to cater for the health needs of the people of Ogun State and its environs in Southwestern Nigeria. The centre is the only tertiary hospital in the city which receives referrals from all the health facilities in the city, state and the neighboring states.

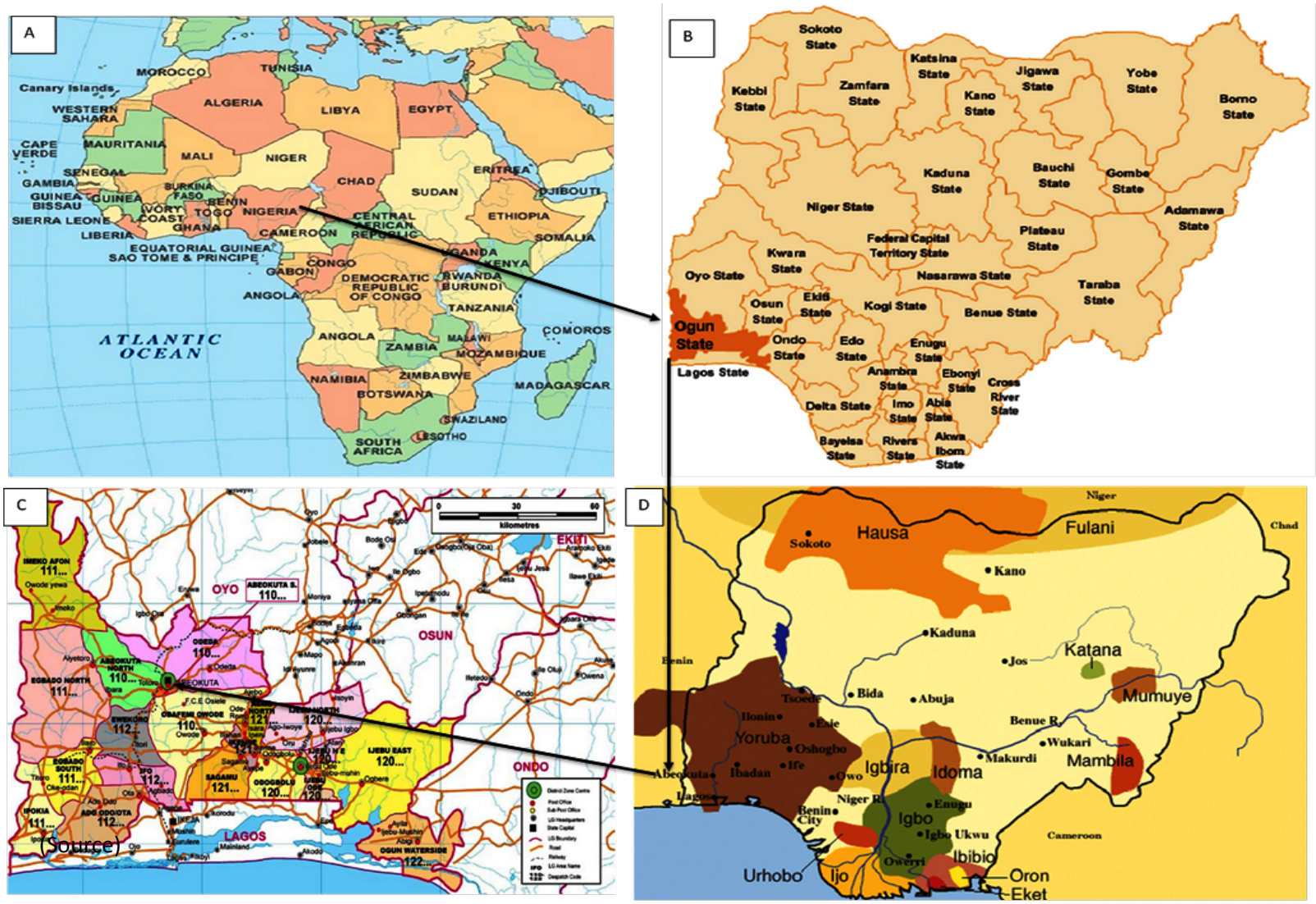


Figure 4.1. A-Map of Africa showing the location of Nigeria, B-Map of Nigeria showing the location of Ogun state, C- Map of Nigeria showing the location of Abeokuta, D- Map of Ogun state showing the location of Abeokuta and other towns

Figure 4.2. Olumo Rock, one of the tourist centres in the city, B. Aerial view of Abeokuta

(Source https://www.google.co.uk/#q=OLUMO+rock)

4.2 Healthcare delivery in the city

Like in other parts of the country the state operates three-tier or level of healthcare: primary (health posts, health centres), secondary (Cottage, General or State hospitals) and tertiary health care (Federal medical centres and University teaching hospitals). Primary health care is constitutionally under the jurisdiction of the Local Government. The remaining two are under the State and Federal Governments respectively.

A significant proportion of health care delivery is carried out by private health institutions and mission or faith-based hospitals.

The costs of healthcare in the city and in most parts of the country are generally borne by the patients through out of pocket expenses. Social health insurance coverage is low in the city and in most parts of the country. On the other hand strong family bonding exist in the city where rich and well-to-do individuals assist their poor family members

A cardiologist covers the cardiac unit assisted by postgraduate resident doctors as well as experienced nurses. Facilities for cardiac evaluation that exist in the centre include: chest radiography, 12-lead electrocardiography (ECG), exercise ECG, Holter ECG, Ambulatory blood pressure monitoring devices, Spirometry and echocardiography (ECHO). All the ECGs and ECHOs were carried out within 72 hours of admission as prescribed by the study protocol.

4.3 Study population

All cases of AHF, both denovo presentations and recurrent decompensation with a pre-established diagnosis of HF were consecutively recruited into the registry between January 1, 2009 and December 2010. (There were no study refusals)

4.4 Enrollment and data collection

Data from each subject was obtained using a uniform and standardized case report form. Detailed clinical documentation on newly diagnosed/ newly presenting cases/ pre-existing cases of HF was carried out. The following data were obtained: 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, 12-lead ECG, echocardiography, medications and intra-hospital and 6-month outcomes.

4.5 Clinical evaluation

Their blood pressures were measured in the right arm with the subjects seated and rested for 5 minutes before the procedure. Measurements were taken using mercury sphygmomanometer (Accosson London). Systolic and diastolic blood pressures were measured at Korotkoff sounds phases I and V respectively. The cuff size used was based on the arm circumference of the subject. The cuff was rapidly inflated to 30mmHg above the level at which the pulse disappeared and then deflated gradually. Blood pressure 140/90 and above was taken as hypertension. Subjects were weighed without shoes and in light clothing on a standard beam balance. Height was measured to the nearest centimetre using anthropometrical plane with subjects not putting on shoes or headgear.

Body mass index (BMI) was calculated using the formula: BMI = Weight (kg) / (height in metres)^2 A BMI of 24-29.9kg/m^2 and >=30kg/m^2 defined overweight and obesity respectively.

Body surface area was calculated using the formula of Dabois(Du Bois and Du Bois, 1916)

Body Surface Area (BSA) (in m^2) =0.0001 x (71.84) x (Weight in kilogram) $^{0.425}$ x height in centimetre) $^{\mathbf{0.725}}$.

4.6 Laboratory Investigations

Urine samples were collected from the subjects with the use of universal bottles for urine analysis using Bayers' uristix test strip. Venous blood samples (5-10ml) was drawn from the antecubital vein of the subjects into serially numbered and appropriate sample bottles for full blood count (potassium EDTA bottle), and for electrolyte, urea and creatinine (Lithium heparin bottle)

After an overnight fasting of 8-14 hours , venous blood samples were drawn from the subjects into appropriate sample bottles for fasting blood glucose (Fluoride oxalate bottle) and for fasting lipid profile (Potassium EDTA bottle)

For consenting subjects, blood samples were also collected with plain sample bottles for HIV screening. All collected samples were immediately sent to the central laboratory of Federal Medical Centre, Abeokuta separation and storage. The blood samples were centrifuged at a rate of 5,000rpm for 10 minutes. The separated plasma was drawn using a pipette into newly labelled sample bottles with study number corresponding to the subjects and CRFs. This was then kept frozen between -2 to 4 degrees centigrade before analysis was performed in batches after a week of sample pooling.

Serum electrolytes were analysed with ISE SFRI 4000 electrolyte analyser (SFRI Medical Diagnostics St.-Jean-d'lllac, France). Urea and creatinine were analysed with Slim SEAC photometer (dar SEAC –Radim , Italy) while Sysmex 5 parts analyser was used to perform full blood count wile ELISA washer and reader (Tecan Group LTD, Seestrasse 103, CH-8708 Maennedorf, Switzerland) was used for the diagnosis of HIV

Anaemia was defined as haemoglobin concentration of less than 10g/dl. Glomerular filtration rate was estimated using the four variables- Modification of Diet in Renal Disease (MDRD) formula.(Levey et al., 1999) Renal dysfunction was defined as eGFR of less than 60ml/min/1.73m^2 . [(same criteria used by Stewart et al.(Stewart et al., 2008)]

4.7 Electrocardiography

A standard 12-lead resting ECG was recorded for each subject using a Schiller ECG machine (Schiller AG, Switzerland). All the 12 lead resting ECG were performed by trained nurses/technicians and analyzed by a reviewer who was blinded to the clinical data of the patients. The Minnesota code classification(Blackburn, 1969) system was used in sorting out the various abnormalities. ECG abnormalities were diagnosed based on standard criteria(Rowlands, 1981).**(Figure 4.3)**

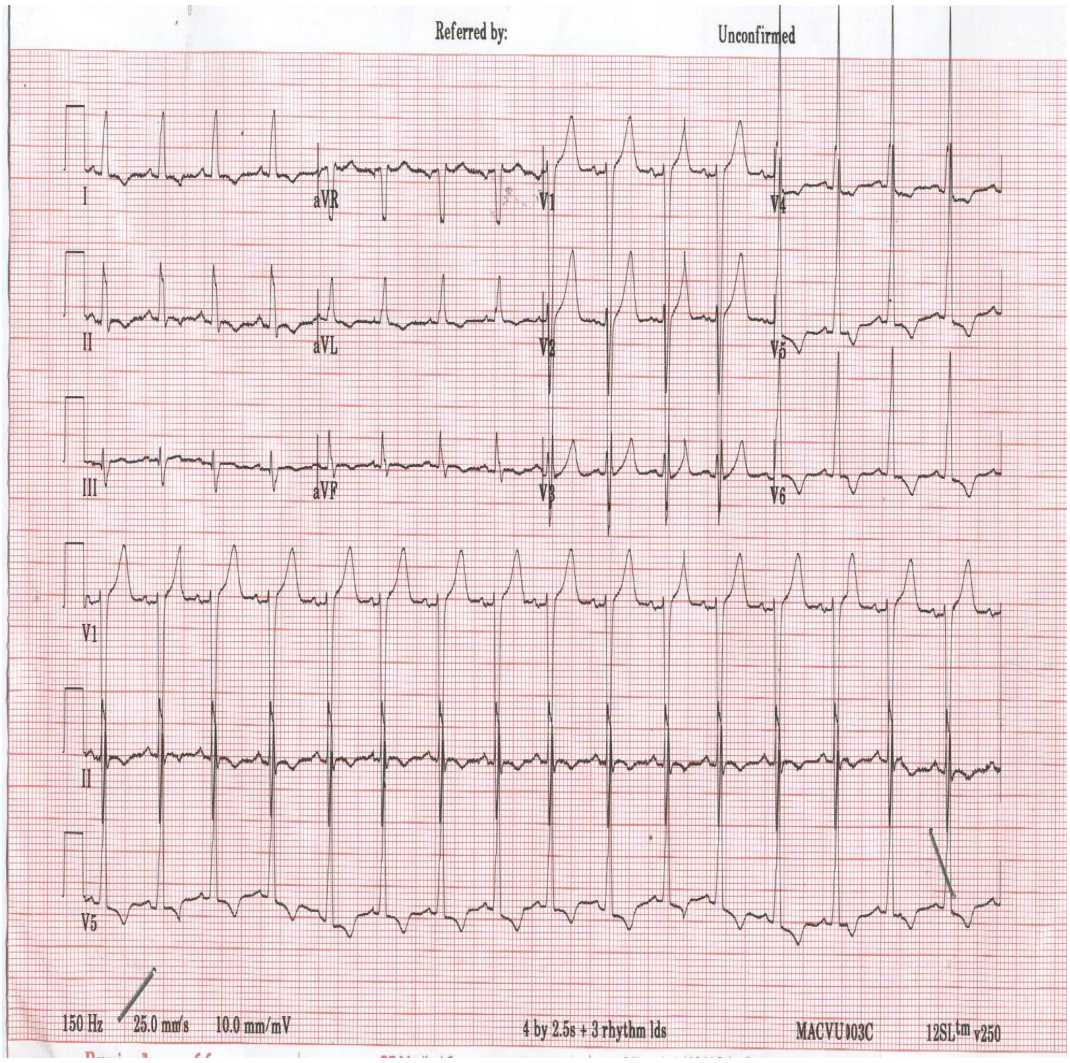


Figure 4.3. 12-lead ECG of a subject with hypertensive heart failure. ECG shows left ventricular hypertrophy with strain pattern

4.8 Echocardiography

An Aloka SSD-4000 echocardiograph (Aloka Co. Ltd., Tokyo, Japan) was used in evaluating the patients. Two dimensional guided M- mode measurements were made according to the recommendations of the American Society of Echocardiography (ASE)(Sahn et al., 1978a). LV internal dimension, posterior wall thickness and interventricular septal thickness were measured at end-diastole and end-systole. Where optimal M-mode imaging could not be obtained, 2D linear measurements were obtained according to the ASE criteria(Sahn et al., 1978a). Left atrial end systolic diameter was obtained from the trailing edge of the posterior aortic – anterior left atrial complex. Measurements were obtained in up to 3 cardiac cycles according to the ASE convention(Sahn et al., 1978a).

Because segmental or regional wall motion was not common in our cohort and LV was uniformly contracting in most cases, Teichholz method(Teichholz et al., 1976) was used for the estimation of LV systolic function. However, where regional or segmental was present, biplane Simpson's method(Schiller et al., 1988) was employed.

Left ventricular mass was calculated using the formula of Devereux and Reichek.(Devereux and Reichek, 1977b) This has been shown to yield LVM closely related to autopsy measurements (r=0.90)(Devereux et al., 1986) and has good interobserver reproducibility (ρ=0.93) in one study(Palmieri et al., 1999). Relative wall thickness (RWT) was derived from 2 X posterior wall thickness/LV internal diameter. Increased RWT was considered to be present when RWT exceeded 0.43 This represents the 97.5^{th} percentile in normal subjects(Roman et al., 1995).

Left ventricular geometric was defined as follows: Normal geometry, when LVMI and RWT were normal; Concentric remodeling, when LVMI was normal and RWT increased; Eccentric hypertrophy, when LVMI was increased but normal RWT; and Concentric hypertrophy, when both LVMI and RWT were increased (Ganau et al., 1992).

The left atrial dimension was measured between the leading edge of the posterior aortic wall and the leading edge of the posterior wall of the left atrium at end systole. The areas of the left atrium was determined by tracing the endocardial border of the left atrium at end systole (ventricular) before the opening of the mitral valve in the apical four chamber view(maximal LA area or A-max), excluding the LA appendage and pulmonary vein confluences.(Lester et al., 1999) (Thomas et al., 2002)

Transmitral flow velocities were obtained with the Doppler sample volume placed just beyond the tip of mitral valve leaflets. The parameters measured were early diastolic peak flow velocity(E), late diastolic peak flow velocity (A), the deceleration time of early mitral velocity and the ratio of E to A (E/A). Isovolumic relaxation time (IVRT) was measured with pulse wave Doppler beam intersecting the LV outflow and inflow tracts,(Nishimura and Tajik, 1997). Tissue Doppler imaging was only applied to identify true pseudonormalised filling pattern. **(Figures 4.4-4.9)**

One experienced cardiologist (OSO) performed all the echocardiography. In our laboratory, the intra-observer concordance correlation coefficient and measurement error have been reported.(Ogah et al., 2006a)

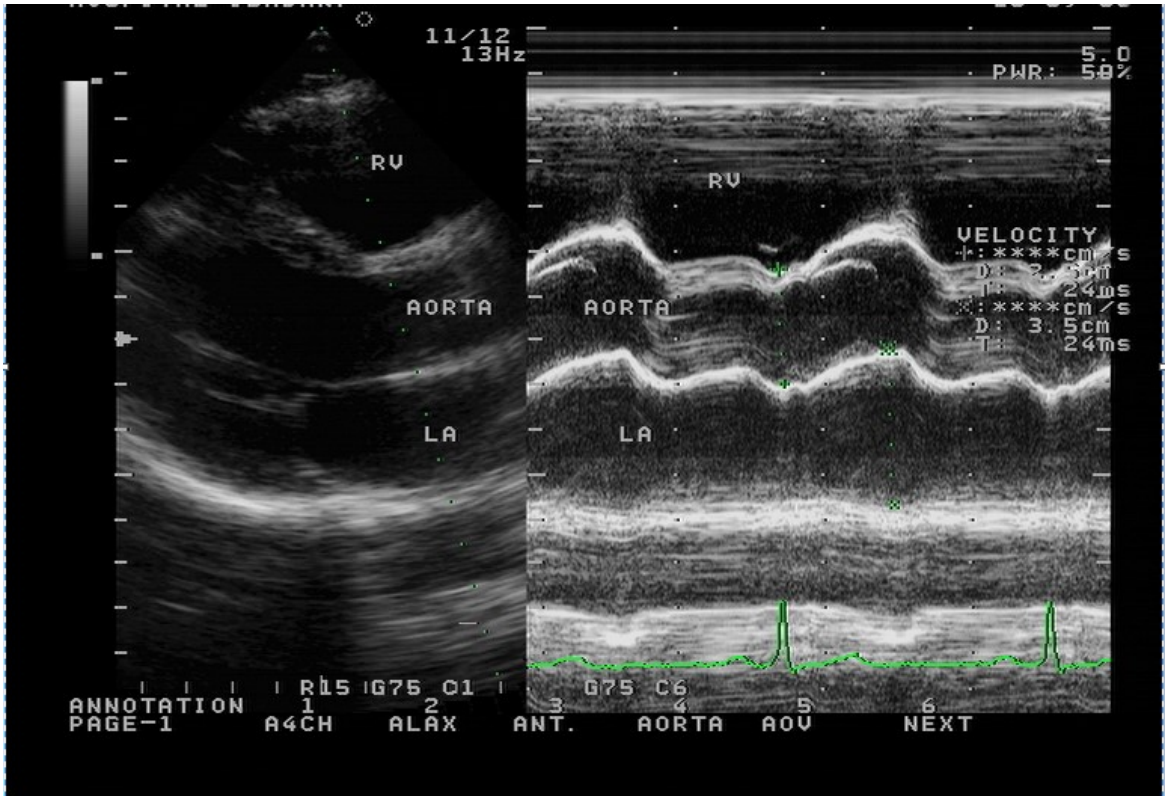


Figure 4.4. M-Mode Echocardiogram Showing Measurement of Aortic Root and Left Atrial Diameter

RV= Right Ventricle, LA= Left Atrium

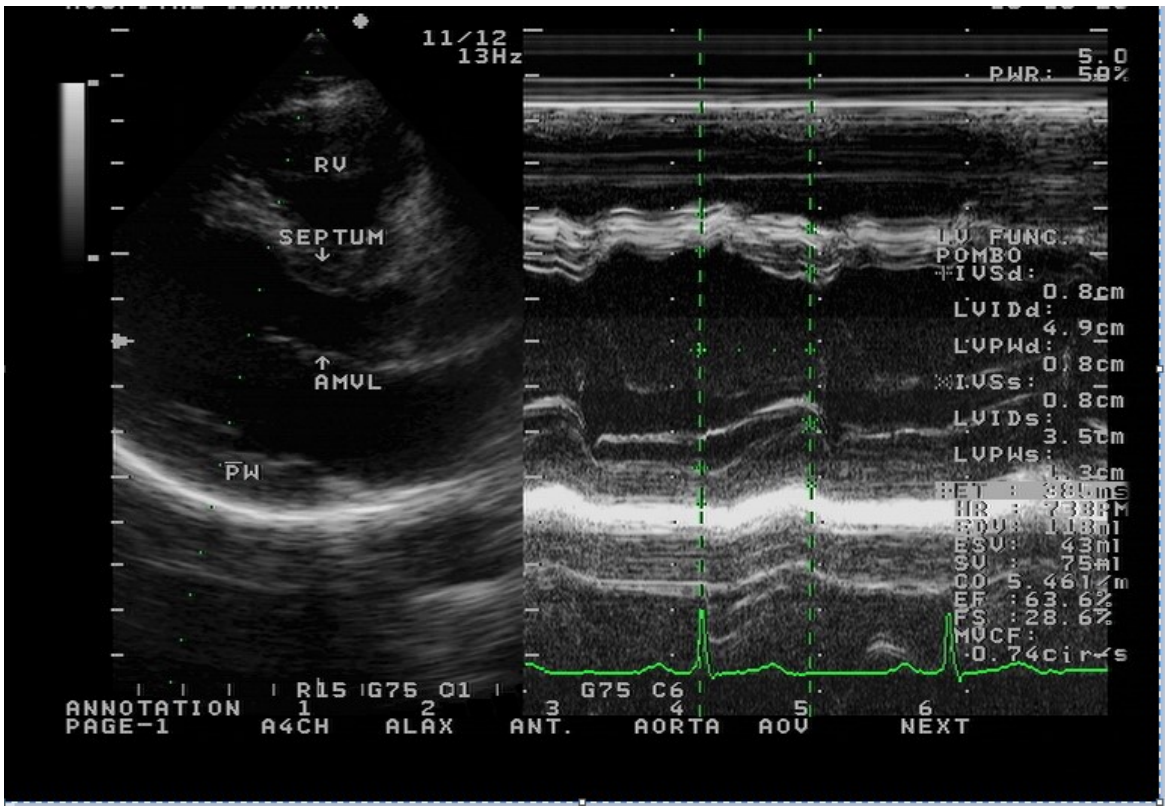


Figure 4.5.M-Mode Echocardiogram Showing Measurement of Left Ventricular (LV) Dimensions and Indices of LV Systolic Function

RV =Right Ventricle, SV=Stroke Volume, AMVL= Anterior Mitral Valve leaflet, EF=Ejection Fraction, IVSD=Interventricular Septum in Diastole, FS=Fractional Shortening, IVSS=Interventricular Septum in Systole, MVCF=Mean velocity of Circumferential Fibre Shortening, LVPWD=Left Ventricular Posterior Wall in Diastlole, LVPWS=Left Ventricular Posterior Wall in Systole, HR=Heart Rate, EDV=End Diastolic Volume, ESV=End Systolic Volume

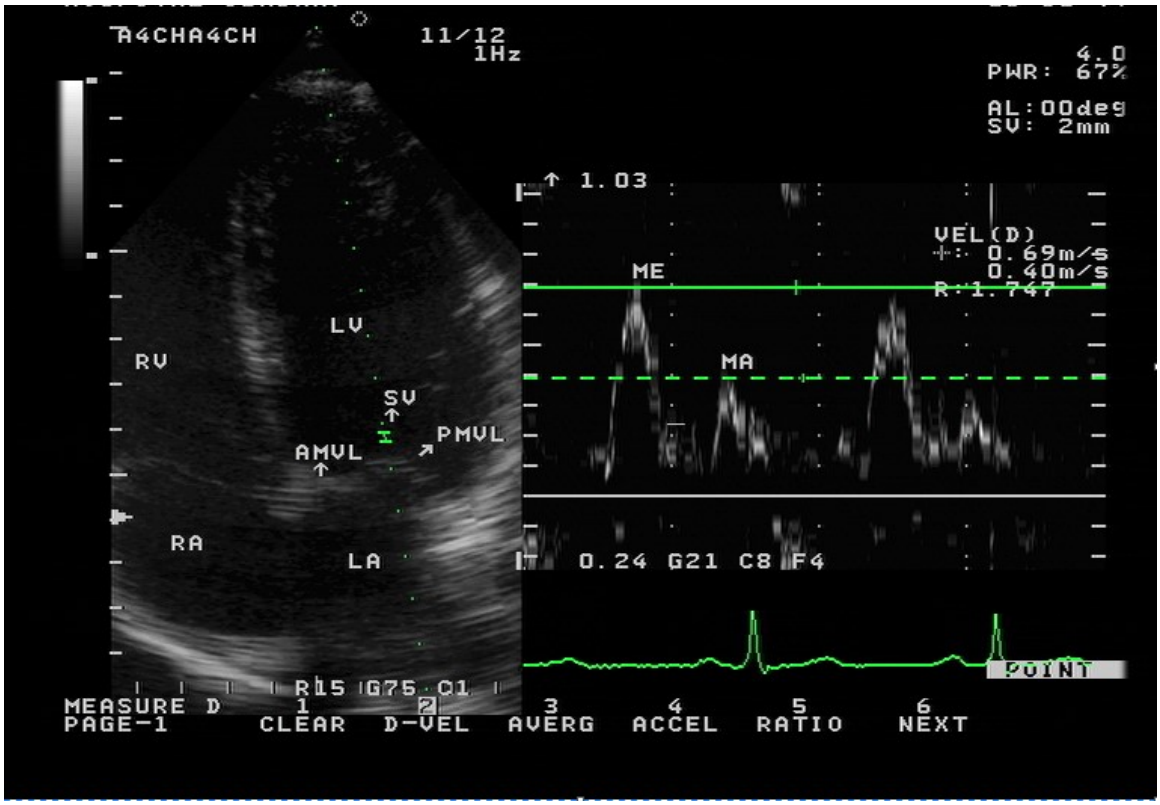


Figure 4.6. Echocardiogram Showing Measurement of Transmitral Flow Velocity Profile ('E' and 'A' Waves). RV =Right Ventricle, LV=Left Ventricle, RA=Right Atrium, LA =Left Atrium, SV=Sample Volume, AMVL=Anterior Mitral Valve Leaflet, PMVL=Posterior Mitral Valve Leaflet, ME=Mitral E wave, MA=Mitral A wave

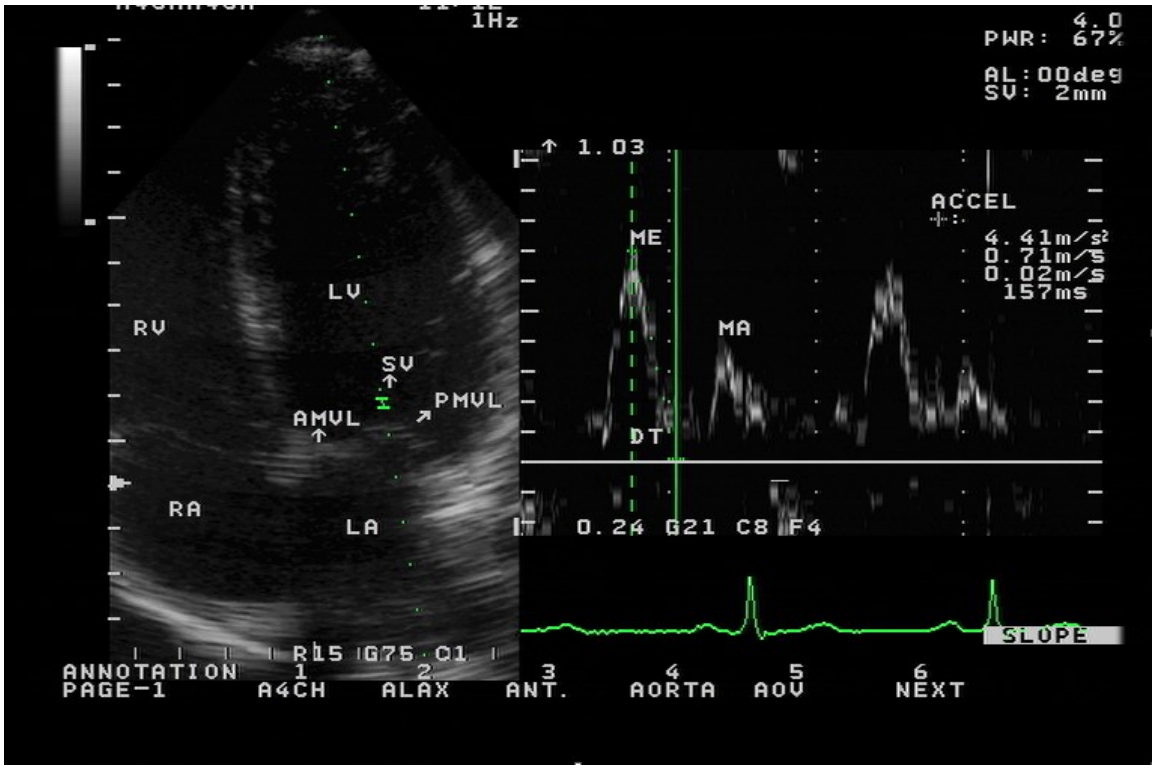


Figure 4.7. Echocardiogram Showing Measurement of Deceleration Time (DT) of the Mitral 'E' Wave.

RV =Right Ventricle, LV=Left Ventricle, RA=Right Atrium, LA =Left Atrium, SV=Sample Volume, AMVL=Anterior Mitral Valve Leaflet, PMVL=Posterior Mitral Valve Leaflet, ME=Mitral E wave, MA=Mitral A wave

A

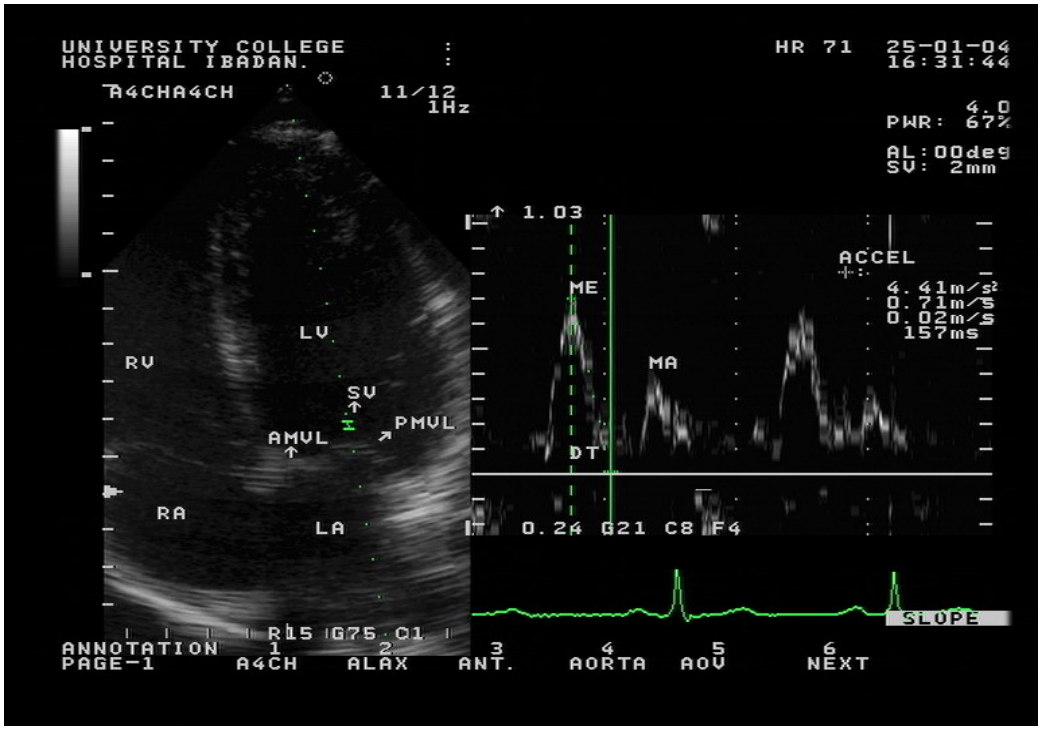


Figure 4.8. A. Echocardiogram Showing Measurement of Deceleration Time (DT) of the Mitral 'E' Wave. RV =Right Ventricle, LV=Left Ventricle, RA=Right Atrium, LA =Left Atrium, SV=Sample Volume, AMVL=Anterior Mitral Valve Leaflet, PMVL=Posterior Mitral Valve Leaflet, ME=Mitral E wave, MA=Mitral A wave. B. Tissue Doppler Imaging (TDI) showing the E' and A' wave

B

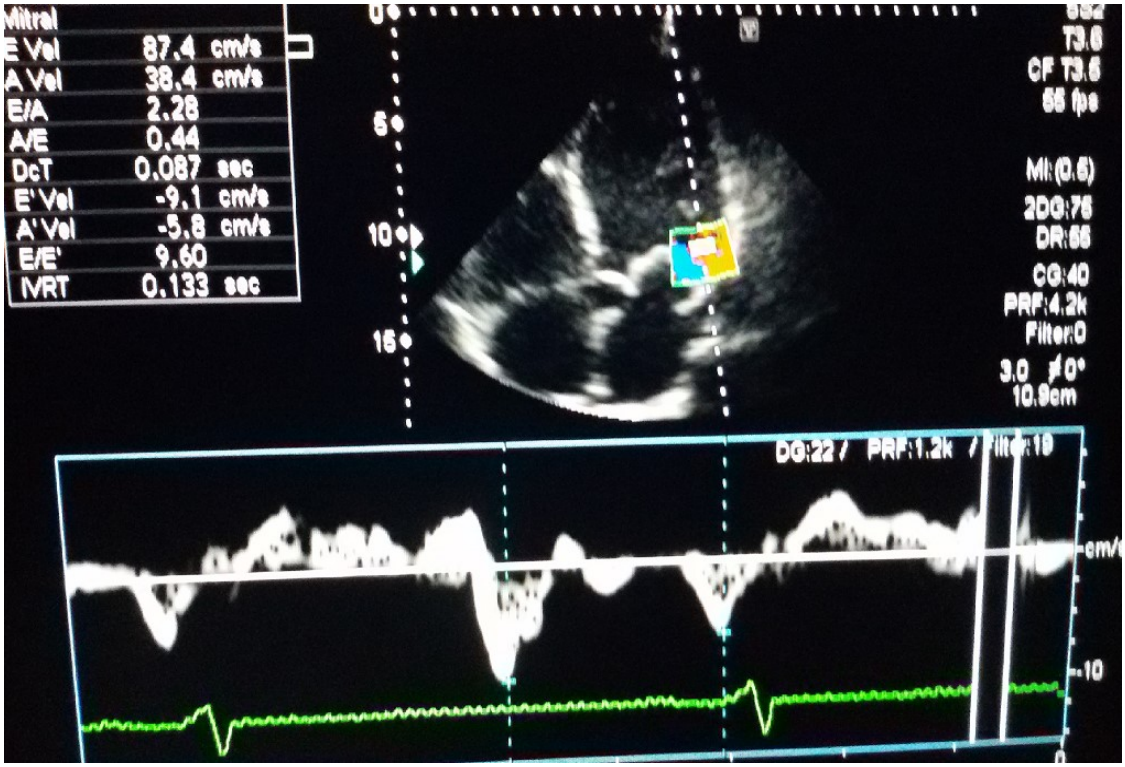


Figure 4.8 B. Echocardiogram Showing Measurement of Tissue Doppler Imaging (TDI) showing the E' and A' wave

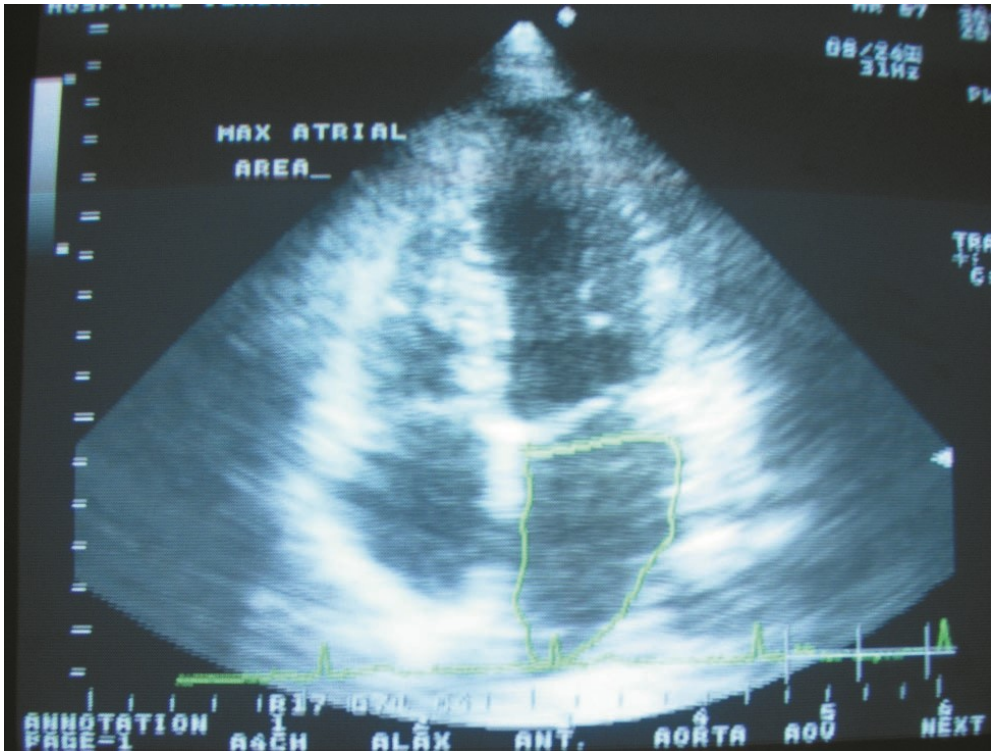


Figure 4.9. Echocardiogram Showing Measurement of maximal left atrial area.

4.9 Diagnoses of Heart Failure/ Case definition

A standardised diagnosis of HF was made using the Framingham criteria(McKee et al., 1971) as well as the according to the guidelines of ESC on the diagnosis and treatment of AHF(Dickstein et al., 2008) **(Table 4.1)** As such, both de novo presentations of AHF as well as recurrent presentations of typically decompensated HF (i.e. acute- on –chronic HF) were included in the registry. **(Figures 4.9-4.11).**

Table 4.1. **Case Definition**

Case definition	**Diagnostic criteria**
Hypertensive HF	Previous history of hypertension or sustained BP of >140/90 mmHg in the presence of symptoms of HF, increased LV mass LV systolic and/or diastolic dysfunction
Valvular HF (mostly rheumatic)	HF in addition to any of the following: i. Mitral stenosis: – presence of thickened and calcified mitral valve leaflets, loss of the classic M-shaped pattern of a normal mitral valve, diastolic dooming and restriction of the mitral valve leaflet motions. ii. Mitral Regurgitation: Poor coaptation of the mitral valve leaflets in systole, thickened leaflets, dilated and hyperdynamic left ventricle, iii. Aortic stenosis: Presence of calcified aortic valve, reduction in aortic cusp separation, highly echo reflectant aortic valve leaflets, iv. Aortic regurgitation: Poor coaptation of the aortic cusps in diastole, dilated left ventricles and fine fluttering of the anterior mitral valve in diastole.
Dilated Cardiomyopathy	Dilated cardiomyopathy was diagnosed when there are dilated heart chambers with normal or decreased wall chambers as well as impaired LV systolic function.
Endomyocardial Fibrosis	Endomyocardial fibrosis (EMF) was documented in the presence of clinical features coupled with dilated atria and thickening of the endocardium especially at the apices of the ventricles
Pericardial Effusion	Pericardial effusion was diagnosed when there is echo free space between the visceral and parietal pericardium. Diagnosis of constrictive pericarditis was based on standard criteria.
Cor-pulmonale or Right Heart Failure	Cor pulmonale was present when there is dilated and hypertrophied right ventricle (RV), evidence of increased RV systolic pressure (D-shaped LV in diastole (diastolic flattening of the LV septum)
Ischaemic Cardiomyopathy	HF associated with diagnosis of myocardial infarction. Diagnosis of MI was based on ECG changes, Cardiac enzyme elevation and regional wall motion abnormality at echocardiography
LV systolic dysfunction	HF in the presence of LV ejection fraction (EF)<=45%
LV diastolic dysfunction	HF in the presence of LVEF >=45% and E/a ratio, deceleration time and isovolumic relaxation time (IVRT) within accepted definition(according to the criteria of the European Society of Cardiology (European Heart Journal (1998) 19, 990–1003), European Journal of Heart Failure (2012) 14, 803–869)

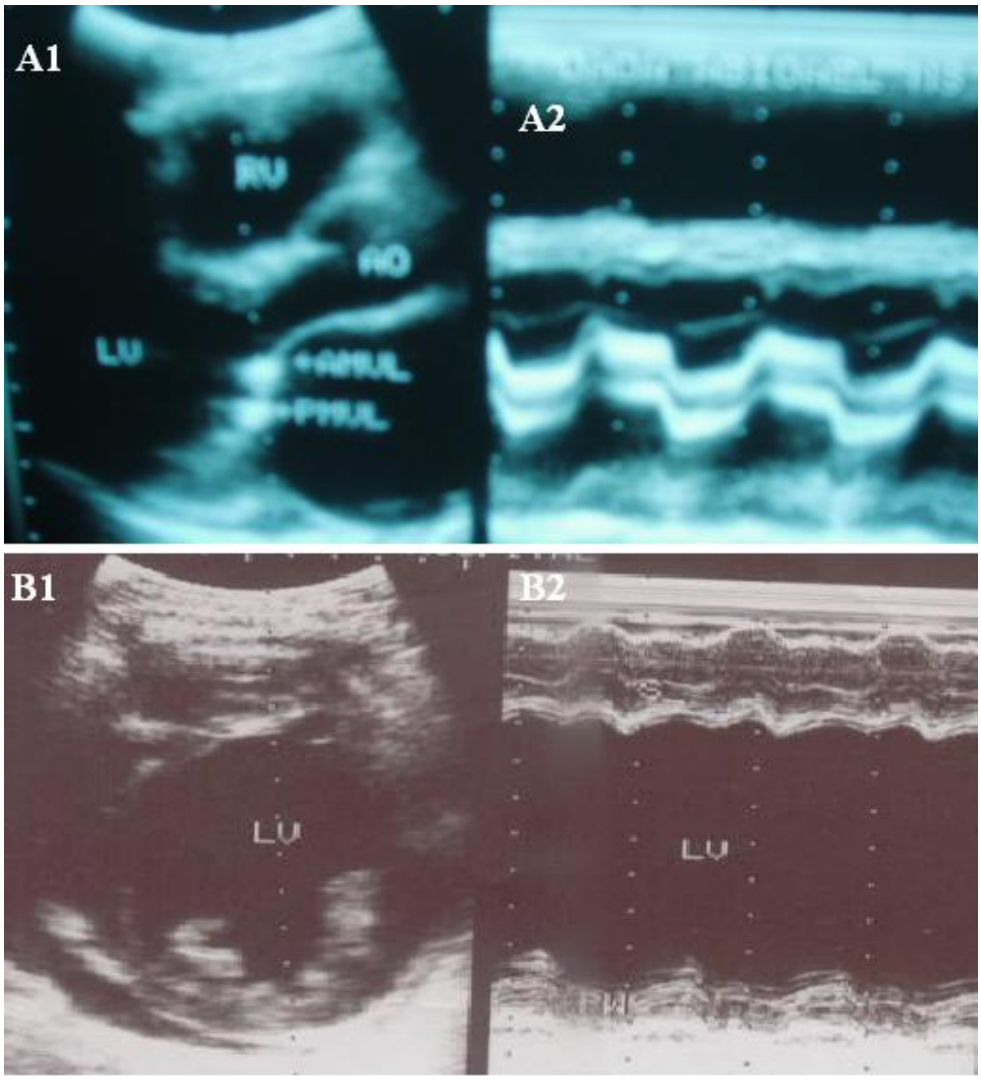


Figure 4.10. A(1&2). 2D and M-mode echocardiogram of a subject with mitral stenosis; B(1&2). 2D and M-mode echocardiogram of a subject with idiopathic dilated cardiomyopathy

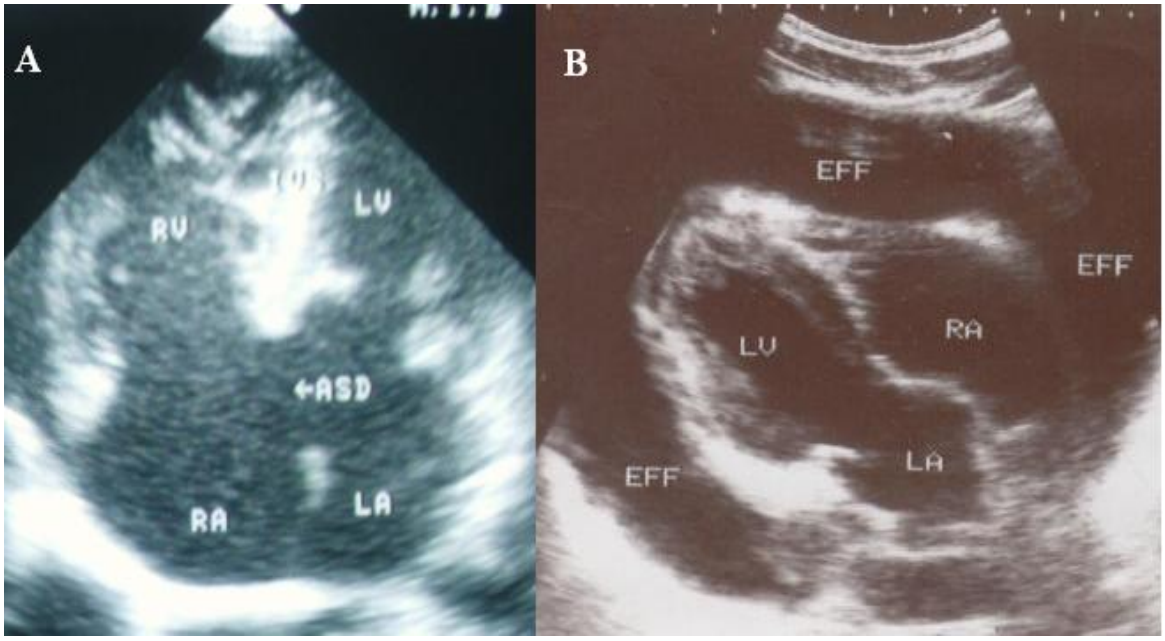


Figure 4.11. Echocardiogram of a subject with a large atrial septal defect; B. 2D echocardiogram of a subject with effusive pericarditis

4.10 Follow-Up

The study cohort was prospectively followed up for six months post index hospitalisation. The subjects were contacted through clinic visit or telephone calls at one, three and six months. Information obtained during follow-up included their wellbeing, prescribed pharmacotherapy, history of re-hospitalization and deaths (from next of kin). In addition to patient or relation's telephone interviews; and where necessary referring physicians were contacted for additional information.

4.11 Health outcomes

The following health outcomes were documented - 1) length of initial hospital stay (LoS) in days, 2) survival status on discharge (dead or alive), 3) short-term case-fatality (30 days), 4) medium-term case-fatality (180 days), 5) re-hospitalization status (180 days).

4.12 Estimation of health care cost of HF

All available costs associated with in-patient care, out-patient cares (both direct and indirect cost) as well as the opportunity costs associated with HF management in the city were computed for the year 2010. An annual, prevalence based approach was employed in estimating the cost of the resources used for the management of HF.(Stewart et al., 2002, Ryden-Bergsten and Andersson, 1999, Czech et al., 2013, Araujo et al., 2005) Healthcare costs were then expressed in the local currency-Naira, (and converted to US Dollar [$US] at a rate of 150 Nigerian Naira to $US1 in 2010)

4.13 Ethical consideration

The study was reviewed and approved by the ethics review boards of Federal Medical Centre Abeokuta, Nigeria and the University of the Witwatersrand. All the subjects gave informed consent and the study was carried out in accordance with the declaration of Helsinki.(Rits, 1964)

4.14 Data management and Statistical Analyses

Data was entered into EpiData software (The EpiData Association, att. Jens Lauritsen, Enghavevej 34, DK5230 Odense M, Denmark) by experienced personnel and analyzed with SPSS version 11.0 (SPSS, Inc. Chicago Illinois). Descriptive statistics for baseline data was performed on continuous variables using mean, standard deviation, range and median where appropriate. Categorical variables are expressed as percentages. MacNemar and chi-square tests (for categorical variables) and Student's t-test or analysis of variance (for continuous variables) were used for comparisons as appropriate.

Survival function estimates was performed using the Kaplan-Meier method and the differences were tested using log-rank test. The follow-up was censored at 6 months post admission. Subjects who died or were readmitted within the period of six months constituted the event of interest for purpose of survival analysis while those still alive/ not readmitted or lost to follow-up were treated as censored. In the survival analysis, censoring meant that the outcome of interest has not been observed. All demographic and clinical profiling variables were examined, on a univariate basis, as potential correlates of death during 180 day follow-up in those who survived the index hospitalisation. Where appropriate, results are expressed as odds ratio (OR) with their 95% Confidence Intervals (95% CI).

A two-sided p value of <0.05 was considered significant.

Results (Published Reports)

Chapter 5: Contemporary clinical profile of acute HF in Abeokuta, Nigeria

Published paper 1.

Ogah OS, Stewart S, Falase AO, Akinyemi JO, Adegbite GD, Alabi AA, et al. Contemporary profile of acute heart failure in Southern Nigeria: data from the Abeokuta Heart Failure Clinical Registry. JACC Heart failure. 2014 Jun;2(3):250-9. PubMed PMID: 24952692.

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Contemporary Profile of Acute Heart Failure in Southern Nigeria

Data From the Abeokuta Heart Failure Clinical Registry

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Ibadan and Abeokua, Nigeria; Johannesburg and Cape Town, South Africa; and Melbourne, Australia

Abstract

Objective

This study sought to determine the contemporary profile, clinical characteristics and intra-hospital outcome of acute heart failure in an African urban community.

Background

There is limited data on the current burden and characteristics of acute heart failure (AHF) in Nigerian Africans.

Methods

We prospectively collected comprehensive and detailed clinical and socio-demographic data from 452 consecutive patients presenting with AHF to the only tertiary hospital in Abeokuta, Nigeria (population 3.2 million) over a two year period.

Results

Mean age was 56.6±15.3 years (57.3±13.4 for men, 55.7±17.1 for women) and 204 (45.1%) were women. Overall, 415 (91.8%) subjects presented with de novo AHF. The most common risk factor for HF was hypertension (pre-existing in 64.3% of cases). Type 2 diabetes mellitus was present in 41(10.0%). Hypertensive heart failure was the commonest etiological cause of HF being responsible for 78.5% of cases. Dilated cardiomyopathy (7.5%), cor-pulmonale (4.4%), pericardial disease (3.3%), rheumatic heart disease (2.4%) and ischemic heart disease were less common (0.4%) causes. The majority (71.2%) of subjects presented with left ventricular dysfunction (mean left ventricular ejection fraction 43.9 ± 9.0%) with valvular dysfunction and abnormal LV geometry frequently documented. Mean duration of hospital stay was 11.4± 9.1 days and intra-hospital mortality was 3.8%.

Conclusions

Compared to high income countries, individuals presenting with AHF in Abeokuta, Nigeria are relatively younger and still of a working age. It is also commoner in men and associated with severe

symptoms because of late presentation. Intra-hospital mortality is similar to other parts of the world.

5.1 Introduction

Although recognized as a significant health problem in high income countries.(Sidney et al., 2013, Mosterd and Hoes, 2007) the syndrome of heart failure (HF), both in its acute(Mosterd and Hoes, 2007) and chronic(Mosterd and Hoes, 2007) forms has emerged as an a issue of global public health importance. It has been established that the burden of HF doubles with each passing decade after the age of 40 years especially in industrialized countries of the world due to aging population and increasing burden of risk factors including hypertension, diabetes mellitus, ischemic heart disease and, more recently obesity .(Cowie et al., 1997). HF is estimated to affect about 15 million people worldwide (0.2% of the world population). Whilst there are robust estimates to describe the incidence, prevalence and overall burden of HF in Europe (Cowie et al., 1999, Cleland et al., 2003, Cleland et al., 2000) and North America, there is a paucity of data to describe the same in other major populations around the globe. For example, HF in Africa (including Nigeria) appears to occur at a relatively younger age, afflicting individuals at the prime of life and mostly due to non-ischemic origin. However, there is limited systematically collected and contemporary data to describe clinical characteristics, outcome and cost of HF for the continent.(Damasceno et al., 2007, Ntusi and Mayosi, 2009b)

As an extension of this, there is limited data derived from systematically and prospectively conducted studies of HF in Nigeria – the most populous region in sub-Saharan Africa. Previous studies in the 60s, 70s and 80s were mainly retrospective and the various diagnoses were not confirmed by echocardiography.(Antony, 1980, Ladipo, 1978, Parry et al., 1977) Moreover, there is even less data to describe acute clinical presentations of HF, to match the clinical registry data derived from large cohorts in Europe and North America(Adams et al., 2008).

Considering the paucity of data on acute HF (AHF) in sub-Saharan Africa, we used the data of the Abeokuta Heart Failure Registry to explore and determine the current etiology and characteristics of

acute (both de novo and recurrent) presentations of the syndrome in southern Nigeria. The possible role of epidemiologic and demographic transition occurring in Nigeria on the profile of HF in the country was also assessed(Omran, 1971).

5.2 Methods

5.2.1 Design and setting

This was a prospective, observational study conducted at the Federal Medical Centre (FMC), Idi-Aba, and Abeokuta, Nigeria. Abeokuta is the capital city of Ogun state, one of the 36 states that make up the Federal Republic of Nigeria. FMC was established in 1993 by the Federal Government of Nigeria to cater for the health need of the people of Ogun State and its environs in Southwestern Nigeria. The center is the only tertiary hospital in the city which receives referrals from all the health facilities in the city, state and the neighboring states. The state has a population of about 3.2 million and a land area of about 16,409.26 square kilometers. The city itself has an estimated population of about 1 million inhabitants.(2006a) The prevalence of HIV antibodies in individual attending the hospital clinics in 2010 was 11.6%(16% in women and 7.3% in men),(Motayo et al., 2012)

Health care cost in Abeokuta, Nigeria (and in fact in all parts of the country) is generally borne by the individual through out of pocket payment. Health insurance in the country is still at a rudimentary stage. Only a very small population has access to this. However strong family tie exist in the country where poor patients are assisted by their wealthy or well-to do family members. This is in fact a very big challenge to health care delivery in the city and the country in general.

A cardiologist (OSO) covers the cardiac unit assisted by postgraduate resident doctors and well as experienced nurses. Facilities for cardiac evaluation that exist in the center include: chest radiography, 12-lead electrocardiography (EKG), exercise EKG, Holter EKG, Ambulatory blood pressure monitoring devices, Spirometry and echocardiography (ECHO). All the EKGs and ECHOs were carried out within 72 hours of admission as prescribed by the study protocol.

5.2.2 Study population

All cases of AHF, both denovo presentations and recurrent decompensation with a pre-established diagnosis of HF were consecutively (there were no study refusals) recruited into the registry between January 1, 2009 and December 2010. All subjects provided written and/or informed consent to participate in the study. Ethical approval was obtained from the ethical committee/ ethical review board of the Federal Medical Centre, Abeokuta. The study was carried out in accordance with international ethical principles(Rits, 1964).

5.2.3 Enrollment and data collection

Data from each subject was obtained using a uniform and standardized case report form. Detailed clinical documentation on newly diagnosed/ newly presenting cases/ pre-existing cases of HF was carried out. The following data were obtained: 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 cardiovascular risk factors, etiology of HF, precipitating factor, co-morbidities, blood investigations, 12-lead EKG, echocardiography, medications and intra-hospital mortality.

5.2.4 Clinical evaluation

Blood pressure measurements were obtained according to standard guidelines with a mercury sphygmomanometer (Accousson London). Body mass index (BMI) was calculated using the formula: BMI = Weight (kg) / [h)] $^{2.}$ A BMI of 24-29.9kg/m^2 ^{and} >=30kg/m^2 defined overweight and obesity respectively. Anemia was defined as hematocrit of less than 10g/dl. Glomerular filtration rate was estimated using the four variables- Modification of Diet in Renal Disease (MDRD) formula.(Levey et al., 1999) Renal dysfunction was defined as eGFR of less than 60ml/min/1.73m^2 (same criteria used by Stewart et al(Stewart et al., 2008))

5.2.5 Diagnoses of Heart Failure

A standardised diagnosis of HF was made using the Framingham criteria(McKee et al., 1971) as well as the according to the guidelines of European Society of Cardiology on the diagnosis and treatment of AHF(Dickstein et al., 2008) As such, both de novo presentations of AHF as well as recurrent presentations of typically decompensated HF (i.e. acute- on -chronic HF) were included in the registry.

5.2.6 Electrocardiography

A standard 12-lead resting EKG was recorded for each subject using a Schiller EKG machine (Schiller AG, Switzerland). All the 12 lead resting EKG were performed by trained nurses/technicians and analyzed by a reviewer who was blinded to the clinical data of the patients. The Minnesota code classification(Blackburn, 1969) system was used in sorting out the various abnormalities. EKG abnormalities were diagnosed based on standard criteria(Rowlands, 1981).

5.2.7 Echocardiography

An Aloka SSD-4000 echocardiograph (Aloka Co. Ltd., Tokyo, Japan). was used to assess all patients. Two dimensional guided M- mode measurements were made according to the recommendations of the American Society of Echocardiography (ASE)(Sahn et al., 1978a). LV internal dimension, posterior wall thickness and interventricular septal thickness were measured at end-diastole and end-systole. Where optimal M-mode imaging could not be obtained, 2D linear measurements were obtained according to the ASE criteria(Sahn et al., 1978a). Left atrial end systolic diameter was obtained from the trailing edge of the posterior aortic – anterior left atrial complex. Measurements were obtained in up to 3 cardiac cycles according to the ASE convention(Sahn et al., 1978a). One experienced cardiologist (OSO) performed all the echocardiography. In our laboratory, the intra-observer concordance correlation coefficient and measurement error have been reported.(Ogah et al., 2006a) Left ventricular mass was calculated using the formula of Devereux and Reichek.(Devereux and Reichek, 1977b) Left ventricular geometric was defined according to standard criteria.(Ganau et al., 1992).

The left atrial dimension and area was measured using standard methods (Lester et al., 1999) (Thomas et al., 2002) .

Transmitral flow velocities were obtained with the Doppler sample volume placed just beyond the tip of mitral valve leaflets and standard measurements were obtained.(Nishimura and Tajik, 1997) Tissue Doppler imaging was only applied to identify true pseudonormalised filling pattern.

5.2.8 Statistical analyses

Data was entered into EpiData software (The EpiData Association, att. Jens Lauritsen, Enghavevej 34, DK5230 Odense M, Denmark) by experienced personnel and analyzed with SPSS version 11.0 (SPSS, Inc. Chicago Illinois). Descriptive statistics for baseline data was performed on continuous variables using mean, standard deviation, range and median where appropriate. Categorical variables are expressed as percentages. MacNemar and chi-square tests (for categorical variables) and Student's t-test or analysis of variance (for continuous variables) were used for comparisons as appropriate. A two-sided p value of <0.05 was considered significant.

5.3 Results

5.3.1 Cohort profile

Table 5.1 summarizes the demographic and past history/risk profile of the study cohort. A total of 452 subjects were recruited into the registry. This constituted 9.4% of the total number of medical admissions during the period. There were 248 (54.9%) men and 204 (45.1%) women. The mean age of the cohort was 56.4±15.2 years. The majority of subjects were aged > 45 years and married; while 67.5% of them had at least primary school education. More than two thirds also lived in an urban community. Few subjects (3.3%) were current cigarette smokers and was more commonly reported in men than women (5.6% and 0.5% respectively) with a similarly low level reporting a positive family history of heart disease. More than half the cohort was being actively treated for hypertension. The overall prevalence of diabetes mellitus was 10.0%. Of note, 415 (91.8%) subjects were de novo presentations of AHF. About 90% of the subjects were in NYHA class II or III, one month prior to evaluation, 27% were either overweight or obese, 21.7% had moderate-to-severe renal dysfunction (eGFR <60ml/min/1.73m^2) and 10.5% of the subjects were anemic. Presenting symptoms and signs are summarized in **Figure 5.1**, respectively.

Table 5.1. Socio-demographic and clinical profile of study cohort

Variable	ALL(n=452)	MEN(n=248)	WOMEN(n=204)	P-value
Mean Age	56.6±15.3	57.3±13.4	55.7±17.1	0.265
Yoruba Tribe	415(91.8%)	225(90.7)	190(93.1)	0.450
Others Tribes	37(8.2%)	23(9.3)	14(6.9)	0.448
Married	363(80.3)	221(89.1)		<0.001
No Education	147(32.5)	63(25.4)	84(41.2)	0.006
Unemployed	13(5.2)	25(12.3)	38(8.4)	0.002
Urban residence	388(74.8)	185(74.6)	153(75.0)	0.922
Current smoker	15(3.3)	14(5.6)	1(0.5)	0.006
Never consumed alcohol	286(63.3)	100(40.3)	186(91.2)	<0.001
Known Hypertension	293(64.3)	174(70.2)	119(58.3)	0.010
Known Diabetes Mellitus	45(10.0)	20(8.1)	25(12.3)	0.157
Asthma	9(2.0)	3(1.2)	6(2.9)	0.311
COPD	16(3.5)	12(4.8)	4(2.0)	0.127
Arthritis	64(14.2)	10()	35(17.2)	0.105
Family History of Heart Disease	14(3.1%)	8(3.2)	6(2.9)	0.862
NYHA Class (n=308)				0.502
Class II	79(17.5)	47(19.0)	32(15.7)	
Class III	284(62.8)	150(60.5)	134(65.8)	
Class IV	89(19.7)	51(20.4)	38(18.6)	
BMI(kg/sqm)	23.9±5.7	24.0(5.1)	23.7(6.4)	0.470
% Obese	41(9.1)	21(10.7)	20(12.4)	0.428
Temperature (^{0}C) (n=299)	36.4±0.8	36.4±0.7	36.4±0.80	0.801

Resp. Rate (c/min) (n=395)	27.8±6.3	27.9±6.3	27.7±6.2	0.706
Pulse Rate (beats/min) (n=418)	96.6±18.3	96.9±17.9	96.3±18.7	0.765
SBP (mmHg) (n=424)	137.5±31.8	138.7±32.2	136.2±31.4	0.416
DBP (mmHg) (n=424)	87.3±20.3	88.5±21.0	85.9±19.4	0.186
PCV (%) (n=381)	37.6±7.0	37.9±7.0	37.2±7.1	0.372
WCC (n=377)	7.13±3.73	7.0±3.8	7.27±3.68	0.519
% Lymphocytes (n=303)	35.8±12.8	35.3±12.4	36.4±13.2	0.452
Serum Sodium (mmol/dl)	135.2±10.0	134.9±10.2	135.6±9.8	0.640
Serum Potassium(mmol/dl)	3.61±0.74	3.63±0.76	3.58±0.72	0.661
Total cholesterol (mg/dl)	171.0±70.5	164.1±72.2	188.6±64.8	0.228
Urea (mg/dl)	44.0±39.6	48.3±44.4	38.8±32.1	0.037
Creatinine (mg/dl)	1.45±2.15	1.67±2.56	1.19±1.46	0.857
Glucose (mg/dl)	112.8±53.3	112.2±46.6	113.4±61.0	0.028
Duration in hospital admission (days)	11.4±9.1	10.8±0.78	6.48±0.52	0.608
Anaemia (n=382)	40(10.5)	18(8.8%)	22(12.4%)	0.169
Renal Dysfunction(n=366)	174(47.5)	97(48.0)	77(47.0)	0.461
HIV positive (n=222)(%)	2.7	3.5	1.9	0.474

*data in bracket are percentages

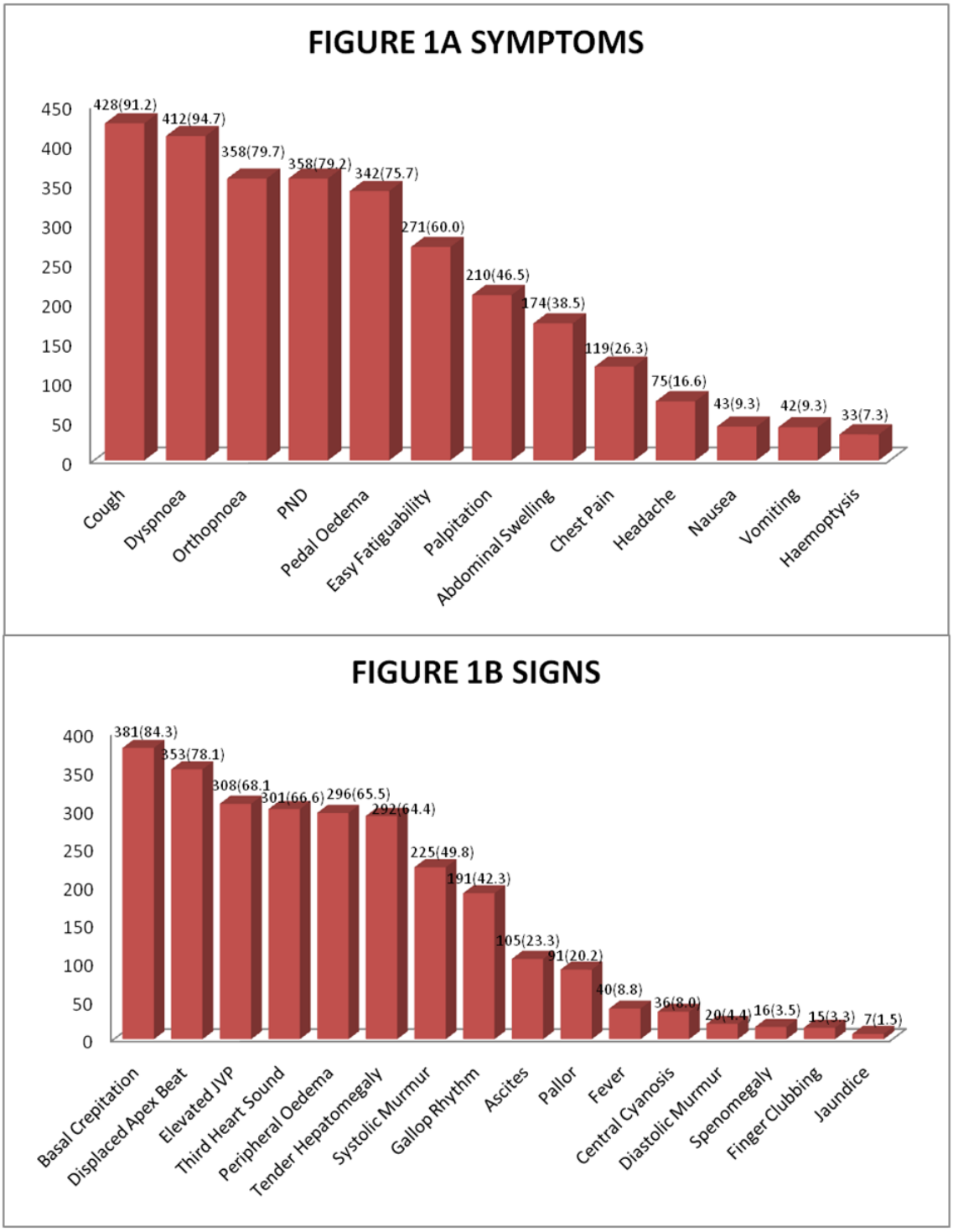

Figure 5.1. Symptoms and signs in the 452 subjects with acute HF

5.3.2 Precipitating factors for acute heart failure

The common precipitating factors for HF in the cohort include infections especially chest infection (n=284, 62.8%), uncontrolled hypertension (n=200, 44.2%) and arrhythmias especially atrial fibrillation (n=123, 27.3%). Less common precipitants included anemia (n=33, 7.3%), excessive physical activity (n=-25, 5.5%) and electrolyte imbalance (e.g. hyponatraemia and hypokalemia n=10, 2.2%). Of note, there was only one case of acute myocardial infarction (0.2%)

5.3.3 12 lead electrocardiography

A majority of subjects presented with an abnormal 12 lead EKG. Axis deviations (most commonly left axis deviation) were determined in 76.1% of cases. Atrial enlargement or abnormality was recorded in 69.7% of EKGs. EKG-defined LVH was observed in 82.8%, out of which 38.5% had EKG LVH with strain pattern, 13.1 % had right ventricular hypertrophy, 28.7% had arrhythmias and atrial fibrillation was also present in 52 (11.5%) subjects.

5.3.4 Echocardiography and etiology of HF

Figure 5.2 shows the etiological risk factors for HF in the cohort. Hypertensive heart disease, dilated cardiomyopathy, cor-pulmonale (right heart disease), pericardial disease and rheumatic heart disease were the common risk factors for HF in the cohort and these constituted 78.5%, 7.5%, 4.4%, 3.3% and 2.4% of cases, respectively. Pericardial diseases and right HF was more common in women, while hypertensive HF and DCM was more common in men. Other causes of HF in the cohort included peripartum cardiomyopathy (1.3%), endomyocardial fibrosis (EMF) (0.9%), thyroid heart disease (0.7%), ischemic heart disease (0.4%) and adult congenital heart disease (0.4%). The echocardiographic features of the subjects according to gender are shown in **Table 5.2**

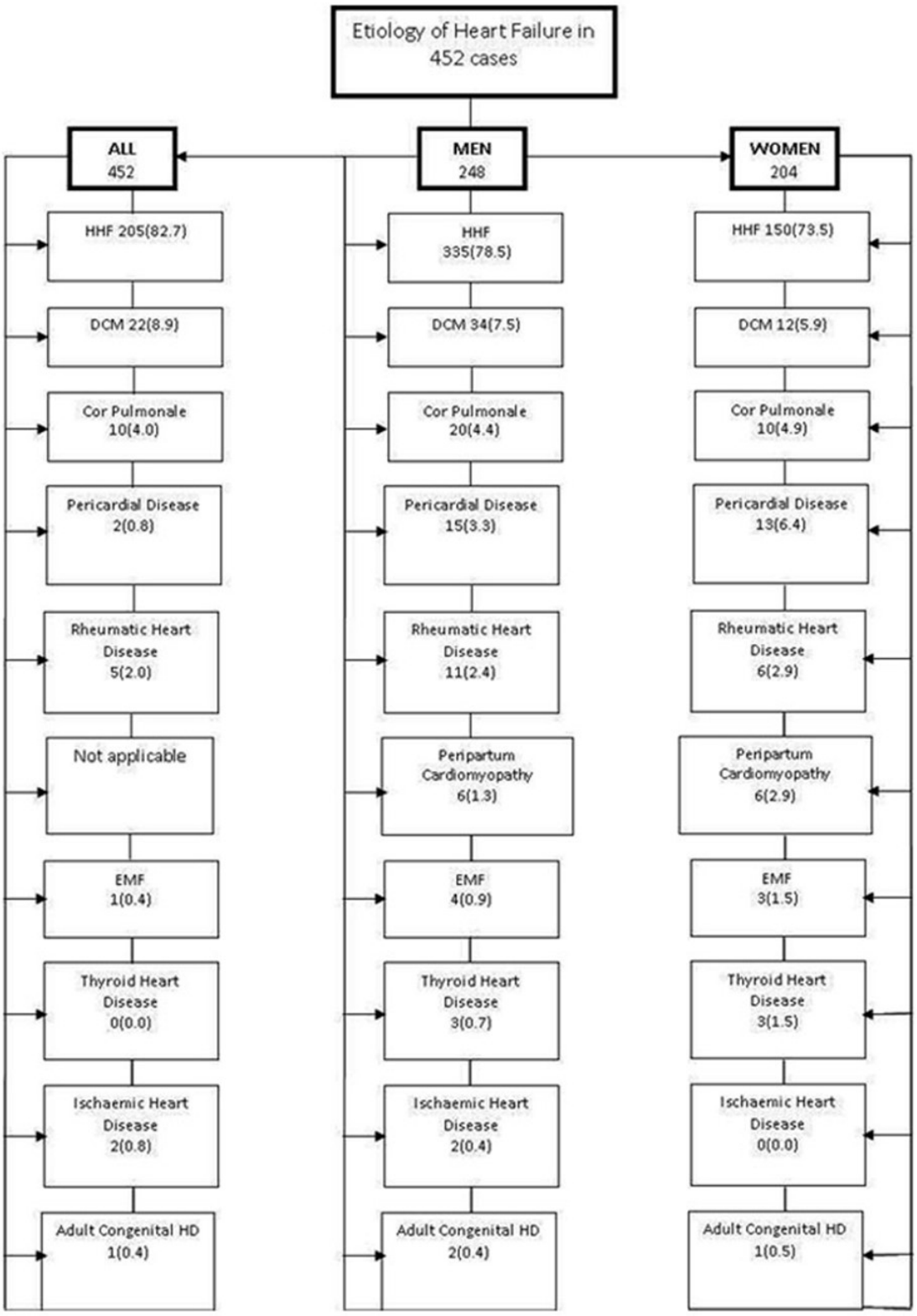

Figure 5.2. Etiology of HF in the 452 subjects

Table 5.2 Echocardiographic variables of the cohort in men and women

Variable	ALL(n=452)	Men(n=248)	Women(n=204)	P-Value
Aortic root (cm)	3.04±0.50	3.22±0.51	2.81±0.39	<0.001
Left atrium(cm)	4.80±0.66	5.00±1.43	4.54±1.05	0.157
IVSTd	1.32±0.37	1.38±0.40	1.25±0.36	0.001
PWTd	1.17±0.35	1.20±0.36	1.12±0.33	0.031
LVIDd	5.48±1.43	5.79±1.44	5.11±1.33	<0.001
LVIDs	4.51±1.40	4.82±1.42	4.14±1.29	<0.001
FS	18.5±9.0	17.6±8.74	19.5±9.12	0.039
EF	43.9±9.0	42.1±16.8	45.9±17.1	0.037
LVM	320.7±132.8	360.0±141.8	272.4±102.4	<0.001
LVMI	86.2±37.0	92.8±40.9	77.9±26.6	<0.001
RWT	0.44±0.15	0.43±0.15	0.46±0.15	0.189
E wave(m/sec)	0.82±0.29	0.79±0.28	0.86±0.31	0.031
A wave(m/sec)	0.52±0.15	0.49±0.22	0.56±0.28	0.017
E/A	2.04±0.40	2.10±1.48	1.97±1.28	0.460
IVRT	145.0±59.7	117.1±35.9	110.6±32.8	0.174
DT	114.4±34.7	142.6±56.0	148.3±64.4	0.397
LV Geometry				
CH (%)	38.3	39.6	36.8	0.069
EH (%)	45.4	47.6	42.8	0.069
MR (%)	77.9	75.5	80.7	0.256
TR (%)	69.7	65.5	74.7	0.068
AR (%)	8.2	8.5	7.8	0.851
Syst HF (%)	66.4	71.2	60.6	0.028
Spontaneous Echoes	6.8	8.5	4.8	0.212

Intramural Thrombi	0.8	1.0	0.6	0.670

IVSTd= Interventricular septal wall thickness in diastole, PWTd= Left ventricular posterior wall thickness in diastole, LVIDd= left ventricular internal diameter in diastole, LVIDs= left ventricular internal diameter in systole, FS= fractional shortening, EF= ejection fraction, LVM= left ventricular mass, LVMI= left ventricular mass index, RWT= relative wall thickness, E =LV early filling velocity, A=Left ventricular late filling velocity, IVRT= isovolumic relaxation time, DT= deceleration time of E velocity, CH= concentric hypertrophy, EH= Eccentric hypertrophy, MR= mitral regurgitation, TR= tricuspid regurgitation, AR= aortic regurgitation

The aortic root diameter, LV septal wall thickness in diastole, posterior wall thickness, indices of LV systolic function and left ventricular mass were significantly higher in men than in women. Men also had significantly higher frequency of systolic HF than women (71.2% vs. 60.6%, p=0.028). **Table 5.3** shows the echocardiographic characteristics of the cohort according to the etiological risk factor for HF. LV wall thickness was higher in the hypertensive HF group while LV dilatation was found to be greatest in the DCM group; which also had the highest frequency of LV systolic dysfunction

In terms of LV geometry, 93.5% of the cohort had abnormal LV geometry (concentric remodeling – 9.7%, concentric hypertrophy – 38.3% and eccentric hypertrophy – 45.4%).

Table 5.3. Echocardiographic characteristics according to etiological factor

	ALL(452)	HHF(n=355)	CMO(n=38)	CORPULMALE(n=26)	PERICARDIAL(n=15)	RHD(n=11)	OTHERS(n=7)
AO*	3.04±0.50	3.10±0.50	2.89±0.48	2.93±0.11	2.76±0.39	2.90±0.42	2.78±0.25
LA	4.80±2.66	4.90±2.99	4.80±1.18	4.26±1.15	3.87±0.96	4.71±1.06	4.20±0.37
LA area (cm^2)	26.9±8.3	26.6±8.1	26.7±6.1	24.8±4.3	21.5±.4.2	33.5±12.0	27.1±14.6
IVSTd*	1.32±0.38	1.35±0.37	1.13±0.28	1.18±0.43	1.18±0.23	1.46±0.37	1.25±0.25
PWTd	1.17±0.38	1.19±0.36	1.05±0.35	1.04±0.16	0.96±0.18	1.21±0.30	1.10±0.34
LVIDd*	5.48±1.43	5.52±1.49	6.19±0.75	4.59±1.28	4.14±0.70	5.72±0.94	4.69±0.97
LVIDs*	4.51±1.40	4.57±1.43	5.33±0.87	3.42±1.23	3.05±0.48	4.50±1.01	3.75±1.15
FS*	18.5±9.0	17.9±8.70	14.3±8.20	26.5±9.0	21.8±9.2	25.9±6.0	21.4±10.5
EF*	43.8±17.0	42.9±16.5	35.4±16.2	58.6±14.6	50.3±16.5	58.6±10.5	49.0±19.8
LVM	320.7±132.8	338.4±133.6	297.5±95.1	217.1±134.3	152.4±90.5	338.2±93.1	204.6±57.5
LVMI	86.2±37.0	90.4±37.7	79.9±31.1	67.1±34.5	38.4±11.0	93.4±24.2	59.2±16.6
RWT	0.44±0.15	0.45±0.15	0.35±0.14	0.49±0.15	0.48±0.13	0.43±0.15	0.49±0.20
Systolic HF*	66.4	68.1	80.0	44.4	57.1	11.1	69.2
ME*	0.82±29	0.82±0.29	0.86±0.21	0.72±0.26	1.03±0.43	0.69±0.22	0.73±0.28
MA	0.52±0.25	0.53±0.25	0.42±0.26	0.57±0.25	0.64±0.23	0.35±0.15	0.61±0.23
E/A	2.04±1.40	2.04±1.45	2.50±1.10	1.64±1.10	1.58±0.89	2.49±1.49	1.38±0.81
DT	145.0±59.7	144.3±57.6	114.6±41.4	183.9±64.6	184.9±91.0	154.0±36.2	146.3±76.8
IVRT	114.4±34.7	116.4±34.8	109.9±38.4	107.2±29.1	89.0±8.7	92.0±7.0	113.1±26.9

AO= aortic root diameter, IVSTd= Interventricular septal wall thickness in diastole, PWTd= Left ventricular posterior wall thickness in diastole, LVIDd= left ventricular internal diameter in diastole, LVIDs= left ventricular internal diameter in systole, FS= fractional shortening, EF= ejection fraction, LVM= left ventricular mass, LVMI= left ventricular mass index, RWT= relative wall thickness, E =LV early filling velocity, A=Left ventricular late filling velocity, IVRT= isovolumic relaxation time, DT= deceleration time of E velocity, CH= concentric hypertrophy, EH= Eccentric hypertrophy, MR= mitral regurgitation, TR= tricuspid regurgitation, AR= aortic regurgitation. *$p<0.05$ considered to be statistically significant.

5.3.5 Intra-hospital medications

On admission 431(95.4%), 419(92.7%), 383 (84.7%), and 338(74.7%) were placed on diuretics, ACE inhibitors, angiotensin receptor blockers and digitalis respectively. Calcium channel blockers, centrally acting anti-hypertensives beta-blockers, anticoagulants (heparin) and hypoglycemic agents were prescribed for 78(17.3%), 54(12.0%), 42(9.4%), 292(64.7%) and 30(6.7%) subjects respectively.

At discharge, four hundred and forty eight individuals (99.1%) were prescribed ACE inhibitors, 398 (88.1%) of the subjects were prescribed a loop diuretic, 327(72.3%) on digoxin, 121(26.8%) on long acting calcium channel blockers, 65 (14.4%) on hydrallazine and isosorbide dinitrate combination, and 41(9.1%) on beta blockers. Ancillary medication which the patients had during the course of admission were aspirin 197(43.6%), centrally acting antihypertensive 79(17.5%), , hypoglycemic agents 49(10.8%), thiazide diuretic 32(7.1%), and amiodarone 10(2.2%)

5.3.6 Intra-hospital outcome

Seventeen subjects died during the course of admission. Causes of death were pump failure (7 cases), sudden death possibly due to arrhythmia (5 cases), pulmonary embolism (3 cases) and stroke (2 cases). All the intra-hospital deaths occurred in those with de novo HF and mostly in women. Those that died were younger (mean age 48.2 vs. 56.8 years, p=0.025). The majority (9 cases) were either hypertensive (52.9%) or had dilated cardiomyopathy (29.4%) and were more likely to present with systolic dysfunction (5 cases) and/or in NYHA Class III or IV (15 cases).

The mean overall length of hospital stay was 10.8±6.1 days (range 2-61, median 9 days).

5.3.7 4.3.7. International Comparisons

Table 17 shows the comparison of our findings with that of other workers in SSA and other parts of the world. The age of presentation ranges from 40 years in a study from Malawi to 57 years in Cameroon.

5.4 Discussion

This is the first detailed, comprehensive and prospective study of AHF in Abeokuta and in Southern Nigeria. Our data shows that acute presentation of HF (predominantly de novo) constitutes just fewer than 10% of all medical admissions in the city. In general cardiological related conditions are responsible for just under one in five emergency medical admissions in Abeokuta only second to infections/infestations that account for almost one in two cases. (Ogah et al., 2012a) These data suggest that AHF in Abeokuta, Nigeria predominantly afflicts young and middle aged in prime of their life and most present as de novo AHF. Clinically late presentation is common, with over 80% presenting in NYHA class III or IV. Over two-thirds of our cohorts had systolic HF with hypertensive heart disease the most common risk factor for HF overall (almost four in five cases). Alternatively, ischemic heart disease is relatively uncommon. Infections and uncontrolled hypertension are the commonest precipitating factors with co-morbidities and secondary valvular dysfunction also common. We also noted low utilization of disease modifying drugs such as beta blockers and hydrallazine – isosorbide combination. Intra-hospital mortality rate was relatively low at just under four percent.

Contrary to the situation in advanced countries of Europe, North America and Japan where HF is essentially a problem of the elderly with a mean age at presentation of 72 years this was a relatively young cohort. Our finding of lesser rate of HF in women is consistent with many previous reports. Alternatively, there have been reports (notably South Africa and the East African countries of Kenya and Uganda)of more women than men presenting with HF. (Stewart et al., 2008, Oyoo and Ogola, 1999, Kuule et al., 2009) Other aspects of this cohort (including precipitating factors, a predominance of de novo cases and late, severe presentations) are similar to equivalent African reports. The etiological pattern in our cohort is also consistent with findings in other parts of Nigeria where hypertensive HF contributes to 52.7-62.6% of cases of HF (Ojji et al., 2009, Laabes et al., 2008, Onwuchekwa and Asekomeh, 2009, Karaye and Sani, 2008).

In a recent systematic review, we have shown that the pooled prevalence of hypertension increased from 8.6 % (CI= 13.7-16.3%) from the only study during the period from 1970-1979 to 22.5% (CI=21.8-23.2%) from 2000 to 2011. Awareness, treatment and control of hypertension were generally low (14.2-30%, 18.6-21% and 9% respectively) with attendant high burden of hypertension related complications.(Ogah et al., 2012b)

Hypertension is also the predominant etiological factor for HF in adjacent Cameroon. (Damasceno et al.) Alternatively, in East Africa (Kenya, Uganda) as well as the horn of Africa (Kuule et al., 2009) cardiomyopathy is more common.

Generally two-thirds of HF patient have systolic dysfunction. This is in keeping with the findings of our study and other workers **(Table 5.4)** Consistent with findings of EHFS II and the Heart of Soweto Study, valvular dysfunctions was also common. The use of ACEIs and spironolactone is quite comparable with findings in advanced countries. This however was not the case with beta blockers and hydrallazine-isosorbide combination. This observation presents an opportunity for improvement in care of HF patients in Abeokuta in particular and Nigeria in general. Previously reported intra-hospital mortality rates from SSA are generally higher than our cohort; ranging from 4.3% to 9.2% (Damasceno et al., 2012, Oyoo and Ogola, 1999, Kingue et al., 2005, Tantchou Tchoumi et al., 2011a) compared to 3.8% to 6.7% (Adams et al., 2005a, Abraham et al., 2008, Nieminen et al., 2006a, Tsuchihashi-Makaya et al., 2009) in high income countries. Length of hospital stay (mean 11 days) was longer than that reported in in the THESUS-HF study (7 days (Damasceno et al.)) but shorter than a Cameroon cohort (13 days (Tantchou Tchoumi et al.)).These are all longer than that is reported in high income countries (4-7 days (Adams et al., 2005a)).

The younger age of presentation of HF patients in our cohort and in many parts of Africa may be related to the etiology of HF. Rheumatic heart disease and cardiomyopathies are essentially problems of the young and middle age. Also hypertension is known to occur early in Africans and African Americans with greater adverse consequences. The gender differences reported from different regions of SSA may be related to patient selection, sex differences in the burden of CV risk

factors and regional variations. In areas with a predominance of rheumatic heart disease and cardiomyopathy (especially peripartum cardiomyopathy), HF rates tends to be commoner in women than in men. Healthcare seeking behaviors may also play an important role. It is more likely that the breadwinner is taken to the hospital in Africa especially where there is no health insurance coverage for the entire family. Some of the possible reasons of under-utilization of standard medications for HF in our cohort may include poor awareness of these therapies in HF in the city, high cost, as well as the late presentation and severity of HF in the subjects. Many physicians are still not comfortable commencing beta blockers or the hydrallazine-isosorbide combination in severely ill HF patients and this presents an opportunity for improved management and outcomes in Abeokuta and wider Nigeria. In the EuroHF Registry, "the best survival was seen in hypertensive HF, as almost all the patients were discharged alive" (Adams et al., 2005a)The fact that hypertension forms the bulk of patients in our cohort may explain, therefore, the lower Intra-hospital mortality rate.. Our data also affords us the opportunity of comparing our findings with similar study in the region of the country reported 41years ago. It does appear that hypertension now plays an increasingly predominant role in driving heart disease in southern Nigeria. Rheumatic heart disease appears to be less prominent. Endomyocardial fibrosis is almost disappearing from the scene while pulmonary heart disease is emerging as a prominent risk factor **(Figure 5.3).**

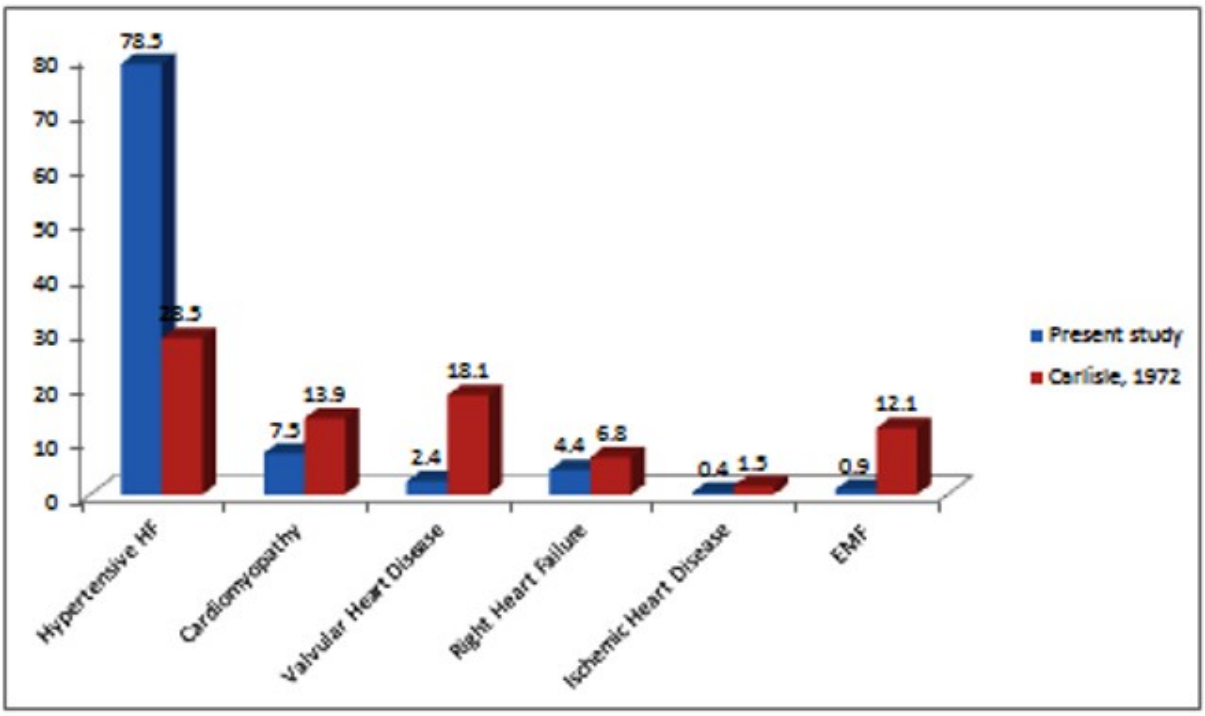

Figure 5.3. Comparison of etiology of HF in present study with similar study in southern Nigeria in the 70s

5.4.1 Study Limitations

This was a cross-sectional study with all the inherent limitations of this methodology. As this was a tertiary cohort, those with milder forms of HF were likely to be under-represented. To overcome this likelihood, all local health facilities were contacted study commencement requesting referral of all HF cases to our clinic (the only centre with cardiologic services (including echocardiography). Cases of ischemic heart disease may also be under-represented due to an increased likelihood of sudden out-of-hospital death and the lack of coronary angiography (all documented cases were investigated with coronary angiography elsewhere). We also did not collect data on the duration of hypertension prior to onset of HF. Finally, we did not assess for nutritional deficiencies and malnutrition as a possible factor for earlier development of heart failure in this population; although in a related study in the country, Olubodun reported that HF patients were more likely to be thiamine deficient, hypoalbuminemic and anemic.(Olubodun, 1992)

5.4.2 Conclusions

In summary, these data suggest that AHF in Abeokuta, Nigeria predominantly affects younger individuals of a working age. Overall, HF is more common in men and associated with severe symptoms because of late presentation. Severe LV systolic dysfunction and abnormal LV remodeling pattern is also common. Intra-hospital mortality was similar to findings in many parts of the world. Hypertension has become the most common (and indeed preventable) antecedent in the region. Because hypertension has been projected to rise by 89% in countries of SSA(Kearney et al., 2005) especially Nigeria which is the most populous country in the region (compared to a projected 24% increase in high income countries) between 2000 and 2025, efforts should be made in the area of primordial and primary prevention as well as health promotion in order to combat the emerging epidemic.

Table 5.4. Comparison of present study with other HF studies in SSA and other parts of the world

Study	No	% women	Mean Age	Smoking	Hypertension	Diabetes	0besity	Cholesterol	Anemia	CKD	NYHA(III&IV)	Mean EF	HHF	DCM	VHDX	RHF	IHD	LOS	M*
Present Study, Nigeria	452	45.1	56.6	3.3	64.3	10	10.7	164.1	8.8	48	82.5	42	78.5	7.5	2.4	4.4	0.4	11	3.8
Stewart, South Africa(Stewart et al., 2008)	844	57	55	48	55	10	34	162.4*	10	25	34	45	33.3	35.3	7.9	14.3	7.9	NR**	NR
THESUS_HF^{S}(Damasceno et al., 2012)	1006	50.7	52	9.8	55.5	11.1	16.3	157.6	15.2	7.7	34.6	39.5	45.4	18.8	14.3	NR	7.7	7	4.2
Laabes, Nigeria(Laabes et al., 2008)	102	68.6	44.8	5.9	44.1	6.9	25.5	NR	NR	NR	93.1	NR	44.1	21.6	22.5	NR	1	NR	NR
Ojji, Nigeria(Ojji et al., 2009)	315	49.1	50.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	62.6	13.8	7.4	1.8	NR	NR	NR
Oyoo, Kenya(Oyoo	91	51.6		NR	NR	NR	NR	NR	NR	NR	37.4	NR	13.	25.	32	NR	2.2	NR	NR

and Ogola, 1999)													2	2					
Kingue, Cameroon(Kingue et al., 2005)	167	40.7	57	NR	NR	NR	NR	NR	NR	NR	NR	NR	54.5	26.3	24.6	NR	2.4	NR	NR
Soliman, Malawi(Soliman and Juma, 2008)	3908	39.9	58.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	24	19	34	NR	0.08	NR	NR
Habte, Ethiopia(Habte et al., 2010)	781	47.6	43.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	24.2	20.2	32.8	3.8	12	NR	NR
Amoah,Ghana(Amoah and Kallen, 2000)	572	NR	42	NR	NR	NR	NR	NR	NR	NR	NR	NR	21.3	16.6	20.1	NR	10	NR	NR
Onwuchekwa, Nigeria(Onwuchekwa and Asekomeh, 2009)	423	42.8	54	NR	NR	NR	NR	NR	NR	NR	NR	NR	56.3	12.3	4.3	2.1	0.2	NR	NR
Kuule, Uganda(Kuul	157	66.2	45	NR	NR	NR	NR	NR	64.3	NR	96.8	NR	25.	27.	28.2	NR	1.9	NR	NR

e et al., 2009)													1	3					
Ogah , NigeriA(Ogah et al., 2008)	1441	48.4	54	NR	NR	NR	NR	NR	NR	NR	NR	NR	56.7	3	3.7	1.6	0.6	NR	NR
TantChou, Cameroon(Tantchou Tchoumi et al., 2011a)	462	42.9	42.5	NR	NR	NR	NR	NR	NR	NR	51	NR	15	32	35	8	NR	13	9.2
Karaye, Nigeria(Karaye and Sani, 2008)	79	44.3	46.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	57	24	12.7	2.5	7.6	NR	NR
EuroHeart failure(Nieminen et al., 2006a)	3580	38.7	69.9	NR	62.5	32.8	NR	NR	14.7	16.8	NR	38	11.4	19.3		3.2	53.6	9	6.7
ADHERE, USA(Adams et al., 2005a)	105,388	52	72.4	NR	73	44	NR	NR	NR	30	76	34.4						4.3	4
OPTIMIZE, USA(Fonarow et al.,	48612	52	73	NR	NR	NR	NR	NR	NR	NR	NR	39							3.8

2007b)																			
ADHERE,INDONESIA(Siswanto et al., 2010)	1687	64.5	60	74	54.8	31.2	NR	NR	NR	NR	NR	37.9	54.8	NR	NR	NR	23.3	7.1	6.7
JCARE-CARD, JAPAN(Tsuchihashi-Makaya et al., 2009)	2675	40.3	71	37.7	52.9	29.9	NR	24.8	20.8	11.7	87.5	42.2	24.6	21.9	15.7	NR	32	NR	NR

*M= mortality, **NR=Not reported, EF= ejection fraction, NYHA= New York Heart Association, CKD= Chronic Kidney Disease, HHF= Hypertensive Heart Failure, DCM= Dilated Cardiomyopathy, VHDX= Valvualr Heart Disease, RHF= Right heart failure, IHD= Ischemic Heart Disease, LOS =Length of Stay in Hospital, M= Miscellaneous

In chapters five and six we sought for the first time to determine the short and medium term outcome of acute heart failure in the city.

The group of subjects who were presenting with acute HF for the first time (Denovo acute HF) was followed up for six months. The mean length of hospital stay was 10.5days. There were 23 deaths while 20 subjects were lost to follow-up. At one month, 4.2% of the subjects had died. This increased to 7.5% at the end of six months. 13.9% of the subjects were readmitted at 6months.

Hypertensive HF patients had the best survival rates while those with pericardial diseases had the highest early mortality. Mortality was associated with female gender, being single, lower blood pressure, higher heart and respiratory rates and higher body temperature. Anaemia, higher creatinine levels, higher while cell count, left atrial diameter, higher NYHA class and valvular dysfunction were also associated with higher mortality.

We also sought to explore the predictors of rehospitalization in patients admitted with denovo acute HF. We observed that about 1.53% and 12.2% of this category of HF subjects were readmitted at 30days and 6-months respectively. Factors associated with rehospitalization, include presence of atrial fibrillation, valvular dysfunction, renal dysfunction, age ≥60yrs female gender and body mass index. After adjusting for possible confounders, only female sex and BMI <19kg/m^2 were the independent predictors of rehospitalization during the 6month follow-up period.

A detailed study of the commonest aetiological risk factor- Hypertensive heart failure was also carried out and reported **(Chapter 7)**.

Chapter 6: Short- and medium-term outcomes after acute HF in Abeokuta, Nigeria.

Published paper 2

- **Ogah OS, Stewart S, Falase AO, Akinyemi JO, Adegbite GD, Alabi AA, et al. Short-term outcomes after hospital discharge in patients admitted with heart failure in Abeokuta, Nigeria: Data from the Abeokuta Heart Failure Registry. Cardiovascular journal of Africa. 2014 Sep 10;25:1-7. PubMed PMID: 25210973.**

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Cardiovascular Topics

Short-term outcomes after hospital discharge in patients admitted with heart failure in Abeokuta, Nigeria: Data from the Abeokuta Heart Failure Registry

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Abstract

Background

Compared to other regions of the world, there is paucity of data on the short-term outcome of acute heart failure (AHF) in Africa's most populous country - Nigeria. We examined six-month outcome (including case-fatality) in patients admitted with HF to a tertiary hospital in Abeokuta, Nigeria.

Methods and Results

A standardized clinical registry captured data on 309 consecutive subjects hospitalized with AHF. These were followed up for at least 180 days (mean follow up period was 205 days). There were 285 subjects with de novo AHF and 24 individuals with decompensated or acute-on-chronic HF. The former were analysed for short-term outcome. Of the 285 individuals with de novo AHF, there were 150 men (52.6%) and 135 women. Mean overall body mass index was 24.0±5.3 kg/m^2 (24.1±5.0 and 23.7±5.5kg/m^2 for men and women, respectively). Mean systolic and diastolic blood pressure were 136.6±30.0 and 87.2±19.1mmHg in men and women, respectively. Women were less likely than men to have formal education (26.0 versus 43.7%), and more likely than men to have never smoked (96.3% vs. 68.7%).

They were also less likely to present with hypertension (77.0% versus 85.3%), diabetes mellitus (12.6 versus 16.7%) and report a family history of heart disease (9.1 versus 12.5%). Most subjects presented in NHYA class III (75.4%).

Mean LoS was 10.5 ±5.9 days. Intra-hospital mortality was 4.2% overall and 4.0% and 5.2% for men and women respectively. Mean follow up was 205 days. Case fatality at 30-days was 4.2% (95%CI, 2.4-7.3%) for the whole cohort comprising 3.9% (95%CI, 1.7-8.5%) in men and 4.5% (95%CI 2.1-9.3%) in women. At 180-days, case-fatality was 7.3% (95%CI, 4.7-11.2%) comprising 7.1% (95%CI, 3.8-12.7%) in men and 7.5% (95%CI 3.9-14.0%) for women. Patients with pericardial diseases had the highest early mortality

which thereafter stabilized. At 180 days, 20.0% of the subjects were re-hospitalised at least once (20.7%for women and 19.3% for men).

Mortality was related to some socio-demographic and clinical characteristics.

Conclusions

The characteristic of HF population in Nigeria is different from similar populations in high income countries. Our patients were younger and have non-ischemic etiological risk factors for HF especially hypertensive heart disease. Mortality is also similar with many of the same clinical correlates of outcomes.

6.1 Introduction

Heart failure (HF) , has emerged as a global epidemic in at risk populations, including those living in high income countries and, as recently described, in low-to-middle income regions of the world such as sub-Saharan Africa.(Damasceno et al., 2012, Al Suwaidi et al., 2012, Santhanakrishnan et al., 2013) Whilst there are well-established HF registries to capture both the characteristics and health outcomes among those hospitalized with acute heart failure (AHF) in Europe(Oliva et al., 2012, Nieminen et al., 2006a), North America(Adams et al., 2005a, Fonarow et al., 2007b) and the Asia-Pacific Region(Sato et al., 2013, Tsutsui et al., 2006b, Santhanakrishnan et al., 2013) there are few reports from sub-Saharan Africa. This includes Nigeria (the most populous country in the region), where HF has emerged as a potentially large public health problem.(Damasceno et al., 2012) Although there have been many therapeutic gains in the management of chronic HF(Scott and Jackson, 2013) leading to improved overall survival rates(Scalvini and Giordano, 2013), there has been very little parallel success (pending further evaluation of the recently reported RELAX Trial(Teerlink et al., 2013)) in respect to AHF. This is particularly important when one considers the high proportion of patients who still require hospitalization for acute HF and associated high levels of in-patient case-fatality and poor short-to-medium term health outcomes.

6.1.1 Study aims

Given the paucity of data describing health outcomes in unselected patients hospitalized with AHF in Nigeria (and indeed wider Sub-Saharan Africa), we examined short (30 day) to medium-term outcomes (180 days) in consecutive patients recruited into the Abeokuta HF registry over a period of 6 months. Standardized data collected via the registry were used to both describe the baseline characteristics of the cohort and identify correlates of mortality during 6 month follow-up.

6.2 Materials and methods

The Abeokuta HF registry is a prospective observational study which consecutively recruited all patients admitted for HF from January 1, 2009 to December 31, 2010. Subjects were enrolled if they were admitted for new onset HF (de novo HF) or worsening of chronic HF (decompensated HF). The main objective of the registry was to characterize the current profile of HF in the community. It was also aimed at determining the mode of care as well as intra-hospital and six months outcomes. Clinical information relating to the socio-demography, medical history, signs and symptoms, medications, results of laboratory investigations including 12 lead ECG and echocardiography were collected. A uniform and standardized case report form was used for data collection. Home addresses and telephone contacts of the subjects as well as their next of next of kin were also collected for study follow-up.

6.2.1 Clinical assessment

Subjects were weighed without shoes and in light clothing using a standard beam balance. Anthropometric plane was used for height measurement to the nearest centre. Body mass index (BMI) was calculated using standard formula. Blood pressure (BP) measurements were done according to international guideline(1999b) with the use of mercury sphygmomanometer (Accousson, London). We defined anaemia as haemoglobin concentration of less than 10g/dl. The modification of diet in renal disease (MDRD) formula (Levey et al., 1999) was used for the estimation of glomerular filtration rate (eGFR); an eGFR value of < 60ml/min/1.73m^2 was the criteria used for defining moderate to severe renal dysfunction.(Stewart et al., 2008)

6.2.2 Diagnosis of HF

A clinical diagnosis of HF was made by the attending Cardiologist based on the Framingham criteria.(McKee et al., 1971) Using recently updated guidelines of the European Society of Cardiology (Dickstein et al., 2008), subjects were categorized into de novo presentation as well as recurrent presentation of typically decompensated HF (i.e. acute-on-chronic HF).

6.2.3 12 lead ECG and Echocardiography

Standard 12-lead resting ECG were recorded for each patient using a Schiller ECG machine (Schiller AG, Switzerland). All ECGs were performed at rest by trained nurses/technicians and analysed by a reviewer who was blinded to the clinical data of the patients. Echocardiography was performed on the subjects with the use of an Aloka SSD – 4000 echocardiography (Aloka Co. Ltd, Tokyo, Japan). Standard views and 2D-guided M-mode measurements were obtained according to international guidelines. Aortic root and left atrial diameter, LV internal dimensions and wall thicknesses were obtained according to ASE criteria. Measurements were obtained in up to three cycles and averaged. One experienced Cardiologist (OSO) performed all the procedures. The intra-observer concordance correlation coefficient and measurement errors from our laboratory have been reported previously.(Ogah et al., 2006a) The formula of Devereux and Recheck was used for LV mass calculation.(Devereux and Reichek, 1977a) Increased relation wall thickness (RWT) was defined as RWT >0.43.(Roman et al., 1995) The different patterns of LV remodelling were defined according to international guideline.(Ganau et al., 1992) Impaired LV systolic function was defined as left ventricular ejection fraction (LVEF) of <50%. Transmitral flow velocities, deceleration time and isovolumic relation time were obtained using standard methods.(Nishimura and Tajik, 1997) Tissue Doppler Imaging (TDI) was applied only to identify true pseudo normalized filling pattern.

6.2.4 Follow-Up

The study cohort was prospectively followed up for 6 months post index hospitalisation. The subjects were contacted through clinic visit or telephone calls at one, three and six months. Information obtained during follow-up included their wellbeing, prescribed pharmacotherapy, history of re-hospitalization and deaths (from next of kin). In addition to patient or relation's telephone interviews, where necessary referring physicians were contacted for additional information.

6.2.5 Health outcomes

The following health outcomes were documented - 1) length of initial hospital stay (LoS) in days, 2) survival status on discharge (dead or alive), 3) short-term case-fatality (30 days), 4) medium-term case-fatality (180 days), 5) re-hospitalization status (180 days) and 6) event-free survival from readmission or death.

6.2.6 Ethical consideration

The study was reviewed and approved by the institution's ethics review board. All the subjects gave informed consent and the study was carried out in accordance with the declaration of Helsinki.(Rits, 1964)

6.2.7 Statistical Methods

Continuous variable are presented as mean and standard deviations (SDs) or medians with their 25^{th} and 75^{th} percentiles when the distribution of the data does not follow Gaussian distribution. Categorical variables are displayed as frequencies and proportions. Group comparison was done with the student's t-test and Chi square statistics was used for comparison of categorical variables. Survival function estimates was performed using the Kaplan-Meier method and the difference were tested using log-rank test. The follow up was censored at 6 months post admission. Subjects who died within the period of six months constituted the event of interest for purpose of survival analysis while those still alive or lost to follow up were treated as censored. In the survival analysis, censoring meant that the outcome of interest has not been observed. All demographic and clinical profiling variables (see Tables 1 and 2) were examined, on a univariate basis, as potential correlates of death during 180 day follow-up in those who survived the index hospitalisation. Given the small number of fatalities overall, multivariate analyses were not performed. Where appropriate, results are expressed as odds ratio (OR) with their 95% Confidence Intervals (95% CI). Data was entered into EpiData software (The EpiData Association, att.

Jens Lauritsen, Enghavevej 34, DK5230 Odense M, Denmark) was used for data entry while SPSS version 15 (and Stata version 11.1) was used for data cleaning and analysis.

6.3 Results

Three hundred and nine (309) subjects were followed up for 6-months after discharge from the index hospital admission.**Figure 6.1** is a flow chart showing the recruitment and main outcome of the subjects. The cohort comprised 285 (92%) de novo cases of AHF and 24 cases of decompensated HF (acute-on chronic HF). The later were excluded in the final analysis.

Two hundred and forty two patients with de novo AHF were known to be alive after 6-months, 23 were known to have died while the remaining twenty were lost to follow-up. Those lost to follow up did not come for follow up after the first admission, they or their relations did not have telephone contacts or they gave addresses that were difficult to assess.

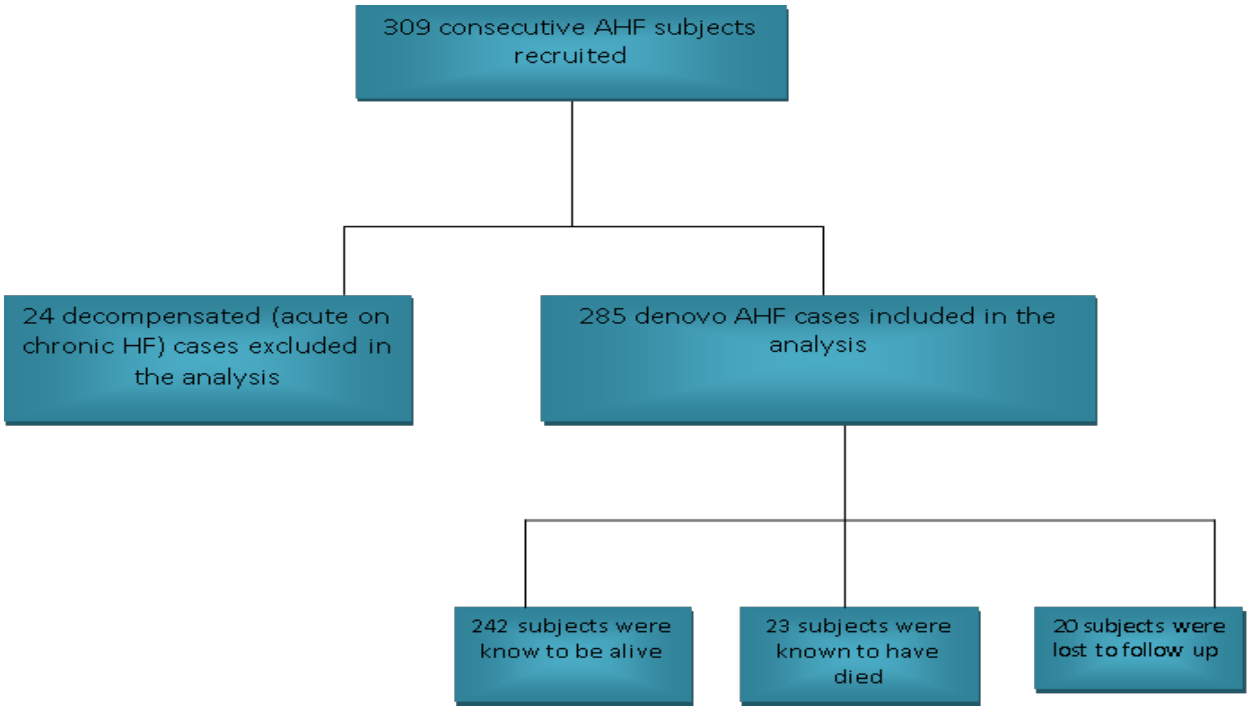

Figure 6.1. Flow chart showing the recruitment of the subjects

6.3.1 Clinical and demographic profile of the subjects

Table 6.1 summarises the clinical and demographic profile of the study cohort**.** Overall, there were 150 men (52.6%) and 135 (47.4%) were women. The mean age for the cohort was 56.3±15.6 years (57.0±13.6 and 55.4±17.6 years for men and women respectively.) Just fewer than 50% of subjects were aged ≥60 years, one third did not have any form of formal education while two thirds were married. A small minority were unemployed and three quarters were urban residents. Mean overall BMI was 24.0±5.3 kg/m^2 (24.1± 5.0 and 23.7± 5.5kg/m^2 for men and women respectively) and mean systolic and diastolic BPs were 136.6±30.0 and 87.2±19.1 mmHg, respectively.

Women were less likely than men to have formal education (26.0 versus 43.7%), and have a current/past history of smoking (68.7 versus 96.3%). They were also less likely to present with hypertension (77.0% versus 85.3%), diabetes mellitus (12.6 versus 16.7%) and report a family history of heart disease (9.1 versus 12.5%).

On the other hand, men were more likely to present with hypertension (85.3 versus 77.0%) and chronic obstructive pulmonary disease (7.3 versus 6.7%) but less likely to be suffering from chronic osteoarthritis (21.3 versus 32.6%). Most subjects were in NHYA class III (75.4%) on presentation; the majority being in either NYHA class III or IV (91.5%).

Table 6.1. Demographic and clinical profile Characteristics of the cohort

Variable	All(n=285)	Men(n=150)	Women(n=135)
Sociodemographic variables			
Age (years)	60.0±13.2	57.0(13.6)	55.6(17.3)
Age >60yrs	46.3%	48.7%	43.7%
No education	98(34.4)	39(26.0)	59(43.7)
% Married	156(67.8)	92(73.0)	64(61.0)
Unemployed	7(2.5)	1(6.7)	6(4.4)
Urban residence	216(75.8)	113(75.3)	103(76.5)
Risk factors and co-morbidities			
Never smoked cigarette	233(81.8)	103(68.7)	103(96.3)
Current alcohol use	17(6.0)	14(9.3)	3(2.2)
Diabetes mellitus	37(13.0)	19(12.7)	18(13.3)
Hypertension	232(81.4)	128(85.3)	134(77)
COPD	20(7.0)	11(7.3)	9(6.7)
Arthritis	76(26.7)	32(21.3)	44(32.6)
Family history of Heart Disease	25(8.8)	9(6.0)	16(11.9)
Clinical/Laboratory parameters			
NYHA Class			
Class II	24(8.4)	16(10.7)	8(5.9)
Class III	215(75.4)	107(71.3)	108(80.0)
Class IV	46(16.1)	27(18.0)	19(14.1)
Cough	254(89.1)	129(86.0)	125(92.6)
Dyspnoea	275(96.5)	145(96.7)	130(96.3)
Orthopnoea	234(82.1)	123(82.0)	111(82.2)
PND	244(85.6)	129(86.0)	115(85.2)
Leg oedema	228(80.0)	121(80.7)	107(79.3)
Palpitation	148(52.1)	77(51.7)	71(52.6)
Basal crepitation	239(83.9)	129(86.0)	110(81.5)
Elevated JVP	229(80.4)	124(82.7)	105(77.8)
Third heart sound	207(72.6)	111(74.0)	96(71.1)
Tender hepatomegaly	204(71.6)	99(66.0)	105(77.8)
Body weight (kg)	66.9±15.4	66.9(13.9)	61.1(14.5)
Height (cm)	162.8±8.1	166.7(7.5)	160.3(6.1)
BMI(kg/m^2)	25.2±5.7	24.1(5.0)	23.7(5.5)
Systolic BP(mmHg)	131.9±25.1	137.9(30.0)	133.3(27.9)
Diastolic BP(mmHg)	85.4±15.9	89.0(19.6)	85.3(17.1)
Pulse pressure(mmHg)	46.5±15.7	49.0(19.0)	47.7(16.6)
Temperature (^oC)	36.3±0.6	36.4±0.8	36.4±0.8
Respiratory rate (c/min)	30.2±6.5	28.5±6.4	27.9±6.7
Pulse rate (bpm)	95.9±16.7	96.2±18.2	96.3±
Packed cell volume (%)	35.9±7.8	37.5±7.2	36.8±7.7
Total white cell count ()	6.4±2.9	7.3±3.7	7.4±3.8
% Lymphocytes	37.9±11.1	36.7±12.7	36.1±12.9

Serum Sodium (mmol/l)	136.5±6.4	135.9±6.7	136.3±6.1
Serum potassium(mmol/l)	3.7±0.8	3.7±0.8	3.6±0.8
Total Cholesterol(mg/dl)	162.5±53.3	157.7±84.0	181.2±64.6
Serum Glucose(mg/dl)	111.7±53.2	115.6±50.6	114.0±58.5
Serum Urea(mg/dl)*	38.5±30.0	50.5±51.4	36.1±29.7
Serum Creatinine(mg/dl)*	1.8±0.4	1.7±2.5	1.2±1.4

Table 6.2 shows the laboratory profile, aetiological risk factors and discharge medications.

Serum urea and creatinine were significantly higher in men compared to women. Except for peripartum cardiomyopathy (PPCM), the aetiological risk factors were similar in men and women. Hypertensive heart disease was responsible for the majority (75.8%) of cases of HF. Other causes (all <10% of cases) included dilated cardiomyopathy, cor-pulmonale, pericardial disease and rheumatic heart disease; with PPCMO, thyroid heart disease, coronary artery disease and endomyocardial fibrosis being responsible for a minority of cases. Discharge medications were similar in men and women except for beta blockers which were more commonly prescribed more in men.

Table 6.3 depicts the 12-lead ECG and echocardiographic parameters according to gender.

Men had higher mean absolute QT intervals, left atrial area, left ventricular internal dimensions as well as absolute and indexed LV mass.

Table 6.2. Aetiology of HF and discharge medications in the 285 subjects

Variable	All	Men	Women
Aetiology of HF (n/%)			
Hypertension	216(75.8)	119(79.3)	97(71.9)
Dilated Cardiomyopathy	24(8.4)	16(10.7)	8(5.9)
Cor pulmonale	16(5.6)	9(6.0)	7(5.2)
Pericardial Diseases	9(3.2)	1.(0.7)	8(5.9)
Rheumatic Heart Disease	7(2.5)	4(2.7)	3(2.2)
Peripartum Cardiomyopathy	6(2.1)	0(0.0)	6(4.4)
Thyroid Heart Disease	3(1.1)	0(0.6)	3(2.2)
Ischemic Heart Disease	1(0.4)	1(0.7)	0(0.0)
Adult Congenital Heart Disease	1(0.4)	0(0.0)	1(0.7)
Endomyocardial Fibrosis	2(6.7)	0(0.0)	2(0.7)
Type of Heart Failure			
Systolic Heart Failure (%)	66.4	71.4	60.9
Heart Failure with normal EF (%)	33.6	28.6	39.1
Medications (n/%)			
Loop diuretics	249(87.4)	132(88.0)	117(86.7)
Digoxin	219(76.8)	114(76.0)	105(77.8)
ACEI/ARBs	281(98.6)	148(98.7)	133(98.5)
Beta-blockers	56(19.6)	35(23.3)	21(15.6)
Spironolactone	247(86.7)	133(87.3)	116(85.9)
Hydrallazine/Isosorbide	33(11.7)	19(12.9)	14(10.4)
Amiodarone	5(1.8)	4(2.7)	1(0.7)

Table 6.3. 12-lead ECG and echocardiographic profile according to gender

Variable	All(n=285)	Men(n=150)	Women (n=135)
Ventricular rate (beats/min)	96.3±22.5	94.3±17.3	101.3±21.8
QRS duration (ms)	116.0±26.2	117.1±24.5	107.8±41.1
QT Interval (ms)	350.7±30.6	374.3±35.0	348.8±45.5
Corrected QT(ms)	442.0±20.9	462.2±38.2	447.6±36.2
Atrial fibrillation (%)	13.3	16.7	9.6
Aortic root diameter(cm)	3.2±0.6	3.26±0.58	2.84±0.38
Left atrial diameter(cm)	5.9±0.8	4.75±0.89	4.50±0.85
Left atrial area (cm^2)	30.15± 9.91	28.8±9.0	24.7±6.3
IVERSUSD(cm)	1.18±0.28	1.33±0.39	1.23±0.32
LVPWd(cm)	1.38±0.35	1.19±0.39	1.10±0.35
LVIDd(cm)	5.52±0.97	5.81±1.61	5.16±1.45
LVISs(cm)	4.51±1.57	4.80±1.63	4.16±1.43
Fractional shortening (%)	14.5±2.97	17.77±13.10	19.80±12.21
Ejection fraction (%)	36.8±6.53	40.57±23.61	45.12±20.11
E-wave (m/s)	0.70±0.24	0.82±0.28	0.84±0.32
A-wave (%)	0.41±0.17	0.49±0.23	0.56±0.28
E/A ratio	2.11±1.55	2.14±1.47	1.90±1.25
DT(ms)	145.8±59.2	144.2±58.3	147.9±60.5
IVRT(ms)	111.0±34.3	114.9±35.8	106.1±32.1
LV Mass (absolute)	449.0±217.5	561.7±106.6	233.0±54.24
LV Mass (indexed)	274.1±117.5	336.4±46.6	160.9±16.1
Mitral Regurgitation (%)	19.6	18.7	20.7
Tricuspid regurgitation (%)	15.1	12.7	17.8

6.3.2 Intra-hospital and follow up outcomes

Mean LoS was 10.5 ±5.9 days, with women having slightly longer hospitalisations than men (10.0±6.3 and 11.0±5.4 days). Intra-hospital mortality was 4.2% overall and 4.0% and 5.2% for men and women respectively. Mean follow up was 205 days. Case fatality at 30-days was 4.2% (95%CI, 2.4-7.3%) for the whole cohort comprising 3.9% (95%CI, 1.7-8.5%) in men and 4.5% (95%CI 2.1-9.3%) in women. At 180-days, case-fatality was 7.3% (95%CI, 4.7-11.2%) comprising 7.1% (95%CI, 3.8-12.7%) in men and 7.5% (95%CI 3.9-14.0%) for women. Patients with pericardial diseases had the highest early mortality which thereafter stabilized. Those diagnosed with hypertensive HF subjects had the best survival profiles **(Figure 6.2, Figure 6.3).** At 180 days, 20.0% of the subjects were re-hospitalised at least once (20.7% for women and 19.3% for men).

Characteristics of subjects that died

Table 6.4 shows the univariate correlates of survival in the cohort. Increased likelihood of case fatality was associated with NYHA classes III and IV, higher total white cell count, renal impairment, higher E/A ratio, larger LA diameter or area and presence of tricuspid regurgitation.

Higher systolic blood pressure was associated with better prognosis.

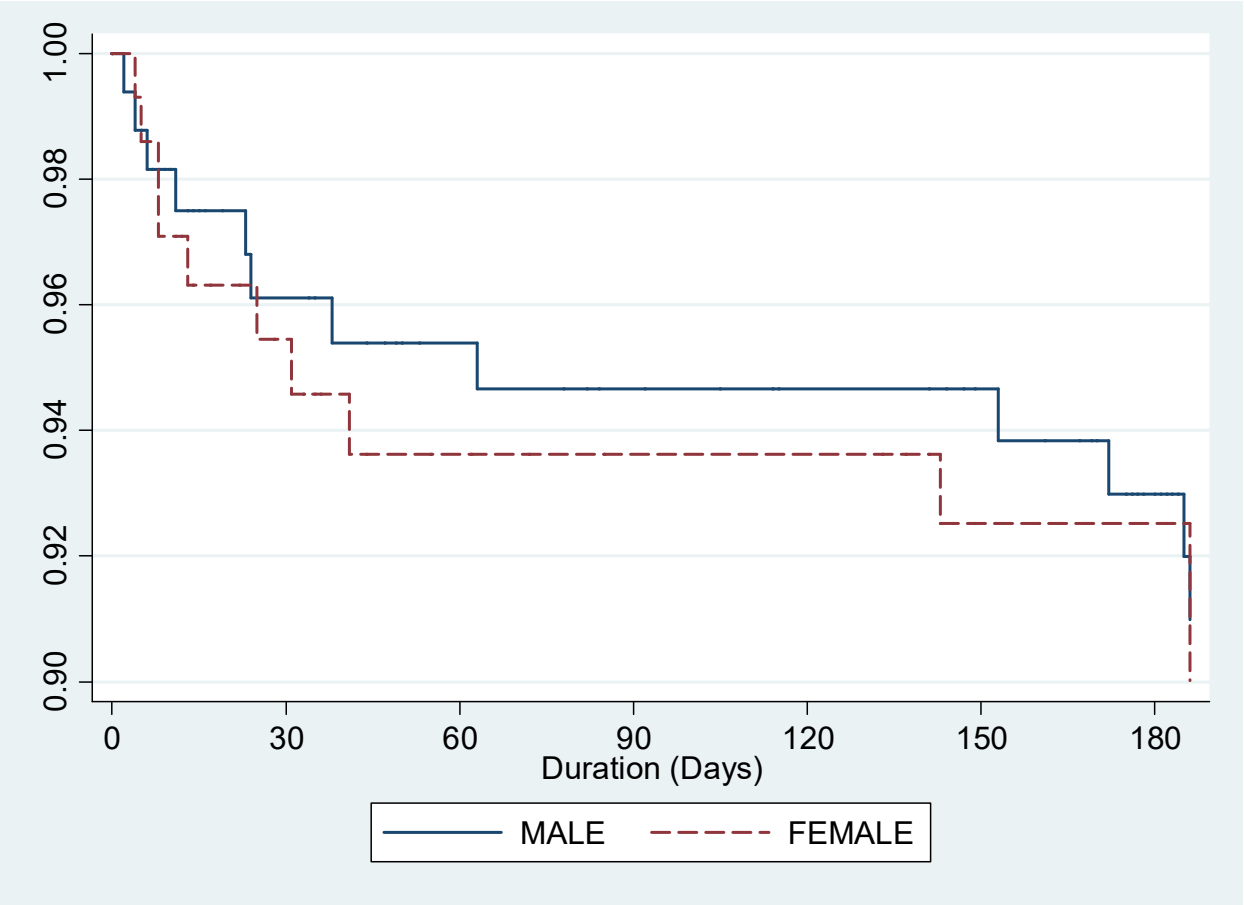

Figure 6.2. Kaplan-Meier survival curve for males and females

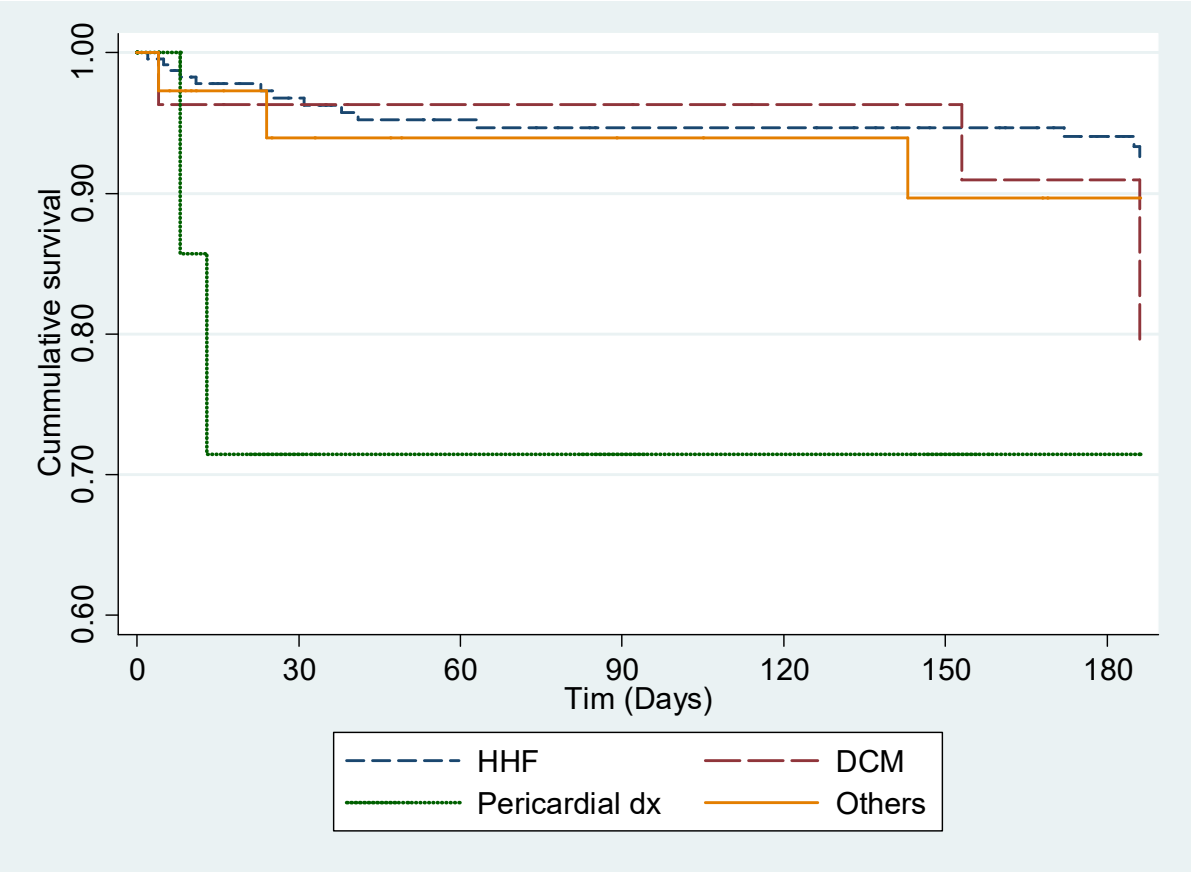

Figure 6.3. Kaplan-Meier survival curve for the different etiological risk facto

Table 6.4. Clinical and demographic predictors of outcome on univariate analysis (6 months survival)

Variable	All (n=285)	Alive(258)	Dead(23)	OR	95% CI	P-VALUE
Age (years)	**57.3**±15.4	57.4±14.0	57.2±19.1	0.99	0.96-1.01	0.324
Female gender(%)	52.6%	54.5%	50%	1.14	0.48-2.70	0.764
No education(%)	33.3%	32.8%	30.0%	0.77	0.26-2.28	0.635
Not married (single)(%)	67.8%	69.6%	52.9%	1.51	0.56-4.07	0.417
Body mass index	24.0±5.4	23.7±4.9	23.4±3.6	0.97	0.87-1.08	0.580
Non-smoker(%)	81.8	82.3%	85.0%	1.51	0.43-5.34	0.521
Alcohol use(%)	6.0%	5.6%	5.0%	0.79	0.32-1.95	0.609
Presence of Diabetes(%)	13.0%	13.1%	10.0%	0.65	0.14-2.92	0.574
Temperature(oC)	36.4±0.8	36.4±0.9	36.4±0.7	1.31	0.65-2.62	0.449
Respiratory rate(cpm)	28.3±6.2	28.0±6.6	29.2±5.3	1.02	0.96-1.08	0.639
Heart rate (bpm)	95.5±17.1	95.0±17.4	100.5±15.9	1.00	0.97-1.03	0.846
Systolic blood pressure(mmHg)	136.1±29.4	137.3±27.7	122.5±20.0	0.98	0.96-6.99	0.017
Diastolic blood pressure(mmHg)	87.1±29.4	88.6±18.7	80.0±13.4	0.98	0.95-1.00	0.085
Pulse pressure>30mmHg	3.3%	2.1%	5.0%	0.42	0.16-1.10	0.078
NYHA (III & IV)(%)	91.5	90.4	95.0	4.03	1.53-10.65	0.005
Serum Sodium (mmol/l)	136.9±4.6	136.0±6.4	137.2±7.4	1.03	0.96-1.11	0.428
Serum Potassium(mmol/l)	3.7±0.5	3.6±0.7	4.0±1.0	1.64	0.72-3.75	0.243
Blood glucose (mg/dl)	112.3±56.0	117.0±58.5	111.8±58.5	1.00	0.99-1.01	0.501
Packed cell volume (%)	41.0±7.6	37.6±7.0	32.2±8.4	0.92	0.86-0.97	0.004
Total white cell count	6.8±3.1	6.9±3.4	9.2±5.1	1.13	1.02-1.25	0.024
% Lymphocytes	42.9±4.1	36.7±12.3	37.5±16.7	1.02	0.98-1.06	0.432
Serum Creatinine(mg/dl)	0.8±0.3	1.2±1.0	2.1±2.5	1.38	1.04-1.83	0.024
QRS duration (ms)	107.1±9.4	110.3±29.5	110.9±32.2	1.01	0.99 – 1.03	0.171
Corrected QT (ms)	439.4±40.9	449.3±34.4	457.3±34.6	1.01	0.99-1.04	0.173
Atrial fibrillation(%)	13.3%	14.6%	20.0%	1.14	0.36-3.55	0.827
E/A ratio	2.2±1.0	2.1±1.3	2.7±1.6	1.40	0.99-1.97	0.060
Left atrial area(cm^2)	26.2±6.7	26.8±7.5	34.2±12.1	1.11	1.01-1.21	0.025
Left atrial diameter (cm)	4.8±0.9	4.6±0.9	5.0±1.1	1.56	0.94-2.60	0.084
LVID(cm)	5.47±1.55	5.6±1.5	5.7±1.2	1.11	0.74-1.67	0.614
HF with systolic dysfunction	66.4%	67.5%	70.6%	0.66	0.27-1.59	0.356
MR(Yes)(%)	19.6%	20.2%	25.0%	1.34	0.50-3.60	0.562
TR(Yes)(%)	15.1%	13.1%	35.0%	2.64	1.00-6.95	0.050

6.4 Discussion

Our data is the first detailed study of clinical profile and short-term outcome of HF in southern Nigeria. The key findings from the study are that HF in our community is a problem of young and middle aged individuals who are in the prime of their lives. Majority presented with de novo AHF and hypertensive heart disease and other non-ischaemic aetiology contributing over 90% of the cases. The use of some disease modifying agents such as beta blockers and nitrate therapy is low although ACE inhibitors or ARBs and aldosterone antagonists are used very frequently. The mortality rates in the short to medium term are relatively low and higher in women than in men but this was not statistically significant. We also noted that socio-demographic and clinical variables are related to mortality.

Our finding of the relative young age at presentation of AHF is similar to reports from many parts of Africa. AHF patients in the continent are about 20 years younger than similar patients in high income countries with a mean age ranging from 40 to 57 years.(Soliman and Juma, 2008, Dzudie et al., 2008) The high frequency of de novo cases is higher than the values in registries in Europe and America which ranges from 24% in the ADHERE registry(Adams et al., 2005a) to 44% in the Italian HF registry.(Tavazzi et al., 2006) A high frequency of de novo HF has been reported from Japan in the ATTEND registry (63%)(Sato et al., 2010) and (64.7%) in the Acute Heart Failure Database (AHEAD) registry. Randomized controlled trails have shown that ACEIs(1987), ARB(McMurray et al., 2003), and beta-blocker(1999a) can improve survival in patients with HF. Furthermore, the African-American Heart Failure trial has shown the efficacy of hydrallazine-isosorbide combination in the treatment of HF in blacks.(Taylor et al., 2004)

The high rate of use of diuretics, ACEI/ARBs and aldosterone antagonists is similar to findings in many parts of the world. On the other hand the rate of use of beta-blockers falls short of the findings from Europe and America.(Fonarow et al., 2007b) (Cowie et al., 1999, Okin et al., 1996,

Adams et al., 2005a) One of the important findings is the comparable or even lower short-term mortality rate of HF in our cohort compared to findings in the advanced countries. Mortality rates were 4.2% (95%CI, and 7.3(95%CI; I4.7-11.2%) at 30 days and 180 days respectively. In our study demographic and clinical variables were also noted to affect short term out-come although many of the variables did not reach statistical significance probably because of the short term follow-up and few fatalities recorded. Unlike finding in advanced countries (Adams et al., 2008, Okin et al., 1996), we noted that age was not associated with poorer outcome in our cohorts. Our finding of better prognosis in obese individuals is similar to the findings of other workers (Cowie et al., 1999, Okin et al., 1996). In the Framingham study, high BMI was associated with better prognosis (HR for mortality per 1SD: 0.88, 95CI =0.75-1.04 for men and 0.86, 95%CI= 0.72-1.03 for women) This is also consistent with the "obesity paradox" in HF.(Arena and Lavie, 2010, Ballo et al., 2013, Komukai et al., 2012) Underweight in HF patients may be indicative of cardiac cachexia and progression of HF and poor prognosis. Lower BP or pulse pressure was associated with poorer outcome. This may reflect advanced HF and decreased stroke volume. This has been noted by previous workers (Senni et al., 2013, Adams et al., 2008). It is now well known that impaired renal function is an independent risk factor for all-cause mortality in HF (Damman et al., 2009, Ghali et al., 2009, Hillege et al., 2006). This is also same in this study. Patients with renal impairment often develop cardio-renal syndrome which is caused by low cardiac output. These patients often develop multiple alterations at the vascular level leading to endothelial dysfunction, coagulation abnormalities, insulin resistance, hyperhomocystinemia and activation of the sympathetic nervous system as well as the renin-angiotensin and aldosterone system. They are prone to unstable HF and susceptible to high catecholamine levels. Furthermore HF patients with renal dysfunction are also less likely to receive proven medications for HF. Lower serum sodium or potassium was associated with better prognosis in this study. This is contrary to most reports from the Western world, although in a Polish study, Biegus et al (Fonarow et al., 2007b) had showed that lower serum potassium was associated with better outcome. This may be related to better response to diuretics in the survivors leading to the

electrolyte derangement. It may also be speculated that sodium may play a lesser role in the pathophysiology of HF in our setting. Hypertension may be associated with relatively less neuro-hormonal activation than ischemic heart disease which is the commonest risk factor for HF in the developed counties of Europe and North America. We observed also that left atrial size, left atrial volume , left ventricular size, higher e/a ratio and presence of mitral and tricuspid regurgitation were associated with poorer outcome. This has been well recognized by earlier workers. Left atrial or ventricular size reflects left atrial or ventricular pressure and volume overload and the severity and duration of increases LV filling in response to cardiac function abnormality associated with HF(Benjamin et al., 1995).

The plausible reasons for the younger age of presentation of HF in our study and many parts of Africa may be related to the aetiology of the condition which are conditions that present in young and middle age. In additions hypertension and related target organ damage present at younger age in Africans and people of African descent. The dominance of de novo presentations in our cohort may be related to poorer long-term outcome of HF in our setting such that few people are living with chronic HF. Another reason is because of poor or inadequate health education; most often patients do not keep to one health facility when they have chronic illnesses such as HF. They often move from one facility to another (including alternative healthcare facilities) seeking for cure. Low mortality in our cohort may be related to the fact that the study was conducted in a cardiology unit and may not reflect what happens in a general medical ward or in private practice in the country. The clinical characteristics of our patients may also be explanatory. Our subjects are younger compared to the typical patients with HF in the Western world who are generally elderly. The average length of hospital stay is longer in our setting (9 days) compared to 6.1 days in the US(Cowie et al., 1999) and nine days in Europe(Adams et al., 2005a). However it is shorter than 21 days reported from Japan (Redfield et al., 2012). It is possible that longer stay in hospital affords patients the opportunity to recover well and get used to medications for HF. Mortality from HF is generally better in Japanese patients compared to other advanced countries. Furthermore it is also

possible that etiology of HF in our cohort could have affected the outcome. Hypertension is predominantly the major risk factor for HF in our cohort. Ischemic heart disease is relatively uncommon. It is well known that mortality rates from CAD are generally worse than those with non-ischemic heart disease. Mitchell et al(Mitchell et al., 2008) reported a total mortality rate of 30% at 3 years in the placebo group of ischemic HF compared to a rate of 15% in the non-ischemic HF group. The poorer outcome of women in our study may be because the women were less educated and more likely to be unemployed and dependent than the men and may not be able to pay for HF medications. Clinic follow up may also be poorer in the women. The main etiological factors for HF in our cohort are non-ischemic in origin with hypertensive heart disease responsible for over 75% of cases. It may be reasonable to suggest that applying guidelines derived from clinical trials in the Western world where the majority of HF are ischemic in origin may be in-appropriate in our population.

6.4.1 Limitations

Our study is a single centre hospital based study and conducted in a cardiology unit and, therefore, may not have captured all the patients with HF in the city during the study period although many referrals were received from surrounding hospitals and clinics during the period due to the awareness that was created for the study. The findings of the study may not be extrapolated to the general population or the practice in other Nigerian hospitals. A national HF registry is needed as has been done in many countries. The use of the Framingham criteria as a screening tool may have missed some patients especially the elderly with HF as the criteria is not sensitive in this population. Due to cost consideration, our subjects did not have NT-proBNP levels done as this has not become a routine practice in the country. NT-proBNP has been shown to be a strong predictor of prognosis in HF.(Adlam et al., 2005) Other prognostic variables such as exercise capacity ($Vo_{2\ and}$ 6-minute walk) were not assessed in our patient. Some of our patients were lost to follow up and may have affected the survival information in this study. However the rate of attrition is similar to other follow up studies. This is complicated by the fact that there is no effective national death registry in the

country. We also could not ascertain the exact cause of death for patients who died outside the hospital environment.

6.4.2 Conclusions

The characteristic HF population in Nigeria is different from similar populations in high income countries. Our patients are about 20-years younger and have non-ischemic etiological risk factors for HF especially hypertensive heart disease. Mortality is similar to findings in many countries and has some similar clinical and laboratory prognostic factors.

Because hypertension is a major risk factor for HF in Abeokuta and in many parts of Nigeria, effort should be made at all levels on regular BP surveillance, treatment and control. Proactive application of agents that have been shown to be particularly effective in African populations or hypertensive subjects should be advocated. There is also need for the development of HF management programmes which at moment is not existent in the city.

Finally, there is need for a national HF registry in the Nigeria to better understand the characteristics, management and outcome of HF in the different regions of the country.

Chapter 7: Predictors of rehospitalisation in patients admitted with heart failure in Abeokuta

Published paper 3

- **Ogah OS, Stewart S, Falase AO, Akinyemi JO, Adegbite GD, Alabi AA, et al. Predictors of rehospitalization in patients admitted with heart failure in abeokuta, Nigeria: Data from the Abeokuta Heart Failure Registry. J Card Fail. 2014 Nov;20(11):833-40. PubMed PMID: 25175695.**

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Predictors of Rehospitalization in Patients Admitted With Heart Failure in Abeokuta, Nigeria: Data From the Abeokuta Heart Failure Registry

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ABSTRACT

Objective: We sought, for the first time, to examine the rate and predictors of hospital readmission in patients discharged after an episode of heart failure (HF) in Nigeria.

Methods: This was a hospital-based, prospective, observational study that used the data from the Abeokuta HF Registry.

Results: Overall, 1.53% (95% confidence interval [CI] 0.58−4.02) and 12.2% (95% CI 8.88−16.8) of patients were re-hospitalized at least once within 30 days and 6 months, respectively (5.3% had multiple readmissions); the latter comprised 21/138 men (15.2%) and 11/124 (8.9%) women. A total of 11 (4.2%) died (all of whom had been rehospitalized). Worsening HF (24 cases, 75%) was the commonest reason for readmission. Among others, factors associated with rehospitalization included presence of mitral regurgitation (odds ratio [OR] 2.37, 95% CI 1.26−4.46), age ≥60 years (OR 2.04, 95% CI 0.96−3.29), presence of tricuspid regurgitation (OR 1.77, 95% CI 0.86−3.61), and presence of atrial fibrillation (OR 1.34, 95% CI 0.59−3.03). However, on an adjusted basis, only female sex (adjusted OR 0.33, 95% CI 0.14−0.79; $P = .014$ vs male) and body mass index <19 kg/m^2 (adjusted OR 3.74, 95% CI 1.15−12.16; $P = .028$ vs ≥ 19 kg/m^2) were independent correlates of readmission during 6 months' follow-up.

Conclusions: HF rehospitalization within 6 months' follow-up occurred in ~12% of our cohort living an environment where HF etiology is predominately nonischemic and the HF population is relatively younger. Higher rates of readmission were noted in those with older age, lower body mass index, low literacy, lower serum sodium level, and presence of atrial fibrillation, renal dysfunction, and valvular dysfunction. (*J Cardiac Fail 2014;20:833−840*)

Key Words: Heart failure, rehospitalization, survival, outcome, predictors, Nigeria.

Abstract

Objective

We sought, for the first time, to examine the rate and predictors of hospital readmission in patients discharged after an episode of HF in Nigeria.

Methods

This was a hospital-based, prospective, observational study that used the data from the Abeokuta HF Registry.

Findings

Overall, 1.53% (95% CI, 0.58-4.02) and 12.2% (95%CI, 8.88-16.8) of patients, respectively, were re-hospitalized at least once within 30 days and 6 months (5.3% had multiple readmissions); the latter comprising 21/138 men (15.2%) and 11/124 (8.9%) women. A total of 11 (4.2%) also died (all of whom had been re-hospitalized). Worsening HF (24 cases, 75%) was the commonest reason for readmission. Among others, factors associated with rehospitalization include presence of mitral regurgitation (OR, 2.37; 95%CI, 1.26-4.46), age ≥ 60 years (OR, 2.04; 95%CI, 0.96-3.29), presence of tricuspid regurgitation (OR, 1.77; 95% CI, 0.86-3.61), and presence of atrial fibrillation (OR, 1.34; 95%CI, 0.59-3.03). However, on an adjusted basis, only female gender (adjusted OR 0.33, 95% CI 0.14-0.79; p=0.014 versus men) and body mass index <19kg/m^2 (adjusted OR 3.74, 95% CI 1.15-12.16; p=0.028 versus rest) were independent correlates of readmission during 6-months follow-up.

Conclusions

HF rehospitalization within 6-months follow-up occurs in about 12% of our cohort living in an environment where HF etiology is predominately non-ischemic and the HF population is relatively younger. Higher rates of readmission were noted in those of older age, lower BMI, low literacy, lower serum sodium level, presence of atrial fibrillation, renal dysfunction and valvular dysfunction.

7.1 Introduction

Heart failure (HF) affects over 23 million people worldwide.(Bui et al., 2011) In the United States of America (USA) alone, about 5.8 million people are affected and up to 2.4 million hospital admissions can be attributed to HF as primary or secondary diagnoses.(Roger et al., 2011) In Europe, over 60% of economic cost of HF is related to hospital admissions.(Stewart et al., 2001a) This is because HF is associated with high rates of recurrent hospitalizations and frequent clinic visits. HF in Nigeria and in most parts of Sub-Saharan Africa commonly afflicts people in the prime of their life, mostly due to non-ischemic origin especially hypertensive heart disease and patients often present late with severe symptoms.(Ogah et al., 2014a, Stewart et al., 2008, Damasceno et al., 2012, Ojji et al., 2009, Laabes et al., 2008, Ojji et al., 2013)

Data from developed countries show that half of HF patients are rehospitalised within 6-months of discharge(Butler and Kalogeropoulos, 2008) and 70% of these are due to worsening of previously diagnosed HF.(Gheorghiade et al., 2005) In a recent report, Jencks et al(Jencks et al., 2009) showed that HF is the number one reason for readmission in the USA. Predictably, HF readmission is associated with higher mortality compared to the index admission. Whether similar patterns of readmission occur in patients affected by HF in Sub-Saharan Africa and specifically West Africa is unknown.

We have previously re-confirmed via the Abeokuta HF Registry(Ogah et al., 2014a) that the risk factors and etiology of HF are not entirely same in sub-Saharan, compared to other parts of the world.(Stewart et al., 2008) The aim of this study was for the first-time, therefore, to identify predictors of rehospitalisation in a Nigerian HF population using the data from the Abeokuta HF Registry.

7.2 Methods

7.2.1 Study design and clinical setting

As described previously (Ogah et al., 2014a), this is a hospital-based, prospective, observational study in which all patients with clinical diagnosis of HF were recruited from January 1, 2009 to December 31, 2010. Patients were enrolled if they met the Framingham(McKee et al., 1971) as well as the European Society of Cardiology(Dickstein et al., 2008) criteria for the diagnoses of HF.

The study was primarily conducted at the Federal Medical Centre (FMC), Abeokuta. The institution is the only tertiary health facility in the city.

Abeokuta is the capital city of Ogun state in Southwestern, Nigeria (one of the 36 states that make up the Federal Republic of Nigeria)

The entire state has an estimated population of 3.2 million inhabitants based on the 2006 national population census, out of which a million are living in Abeokuta alone.(2006b)

Like in other parts of the country the state operates three-tier or level of healthcare: primary (health posts, health centers), secondary (Cottage, General or State hospitals) and tertiary health care (Federal medical centers and University of teaching hospitals) Primary health cares is constitutionally under the jurisdiction of the Local Government. The remaining two are under the State and Federal Governments respectively.

A significant proportion of health care delivery is carried out by private health institutions and mission hospitals.

The costs of healthcare in the city and in most parts of the country are generally borne by the patients through out of pocket expenses. Social health insurance coverage is low in the city and in most parts of the country. On the other hand strong family bonding exist in the city where rich and well-to-do individuals assist their poor family members

Referrals were received from private as well as public primary and secondary health care facilities within the city of Abeokuta who were informed of the existence and importance of the registry.

Patients aged 18-years and above were enrolled and all gave written informed consent and the institution's ethics review board approved the study. The study was carried out according to international laid out guidelines as enshrined in the Declaration of Helsinki.(Rickham, 1964)

7.2.2 Clinical evaluation

A standard case report form was used in data collection. Baseline clinical and demographic variables such as age, gender, contact addresses, telephone number of patients and their relations, marital status, occupation, educational background, history of cardiovascular risk factors such as hypertension, family history, cigarette smoking etc. were collected.

Also collected were the signs and symptoms, clinical diagnoses, co-morbidities, medications, result of investigation, date of discharge and intra-hospital outcome.

Blood pressure was recorded according to standard guideline(1992b) with the use of Mercury Sphygmomanometer (Accosson, London). Systolic and diastolic blood pressures were measured at Korotkoff sound phases I and V respectively. An average of three readings was taken after 5 minutes of rest. Patients were weighed without shoes and in light clothing on a standard beam balance. An anthropometric plane was used for height measurement with patients not putting on shoes or headgear.

Body mass index (BMI) was calculated using the formula: BMI = Weight (kg) / [height (m)] $^{2.}$ A BMI of 24-29.9kg/m^2 and >=30kg/m^2 defined overweight and obesity respectively. Anemia was defined as hematocrit of less than 10g/dl. Glomerular filtration rate was estimated using the four variables-Modification of Diet in Renal Disease (MDRD) formula(Levey et al., 1999) Renal dysfunction was defined as eGFR of less than 60ml/min/1.73m^2 (same criteria used by Stewart et al(Stewart et al., 2008)

12 lead ECG tracing was obtained with Schiller ECG electrocardiograph (Schiller AG, Switzerland) and the reports were analyzed by the authors blinded to the clinical history of the patients. M-mode, 2D

and Doppler echocardiography were performed using an ALOKA 4000 SSD machine (ALOKA co. Ltd, Tokyo, Japan) according to standard criteria.(Henry et al., 1980)

The criteria employed for diagnoses of the different etiologies have been previously reported.(Ogah et al., 2014a)

7.2.3 Follow up

The patients were followed up for a period of six months. Information on readmission was assessed through: hospital case record, telephone contact of patients or their relatives (Cell phone coverage in Nigeria is quite extensive and remarkable), telephone calls to their private doctors (where necessary) and occasional home visits by research assistants.

Follow up was done at 1- and 6-months after the index admission. Information collected during follow up among other things included patients' wellbeing (subject's feeling about his or her general health which was graded from markedly improved to markedly worse), medications as well as information on rehospitalization. At the end of 6 months, 233 out of the 262 patients were known to be alive, 18 were lost to follow up and 11 patients were known to have died (all during hospital readmission). Thirty two patients were readmitted at least once, 13 patients twice and one was readmitted thrice within 6 months.

7.2.4 Data management and statistical analysis

Data management was with the use of EpiData data management software (The EpiData Association, att. Jens Lauritsen, Enghavevej 34, DK5230 Odense M, Denmark). Data analysis was with IBM SPSS version 20 (SPSS, Inc. Chicago Illinois) and STATA version 11 (Stata Corp LP 4905 Lakeway Drive College Station, Texas 77845-4512 USA) statistical softwares.

Continuous data are expressed as mean ± SD, (or median ± IQR where necessary) and 95% confidence interval. Categorical variables are expressed as proportions. The patients were grouped into two (group 1, those not rehospitalised; and group 2, those rehospitalised). They were compared accordingly. Univariate regression analysis was used to identify factors associated with

rehospitalization. Forest plot was constructed for the result of the univariate analysis. Multiple logistic regression analysis was used to determine the independent predictors of readmission. The criteria for inclusion in the multiple logistic regression analysis was a p-value <0.15 in the univariate analysis.P<0.05 was adjudged statistically significant.

7.3 Results

7.3.1 Sociodemographic characteristics

Two hundred and sixty two patients, comprising 138 men (53%) and 124 (47%) women, who survived admission for de novo HF were followed up for six months. **Table 7.1** compares the socio-demographic and clinical profile of the cohort according to 6-month readmission status. The group readmitted were significantly older (mean age 61.7±14.0 vs.56.1±15.4, p=0.026). Except for body mass index and serum sodium, which were significantly higher in the readmitted group (p=0.029 and 0.039 respectively), all the other parameters were similar between the two groups. **(Table 7.1)**
The overall mean length of hospital stay was 10.5 +- 6.1 days (range 2-61 days; median 9 days). Eleven (12.2%) of the 90 patients who were on admission for 7 days or less (short stay) compared to 21 (12.2%) of the 172 patients who had length of hospital admission (>7days) were rehospitalised.

7.3.2 Readmission rates

The readmission rates at 30- and 180-days were 1.53% (95% CI, 0.58-4.02) and 12.2% (95%CI, 8.88-16.8) respectively. **Figure 7.1** is a Kaplan-Meier survival curve for re-admission in our cohort.

7.3.3 Reasons for 6 month readmission

Twenty four (75%) of the 32 patients were admitted on account of worsening HF. Three were due to arrhythmias (atrial fibrillation) while one each was due to pneumonia, lower gastrointestinal bleeding, renal failure, angioedema and severe hypertension.

7.3.4 Clinical correlates of readmission

Those readmitted were older, more likely to be men and non-smokers, took less alcohol (59.4% vs. 61.7%), and had lower frequency of diabetes mellitus (DM) (9.4% vs.13.5%). They also tended to

have more severe symptoms and signs of HF such as orthopnea (87.5 vs. 81.2%), paroxysmal, nocturnal dyspnoea (93.8 vs. 84.2%). virtually all the readmitted cases were in NYHA Class III or IV (100 vs. 91.4%). They also had lower body mass index (22.0 vs.24.3kg/sqm) – **see Table 7.1.** Total white cell count, lymphocyte count, serum sodium, total cholesterol, blood sugar were also higher in the readmitted group. Alternatively, serum potassium, creatinine, and packed cell volume levels were lower in rehospitalised patients. The frequency of atrial fibrillation was also higher in the readmitted group (18.8% vs. 11.7%)

7.3.5 Echocardiography

Accordingly to echocardiography, the left atrial diameter and left atrial area left ventricular diameter in systole were significantly higher in the readmitted group compared to the rest. Alternatively, LVEF was lower with 76.7% in those rehospitalised with those recording a LVEF <50% compared to 62.6% for the rest. Significantly the rehospitalised group also had higher rates of valvular dysfunction **(Table 7.2)** In terms of prescribed pharmacotherapy the two groups were similar; with the notable exception of more digoxin prescribed in those rehospitalised (84.4% vs. 67%, p=0.046).

Table 7.1 . Baseline socio-demographic and clinical profile of the subject

Variable	All (n= 262)	Rehospitalised (n=32)	Rest (n=230)	p-value
Socio-demography				
Gender (n/%) Men	138(52.7)	21(65.6)	117(50.9)	0.133
Age (years)	56.1(15.4)	61.7(14.0)	55.3±15.5	0.026
Single marital status (n/%)	45(21.5)	5(17.9)	40(22.1)	0.735
Urban residence (n/%)	201(76.7)	21(65.6)	180(78.3)	0.122
CV risk factors/co-morbidities (n/%)				
Never Smoked	214(81.7)	26(81.2)	188(81.7)	0.800
Current alcohol user	161(61.5)	19(59.4)	142(61.7)	0.305
Diabetes mellitus (Yes)	34(13.0)	3(9.4)	31(13.5)	0.779
Hypertension (Yes)	213(81.3)	27(84.4)	181(80.9)	0.810
Atrial fibrillation (%)	33(12.6)	6(18.8)	27(11.7)	0.263
COPD (Yes)	19(7.3)	4(12.5)	15(6.5)	0.265
Arthritis (Yes)	67(25.6)	12(37.5)	55(23.9)	0.128
Family history of heart disease	23(8.8)	4(12.5)	19(8.3)	0.500
Symptoms and signs (n/%)				
Cough	232(88.5)	27(84.4)	205(89.1)	0.385
Dyspnoea	253(97.3)	30(93.8)	223(97.8)	0.388
Orthopnoea	214(82.0)	28(87.5)	186(81.2)	0.470
Paroxysmal nocturnal dyspnoea	222(85.4)	30(93.8)	192(84.2)	0.189
Leg oedema	209(80.1)	26(81.2)	183(79.9)	0.859
Basal crepitation	218(83.2)	29(90.6)	189(82.2)	0.315
Elevated Jugular venous pressure	209(79.8)	28(87.5)	181(78.7)	0.348
Third heart sound	189(72.1)	24(75.0)	165(71.7)	0.834
Systolic murmur	123(46.9)	15(46.9)	108(47.0)	0.993
Hepatomegaly	186(71.0)	23(71.9)	163(70.9)	0.907
Ascites	59(22.5)	8(25.0)	51(22.2)	0.821
NYHA III or IV on admission	242(92.4)	32(100)	210(91.4)	0.325
Body mass index (kg/m^2)	24.0(5.2)	22.0±4.2	24.3±5.3	0.029
Temperature	36.4(0.8)	36.2±0.5	36.4±0.9	0.186
Respiratory rate	28.7(6.6)	29.7±8.8	28.5±6.3	0.335
Pulse rate	96.3(18.0)	96.1±18.1	96.4±18.0	0.942
Systolic blood pressure (mmHg)	136.2(29.7)	87.8±21.8	134.0±18.3	0.678
Diastolic blood pressure (mmHg)	87.6(18.8)	87.8±21.8	87.5±18.3	0.935
Pulse pressure	48.7(18.3)	50.5±16.0	48.5±18.6	0.568
Packed cell volume (%)	37,1(7.3)	37.6(6.8)	37.1(7.3)	0.719
White cell count	7.5(3.7)	7.6(3.9)	7.6(3.9)	0.194
Lymphocytes (%)	35.6(12.8)	35.1(11.4)	35.6(13.0)	0.833
Serum Sodium (mmol/L)*	136.0(6.5)	133.4(6.2)	136.5(6.5)	0.039
Serum Potassium (mmol/L)	3.65(0.8)	4.0(0.9)	3.6(0.7)	0.102
Total Cholesterol (mg/dl)	166.0(80.4)	139.4(49.7)	169.5(83.4)	0.437
Blood Glucose (mg/dl)	115.9(55.9)	116.8(65.2)	116.0(54.5)	0.990
Blood Urea(mg/dl)+	43.7(4.1)	56.2(8.4)	42.0(3.1)	0.105
Blood creatinine(mg/dl)+	1.50(0.11)	1.36(0.15)	1.53(0.16)	0.683
QRS duration (msec)	109.7(29.5)	100.3(21.0)	112.2(31.1)	0.220

QT Interval (msec)	358.9(37.6)	355.3(37.1)	359.8(38.1)	0.716
QTc (msec)	453.3(35.8)	449.9(30.4)	454.1(37.3)	0.720
Etiology of Heart failure (n/%)				
Hypertensive heart disease	199(76.0)	24(75.0)	175(76.1)	0.866
Dilated Cardiomyopathy	22(8.4)	2(6.2)	20(8.7)	
Right heart failure	15(5.7)	3(9.4)	12(5.2)	
Pericardial diseases	8(3.1)	2(6.2)	6(2.6)	
Rheumatic heart disease	7(2.7)	0(0.0)	7(3.0)	
Others	11(4.2)	1(3.1)	10(4.3)	

Table 7.2. Echocardiographic profile of the subjects

Variable	All subjects (n= 262)	Readmitted (n=32)	Rest (n= 230)	p-value
Left atrial diameter (cm)	4.62(1.0)	4.8(0.7)	4.60(1.0)	<0.001
Left atrial area (sq.cm)	26.9(8.4)	27.1(8.0)	26.8(8.5)	0.006
Septal wall thickness in diastole(cm)	1.31(0.69)	1.72(0.67)	1.26(0.37)	0.050
Posterior wall thickness in diastole(cm)	1.20(0.82)	1.21(0.21)	1.20(0.87)	0.803
LV internal diameter in diastole (cm)	5.63(3.01)	5.68(0.88)	5.63(0.61)	0.490
LV internal diameter in systole (cm)	4.45(1.57)	4.74(0.93)	4.41(0.64)	0.004
Fractional shortening (%)	19.2(11.0)	17.3(10.4)	19.6(11.2)	0.099
Ejection fraction (%)	39.7(18.5)	36.8(18.1)	40.1(18.6)	0.020
Mitral ‘E’ wave velocity (m/sec)	0.81(0.29)	0.87(0.32)	0.80(0.30)	0.880
Mitral ‘A’ wave velocity	0.53(0.26)	0.53(0.25)	0.53(0.26)	0.905
E/A ratio	1.94(1.35)	1.96(1.20)	1.93(1.37)	0.088
Systolic dysfunction (%) (n=236)	152(64.4)	23(76.7)	129(62.6)	0.156
Mitral regurgitation (n=219)	165(75.8)	25(92.6)	140(72.9)	0.056
Tricuspid regurgitation (n=219)	152(69.4)	23(85.2)	129(67.2)	0.232

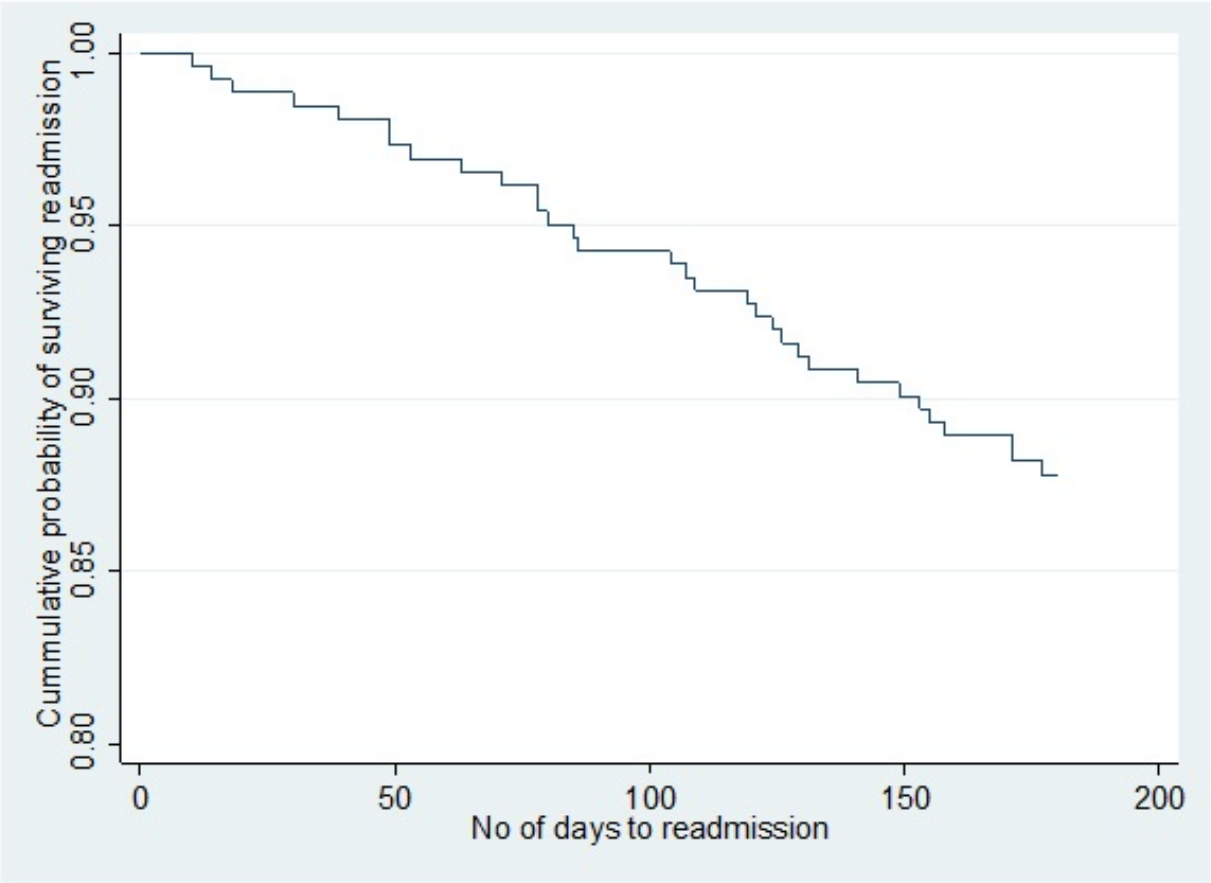

Figure 7.1 Kaplan-Meier survival curve for re-admission

7.3.6 Predictors of rehospitalisation

According to univariate analysis **(Table7.3,Figure7.2)** Low BMI (OR, 2.95; 95%CI, 1.16-7.47; p=0.018), low literacy (none or less than 6-years of formal education), serum sodium <130mmol/L (OR, 4.11; 95%CI, 1.58-10.75; p=0.002), and presence of mitral regurgitation (OR, 4.64; 95%CI, 0.1.06-20.29; p=0.026) were significantly associated with higher risk of rehospitalization. Factors associated with lower risk of rehospitalisation include: female gender, history of smoking, presence of DM, higher random blood sugar, and higher packed cell volume. On an adjusted basis **(see figure 7.2),** only female gender (adjusted OR 0.33, 95% CI 0.14-0.79; p=0.014 versus men) and body mass index <19kg/m^2 (adjusted OR 3.74, 95% CI 1.15-12.16; p=0.028 versus rest) were independent correlates of readmission during 6-months follow-up.

Table7.3. Univariate correlates of readmission in the 262 denovo HF subjects

Variable	OR	95% CI	P-value
Age >60years	2.04	0.96 – 4.29	0.058
Female gender	0.54	0.25 – 1.18	0.117
Body mass index <19	2.95	1.16 – 7.47	0.018
No education	1.47	0.62 – 3.46	0.376
Not married	0.73	0.30 – 1.75	0.481
History of smoking	1.06	0.41 – 2.74	0.907
Alcohol use	1.10	0.52 – 2.35	0.796
History of diabetes mellitus	0.66	0.19 – 2.31	0.518
Serum Sodium (<130mmol/l)	4.11	1.58 – 10.75	0.002
Random blood glucose (>140mmHg)	0.67	0.22 - 2.02	0.459
Packed cell volume (<=30%)	0.53	0.15 – 1.85	0.313
Serum Cr (> 2mg/dl)	1.20	0.43 – 3.39	0.729
Presence of atrial fibrillation	1.74	0.65 – 4.59	0.263
Ejection fraction<35%	1.36	0.61 – 3.04	0.459
Presence of mitral regurgitation	4.64	1.06 – 20.29	0.026
Presence of tricuspid regurgitation	2.81	0.93 – 8.45	0.057

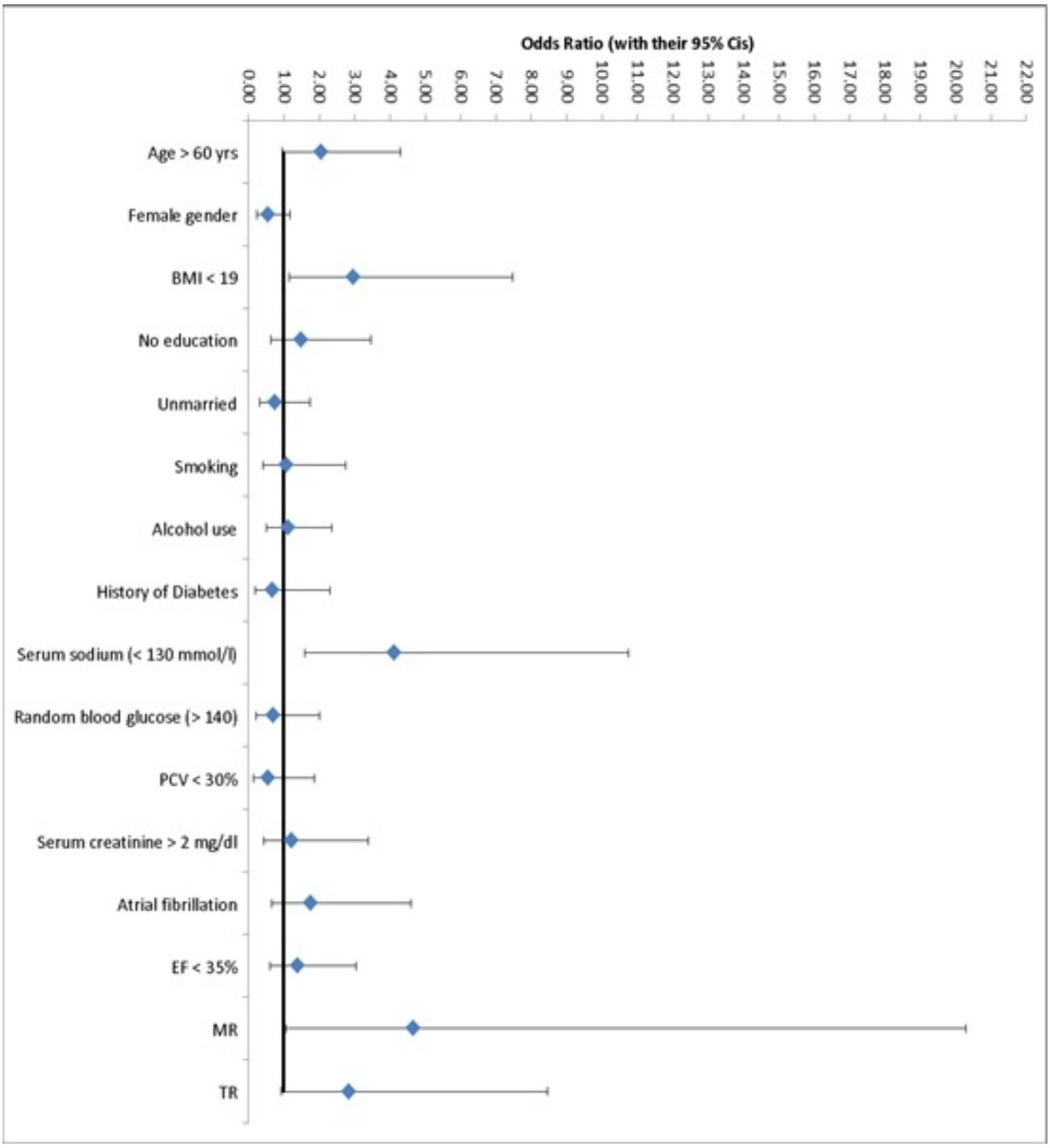

Figure7.2. Shows univariate variables associated with readmission represented with forest plot. (Adjusted OR for women= 0.33 (95%CI, 0.14-0.79), Adjusted OR for BMI=3.74(95%CI, 1.15-12.16)

7.4 Discussion

This represents one of the first-ever reports from the city of Abeokuta, Nigeria to prospectively determine medium-term outcomes in adults who survive a de novo hospitalization for HF. Our sample represents a unique population of HF patients from the south-western zone of Nigeria.

As in other parts of Africa (Stewart et al., 2008, Damasceno et al., 2012) and in contrast to reports from high income countries (Adams et al., 2005b, Nieminen et al., 2006a) this was a relatively young cohort with HF of predominantly non-ischemic causes. With full follow-up in the majority of case, we found a low-rate of 6 month mortality (4.2%), as well as relatively low-rates of rehospitalisation (predominantly recurrent HF) at 30 days (1.53%) and 6 months (12.2%). In this Nigerian population and HF cohort, there were a number of characteristics that appeared to modulate the risk of rehospitalisation. Higher rates of rehospitalisation were observed in those of older age, lower BMI, low literacy , lower serum sodium level, presence of atrial fibrillation, renal dysfunction and valvular dysfunction were associated with higher likelihood of readmission. Conversely, women, being single, history of DM and lower packed cell volume were associated with lower rates of rehospitalisation. Given the size of the cohort and relatively low number of rehospitalised patients, it was difficult to determine independent predictors of such an event. However, further analyses did show that on an adjusted basis, women were two-thirds less likely to be readmitted compared to men, while those with a low BMI were almost four times more likely to be readmitted to their heavier, potentially more nourished counterparts.

The readmission rate of 12% in the present study is generally lower than the rates reported from North America and Europe. In a study by Krumholz et al(Krumholz et al., 1997), it was reported that about 50% of HF patients were readmitted within 6-months after the initial admission. Ross et al(Ross et al., 2010) showed from Medicare data, that all cause readmission ranges from 22.9% to 23.3% between 2004 and 2006 in the United States. However, consistent with other data from sub-Saharan Africa (Damasceno et al., 2012, Stewart et al., 2008) this was a relatively young cohort with

HF caused by predominantly non-ischaemic causes. In other parts of the world hospital readmission risk increases with age. Patients aged ≥65 years are far more likely to experience recurrent hospitalization. A 4-fold increase in 30-day readmission rate was reported for elderly populations who were 80-years or older. Blackledge et al(Blackledge et al., 2003a) and Koitabachi et al(Koitabashi et al., 2005) observed a 24% increase per 10-year age increment in the annual readmission rate. The reported impact of gender on readmission rates in those with HF is inconsistent. While some authors reported higher rates in women (Howie-Esquivel and Dracup, 2007), others reported higher rates in men similar to our finding.(Alla et al., 2007, Nieminen et al., 2008)

Arrhythmias especially atrial fibrillation (AF) is common in HF and adversely affects hemodynamics in patients. Several studies have shown that this rhythm disorder is associated with higher risk of readmission in individuals with HF irrespective of ejection fraction or rhythm control.(Middlekauff et al., 1991, Rivero-Ayerza et al., 2008) Recent findings from Africa suggest that AF occurs in 4.6% of cardiac cases(estimated 5.6 cases/100,000/year)(Sliwa et al., 2010a) The mean age of occurrence is 57.2 ±18.8 years in Africa compared to70.1±13.4 years in North America.(Oldgren et al., 2014) Common risk factors include hypertension, heart failure and valvular heart disease.(Sliwa et al., 2010a, Shavadia et al., 2013, Ntep-Gweth et al., 2010, Oldgren et al., 2014) Our finding of higher risk of readmission in patients with poor LV function is similar to the findings of many workers.(Babayan et al., 2003, Harjai et al., 1999) However some recent reports indicate similar risk in HF with preserved ejection fraction.(Agoston et al., 2004, Malki et al., 2002) Our study also confirmed previous reports that presence of valvular dysfunction is associated with 4-fold higher risk of HF related readmission.(Berry et al., 2005)

Some plausible reasons for lower rate of readmission in our cohort compared with data from developed countries may be related to the younger age of our patients as well as the fact that majority of the patients had hypertensive heart failure related HF and other forms of non-ischemic related HF. Several studies have documented higher readmission rates with ischemic etiology.

(Blackledge et al., 2003a) Our patients also stayed longer on the ward (mean length of hospital stay was 9 days compared to 4 days in the USA) before discharge. This could have afforded them the opportunity of better stabilization. The fact that the study was carried out in a cardiology unit/tertiary institution may account for our finding and may not reflect the situation in the general Nigerian population. The higher rate of readmission in lean patients may be related to cardiac cachexia and severe HF. It may also support the concept of obesity paradox in HF. Hyponatremia has been linked to frequent ventricular ectopics and sudden death. Hyponatremia in HF is due to activation of the renin-angiotensin-aldosterone axis, decreased sodium and water delivery to the collecting ducts of the nephron, coupled with resistance to the action of natriuretic peptides. Hyponatremia in HF is also linked to increased vasopressin levels in HF as a result of increase in number of aquaporin water channels in the collecting duct of the kidney(Mielniczuk et al., 2008). We also observed that the group rehospitalised had higher frequency of osteoarthritis. This may be related to age. It may also be due to concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) which can worsen their HF.

The impact of current smoking status on HF readmission is inconsistent. Similar to our finding, the "smoker's paradox" has been demonstrated by other workers where a 23% lower risk of 90-day rehospitalization risk was reported in current cigarette smokers.(Fonarow et al., 2008) It has been postulated that current smoking has a preconditioning-like effect on HF patients, allowing a better outcome during acute decompensation. Furthermore sudden or recent cessation of smoking during hospitalization allow for more rapid stabilization and compensation among patients who were smoking up until the time of HF hospitalization. The paradox could also be explained by the beneficial or lower dimethyl arginine (ADMA- a potential nitric oxide synthase inhibitor) profile which has been documented in smokers by some authors.(Onat and Hergenc, 2008, Eid et al., 2004) ADMA is increased in HF patients and it is associated with the severity of HF and also predicts adverse outcomes.(Duckelmann et al., 2008)

Presence of DM or high blood glucose is an established predictor of readmission in HF patient. (Montero Perez-Barquero et al., 2007, Krumholz et al., 2000, Greenberg et al., 2007, Dungan et al., 2010) This is due to the role of hyperglycemia and insulin resistance in the development of diabetic heart disease partly as a result of in-efficient myocardial fuel metabolism.(Aneja et al., 2008) Hyperglycemia could also induce shifts in the fluid and electrolytes that may affect the outcome of HF patients.

In the present study we observed that DM patients were less likely to be readmitted. This could be a statistical chance finding. It could also be due to the higher prevalence of HF with preserved EF in DM patients. These are generally less likely to be readmitted compared to those with reduced EF.

The implication of our finding is that simple socio-demographic and laboratory variables especially BMI, age , serum sodium ,presence of atrial fibrillation and valvular dysfunction could be used to predict patients who are at risk of rehospitalisation in our environment. It may be worthwhile to look at the impact of nutritional rehabilitation in our HF patients.

The process of care, access to health care, low literacy, poverty and cultural practices may also affect the timing of presentation of patients to health care facilities as well as adherence to clinic attendance and drug therapy.

Because of ignorance coupled with poverty or lack of access to healthcare, patients in developing countries such as in Africa often present late to the hospital and when they do, catastrophic spending for care of chronic conditions such as HF is often a major challenge. This consequently affects adherence.

Cultural practices as well as superstitious beliefs also affect health seeking behavior in Africa. Patients often visit hospitals as a last option (after trying other alternatives including native or traditional medicine). For chronic conditions such as HF, they often move from one center to the other seeking for permanent cure. This also affects compliance.

It will be worthwhile to explore the impact of these factors in future outcome studies on HF or other chronic non-communicable diseases in our environment.

7.4.1 Limitations

As noted in a previous report (Stewart and Sliwa, 2009), research is often problematic and challenging in a resource-poor environment and there are a number of limitations that require comment. The first of these is the sample size and fewer events which did not allow for the development of models of risk prediction for the population. A larger and multicentre study is therefore advocated to provide this information.

Heart rate variability and newer echocardiographic parameters such as tissue Doppler imaging were also not assessed. We also did not assess the impact of quality of life and psychosocial factors.

Finally, because our sample is limited to Abeokuta (south-western part of the country), our findings cannot be generalized to other parts of Nigeria.

7.4.2 Conclusions

HF rehospitalization within 6-months follow-up occurs in about 12% of patients in our cohort living in an environment where HF etiology is predominately non-ischemic. Higher rates of readmission were noted in those of older age; lower BMI, low literacy, lower serum sodium level, presence of atrial fibrillation, renal dysfunction and valvular dysfunction.

Chapter 8: Hypertensive heart failure in Abeokuta, Nigeria.

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ORIGINAL PAPER

Hypertensive Heart Failure in Nigerian Africans: Insights from the Abeokuta Heart Failure Registry

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Data from the Abeokuta Heart Failure Registry were used to determine the clinical characteristics, mode of treatment, and short- and medium-term outcomes of patients with hypertensive heart failure. A total of 320 patients were consecutively studied, comprising 184 men (57.5%) and 136 women (42.5%) aged 58.4±12.4 and 60.6± 14.5 years, respectively. Most patients (80%) presented with New York Heart Association functional class III or IV and around one third (35%) had preserved systolic function. Median hospital stay was 9 days (interquartile range 5–21) while intra-hospital mortality was 3.4%. The 30-day, 90-day, and 180-day mortality rates were 0.9% (95% confidence interval, −0.2 to 3.5), 3.5% (95% confidence interval, −1.7 to 7.3), and 11.7% (95% confidence interval, −7.8 to 17.5), respectively. In a multiple logistic regression analysis, only serum creatinine was an independent predictor of mortality at 180 days (adjusted odds ratio, 1.76; 95% confidence interval, −1.17 to 2.64). Hypertension is the most common etiological risk factor for heart failure in Nigeria. Most patients present in the fourth decade of life with severe heart failure and secondary valvular dysfunction and significant in-hospital mortality. *J Clin Hypertens (Greenwich).* 2015:1–10. © 2015 Wiley Periodicals, Inc.

Abstract

Data from the Abeokuta Heart Failure Registry were used to determine the clinical characteristics, mode of treatment as well as intra-hospital outcome of hypertensive heart failure (HT-HF).

Three hundred and twenty subjects were consecutively studied; comprising 184 (57.5%) men and 136 (42.5%) women aged 58.4±12.4 and 60.6±14.5 years, respectively. Most (80%) presented in NYHA Class III or IV and around one third (35%) had preserved systolic function. Median hospital stay was 9 (IQR 5 to 21) days whilst intra-hospital mortality was 3.4% . The 30-day, 90-day and 180-day mortality rates were 0.9% (95%CI-0.2-3.5), 3.5% (95%CI-1.7-7.3) and 11.7% (95%CI-7.8-17.5) respectively. In a multiple logistic regression analysis, only serum creatinine was the independent predictor of mortality at 180-days (adjusted OR=1.76, 95%CI-1.17-2.64)

Hypertension is the commonest etiological risk factor for heart failure in Nigeria. Most present in their prime of life with severe heart failure and secondary valvular dysfunction and significant in-hospital mortality.

8.1 Introduction

High blood pressure is the leading risk factor for cardiovascular diseases (CVDs) and CV related morbidity and mortality globally. It is responsible for about 7.5 million deaths every year worldwide. (Danaei et al., Kearney et al., 2005, Mancia et al., 2013) Over 80% of these deaths occur in young and middle aged men and women in developing/ low income countries.(Kearney et al., 2005, Modesti et al., 2014) It has been projected that hypertension will increase by 89% in countries in sub-Saharan Africa compared to a rate of 24% in advanced countries(Kearney et al., 2005)

In a recent report on the national, regional and global trends in systolic BP (SBP) since 1980, Danaei et al(Danaei et al.) showed that while SBP fell in many developed countries, it actually rose in many developing countries including countries in East and West Africa.

In Nigeria for example, the pooled prevalence of high blood pressure in the country increased from 8.6% during the period from 1970-1979 to 22.5% (2000-2011). Awareness, treatment and control of hypertension are generally low with attendant high burden of hypertension related complications. Hypertension is the commonest risk factor for heart and kidney disease in Nigeria.(Ogah et al., Ogah, 2006, Ojji et al., 2009, Ojji et al., 2013, Damasceno et al., 2012, Ogah et al., 2014a)

Recently hypertension and other non-communicable diseases (NCDs) have been included as a point of emphasis for global initiative. It has been added to the agenda of the World Health Organisation (WHO) and the United States' Center for Diseases Control and Prevention (CDC) especially the new global standardized treatment initiative for hypertension.(2014b)

The aim of this study is to describe the socio-demographic characteristics, clinical features and echocardiographic characteristics and clinical outcome of individuals with hypertensive HF in Abeokuta, South western, Nigeria.

8.2 Material and methods

This was a hospital-based, prospective and observational study which was conducted at the Cardiology Unit, Department of Medicine, Federal Medical Centre Abeokuta, Nigeria as part of the Abeokuta Heart Failure Registry. The baseline characteristics and clinical profile has been published.(Ogah et al., 2014a) The center is a tertiary institution located in the Capital of Ogun State in the South Western Region of Nigeria, which is one of the 36 States that make up the Federal Republic of Nigeria.

The center receives referrals from primary and secondary health facilities within and outside the state. The city has a population of about a million people .(2006a)

During a 2-year period (January 2009- December 2010), a total of 452 patients who were admitted for HF (constituting 9% of total medical admissions for the period) at the centre were recruited into the registry.(Ogah et al., 2014a) Three hundred and fifty five cases (78.5%) were due to hypertensive heart disease. 320 (90.1%) of these were included in the current sub-analysis. Thirty five subjects were excluded because of insufficient BP data.

A standardised diagnosis of HF was made using the Framingham criteria(McKee et al., 1971) as well as the according to the guidelines of European Society of Cardiology on the diagnosis and treatment of AHF.(Dickstein et al., 2008) As such, both denovo presentations of AHF as well as recurrent presentations of typically decompensated HF (i.e. acute- on -chronic HF) were recruited.

All the subjects gave consent before they were enrolled into the study. Ethical clearance was obtained from the institution's ethics review board and the study conformed to international ethics standards(Rickham, 1964)

8.2.1 Clinical Evaluation

A standard case report form was used in data collection. Baseline clinical and demographic variables such as age, gender, contact addresses, telephone number of subjects and their relations, marital status, occupation, educational background, history of cardiovascular risk factors such as hypertension, family history, cigarette smoking etc. were collected.

Also collected were the signs and symptoms, clinical diagnoses, co-morbidities, medications, result of investigation, data on discharge and intra-hospital outcome.

Blood pressure was recorded according to standard guideline(1992b) with the use of Mercury sphygmomanometer (Accousson, London). Systolic and diastolic blood pressures were measured at Korotkoff sounds phases I and V respectively.

Blood pressure was measured at the right arm in the sitting position and cuff size was based on the size of the subjects arm. An average of three readings taken after 5 minutes rest was recorded.

Diagnosis of hypertensive heart failure was made if the following criteria were met: clinical and echocardiographic confirmed diagnosis of HF in a known hypertensive or a persistent blood pressure of ≥140/90 in those who were not previously known hypertensive. Denovo hypertensive heart failure (HHF) were those presenting for the first time with HF while decompensated HHF were those who have had previous history of HF due to hypertensive heart disease.(2003, Nieminen et al., 2006b)

Patients with clinically overt renal failure or on dialysis therapy were excluded from the study. Others excluded were those with HF due primarily to ischaemic heart disease and right heart failure due to COPD. The criteria for the diagnosis or exclusion of other causes of HF in our environment have been reported previously.(Ogah et al., 2014a)

Body mass index was calculated using standard formula.

A BMI of 25-29.9kg/m^2 and >=30kg/m^2 defined overweight and obesity respectively. Anemia was defined as hematocrit of less than 10g/dl. Glomerular filtration rate was estimated using the four variables- Modification of Diet in Renal Disease (MDRD) formula. (Levey et al., 1999) Renal dysfunction was defined as eGFR of less than 60ml/min/1.73m^2.

12-lead ECG tracing was obtained with Schiller ECG electrocardiograph. (Schiller AG, Switzerland) The ECG paper speed was adjusted to 25mm/sec All the ECGs were recorded in the supine position. For each recording, the styli control was set at 10mm/mV (except in very high voltages when it was set at 5mm/mV). ECG reports were analyzed by one of the authors blinded to the clinical history of the subjects.

Electrocardiographic LVH by voltage was based on Sokolow-Lyon (SV1+RV5 or V6)(Sokolow and Lyon, 1949), and/or Cornell (SV3+RaVL with 0.6mV added in women)(Casale et al., 1987)

Repolarization abnormalities in the lateral leads (V5-V6, 1, and aVL) indicated typical strain when there is a down-sloping convex ST segments depression (≥0.1mV) with an inverted asymmetrical T-wave opposite to the QRS axis.(Okin et al., 2001, Ogah et al., 2006b)

Voltages in individual leads were calculated as the mean of three complexes wherever possible.

M-mode, 2D and Doppler echocardiography were performed using an ALOKA 4000 SSD machine (ALOKA co. Ltd, Tokyo, Japan). Two dimensionally guided M-mode measurements were made according to standard guidelines. The left atrial dimensions and area were measured according to standard guidelines(Lester et al., 1999) (Thomas et al., 2002) .

Measurements of the left ventricular (LV) dimensions were made from M-mode readings, according to the recommendations of the American Society of Echocardiography.(Sahn et al., 1978b)

Measurements were averaged over 3 cardiac cycles. Where optimal M-mode imaging could not be obtained, 2D linear measurements were obtained according to ASE guidelines. LV fractional

shortening fraction was calculated accordingly. Where there is regional wall motion abnormality, the Simpsons method of disc was used for LV function assessment.

Left ventricular mass (LVM) was calculated by the equation(Reichek, 1994):

LV mass = 0.8[1.05 (IVSTd+LVIDd+PWTd) 3 - (LVIDd) 3] +0.6g. This formula has good interobserver reproducibility (ρ=0.93) in one study(Palmieri et al., 1999).

Left ventricular mass index (LVMI) was calculated by dividing the value of LV mass by height to its allometric growth rate of 2.7 (LVMHt2.7)(de Simone et al., 1992, de Simone et al., 1995) The partition value of 51g/$ht^{2.7}$ was used since this was the only criterion that demonstrated as the optimal threshold value for left ventricular hypertrophy in blacks irrespective of gender in two previous studies(Nunez et al., 2005, Adebiyi et al., 2006)

Relative wall thickness (RWT) was derived from 2 X posterior wall thickness/LV internal diameter. Increased RWT was considered to be present when RWT exceeded 0.43. This represents the 97.5th percentile in normal subjects (Roman et al., 1995). Left ventricular geometric was defined accordingly(Ganau et al., 1992).

Doppler flow mapping was used in the assessment or absence of presence of valvular regurgitation. Left ventricular diastolic function was evaluated by studying the filling dynamics of the left ventricle. This was quantified by measuring the transmitral 'E' wave velocity (peak early mitral inflow velocity) and the 'A' wave velocity (peak atrial inflow velocity), the E/A ratio and the deceleration time (DT): time interval of peak E wave velocity to its extrapolation to the baseline. The E/A ratio were not evaluated in individuals with atrial fibrillation or marked tachycardia.

8.2.2 Follow-Up

The cohort was prospectively followed up for 180 days. The subjects were contacted through clinic visit, telephone calls or home visits at 30-days, 90-days and 180-days. Information obtained during follow-up included their wellbeing, medications, history of re-hospitalization and deaths (from next

of kin). In addition to patient or relation's telephone interviews, where necessary referring physicians were contacted for additional information.

8.2.3 Outcomes measures

These included: 1) length of hospital stay (LoS), 2) Intrahospital outcome, 3) rehospitalisation at 180 days, and 4) survival within 180 days.

8.2.4 Quality Control

One of the authors (OSO) performed all the echocardiography. In our laboratory, the intra-observer concordance correlation coefficient and measurement error have been reported.(Ogah et al., 2006a)

8.2.5 Data analysis and statistics

All data collected were entered into Epi-data data management software. Analysis was done with SPSS statistical package. Categorical variables are expressed as percentages. Continuous variables are presented as mean and SDs or median and inter-quartile ranges where applicable. Comparison of continuous variables was with the use of student's t-test while categorical variables were done with chi square statistics. Non-parametric tests were used where necessary.

Survival function estimates was assessed by the Kaplan-Meier method and the difference were tested using log-rank test. The follow up was censored at 180-days post admission. Subjects who died within the period of 180-days constitued the event of interest for purpose of survival analysis while those still alive or lost to follow up were treated as censored.

Predictors of survival were determined using univariate Cox-proportional regression analyses. Thereafter multiple logistic regression analysis was performed to identify independent predictors of survivals ($p<0.1$ used for selection of variables). Results were expressed as odds ratio (OR) with their 95% Confidence Intervals (95% CI).

A 2- tailed p value of <0.5 was assumed as statistically significant.

8.3 Results

A data of three hundred and twenty subjects were analysed. There were 184 (57.5%) men and 136 (42.5%) women who were aged 58.4±12.4 and 60.6±14.5 years respectively. The mean age for all the subjects was 59.3±13.4 years. **Figure 18** shows histogram of the age distribution of all the subjects and in men and women. **Table 8.1** shows the socio-demographic characteristics of the patients. Over 90% of them were of the Yoruba tribe (the dominant tribe in the South Western region of Nigeria). Majority were married (72.8%); had at least primary education (63.5%); employed (95%) and resided in the urban area (73.4%)

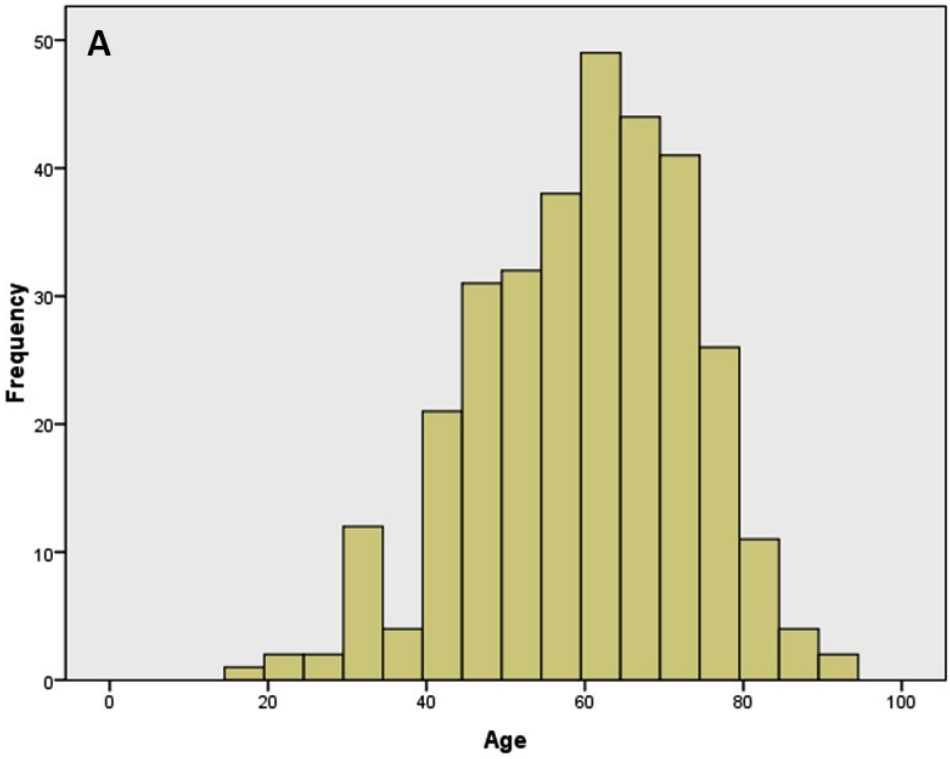


Figure 8.1. Histogram showing the age distribution of the 320 hypertensive subjects.

Men significantly attained higher levels of education than their female counterpart and were more in the skilled and professional occupation category. In terms of CVD risk factors, women had higher body mass index than the men. On the other hand cigarette smoking and alcohol consumption were significantly higher in men. Only about 15% had acute on chronic hypertensive HF. Two hundred and ninety (90.6%) of the subjects were known hypertensives, 70(92.4% of the men and 120(88.2%) of the women. There was history of diabetes mellitus (DM) in 12.2% of the subjects

The commonest co-morbidity was osteoarthritis (67, 20.9%) which was significantly commoner in women than men [29(15.8%) vs. 38(27.9%), p=0.006]. Chronic obstructive pulmonary disease (COPD), asthma, and stroke were present in 8(2.5%), 7(2.2%), and 1(0.3%), respectively. One patient each had stroke, migraine, inguino-scrotal hernia and psychosis. Dyspnoea on exertion was the commonest symptoms and was present in 94.4% while basal crepitation /crackles were seen in 84.4%). Over 80% were in NYHA classes III or IV.

Figure 19 shows the identified precipitating factors for decompensation.

The mean heart rate on admission was 96.2 beats /min while the mean systolic and diastolic blood pressures were 143.5 and 90.5mmHg respectively. The mean packed cell volume, total white cell count, serum sodium, serum potassium and blood glucose were similar between men and women. Total cholesterol was higher in women but not statistically significant. Blood urea and creatinine were higher in men (49.9 versus 38.2mg/dl) and 1.8 versus 1.3mg/dl respectively. 2.7% of those who had HIV screening tested positive. **(Table 8.1)**

QRS duration and QT intervals were higher in men but this was not statistically significant. 12.8% of the cohort was in atrial fibrillation.

Almost all the echocardiographic measures of chamber size and wall thickness were statistically higher in men compared to women **(Table 8.2)**

Table 8.1. Baseline socio-demographic and clinical profile of the 320 hypertensive subjects

Variable	All (n=320)	Men (n=184)	Women (n=136)
Demographic characteristics			
Age (years)	59.3±13.4	58.4±12.4	60.6±14.5
Married (n/%)**	233(72.8)	149(81.0)	84(61.8)
No education (n/%)*	85(37.3)	36(27.1)	49(51.6)
Unemployed (n/%)	16(5.0)	6(3.3)	10(7.4)
Rural dweller (n/%)	85(26.6)	48(26.1)	37(27.2)
CV Risk factors & Comorbidities			
Never smoked (n/%)**	260(81.3)	131(71.2)	129(94.9)
Ever consumed alcohol**	156(48.7)	118(64.2)	38(28.0)
Current alcohol consumption (n/%)	42(13.1)	34(18.5)	8(5.9)
Diabetes mellitus (n/%)	39(12.2)	22(12.0)	17(12.5)
Bronchial asthma (n/%)	7(2.2)	3(1.6)	4(2.9)
COPD (n/%)	8(2.5)	6(3.3)	2(1.5)
Arthritis (n/%)*	67(20.9)	29(15.8)	38(27.9)
Family history of heart disease (n/%)	20(6.3)	13(7.1)	7(5.1)
Clinical & laboratory features			
NYHA Class			
II (n/%)	57(17.8)	36(19.6)	21(15.4)
III (n/%)	201(62.8)	109(59.2)	92(67.6)
IV (n/%)	62(19.4)	39(21.2)	23(16.9)
Symptoms and signs			
Nocturnal cough(n/%)	292(91.3)	166(90.2)	126(92.6)
Dyspnea on exertion (n/%)	302(94.4)	172(93.5)	130(95.6)
Leg edema (n/%)	242(75.6)	140(76.1)	102(75.0)

Paroxysmal nocturnal dyspnea(n/%)	262(81.9)	157(82.1)	111(81.6)
Raised JVP(n/%)	210(65.6)	128(69.6)	82(60.3)
Basal crepitation(n/%)	270(84.4)	160(87.0)	110(80.9)
Hepatomegaly (n/%)	210(62.8)	116(63.0)	85(62.5)
Third heart Sound(n/%)	207(64.7)	115(62.5)	92(67.6)
Temperature (^{o}C).	36.4±0.82	36.4±0.77	36.3±0.88
Respiratory rate (c/min)	28.7±8.9	29.2±10.3	28.0±6.6
Pulse (beats/min)	96.2±18.9	97.4±19.1	94.7±18.7
Systolic BP(mmHg)	143.5±32.1	143.8±32.9	143.0±19.4
Diastolic BP	90.5±20.6	91.1±21.5	89.6±19.4
Body mass index(kg/m^2	24.2±5.3	24.0±5.0	24.5±5.7
Overweight(n/%)	43(23.3)	41(30.3)	84(26.1)
Obese(n/%)	19(10.1)	19(13.8)	38(11.6)
Denovo HF(n/%)	274(85.6)	115(84.2)	119(87.5)
Length of admission in days	10.4±5.2	10.1±4.8	10.8±5.5
Laboratory findings			
Packed cell volume(%)	37.4±6.9	37.3±6.7	37.5±3.3
White cell count	6.9±3.6	7.1±3.8	6.9±3.3
Serum sodium (mmol)	135.8±6.9	135.3±7.1	136.4±6.7
Serum potassium (mmol/l)	3.66±0.79	3.71±0.81	3.60±0.78
Total cholesterol (mg/dl)	166.2±74.1	162.9±76.7	174.7±68.6
Blood glucose (mg/dl)	113.3±51.2	113.4±47.6	113.3±56.2
Urine protein(164 tested)	58(35.4%)	26(25%)	32(42.1%)
Blood Urea (mg/dl)+	44.5± 42.8++	49.9±49.7	38.2±32.0
	32.8(27.5)+++	37.0(29.7)	28.0(22.0)
Blood Creatinine (mg/dl)+	1.5±2.0++	1.8±2.4	1.3±1.5
	0.9(0.8)+++	1.0(0.8)	0.8(0.5)

Estimated glomerular filtration rate+	94.6±51.7++ (90.2)&	95.2±52.6 (89.1)	93.8±50.7 (91.2)
HIV positive(150 tested)	4(2.7%)	3(3.4%)	1(1.5%)

Abbreviation: *=p<0.05, **p<0.001, NYHA= New York Heart Association, COPD=Chronic Obstructive Pulmonary Disease, BP= Blood Pressure, HF= Heart Failure + Data is skewed. ++ reflect mean (SD), +++ reflect Median(IQR), &= median value

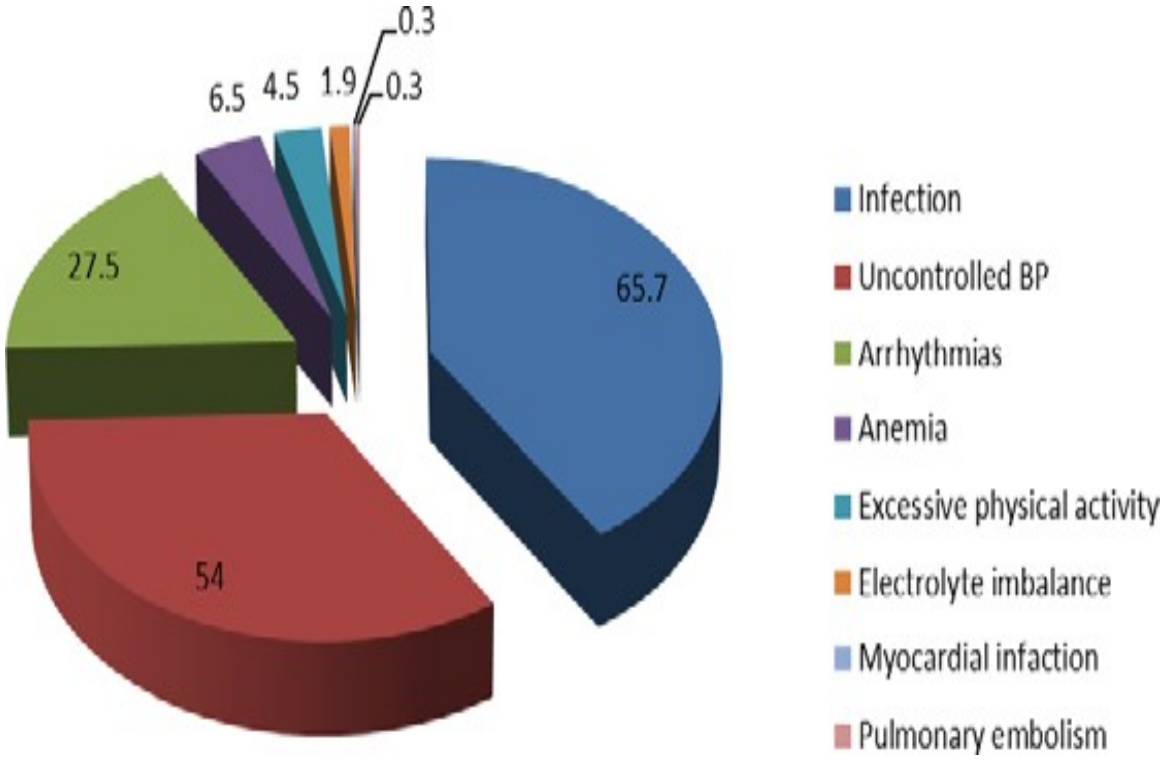


Figure 8.2. Pie chart showing the precipitating factors identified in the 320 hypertensive subjects

Table 8.2. 12-Lead ECG and Echocardiographic abnormalities in the 320 hypertensive subjects

Variable	All (n=320)	Men (n=184)	Women (n=136)
Ventricular Rate (beats/min)	96.8±20.4	95.8±17.1	98.4±25.2
QRS Duration (msec)	109.8±24.7	113.1±23.9	104.4±25.5
QT Interval (msec)	364.8±44.3	368.5±36.6	358.8±54.6
Corrected QT(msec	454.8±35.4	457.5±35.5	450.3±35.5
Atrial Fibrillation /Flutter	41(12.8)	23(12.5)	18(13.2)
ECG LVH++	309(96.5)	173(94.3)	136(100)
ECG LVH with Strain	138(43.0)	87(47.2)	49(36.4)
Aortic root diameter (cm)	3.10±0.50	3.24±0.50	2.90±0.39
Left atrial diameter (cm)	4.68±0.85	4.77±0.86	4.55±0.81
Left atrial Area*	26.6±8.1	27.7±8.3	24.8±7.36
IVSTd (cm)*	1.35±0.37	1.40±0.41	1.28±0.29
IVSTs (cm)*	1.60±0.85	1.67± 0.55	1.48±034
LVIDd (cm)*	5.52±1.49	5.84±1.47	5.08±1.40
LVIDs (cm)*	4.57±1.49	4.86±1.43	4.15±1.31
PWTd (cm)*	1.19±0.36	1.22±0.30	1.15±0.35
PWTs (cm)*	1.65±0.37	1.66±0.38	1.65±0.37
Fractional shortening (%)	17.9±8.7	17.4±8.7	18.7±8.6
Ejection fraction (%)	42.9±16.5	41.8±16.6	44.5±16.3
LV Mass (g)*	338.4±133.6	376.4±140.8	283.9±100.4
Indexed LV Mass ($g/ht^{2.7}$)*	90.4±37.7	96.7±41.8	81.1±28.0
Relative wall thickness	0.45±0.15	0.44±0.15	0.47±0.15
LV geometry (n=263)			
Normal geometry (%)	4.2	4.5	3.7
Concentric remodeling (%)	7.2	3.9	12.0

Concentric hypertrophy (%)	42.6	43.2	41.7
Eccentric hypertrophy (%)	46.0	48.4	42.6
Mitral 'E' Wave	0.82±0.29	0.80±0.28	0.85±0.32
Mitral 'A' Wave	0.53±0.25	0.50±0.23	0.57±0.28
E/A ratio	2.05±1.45	2.11±1.52	1.95±1.35
Deceleration Time (msec)	144.3±57.6	141.5±55.1	148.6±61.4
IVRT(msec)	116.4±34.8	118.5±36.5	113.0±31.9
LV filling pattern (n=262)			
Impaired relaxation(%)	26.7	26.4	27.2
Pseudonormalised filling(%)	45.5	45.3	45.6
Restrictive filling(%)	27.9	28.3	27.2
Mitral regurgitation (%)**	79.1	78	80.3
Tricuspid regurgitation(%)**	60.8	58.2	63.9
Aortic regurgitation(%)**	47.7	43	46.7
Systolic HF(n/%)	182(65.5)	114(69.9)	68(59.1)
Diastolic HF(n/%)	96(34.5)	49(30.1)	47(40.9)

Abbreviation: *=p<0.05.++ LVH diagnosed by Sokolow-Lyon and or Cornel Criteria. IVSTd= Interventricular septal wall thickness in diastole, PWTd= Left ventricular posterior wall thickness in diastole, LVIDd= left ventricular internal diameter in diastole, LVIDs= left ventricular internal diameter in systole, FS= fractional shortening, EF= ejection fraction, LV= left ventricular, E =LV early filling velocity, A=Left ventricular late filling velocity, IVRT= isovolumic relaxation time, HF= Heart Failure. **Moderate/severe AR, MR and TR were present in 3.6, 31.6 and 21.1% respectively

In terms of drug administration 278(86.9%) were on loop diuretics, 25(7.8) on thiazide diuretics, 319(99.1%) were on ACEI/ARBs while 98(30.6%) were placed on long acting calcium channel blockers (CCBs). 81.3%, 73.1%, 15.3% and 2.7% were on spironolactone, digoxin, hydrallazine – isosorbide combination and beta blockers respectively. (**Figure 8.3)**

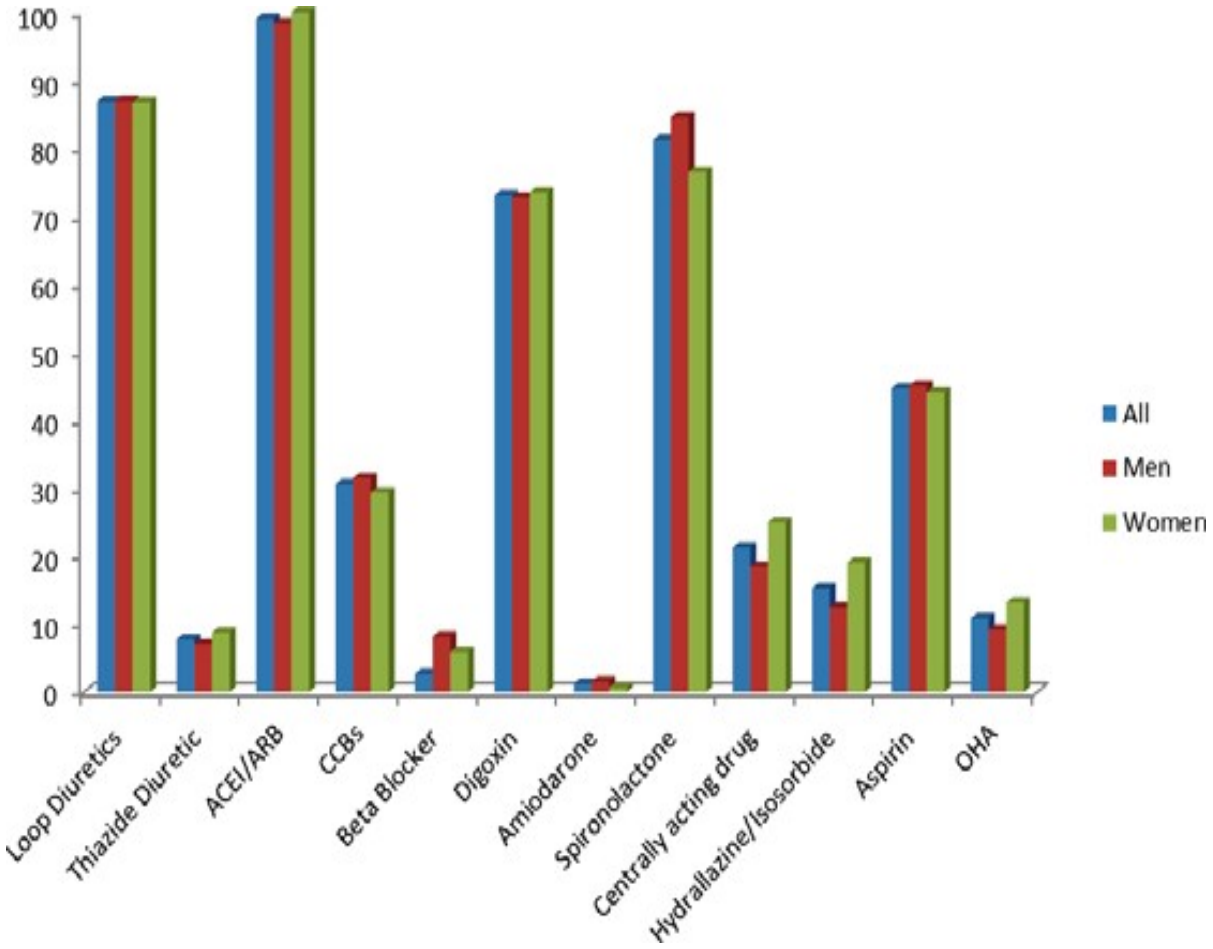


Figure 8.3. Bar chart showing the pattern of drug prescription in the 320 hypertensive subjects.

7.3.1. Outcome

The median length of hospital stay was 9-days and this was same in both men and women. There were eleven intrahospital deaths (5 men and 6 women) giving in-hospital mortality of 3.6% (3.4 and 3.8% for men and women respectively)

The rehospitalisation rates at 30-day, 90-day and 180-day were 4.2% (95%CI-2.3-7.6), 5.6% (95%CI-3.3-9.5), 7.3% (95%CI-4.5-11.7) respectively **(Figure 8.4A)**

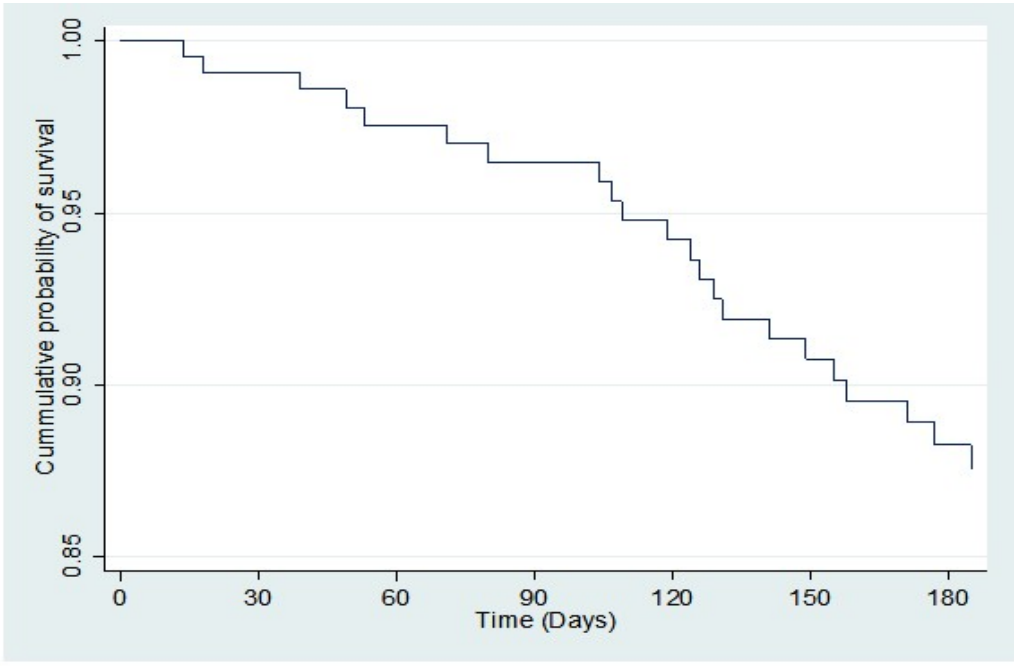
Similarly, the 30-day, 90-day and 180-day mortality rates were 0.9% (95%CI-0.2-3.5), 3.5% (95%CI-1.7-7.3) and 11.7% (95%CI-7.8-17.5) respectively **(Figure 8.4B)**

Compared to those that survived at 180-days, subjects who died were in worse NYHA class –III & IV (86.7% vs. 38.7%, p<0.001). They also had significantly lower systolic blood pressure (130.7± 20.9 vs. 144.1 ± 32.4mmHg, p=0.030), lower diastolic BP (80.0 ±13.7 vs. 89.3 ± 18.9, p=0.044),and pulse pressure (42.7±13.3 vs. 53.5 ± 12.1 mmHg, 0.009), lower packed cell volume (31.7 ±8.8 vs. 37.7 ± 6.6, 0.011), higher serum creatinine 2.2 ± 2.6 vs. 1.2 ± 1.0, p=0.005) and higher total white cell count (9.4 ±5.2 vs. 7.0 ± 3.5, p=0.019).

Subjects that died also had significantly larger left atrial size, lower mitral A-wave and higher E/A ratio.

In a multiple logistic regression analysis, only serum creatinine was the independent predictor of mortality at 180-days (adjusted OR=1.76, 95%CI-1.17-2.64)

The only significant difference in the rehospitalisation status of the cohort was the serum potassium level. This was significantly higher in the rehospitalised group (4.3 ± 0.9 vs. 3.6 ± 0.7, p=0.011)



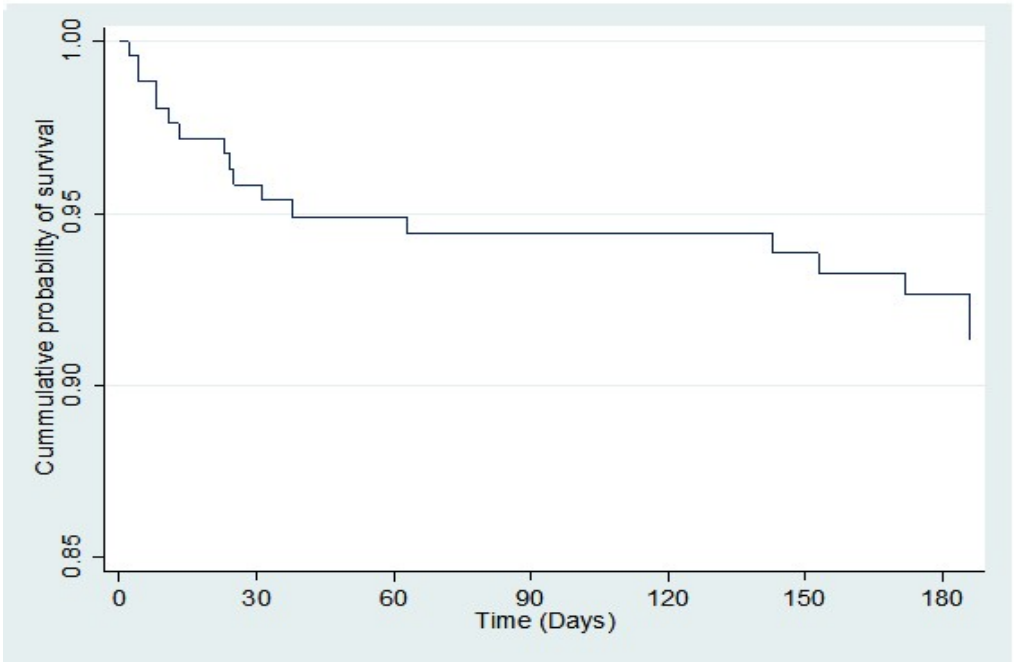


Figure 8.4. A. Kaplan Meier curve showing the rate of mortality of the cohort in 180-days. B. Kaplan Meier curve showing the rate of rehospitalisation of the cohort in 180-days.

8.4 Discussion

There has been limited study on the characteristics and outcome of HT-HF in Nigeria and this is the first comprehensive study of this disorder in the country.

Our findings from this study indicate that HT-HF is a problem of middle aged Nigerians. Only 46% were above the age of 60-years. Majority of the patients present with severe symptoms and are in worse NYHA functional class (82% were in NYHA III or IV). We also noted that severe LV remodeling patterns and frequent functional valvular dysfunction were common in a predominantly denovo HF (Moderate/severe AR, MR and TR were present in 3.6, 31.6 and 21.1% respectively). Co-morbid conditions were common. While the use of disease modifying drugs such as ACEI/ARB and spironolactone was high, the rate of use of beta-blockers and hydrallazine – isosorbide was abysmally low. Finally intra-hospital mortality of 3.4% (95% CI 1.5-6.6%) was recorded.

Table 8.3 depicts the comparison of our data with previous studies in other parts of Africa and high income countries. While our subjects were slightly older than a Cameroonian study (59.3 vs. 54.9 years) (Dzudie et al., 2008), they were younger than hypertensive subjects in South Africa (61years) (Stewart et al., 2008), Europe (69.8years) (Nieminen et al., 2006b) or North America (74.8 years) (Sato et al., 2010)

The male preponderance in our cohort is similar to the report from Europe.(Nieminen et al., 2006a, Nieminen et al., 2008). Higher frequency in women has been reported elsewhere.(Stewart et al., 2008, Sato et al., 2010) The rate of co-morbidities (diabetes mellitus, CAD, COPD, stroke, atrial fibrillation) is lower in our cohort compared with similar data in Europe and America (Table III). This not unconnected with higher rate of CVD risk factors in Europe and America such as cigarette smoking, obesity, dyslipidemia etc. The frequency of anemia is similar. The mean blood pressure compares well with the report from South Africa(Stewart et al., 2008) but lower than the mean blood pressure in the ATTEND registry.(Sato et al., 2010) Our subjects had more severe LV systolic

dysfunction and larger LA size (surrogate of LV diastolic dysfunction) compared to previous reports elsewhere.(Stewart et al., 2008, Nieminen et al., 2006a, Sato et al., 2010)

The use of disease modifying drug such as ACE inhibitors is comparable to previous reports however beta-blocker utilization is very low in our report.

The intrahospital outcome is better than the report from a Polish report but worse than that of EuroHF survey and that ATTEND registry.

Several factors could explain the severity of the disease in our cohort. Late presentation is one reason. Most often the patients are unaware that they have high blood pressure. In a recent review it was found that only 14.2-30% of Nigerian are aware that they are hypertensive, 18-21% are on treatment and only 9% are controlled.(Ogah et al., 2012b) Other factors may include ignorance, lack of health education, weak healthcare system and poor social support.

Some reasons may account for lower history of stroke in our study compared to data from high income countries. It is possible that most of our stroke patients die and do not live long enough to develop HF. Better facilities available for care of stroke patients may have accounted for higher number of subjects with previous history of stroke in advanced countries. In a 10-year review of stroke, Ogun et al(Ogun et al., 2005) documented that that the case fatality at 24-hours , 7-days, 30-days and 6-months were 9%, 28%, 40% and 46%, respectively[154]. In 2007, mortality from stroke in the country was put at 126/100, 000 population.(Strong et al., 2007)

An important feature of our study is the assessment of LV geometry and filling pattern in hypertensive HF patients which has been scarcely studied in Africa. Severe forms of LV geometry (concentric or eccentric hypertrophy) were frequent which is indicative of severe myocardial remodeling in our HF patients.

Presence of high frequency of pseudo-normalized and restrictive LV filling pattern indicates severe degrees of LV diastolic dysfunction. This may also explain the high frequency of valvular abnormalities in our cohort.

Some of the potential reasons for the high prevalence of severe diastolic dysfunction in our study population may include severity of the hypertension and LVH. Race as well as salt sensitivity may also be responsible.

The commons reasons for the low utilization of beta-blockers in our cohort could include severity of disease and oedema at presentation, low blood pressure on admission, poverty (since patients pay out of their pocket and sometimes ignorance on the side of the care givers. The high rate of use of digitalis could be related to the high burden of systolic HF as well as ignorance on the part of health professionals

These finding s provide an opportunity for intervention (education and training of health care providers) The finding that presence of renal impairment is an independent predictor of outcome in our cohort supports the known abysmal outcome of patients with chronic kidney disease (CKD) in Nigeria and in most African countries.(Seck et al., 2013, Ulasi and Ijoma, 2010) In most cases renal replacement is out of the reach of patients because of high cost or non-availability.

Table 8.3. Comparison of our findings with similar studies in other parts of the world

Characteristics	**Present study (n=320)**	**HOS(Stewart et al., 2008) (n=281)**	**EHFS II(Nieminen et al., 2006b) (n=200)**	**AHEAD(Sato et al., 2010) (n=149)**	**Venskutonyte et al(Venskutonyte et al., 2009) (n=65)**
Female (%)	42.5	61	39.6	65.4	33.3
Mean age (yrs.)	59.3	61	69.8	74.8	65.5
Denovo HF (%)	85.6	NA	37.3	74.3	66.7
NYHA III+IV (%)	82.2	29	NA	34.0	NA
Previous history of hypertension (%)	90.6	100	94.6	94.3	100
Diabetes mellitus (%)	12.2	14	34.5	43.1	33.3
Previous MI or CAD (%)	0.3	1.0	53.8	26.4	46.7
COPD (%)	2.5	NA	18.0	17.8	26.7
Stroke or TIA in History (%)	0.3	12	16.0	26.4	20
Atrial Fibrillation (%)	12.8	9	37.7	19.0	46.7
Mean systolic BP(mmHg)	144	140	NA	198	NA
Mean diastolic BP(mmHg)	91	80	NA	100	NA
Heart Rate (beats/min)	96	NA	NA	93	NA

Body Mass Index (kg/m^2)	24.2	NA	NA	28.0	33.9
Hospitalization for HF within last 12 months (%)	82.2	NA	NA	45.1	46.6
Renal Failure (%)	14.4	27	18.7	NA	NA
Anaemia (%)	11.5	10	11.3	NA	NA
Infection (%)	63.4	NA	15.6	NA	13.3
Non-Compliance with Therapy (%)	74.1	NA	21.9	NA	66.7
ACE Inhibitors (%)	99.1	NA	NA	71.3	NA
Beta-blockers (%)	2.7	NA	NA	77.0	NA
Calcium antagonists (%)	30.6	NA	NA	51.1	NA
Diuretics (%)	86.9	NA	NA	88.5	NA
Spironolactone (%)	81.3	NA	NA	36.2	NA
Digoxin (%)	73.1	NA	NS	13.8	NA
LVEDD (mm)	55	46	56	NA	50*
Mean ejection fraction	42.7	53	44	55	50.5
LA (mm)	47	NA	45	NA	42*

Mitral regurgitation (%)	79.1	7	77.6	NA	100
Tricuspid regurgitation (%)	60.8	6	53.7	NA	93.3
LOS days, median	9	NA	8	NA	13
Intra-hospital mortality (%)	3.4	NA	1.5	2.2	6.6

8.4.1 Perspectives

The study has some important clinical and public health implications. In view of the rising burden CVD risk factors especially hypertension in Nigeria, our finding may indicate possible increase in the burden of heart failure and other hypertensive target organ damage. This is against the background of high burden of HIV/AIDs and other communicable disease that has place a lot of strain on the weak health system of the country.

There is therefore need for regular and systematic national and regional data necessary for policy. It is important to set up chronic disease clinics at the community level to cater for diseases such as hypertension and the twin sister- diabetes mellitus. This will reduce the burden on general physicians as well as reduce the waiting time encountered by hypertensive patients in most general clinics. Government can also subsidize the cost of drugs as the burden of out-of-pocket purchasing of medications often lead to non-compliance.

Basic equipment for measuring BP should be made available at all levels of care in the country especially at the PHC. Capacity building in the form of training and retraining of health workers as well as education of the general population on the significance of causes and control of hypertension is important.

At the individual level, the use of nurse led PHC for the diagnosis and follow-up has been shown to be effective.(Sindhu et al., 2010) Integration of blood pressure control into other control programmes such as HIV/AIDS control programmes have been demonstrated to be useful and effective in some countries such as Cambodia and South Africa.(Levitt et al., 2011) The national policy on non-communicable disease must be put into use especially at the primary health care (PHC) level. The national guideline on the management of hypertension has to be tailored to the needs and peculiarities of the Nigerian environment. The guideline should also be available and accessible to healthcare providers at all levels of care. The process of procurement and distribution of anti-hypertensive medications has to be standardized in order to prevent “out of stock”

syndrome. There must also be quality control in order to stop the flow of counterfeit medications in the country.

Reduction of salt intake is one of the most cost effective approaches to BP control. In this regard Nigeria can learn from South Africa that recently passed a law that will regulate the amount of salt in processed foods in the country.(2012b)

The global risk management approach must remain the key message in Nigeria. This has been shown to be economically beneficial in many third world countries.(Gaziano et al., 2008)

Finally community participation is an important approach in public health control programmes in SSA. The use of traditional and religious rulers has produced good results in many primary healthcare programmes and this can be applied to BP control.

8.4.2 Limitations

This study has some limitations. Because the study was hospital based, it may not have captured all cases of heart failure in the community especially those with mild disease as well as chronic stable HF cases. However, effort was made by the group to inform healthcare providers (both in public and private health institutions) in the community about the registry. More so our institution was the only one that had the services of a cardiologist and that has cardiac evaluation tools in the city. We may not have captured some of the heart failure cases that presented to the out-patient department. A community based data is better in order to estimate the true burden of the disease in the state.

We could not assess biomarkers in this study due to cost constraint.

LV systolic function evaluation did mid include mid-wall function assessment which has been repeatedly shown to be prognostically valuable and to respond to treatment in hypertensive heart disease.(Verdecchia et al., 2001, Wachtell et al., 2010) Finally some of the newer parameters for accessing diastolic function were not used in this study.

8.4.3 Conclusion

In conclusion, HT-HF afflicts Nigerians in their productive age group with attendant economic loss high disability adjusted life years. The disease is often severe due to late presentation. Efforts should be made at the community level to ensure primordial prevention, early detection, treatment and control of hypertension in the country.

In the previous chapters, we explored the contemporary profile of Nigerian patient presenting with acute HF including their antecedents, clinical presentation and indeed health outcomes following their initial admission with acute HF. In order to respond to increasing burden of acute and chronic forms of HF in the region, it is imperative to understand the economic burden of acute HF.

In this chapter we describe the economic cost of HF (both direct and indirect cost) in Abeokuta for the year 2010. The annual cost per person was calculated.

Chapter 9: The economic cost of acute HF in Abeokuta, Nigeria

Published paper 5.

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RESEARCH ARTICLE

Economic Burden of Heart Failure: Investigating Outpatient and Inpatient Costs in Abeokuta, Southwest Nigeria

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Abstract

Background: Heart failure (HF) is a deadly, disabling and often costly syndrome world-wide. Unfortunately, there is a paucity of data describing its economic impact in sub Saharan Africa; a region in which the number of relatively younger cases will inevitably rise.

Methods: Heath economic data were extracted from a prospective HF registry in a tertiary hospital situated in Abeokuta, southwest Nigeria. Outpatient and inpatient costs were computed from a representative cohort of 239 HF cases including personnel, diagnostic and treatment resources used for their management over a 12-month period. Indirect costs were also calculated. The annual cost per person was then calculated.

Results: Mean age of the cohort was 56.0 ± 15.1 years and 53.1% were men. The total computed cost of care of HF in Abeokuta was 76, 288,845 Nigerian Naira (US$505, 595) translating to 319,200 Naira (US$2,126 US Dollars) per patient per year. The total cost of in-patient care (46% of total health care expenditure) was estimated as 34,996,477 Naira (about 301,230 US dollars). This comprised of 17,899,977 Naira- 50.9% ($US114,600) and 17,606,500 naira −49.1%($US118,710) for direct and in-direct costs respectively. Out-patient cost was estimated as 41,292,368 Naira ($US 275,282). The relatively high cost of outpatient care was largely due to cost of transportation for monthly follow up visits. Payments were mostly made through out-of-pocket spending.

Conclusion: The economic burden of HF in Nigeria is particularly high considering, the relatively young age of affected cases, a minimum wage of 18,000 Naira ($US120) per month and considerable component of out-of-pocket spending for those affected. Health reforms designed to mitigate the individual to societal burden imposed by the syndrome are required.

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9.1 Introduction

Heart failure (HF) has recently emerged as a global health problem.(Cook et al., 2014) It is a highly symptomatic syndrome that affects 2-3% of the population in high income countries especially in people above the age of 65 years.(Redfield et al., 2003, Mosterd et al., 1999) Approximately 15 million (out of 900 million) Europeans and 5.8 million (out of 300 million) Americans are affected by HF.(Wijeysundera et al., 2010, McMurray et al., 2012) The burden of HF has increased due to increasing elderly population as well as improved survival of patients with risks of HF such as acute myocardial infarction, hypertension and diabetes mellitus.(Nagamine et al., 2006, Hines et al., 2006) In response, strategies for the effective management of the disease in the outpatient setting have been developed and applied.(McMurray et al., 2012) This has led to improved survival in some countries.(Wijeysundera et al., 2010, MacIntyre et al., 2000, Schaufelberger et al., 2004) In high-income countries, the economic burden of HF is high because it is associated with frequent hospital admissions.(Stewart et al., 2002, Ryden-Bergsten and Andersson, 1999) Moreover, management of HF places significant financial burden on patients, their families/ care-givers and, as indicated, society as a whole.(Araujo et al., 2005, Stewart et al., 2002, Stewart, 2005)

Until recently, little was known about the emerging problem of non-communicable forms of HF supplementing traditional pathways to the syndrome in sub-Saharan Africa. Contemporary studies from South Africa(Stewart et al., 2008, Sliwa et al., 2008) and Nigeria(Ojji et al., 2013, Ojji et al., 2009, Laabes et al., 2008, Ogah et al., 2014a) have built on historical reports to demonstrate that the aetiology, natural history and indeed case profile of HF (i.e. more women and younger individuals affected in the prime of their life) is different from high-income countries. As such, HF is now responsible for 7-10% of medical admissions in the region.(Ojji et al., 2013, Oyoo and Ogola, 1999, Ogah et al., 2014a) Significantly, given its potential enormous cost implications (both related to direct health care costs and economic burden on affected individuals and their families) there is

virtually no data on the economic burden of HF in sub-Saharan African countries and major populaces such as Nigeria.

9.1.1 Study Aims & Objectives

The aim of this study, therefore, was to determine the consumption of health care resources for the treatment of HF in Abeokuta, Nigeria and to estimate overall healthcare costs associated with its management in a large and representative cohort of affected cases. Data were used to estimate the annual cost of HF in the region to inform health care policy towards efficient use of resources to mitigate the individual to societal impact of the syndrome.

9.2 Material and Methods

9.2.1 Ethics Statement

This study was approved by the Federal Medical Center Abeokuta and University of Witwatersrand Health Research Ethics Review Committees and all the participants provided informed consent in writing, in accordance with the Declaration of Helsinki. (Rits, 1964)

9.2.2 Study site

The study was undertaken at the Federal Medical Centre, Abeokuta, Ogun state, southwest Nigeria. The state has a population of about 3,751,140 inhabitants.(2014c) Abeokuta is the state capital and has a population of about a million people.(2014a) As described previously (Ogah et al., 2014a), Federal medical center Abeokuta is a tertiary institution that receives referrals from primary and secondary health facilities within and outside the state. All the patients that were discharged alive were given monthly appointments for clinical review as well as for refill of their medications. Patients pay out of pocket and many may not be able to buy medication that will last for longer period. Home based nursing care is not in existence in the city and in many parts of the country. Patients are often taken care of by their relations. Healthcare cost in the city of Abeokuta and in most parts of Nigeria is generally borne by the patient through out of pocket payment payments.

Only a small proportion of the Nigerian population has access to social health insurance.(Soyibo et al., Lawanson et al., 2012, 2012a) However, there exist very strong family bonding and extended family systems where poor patients are assisted by their wealthy or well-to-do family members. The limited coverage of social health insurance in Nigeria is a very big challenge to the achievement of universal health coverage and health care delivery in the country.

9.2.3 Study design and sample

As described previously(Ogah et al., 2014a), the Abeokuta HF registry was a hospital based, prospective, observational registry that ran from January 2009 to December 2010 which was established to determine the current clinical profile of HF in the city as well as to assess typical clinical outcomes and healthcare costs (the focus of this report) associated with HF. A more detailed description of the registry has been documented.(Ogah et al., 2014a) Briefly, all cases of HF presenting to the hospital were captured into the database. Private health facilities, primary health centres as well as health workers were sensitized on the existence of the registry with good response. To a large extent, the sample was fully representative of the population. During the period, HF was responsible for 9% of total medical admission (Ogah et al., 2014a) a figure that is consistent with equivalent reports from other parts of Africa.(Oyoo and Ogola, 1999, Laabes et al., 2008, Stewart et al., 2008)

9.2.4 Data collection

A specific data extraction proforma was developed and used to obtain data on resource consumption in those cases enrolled in the Abeokuta HF registry. The clinical diagnostic criteria employed in the diagnosis of HF have been described elsewhere.(Ogah et al., 2014a) Clinical diagnoses were coded using the International Classification of Diseases (ICD-10) coding system.(2010) The proforma was used to extract the following direct outpatient and inpatient cost categories as shown in the textbox below.

9.2.5 Health Care Expenditure

i. Direct Health Care Costs

The inpatient costs include the cost of medical and nursing care, cost of investigations and drugs. It also includes the cost of surgery and procedures as well transportation to and from the hospital. Personnel costs include the opportunity cost of medical care, nursing as well as ancillary support by other health workers. The wages of these health workers were derived from the Federal Government of Nigeria salary scales. This included their basic salary; call duty allowance, hazard allowance and housing allowance. We did not capture cost associated with purchase of medications over the counter, cost of alternative medical care which is common in Africa, aids, home modifications etc. We assume that these categories are likely to represent a very small percentage of the total costs identified from this study. We also did not capture capital costs.

ii. Indirect Health Care Costs

For indirect costs, the days of lost work (productivity loss) were calculated and the minimum wage used to monetize them.

Cost Component

A. In-patient care

i. Direct cost

- Hospital care (Medical consultation, Nursing care, utility fees, accommodation and feeding and ward consumables including oxygen)
- Laboratory investigations
- Medications
- Surgery and procedures
- Transportation

ii. Indirect cost(the days of lost work (productivity loss)

B. Out-patient care

i. Direct cost

- Clinic visits
- Laboratory investigations
- Medications

Transportation

ii. Indirect cost: the days of lost work (productivity loss)

Text box showing summary of the cost components.

In-patient cost

The standard costing table (unit costs) of the Federal Medical Center, Abeokuta for the year 2010 was used for computing the cost of consultations, hospital admissions, medical consumables, medical investigations, and drug therapy **(see Text box above).** It was assumed that the cost of single hospital admission covers the cost of treatment in the emergency room as well as in the medical ward. The cost of medications was taken as a whole. We assumed that the cost of medications had remained unchanged throughout the year.

Out-patient costs

This was also grouped into direct and indirect costs. All the patients that were discharged alive were given monthly appointments for clinical review as well as for refill of their medications **(see Text box).**

Specific costs

i. **Cost of drugs**

The costs of drugs were based on the hospital's price list (which includes the tender prices plus a 10% mark up or dispensing fee). The frequency of use of the various categories of drugs was based on the findings from the HF registry. The most frequent dosage was used for cost calculation. We did not account for increase or reduction in dose of the drugs during the course of treatment. We assumed that substitution of one class or brand of medication occurred without additional costs.

ii. **Cost of Laboratory and diagnostic tests**

The cost of all laboratory and diagnostic tests (haematological, biochemical, microbiological, chest radiography, electrocardiography and echocardiography) were based on the price list of the hospital in 2010. The rate of consumption of these items was also garnered from the HF registry.

iii. Cost of Surgery and Procedures

The cost of surgeries and procedures were obtained from the Lagos State University Teaching Hospital (LASUTH), as well the Reddington multi-specialist hospital, Lagos where majority of the surgeries and procedures were performed.(Falase et al., 2013, Johnson et al., 2014) The surgeries and procedures include valve surgeries, coronary angioplasty/stenting, pericardiectomies etc. Total cost was multiplied by the frequency of the surgeries and procedures.

9.3 Estimation of indirect costs

The human capital approach was used to estimate the indirect cost. The average annual earning of the patients was estimated based on their occupational group. These were used to calculate their average daily earnings. The product of the working days lost and average daily earnings provided the productivity losses associated with HF in the study and these were assigned monetary values.

Cost analyses

All available costs (as detailed above) associated with in-patient care, out-patient care as well as the opportunity costs associated with HF management in the city were computed for the year 2010. An annual, prevalence based approach was employed in estimating the cost of the resources used for the management HF.(Stewart et al., 2002, Ryden-Bergsten and Andersson, 1999, Czech et al., 2013, Araujo et al., 2005) Healthcare costs were then expressed in the local currency-Naira, (and converted to US Dollar [$US] at a rate of 150 Nigerian Naira to $US1 in 2010).

9.4 Results

Outpatient and inpatient costs were computed from a representative cohort of 239 HF cases over a 12-month period for the year 2010. **Table 9.1** provides a summary of the study cohort used to derive all HF-related health care activities. Mean age was 58.0±15.1 years, 46.9% were female and around one third were aged ≤ 55 years and in the prime of their potential working life.

9.4.1 Cost of components of in-patient care

i. Cost of hospital care

The following were computed for the subjects: medical consultation (N300/day), nursing care (N200/day), utility fees(N400/day), accommodation and feeding (N900/day) and average cost of ward consumables/patient/ admission (N3500/patient)The estimated cost of hospital care for the year was about 5.5 million naira (about $U36,500)

ii. Cost of laboratory investigations

The laboratory investigations considered in the costing is as shown in **Table 9.2.**The estimated cost was approximately 3.8 million naira (about $US28,000).

iii. Cost of medications

This includes cost of standard drugs for the management of HF, as well as other drugs such as antituberculous drugs used for the management of T.B pericarditis. The estimated cost of drugs was N6,565,527 (about $US43770) **(Table 9.3).**

iv. Cost of Surgery/Procedures

As stated earlier, we estimated the cost of surgery/ procedures for the few patients who were able to afford them. This was estimated to cost N1, 092, 000 (about $US72800) – see **Table 9.4.**

v. Cost of transportation

This was calculated to cost N216, 600 (about $US1, 444) **(see Table 9.5)**

vi. Indirect in-patient care cost

This was estimated to cost N17, 806,500 Naira ($US118, 710) – **(Table 9.6)**

Table 9.1. Sociodemographic profile of the HF subjects seen in 2010

Variable	Value
Gender	
Male (n/%)	127(53.1)
Female (n/%)	112(46.9)
Mean age (years)	58.0(15.1)
Median age(years)	60
Age range (years)	
<24	8(3.3)
25-34	15(6.3)
35-44	21(8.8)
45-54	40(16.7)
55-64	59(24.7)
65-74	63(26.4)
>=75	33(13.8)
Marital status	
Single	32(13.4)
Married	168(70.3)
Widow/widower	5(2.1)
Separated/ Divorced	34(14.2)
Educational level	
No formal education	88(36.8)
Primary (<=6 years)	60(25.1)
Secondary (6-12 years)	44(18.4)
Post-Secondary/University/Postgraduate (>12years)	47(19.7)
Occupation	
Unemployed	20(8.4)
Unskilled labour	146(61.1)
Skilled labour	18(7.5)
Professional	24(10.0)
Pensioner/Retiree	31(13.0)
Place of residence	
Within Abeokuta city	138(57.7)
Outside Abeokuta but within Ogun State	53(22.2)
Outside Abeokuta and outside Ogun State	48(20.1)
Monthly Income of subjects in Naira(Median value)	
Unemployed*	18000(120USD)
Unskilled labour	90,000(600USD)
Skilled labour	240,000(1600USD)
Professional	480,000(3200USD)
Pensioner/Retiree	330,000(2200USD)
Aetiology of HF	
Hypertensive HF	195(81.6)
Dilated Cardiomyopathy	14(5.9)
Pericardial Diseases	8(3.3)
Rheumatic Heart Disease	4(1.7)
Others	4(1.7)
Co-morbidities	
Hypertension	185(77.4)

Osteoarthritis	49(20.9)
Atrial fibrillation	37(15.5)
Diabetes Mellitus	24(10.0)
Chronic Obstructive pulmonary disease	7(2.9)
Others	6(2.4)

*Allocated minimum wage in the country

Table 9.2. Cost of investigations (In-patient)

A. In-patient Investigations					
Investigation	**Cost per test**	**Percent***	**Number**	**Cost (Naira)**	**Cost (US Dollars)**
Urinalysis	200	88	225	45000	300.0
Full blood count	1350	96	229	309150	2061.0
Blood sugar	400	96	229	91600	610.7
Electrolyte and Urea	2500	96	229	572500	3816.7
Lipid profile	3500	65	155	542500	3616.7
Electrocardiography	2500	96	229	572500	3816.7
Echocardiography	5000	92	220	1100000	7333.3
Chest X-Ray	2000	96	229	458000	3053.3
Cardiac enzyme	5000	0.8	2	10000	66.7
INR	3500	10	24	84000	560.0
HIV screening	500	46	111	55500	370.0
Liver function tests	3000	50	120	360000	2400.0
Total Cost				3840750	28005.0
Note: Cost based on the hospital costing list for 2009					
B. Out-patient investigations					
Investigation	Cost per test	Percent*	Number	Cost (Naira)	Cost (US Dollars)
Electrocardiography	2500	96	197	492500	3283.3
Electrolyte and Urea	2500	96	197	492500	3283.3
Total	5000	96	394	985000	6566.7
Note: Calculation based on those that survived, it is assumed that same proportion on admission performed these investigations during follow up					

Table 9.3. In-patient cost of medications

Drug	Route	Dose	Dosing	Unit cost (Naira)	Cost per daily dose(Naira)	Total Cost(Naira)	Number of subjects	Total cost in US Dollars
Frusemide	IV	40mg	3	20	60	13620	227	90.8
Frusemide	Oral	40mg	3	5	15	3405	227	22.7
Amlodipine	Oral	5mg	1	15	15	615	41	4.1
Lisinopril	Oral	10mg	1	15	15	3330	222	22.2
Spironolactone	Oral	25mg	1	10	10	2030	203	13.5
Digoxin	Oral	0.125mg	1	5	5	1015	203	6.8
Carvedilol	Oral	6.25mg	1	25	25	550	22	3.7
Hydrallazine	Oral	25mg	1	5	5	90	18	0.6
Isosorbide dinitrate	Oral	10mg	1	220	220	3960	18	26.4
Heparin (LMW)	SC	40mg	1	1350	1350	209250	155	1395.0
Warfarin	Oral	2.5mg	1	40	40	1120	28	7.5
Atorvastatin	Oral	10mg	1	180	180	7380	41	49.2
Amiodarone	Oral	200mg	2	20	40	200	5	1.3
Antibiotics (Augmentin)	IV	600mg	3	600	1800	399600	222	2664.0
Antibiotics (Augmentin)	Oral	625mg	2	170	340	75480	222	503.2
Prednisolone	Oral	30mg	1	30	30	7170	239	47.8
Anti-tuberculous therapy	Oral	Multiple drugs	1	60	60	480	8	3.2
Aspirin	Oral	75mg	1	2	2	208	104	1.4
Total						729503		4863.4
Grand Total						6565527		43770.2

Source: Federal Medical Centre, Abeokuta costing list, Median length of hospital stay= 9 days, 1 US Dollar = 150 naira (2010)

Table 9.4. Cost of procedures (In-patient)

Procedure	Number	Cost per procedure	Total cost(Naira)	Cost (US Dollar)
Pericardiocentesis	11	20,000	220000	1466.7
Pericardiectomy*	2	150,000	300,000	2000.0
Coronary angioplasty/Stenting*	2	700,000	1,400,000	9333.3
Valve surgery*	5	1,800,000	9000000	60000.0
Total			10,920,000	72800.0

*Source= Lagos State University Teaching Hospital and Reddington Hospital Lagos (Ref),
1 US Dollar = 150 Nigerian Naira,

Table 9.5. Cost of transport (In-patients)

Residence	Number	Mean Cost*	Total(Naira)	Total Cost (Dollars)
Within Abeokuta	138	250	34500	230
Outside Abeokuta but within Ogun State*	53	900	47700	318
Outside Ogun State*	48	2800	134400	896
Total			216600	1444

*Mean Cost= Cost per visit = (to and fro), Source= Transport fair at the city motor park,
1 US Dollar= 150 Nigerian Naira

Table 9.6. Indirect cost (In-patient/ outpatient)

A. Indirect in-patient care cost							
Occupation	Monthly Income	Daily income	Daily income(Dollars)	No of Subjects	Total Income lost/day(Naira)	Income lost (Naira)**	Income lost (Dollar)**
Unemployed*	18000	900	6	20	18000	162000	1080
Unskilled	90000	4500	30	146	657000	5913000	39420
Skilled	240000	12000	80	18	216000	1944000	12960
Professional	480000	24000	160	24	576000	5184000	34560
Pensioners	330000	16500	110	31	511500	4603500	30690
Total	1158000	57900	386	239	1978500	17806500	118710
Note: Income loss was based on 5 working days in a week, **Income loss was based on median Los of 9 days							
B. Indirect out-patient care cost							
Occupation	Monthly Income	Daily income	Daily income(Dollars)	No of Subjects	Total Income lost/day(Naira)	Income lost (Naira)**	Income lost (Dollar)**
Unemployed*	18000	900	6	14	12600	151200	1008
Unskilled	90000	4500	30	130	585000	7020000	46800
Skilled	240000	12000	80	15	180000	2160000	14400
Professional	480000	24000	160	21	504000	6048000	40320
Pensioners	330000	16500	110	25	412500	4950000	33000
Total	1158000	57900	386	205	1694100	20329200	135528
Note: *Assigned the minimum wage in Nigeria, Income loss was based on 5 working days in a week , Because most mortality occurred early, it was assumed that 205 subjects completed follow up, 1dollar =150Nigerian Naira							

9.4.2 Cost of components of out-patient care

i. Out-patient clinic visit

This was based on the cost of medical consultations (N250/visit) and nursing/ ancillary services (N200/visit).The calculated total cost was N29, 700 ($US198 US dollar) – **see Table 9.7.**

ii. Cost of out-patient investigations

This was calculated for subjects who survived initial hospital admission. It was assumed that the proportion of subjects who had these tests during admission were also able to have them done during the follow up period. It was estimated to cost N985, 000 ($US 6567 – see **Table 29B.**

iii. Cost of outpatient medications

This is shown in **Table 9.8.** It was estimated to cost N9, 154,168 ($US61, 028)

iv. Cost of outpatient transportation

This constituted a greater proportion of the out-patient care cost. It was calculated as N9, 717, 000 ($US 64,780) – **see**

v. Indirect out-patient care cost

This was estimated to cost about 20,329,200 Naira ($US135, 528) – **Table 9.6.**

Table 9.7. Cost of clinic visits (Out-patient)

Month (Year_2010)	No of admissions	Mortality	No followed up	No of months followed up	Cost (Naira)	Cost (Dollars)
January	34	0	34	11	4950	33
February	20	0	20	10	4500	30
March	16	1	15	9	4050	27
April	25	5	20	8	3600	24
May	29	1	28	7	3150	21
June	20	2	18	6	2700	18
July	21	1	20	5	2250	15
August	18	0	18	4	1800	12
September	12	1	11	3	1350	9
October	21	2	19	2	900	6
November	9	1	8	1	450	3
December	14	0	14	0	0	0
Total	239	14	225	66	29700	198

Assumption= All the mortalities occurred early in the process of follow up,

Cost of medical consultation= N250. Cost of nursing and ancillary services =N200

Table 9.8. Cost of medications (Out-patient)

Drug	**Route**	**Most frequent dose**	**Most frequent Dosing**	**Unit cost (Naira)**	**Cost per daily dose(Naira)**	**Number of subjects**	**Total Cost(Naira)**	**Total cost in US Dollars**
Frusemide	Oral	40mg	3	5	15	148	2220	14.8
Amlodipine	Oral	5mg	1	15	15	30	450	3.0
Lisinopril	Oral	10mg	1	15	15	203	3045	20.3
Spironolactone	Oral	25mg	1	10	10	203	2030	13.5
Digoxin	Oral	0.125mg	1	5	5	55	275	1.8
Carvedilol	Oral	6.25mg	1	25	25	30	750	5.0
Hydrallazine	Oral	25mg	1	5	5	30	150	1.0
Isosorbide dinitrate	Oral	10mg	1	220	220	30	6600	44.0
Warfarin	Oral	2.5mg	1	40	40	28	1120	7.5
Atorvastatin	Oral	10mg	1	180	180	41	7380	49.2
Amiodarone	Oral	200mg	2	20	40	5	200	1.3
Centrally acting drugs (Alpha methyldopa)	Oral	500mg	2	10	20	36	720	4.8
Aspirin	Oral	75mg	1	2	2	89	178	1.2
Antidiabetic agent (Metformin)	Oral	500mg	2	10	20	22	440	2.9
Antituberculous therapy	Oral	Multiple drugs	1	40	40	8	320	2.1
Total							25878	172.5
Grand Total (for 365-9 days) OR 356 days except for antiTB which were for 6 months							9154168	61417.1

Table 9.9. Cost of transport (Out-patient)

Residence	Number of subjects	Mean Cost per visit(to and fro)	Mean cost for 12 visits in a year	Total Cost in Naira	Total Cost in Dollars
Within Abeokuta	138	250	3000	615000	4100
Outside Abeokuta but within Ogun State*	53	900	10800	2214000	14760
Outside Ogun State*	48	2800	33600	6888000	45920
Total	239	3950	47400	9717000	64780

*Source: Transport fare at the main motor park in the city, 1 US Dollar = 150 Naira,

Assumptions: Almost all the patients came for follow up

9.4.3 Summary of in-patent and out-patient care cost

The total cost of in-patient care was estimated as N34,996,477 ($US301,230). This comprised of N17,899,977 (50.9%, $US114,600) and N17,806,500 (49.1%, $US118,710) for direct and in-direct costs respectively. Direct costs were responsible for 61% of in-patient care costs. About 40% of the direct cost was due to surgery / procedures. Hospitalization, medical investigations, drug therapy, and transportation accounted for 20%, 24%, 15%, and 1% respectively, of costs –**see Table 9.10 and Figure 9.3.**

Table 9.10 summarizes the components and total estimated cost of out-patient care. It was estimated as N41,292,368 ($US 275,282 UD dollars). Direct and in-direct costs were N20,963,168 ($US139,754) and N20,329,200 ($US135,528) respectively, constituting 51% and 49% of total out-patient care costs. Transportation, medications, clinic visits and medical investigations contributed 46%, 44%, 5% and 5% respectively to these costs (**Figure 9.3)**.

9.4.4 Total cost

The total estimated cost of care of HF in Abeokuta for the year 2010 was N76, 288,845 ($US508, 595) translating to N319,200 ($US2,128) per patient per year. The proportional contribution of in-patient and out-patient cost were 46% and 54% respectively. The contribution of various components to the total cost is shown in **Figure 9.3**.

Table 9.10. Summary of various aspects of costs of in-patient/out-patient care

A. Summary of various aspects of costs of in-patient care		
Item	Total cost (in Naira)	Total Cost in US Dollars
Hospitalization	5475100	36500.7
Investigations	3840750	28005
Medications	6565527	43770.2
Surgery and procedures	10920000	72800
Transportation	216600	1444
Total Direct Cost	17189977	114600
Total Indirect Cost	17806500	118710
Grand total	34996477	233310
B. Summary of various aspects of costs of out-patient care		
Item	Total cost (in Naira)	Total Cost in US Dollars
Clinic visit	1107000	7380
Investigations	985000	6567
Medications	9154168	61028
Transportation	9717000	64780
Total Direct cost	20963168	139754
Indirect cost	20329200	135528
Grand total	41292368	275282

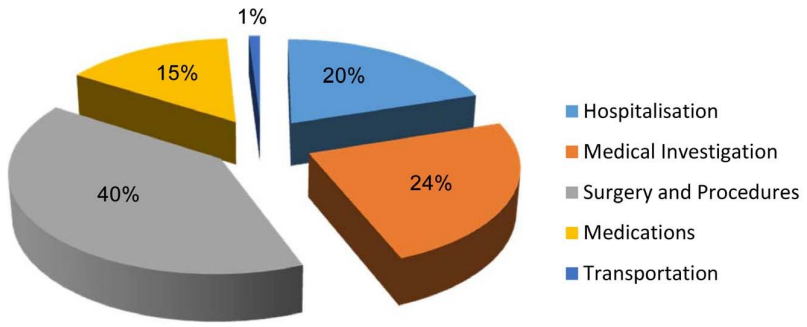

Figure 9.1. Components of direct cost (In-patient)

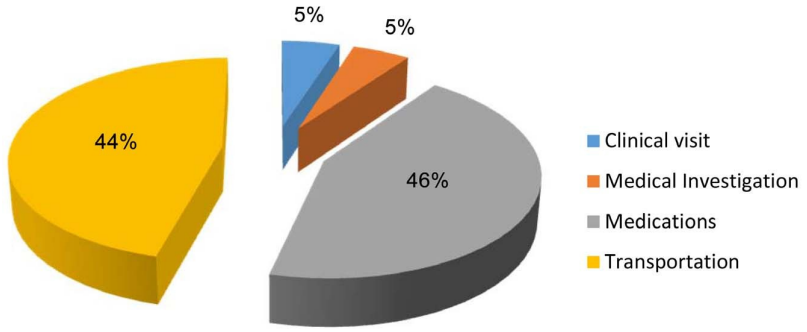

Figure 9.2. Components of direct cost (out-patient)

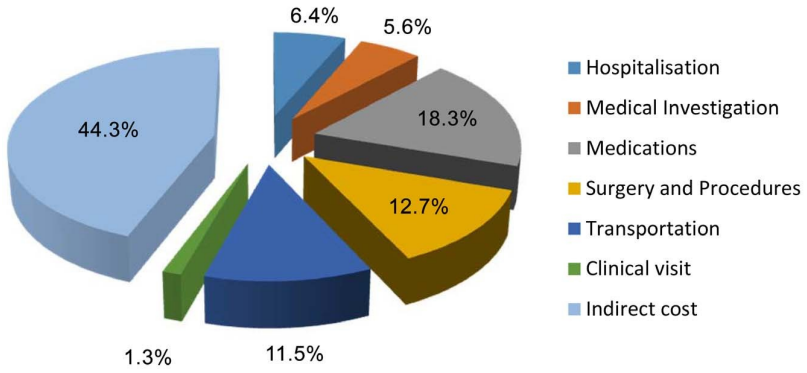

Figure 9.3. Percentage contribution of different components to total cost.

9.5 Discussion

To our knowledge this is the first systematic attempt at estimating the cost of HF in Nigeria; a major populace of sub-Saharan Africa. We have calculated the cost from an individual perspective whilst calculating the total cost per annum overall from a societal perspective. Effort was made to capture all the HF patients in the city of Abeokuta during the study period. All cases of HF presenting to the two major hospitals in the city were captured into the database. Private health facilities, primary health centres as well as health workers were sensitized on the existence of the registry with good response. To a large extent, the sample was representative of the population. During the period, HF was responsible for 9% of total medical admission similar to earlier report from other parts of Africa.(Stewart et al., 2008, Oyoo and Ogola, 1999, Laabes et al., 2008) The main findings of the study are - 1. The total cost of HF or cost per patient per year is enormous considering the context of a developing economy where out-of-pocket expenses is the main means of health care financing;2. Furthermore the estimated cost of HF was fairly distributed between in-patient and out-patient care; 3. A large proportion of direct cost for in-patient care was due to surgery and medical procedures and; 4. Out-patient medications and transportation was responsible for 90% of direct cost of out-patient care. The huge cost of HF has been well documented by several reports both at the individual and population levels. Data from the National Heart and Lung Institute of the United Kingdom shows that the cost of HF per person is approximately 8500 Pounds. At the national level HF costs about 39.2 billion US dollars in America (about 2% of US healthcare budget).(Writing Group et al., 2010) Similar data have been reported from other countries.(Ryden-Bergsten and Andersson, 1999, Stewart et al., 2002) (Araujo et al., 2005, Fagnani et al., 2001)

The distribution of cost of HF in our setting is different from that observed in high income countries(Fagnani et al., 2001, Stewart et al., 2002, Ryden-Bergsten and Andersson, 1999) but similar to one report from Brazil.(Araujo et al., 2005) There has not been any report from Africa to compare our findings with. The contribution of hospital care cost in these countries ranged from 53-75%. Cost of outpatient care was in the range of 4-31% while the cost of drug therapy was between 6-8%

of the total cost of care. The pattern of heart diseases as well as level of technological development influences the mode of care as well as utilization of sophisticated and expensive medical equipment, procedures and consumables which are obviously needed for the care of HF patients. The consumption of these is higher in high income countries than in our setting. This is clearly shown by the impact of surgery/procedures on the cost of hospital care. The few cases (out of the many that needed this) that had surgery for valvular diseases or coronary interventions escalated the hospital care cost in our study.

Other determinants of hospital cost will also include length of hospital stay.(Stewart et al., 2002, Stewart, 2005) (in which our report is similar to European data but longer than the mean length of hospital stay in the USA) Cost of management of co-morbidities has also been shown to account for higher cost of hospitalization in high income countries. In one report on Medicare claims, HF accounted for only15% of the total in-patient cost while 57% were associated with other co-morbid conditions.(Whellan et al., 2010) This may probably be responsible for the huge cost of hospitalization in high income countries compared to our environment.

Due to lack of community based or nurse-led or home care of HF patients in our setting, our patients are given shorter out-patient appointments in order to refill their medications. This is responsible for the high cost attributable to transportation in our report. Because of the younger age of our subjects, HF in our setting is, therefore, associated with longer disability adjusted life years and by extension a huge cost to the society at large.

With the changing demographic and epidemiological landscape in Nigeria coupled with the rising burden of cardiovascular risk factors and non-communicable diseases (especially hypertension) in the country, the rate of HF is predicted to rise if preventive measures are not put in place at all levels. This will put a lot of strain in an already weak health system. The high cost of surgical interventions and procedures is out of the reach of the average Nigerian. Prevention of conditions requiring this mode of care such as rheumatic heart disease, tuberculosis (because of pericarditis)

and coronary artery disease should be a priority for the country at large. Furthermore the need for a functional, effective and efficient social health insurance system in the country cannot be overemphasized considering the fact that majority of those afflicted by HF are poor and are not likely to sustain the treatment of their illness for a long time. There is also need to develop community based HF care in the country as this will reduce the cost of outpatient care which is largely contributed by the cost of frequent transport to-and-from the health facility.

9.5.1 Limitations

This is a hospital based study. Although we tried as much as possible to capture all the HF cases in the city during the study period, there is still the possibility that mild cases may have been missed out especially those that were managed in the out-patient clinic.

"The assumption that the same proportion of patients have investigations (ECG etc.) for the outpatients and inpatients, and that almost all the patients came for follow-up may not be correct. It is likely that a lower proportion of the outpatients (compared with inpatients) will undergo investigations and follow-up (given that the in-patients are not able to miss appointments when in hospital)"

We also did not assess cost based on the severity of HF (NYHA class). Studies have shown that those in NYHA class IV were 8-30 times more expensive to manage compared to those in NYHA class II.(Czech et al., 2013, McMurray and Davie, 1996, McMurray et al., 1993b) Age and sex-specific cost analysis was also not carried out. We also did not include the cost of co-morbidities neither did we capture cost due to alternative medicines (which is common in Africa), over the counter purchases, capital cost and indirect cost by care givers as well as the general cost to the society. These are potential areas of research in our community in the future.

9.5.2 Conclusion

Our data shows the profound impact and importance of HF as a major public health problem in a developing economy like Nigeria that is still battling with communicable diseases. The annual

individual cost of HF is high coupled with the fact that of pocket expenses in the country is over 90%. There is therefore need to reduce this expenditure through control of risk factors for HF in the society especially high blood pressure, reduction in hospital as well as out-patient care cost through the development of community HF care programmes in the country.

Chapter 10: Summary, general discussion, future directions and conclusions

10.1 Summary

We have been able to explore the contemporary profile(Ogah et al., 2014a), intra-hospital outcome(Ogah et al., 2014a), short and medium term outcomes(Ogah et al., 2014c, Ogah et al., 2014d) as well as the economic cost of acute HF(Ogah et al., 2014e) in Abeokuta, South West Nigeria.

We have documented that acute presentation of HF (predominantly denovo) constitute about 10% of all medical admission. We have also shown that the mean age of presentation is about 57-years which is 20-years lower that the age of presentation of acute HF in Europe and North American.(Nieminen et al., 2006a, Adams et al., 2005a)

Individuals with acute HF in the city often present late with severe HF (NYHA III and IV). HF with impaired systolic function is commoner and the risk factors for HF are non-ischaemic especially hypertensive heart disease, dilated cardiomyopathy, rheumatic valvular heart disease and cor-pulmonale. Intra-hospital outcome is similar to findings in other regions of the world.(Ogah et al., 2014a)

In terms of outcomes, the mean length of hospital stay was about 11.4days. Mortality at one month was 4.2% rising to 7.3% at 180-days. Rehospitalization at 180-days was 12.2%. Both socio-demographic and clinical variables affect mortality as well as readmission rates.(Ogah et al., 2014c, Ogah et al., 2014d)

The economic cost of HF in Abeokuta Nigeria is huge considering the early age of presentation and longer disability adjusted life years (DALYs) and paucity of social health insurance in the Nigerian milieu. Unlike in high income countries where cost of care is mainly due to hospitalization, this is fairly shared between in-patient and outpatient care cost in Nigeria (46% and 54%) respectively.(Ogah et al., 2014e)

10.2 Profile of acute HF in the city

The work provides the first comprehensive and detailed profile of acute HF in the city in particular and in Nigeria in Nigeria. Non-ischaemic causes such as hypertensive HF, dilated cardiomyopathy

and rheumatic heart disease constitute a greater proportion of the aetiological risk factor for HF in the city. This is consistent with similar studies in Nigerian(Laabes et al., 2008) and SSA.(Damasceno et al., 2012) Contrary to the findings in this study, HF in high income countries of Europe and America is essentially a disease of the elderly.(Nieminen et al., 2006a)

This portends a huge public health burden as our subjects have higher disability adjusted life years with regards to HF. The younger age of presentation may not be unrelated to the pattern of heart disease in our cohort. Diseases such as rheumatic heart disease and cardiomyopathies are essentially problems of young people and those in the middle age. In addition, it has been shown that hypertension and hypertensive heart disease present earlier in Africans and people of African origin.(Opie and Seedat, 2005)

Secondary valvular dysfunction was a common finding in our cohort. This may explain the severity of symptoms at the time of presentation in our subjects. This may also be due to the severity of cardiac damage prior to presentation. This has also been documented by other workers.(Stewart et al., 2008, Nieminen et al., 2006a)

The study documented and provided an area of public health intervention and improvement of care in the management of HF in the city and Nigeria. The finding of low use of disease modifying therapy in the treatment of HF in out cohort provides opportunity for improvement of care through public education especially amongst heart care providers. This also calls for subsidization of cost of treatment of a chronic condition such a HF by the Government of Nigeria and other countries in SSA.

A comparative analysis of our finding with previous study in Nigeria about 40 year ago shows that hypertension now appears to play a predominant role in the aetiology of HF in Southern Nigeria; infection related heart disease such as rheumatic heart disease, pericardial diseases and endomyocardial fibrosis appear to be less prominent.

The study also provided an in-depth and comprehensive analysis of the commonest aetiology for HF in Abeokuta and Nigerian in general: hypertensive heart failure (HHF).

Less than half of those afflicted were younger than 60years and majority presented in severe HF. Abnormal LV geometric pattern, severe diastolic filling pattern and valvular dysfunction were common. Similar to the general HF cohort our subjects were younger than the average HHF patient in high income country (Nieminen et al., 2006a) but younger than those in some SSA countries.(Tantchou Tchoumi et al., 2011a)

The burden of CV risk factors and co-morbidity was however lower in our cohort compared to finding from high income countries.

Poor hypertension awareness, treatment and control are possible reasons for the severity of the condition in this study. Other factors may include ignorance, weak health system and poor social support system.

10.3 Outcome of acute HF in Abeokuta

There is generally paucity of data on short/ medium term outcome of acute HF in Nigeria.

The finding from the study shows that the mean length of hospital stay (LOS) was 10.8 ± 6.1 (range: 2-61 days medium 9 days).(Ogah et al., 2014c) This is longer than data from the THESUS-HF study(Damasceno et al., 2012) but short than data from elsewhere in Africa. LOS in our study was generally longer than report from high income countries (4-7days).

Intrahospital mortality rate of 3-8% was comparable to 3.8-6.7% reported by several studies in Europe(Siirila-Waris et al., 2006, Nieminen et al., 2006a) and America(Adams et al., 2005a) but lower than several reports from SSA (4.3-9.2%).(Damasceno et al., 2012, Tantchou Tchoumi et al., 2011a)

The findings of HHF constituting majority of our HF population may be responsible for low intrahospital mortality rate. This has been previously documented in the EURO HF survey II.(Nieminen et al., 2006a)

The 30- and 180-days mortality rates were 4.2% (95% CI : 2.4 – 7.3%) and 7.3% (95% CI : 14.7 – 11.2%) respectively. Mortality was associated with lower systolic blood pressure, higher NYHA functional class, lower packed cell volume, higher serum creatinine and larger left atrial area. This is

similar to finding from previous studies.(Nieminen et al., 2006a, Siirila-Waris et al., 2006, Rudiger et al., 2005)

In line with the "obesity paradox", higher BMI was associated with better prognosis.(Fonarow et al., 2008)

The fact that this study was conducted in a cardiology service, as well as the young age of our cohort many explain the relatively low mortality.

It is also possible that the longer stay of our patients in hospital may afford them the opportunity to recover well and get used to their medication before discharge.

HF outcome is generally better in Japan(Sato et al., 2010) where the average LOS is 21 days compared to 6.1-9.0 days in USA(Adams et al., 2005a) and Western Europe.(Nieminen et al., 2006a, Rudiger et al., 2005)

We also report lower rate of readmission (predominantly recurrent HF) at 30days (1.53%) and 180 days (12.2%).(Ogah et al., 2014b) A higher rate of rehospitalization was commoner in the elderly, those with lower BMI, lower literacy and lower serum sodium. Others include presence of atrial fibrillation, as well as presence of valvular and renal dysfunction.

On the other hand, female sex, being single, presence of diabetes mellitus and lower packed cell volume were associated with lower rates of readmission. These are similar to findings by other workers.(Nieminen et al., 2006a, Rudiger et al., 2005, Siirila-Waris et al., 2006)

The readmission rate reported in this study is similar to the finding in the THESUS-HF study(Damasceno et al., 2012) but lower than reports from high income countries.(Adams et al., 2005a, Nieminen et al., 2006a)

The younger age of the cohort, the fact that majority of our subjects had HHF and other forms of non-ischaemic HF and the longer LOS may be responsible for the lower readmission rate in our study. The conduct of this work in a cardiology service may also be another reason. The findings may not reflect the picture in the general population in Nigeria. Nevertheless, the study revealed that

simple sociodemographic and laboratory variables such as age, BMI, serum sodium, presence of atrial fibrillation and valvular dysfunction could be used to predict HF subjects who ae at increased risk of readmission.

10.4 Cost of HF in Abeokuta

The study also for the first time in Nigeria estimated the cost of HF in Nigeria using the data of the Abeokuta HF registry.

The cost of HF per patient per year was found to be huge considering the fact that Nigeria is a developing economy and out-of-pocket expenses is the main means of health care financing. HF cost was fairly and proportionally distributed between in-patient and out-patient care.

The direct cost of in-patient care becomes very huge when surgery and medical procedures are utilized in the care. Medications and transportation constituted over 90% of outpatient care cost.

The finding of huge cost of HF corroborates previous data from many part of the world such as UK(Stewart et al., 2002), Sweden(Ryden-Bergsten and Andersson, 1999) etc.

The almost equal distribution of in-patient and outpatient care cost is similar to a data from Brazil.(Araujo et al., 2005) On the other hand in-patient care cost makes up a large proportion of cost of HF in high income countries of Western Europe and North America.(Agvall et al., 2005, McMurray et al., 1993b, Cook et al., 2014)

The pattern of heart diseases (which are predominately non-ischaemic), LOS, burden of co-morbidities as well as the level of technological development may explain the observed difference.

The burden of co-morbidities is higher in high income countries than in our study. In one USA report, management co-morbid conditions contributed 57% of HF care.

A significant proportion of the outpatient cost is due to transportation. This is because patients are often given short appointments in our setting to refill their drugs.

The establishment of community based or nurse-led or home care of HF patients in our setting could curtail this cost. This has been demonstrated in many high income countries of the world.(Agren et al., 2013, Stromberg et al., 2003)

On the societal point of view, the cost of HF in Nigeria is huge considering the younger age at presentation by our subjects coupled with a longer disability adjusted life years.

Considering the epidemiologic and demographic transition occurring in Nigeria as well as the risking burden of CV risk factors, the burden of HF is likely going to rise. This will put a lot of strain on the already weak heath system with catastrophic consequences.

In view of the high cost of cardiac surgery and cardiac procedures, there is need for government to subsidize the cost associated with this.

Preventive measures are also needed to curtail the burden of conditions such as rheumatic heart disease and coronary artery disease that most often require these procedure.

There is need for implementation of the national health coverage and the health insurance scheme in the country must be made to work in order to sustain the treatment of chronic conditions such as HF.

10.5 Limitations of the study

The cross-sectional nature of this study is a limitation. In addition subjects were recruited mainly from the ward in a tertiary health facility. Individuals with milder forms of HF and those who were seen at the out-patient clinic may, therefore, have been under-represented. In addition, cases of ischaemic heart disease may also have been under-reported because of possibility of sudden death at home and for the fact that the centre does not have facility for coronary angiography.

Furthermore, since it is a single centre study, the findings may not be extrapolated to the general Nigerian population. A regional or national HF registry is therefore needed.

The Framingham criteria used for the screening of the subjects has the limitation in that it has been found to be less effective in the elderly population. Some of the other limitations were highlighted in the previous chapters.

10.6 Future directions

- The study is a single centre, single city urban hospital based one. Future study will explore the regional as well as national burden of HF in Nigeria using a multicentre regional or national registry or survey.
- There is generally no population based incidence or prevalence data on HF in SSA in general and Nigeria in particular. The community or population based data on the burden of systolic or diastolic dysfunction using echocardiography is unknown. In addition, apart from high blood pressure the community burden of other aetiological risk factors for HF such as EMF, rheumatic heart disease and right heart failure is largely unknown. This will also be the focus of future studies.
- The molecular pathobiology of HF in SSA is largely unexplored. This is one area I will to explore in the future.
- The secular trend in HF in the country or in SSA is unknown. This has been well studied in high income countries of Europe and North America.(Chen et al., 2011, Stewart et al., 2001b, Neumann et al., 2009, McMurray et al., 1993a) This is worth studying in the future.
- There is also need for research into best strategies for treatment and prevention of common causes of HF in the country.
- More cohort studies and longer follow up of HF patients is needed in the country to fully describe the natural history of HF in Nigeria.
- An in-depth cost analysis or economic analysis as well as data on quality of care are also not available and needs exploring.
- Clinical trials on HF as well as on risk factors for HF in Nigeria are generally lacking.
- Finally, in-depth scientific approaches to better understand the epidemiology, pathobiology socio-cultural factors, treatment patterns as well as outcome of HF and diseases leading to HF will be the focus of my future research. As suggested by Fonn, “research conceptualized,

conducted, analysed and published by Africans is crucial for Africa to meet the health needs of her people"(Fonn et al., 1991)

The identified gaps/challenges and future directions and possible solutions are summarised in table 10.1.

10.7 Conclusions

Compared to high income countries, individuals presenting with AHF in Abeokuta, Nigeria are relatively younger and still of a working age. It is also commoner in men and associated with severe symptoms and severe LV systolic dysfunction. Hypertension is by far the commonest aetiological risk factor.

With the projected increase in hypertension in the region in the coming years, the burden of hypertension and other complications is expected to rise. There is therefore need to increase awareness, identification, treatment and control of hypertension in the city and Nigeria at large.

Intra-hospital and short- and medium-term outcomes is similar to findings in other parts of the world and has similar clinical and laboratory prognostic factors.

The economic burden of heart failure in the study setting is high considering the minimum wage of 18,000 Naira (120 US dollars) per month in the country. This calls for financing reforms for the control of the disease, which may include a reduction or waiver of user fees in government hospitals, scaling up of financial risk protection pre-payment mechanisms such as health insurance and use of primary healthcare centres for follow-up visits for mild cases. The development and adequate funding of community HF care programmes in the country is also a possible panacea.

10.1. Other identified gaps/challenges and future directions and possible solutions

GAP/CHALLENGE	FUTURE DIRECTION/POSSIBLE SOLUTION
Chronic HF case were not included in this study	A study targeting chronic "stable" HF case will be one of the future projects
No data on population based study of HF either in urban or rural areas of SSA	Further study at the population level is needed
Lack of public health policies in SSA that can promote equity in health care delivery	Multi-dimensional and multi-sectional approach is needed to address this. This requires improvement in finance, education, health, infrastructure, agriculture etc. This will play vital role in primordial prevention of CVDs. It will also improve fetal as well as early childhood nutrition.
Lack of access to CVD care in the rural areas and among the poor in urban areas.	There is need for strengthening of primary and community health programme. This will include training of community health offices and nurses to be able to identify and monitor HF cases in the community.
HF related care is associated with catastrophic experiences	Nigeria and other SSA countries which do not have universal health coverage should work to achieving this.
Weak health systems and inadequate human resources for health	There is need for improvement in the health system especially at the community level. Data is needed to assess the usefulness/effectiveness of task sharing/ shifting in the management of HF in Nigeria in particular and in SSA in general.
Lack if clinical guidelines and protocols for the management of HF and many CVDs in Nigeria and SSA.	There is need for development of locally adapted as well as appropriate practice guidelines and protocols for management of HF and other NCDs in SSA.

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Appendix I (Published Review Articles)

Appendix I is the published review of some of the common risk factors for heart failure in SSA: Hypertension and cardiomyopathy.

Recent advances in hypertension in sub-Saharan Africa

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Recent advances in hypertension in sub-Saharan Africa

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ABSTRACT

Background Hypertension was once considered rare in sub-Saharan Africa (SSA), but currently it has become a widespread problem with immense socioeconomic importance. The purpose of this review is to summarise new information on hypertension in SSA that has been published since the last major review in 2008.

Methods and results A literature search was performed in Pubmed, Embase, WHO Global Cardiovascular Infobase, African Journal On-Line, and African Index Medicus using the following search criteria: hypertension, high blood pressure, and Africa/SSA. Epidemiological surveys that used the WHO STEPS approach or similar methods were also included. The overall prevalence of hypertension in SSA was estimated at 16.2% (95% CI 14.2% to 20.3%) with an estimated number of hypertensive individuals to be 74.7 million. The prevalence of hypertension varies widely from country to country. It is projected that the number of affected individuals will increase by 68% (125.5 million) by 2025. Mass migration of rural Africans to urban areas and rapid changes in lifestyle and risk factors account for the rising prevalence of hypertension.

Conclusions Proactive public health interventions at a population level need to be introduced to control the growing hypertension epidemic, and there needs to be a major improvement in access to hypertensive care for the individual. There is an important need for better epidemiological data and hypertension related outcome trials in SSA.

INTRODUCTION

High blood pressure (BP) is the most common single risk factor for cardiovascular related events and deaths worldwide.[1] In the analysis of the global burden of hypertension, Kearney *et al*[2] estimated that the total number of people affected by the condition will increase between 2000 and 2025, resulting in an additional 560 million people being affected by high BP.

Although Kearney *et al*[2] predicted that the prevalence of hypertension may not rise in sub-Saharan Africa (SSA) compared to other regions of the world, emerging data and recent projections do not support this view. In a recent systematic review it was observed that in the last 10 years systolic BP has risen highest in east, west, and central and southern Africa more than in any other region of the world.[3]

Hypertension is the most common risk factor for development of stroke, congestive heart failure (HF), chronic kidney disease, and coronary artery disease in SSA.[4] Unfortunately, the prevention and control of non-communicable diseases such as hypertension are rarely on the agenda of countries in the region. Thus, the condition is largely under-detected and under-treated due to ignorance and poverty. Complications are often common and severe leading to chronic disability and premature mortality.[5]

The aim of this review is to update information on the epidemiology, pathophysiology, treatment, complications, control, and outcome of hypertension in the SSA region since the last major review in 2008.[6]

METHODS

A literature search was performed using the following search criteria: hypertension, high BP AND Africa/SSA. The following databases were searched: Pubmed, Embase, WHO Global Cardiovascular infobase, African Journal On-Line, and African Index Medicus.

The search criteria were limited to literature published between 1 January 2005 and 31 December 2012. Additional references were obtained through the review of references of articles obtained in the initial search.

Epidemiological surveys that used the WHO STEPS approach[7] or similar methods were included in the analysis.

RESULTS

What is new on the epidemiology of hypertension in Africa?

New surveys and meta-analyses that have been published over the past 5 years and what they add to knowledge

Online supplementary file 1 depicts recent surveys of hypertension conducted in different regions/countries in SSA from January 2008 to December 2012.[w1–w32] It is important to state that in most of the studies, the crude prevalences were presented.

We identified 38 publications from SSA mostly conducted in urban areas: two national surveys (Malawi and Mozambique), 14 in rural settings, 16 in urban communities, one each in semi-urban and semi-urban/rural settings, and four in both rural and urban communities (figure 1).

In the two national studies, the prevalence of high BP was about 31% (35.7% and 37% in men and 37% and 29% in women in Mozambique and Malawi, respectively). In studies carried out 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 Nigerian study was conducted in a middle aged/elderly population (mean age of 61.2 years), which could explain the high prevalence. The values for urban studies ranged from 15.2% in the Democratic Republic of Congo to as high as 47.5% in Cameroon.

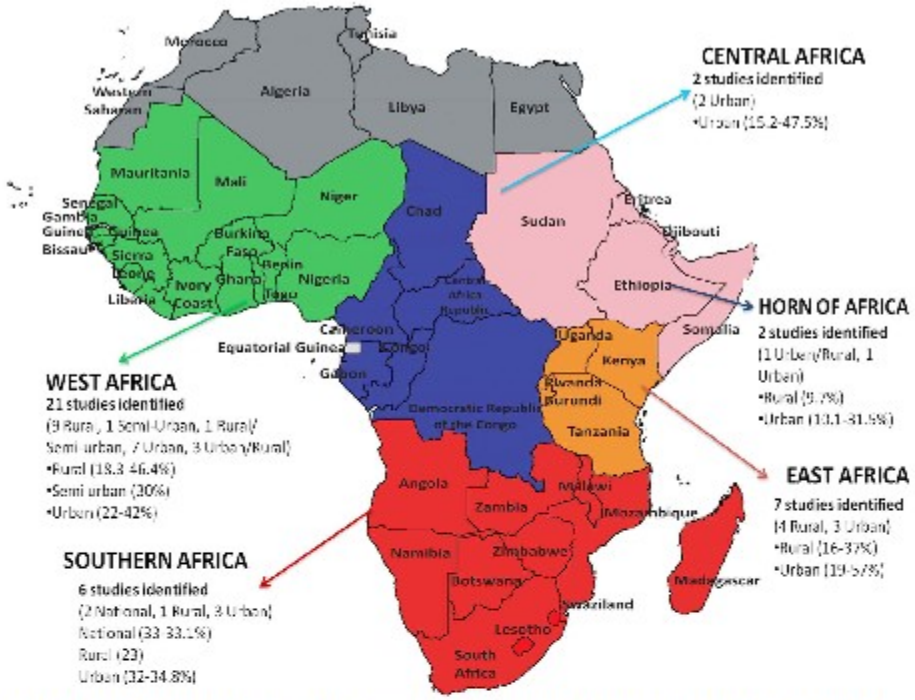

Figure 1 Map of sub-Saharan Africa (SSA) showing the crude prevalence of hypertension in 38 recent studies in different parts of SSA.

Data from studies carried out simultaneously in rural and urban communities show that the prevalence of high BP was generally greater in urban compared to rural settings.

The prevalence of hypertension is generally higher in men than women in most of the studies (see online supplementary file 1).

Recently Twagirumukiza *et al*[8] published the estimates of the current and projected prevalence of hypertension in SSA from population based studies in the region. The authors pooled 15 studies conducted in 11 SSA countries from 1998 to 2008. This included three studies with urban and rural data, four studies with rural data alone, and eight studies with data only from urban areas. The studies were from Ethiopia, Gambia, Ghana, Ivory Coast, Mauritania, Nigeria, Democratic Republic of the Congo, and South Africa.

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%.

The prevalence of hypertension varies from country to country and from one part of SSA to the other. The lowest national estimated prevalence was 10.3% in Ethiopia and the highest was 23.0% in Ghana.

The low prevalence of hypertension in Ethiopia may due to the diet, which is low in sodium but high in potassium.[9] Country variation in the prevalence of hypertension may also be related to differences in the levels of urbanisation and acculturation, diets, cultural habits, and ethnicity. For example, the prevalence of hypertension in SSA is higher in urban than rural populations (22.4% vs 18.2% respectively), but showed pronounced regional differences. In Madagascar the odds ratio (OR) for urban versus rural populations was 1.40 (95% CI 1.04 to 2.17) while in Cameroon it was 2.66 (95% CI 1.90 to 3.74).

The prevalence of hypertension was higher in men than in women (16.8% vs 15.7%, respectively), which was more pronounced in urban areas.

The reasons for these differences are probably related to changes in risk with the adoption of a Western lifestyle, reduced physical activity, and increased salt consumption with reduced potassium intake in urban communities, but also increased sympathetic activity.

Projected prevalence of hypertension in SSA for 2025

Twagirumukiza *et al*[8] used the United Nations Population Fund (UNFPA) data[10] to predict the prevalence of hypertension in the region by 2025. The calculated number of hypertensive individuals living in SSA by 2025 was estimated at 125.5 million (95% CI 111.2 to 162.8 million), which corresponds to an increase of about 68% from 2008 to 2025. The prevalence of hypertension in SSA will rise from 16.2% to 17.4% (CI 15.4% to 22.6%).

Compared with the previous work by Kearney *et al*[2] (which related to the year 2000), the latest report showed a lower age adjusted prevalence rate (27.6% vs 23.3%) and fewer affected individuals (79.8 vs 75 million), and a lower projected prevalence (150.7 vs 125.5 million).

The view of some authorities is that the earlier estimates by Kearney *et al*[2] and the latest by Twagirumukiza *et al*[8] are conservative since they did not allow for any age/gender stratified increases in the prevalence of high BP due to increased exposure to risk factors such as overweight/obesity, increased salt intake, reduced physical activity, reduced intake of fruits and vegetable, and increased alcohol and fat consumption—all of which are associated with development or urbanisation.

Accordingly the current WHO estimates are higher and range from 47.8% in Niger to 31.7% in Eritrea[11] (table 1).

Recent data on hypertension awareness, treatment and control in SSA

Some recent data are available on the rate of awareness, treatment and control of hypertension in SSA. Table 2 shows the results of five publications.[12–16] Like in most parts of the world, awareness, treatment and control of hypertension is still low in SSA. Hypertension awareness ranges from 10.6% among men in Mozambique[13] to 40.3% in Nigerian men.[15] Treatment rates range from as low as 3.5% in Mozambican men[13] to about 60% in a recent study in Cameroon.[16] BP control is also very low in the region, ranging from 1.0% in Mozambican men[13] to 24.6% in an urban setting in the Cameroon.[16]

What the THESUS-HF study has revealed about the contribution of hypertension to HF

The SSA Survey of Heart Failure (THESUS-HF) was a prospective, multicentre, observational survey of patients with acute HF admitted to 12 hospitals in nine countries in the sub-region. Data from the study show that hypertension is the strongest as well as an emerging risk factor for HF in Africa, being responsible for 45.4% of cases.[17]

This implies that the optimal strategy for the prevention of HF in SSA lies in the treatment and control of high BP. This is critically important as hypertension rates will rise in Africa by 89% between 2000 and 2025 compared to a 24% increase in more developed countries.[2]

What INTERSTROKE has revealed about the contribution of hypertension to stroke

INTERSTROKE is an international, multicentre, case–control study designed to establish the relationship of traditional and emerging risk factors to stroke in 84 centres in 22 countries of the world. It is the first large standardised case–control study of the risk factors for stroke in which countries of middle and low income were included.[18]

The initial report from this study shows that stroke occurs at a relatively younger age in Africa compared to other regions of the world (mean age 57.7±15.3 years for Africa, 58.5 ±11.6 years for South East Asia, 58.9±12.0 years for India, 65.6±13.4 years for South America, and 66.0±13.3 years for high income countries). The mean age for all the subjects in the initial report was 61.1±12.7 years.

On the whole a seventh of the subjects were aged 45 years or younger, with the highest proportion in Africa. The study also revealed that hypertension was more associated with stroke in individuals younger than 45 years, meaning therefore that hypertension is the strongest risk factor for stroke in SSA.

This has implications in population based approaches in controlling stroke prevalence in resource poor countries in SSA, because screening programmes require cheap/modest equipment and little expertise. Furthermore, BP can be controlled by cheap drug and non-drug approaches.

Table 1 Recent estimated prevalence of raised blood pressure in Africa according to countries by the WHO

Serial number	Country	2010 population	Men	Women	All
1.	Algeria	35468208	38.3	37.6	38.0
2.	Angola	19081912	–	–	–
3.	Benin	8849892	40.4	37.0	38.7
4.	Botswana	2006945	41.0	40.6	40.8
5.	Cameroon	19598839	39.6	34.2	36.9
6.	Cape Verde	459999	46.8	41.9	44.1
7.	Central African Republic	4401051	–	–	–
8.	Chad	11227208	39.2	34.6	36.8
9.	Comoros	734750	–	–	–
10.	Congo	4042899	41.4	38.6	40.0
11.	Cote d'Ivoire	19737800	44.1	38.6	41.5
12.	Burkina-Faso	16468714	–	–	–
13.	Burundi	8383849	–	–	–
14.	Democratic Republic of Congo	65965795	39.4	35.8	37.6
15.	Djibouti	888716	–	–	–
16.	Egypt	81121077	35.5	34.5	35.0
17.	Equatorial Guinea	700401	–	–	–
18.	Eritrea	5253676	33.9	29.8	31.7
19.	Ethiopia	82949541	33.7	33.2	35.2
20.	Gabon	1505463	43.9	38.7	41.3
21.	Gambia	1728394	43.6	38.7	41.1
22.	Ghana	24391823	37.6	35.2	36.4
23.	Guinea	9981590	–	–	–
24.	Guinea Bissau	1515224	–	–	–
25.	Kenya	40512682	38.9	35.1	37.0
26.	Lesotho	2171318	–	–	–
27.	Liberia	3994122	–	–	–
28.	Libya	6355112	45.9	39.1	42.6
29.	Madagascar	20713819	43.2	40.4	41.8
30.	Malawi	14900841	45.6	41.4	43.4
31.	Mali	15369809	34.0	35.3	34.7
32.	Mauritania	3459773	–	–	–
33.	Mauritius	1299172	–	–	–
34.	Morocco	31951412	40.7	41.7	41.2
35.	Mozambique	23390765	46.7	43.3	44.9
36.	Namibia	2283289	45.1	41.8	43.4
37.	Niger	15511953	52.5	42.8	47.8
38.	Nigeria	158423182	41.5	44.0	42.8
39.	Rwanda	10624005	–	–	–
40.	Sao Tome and Principe	165397	46.0	43.2	44.5
41.	Senegal	12433728	–	–	–
42.	Seychelles	86518	46.6	41.8	44.2
43.	Sierra Leone	5867536	44.1	43.9	44.0
44.	Somalia	9330872	–	–	–
45.	South Africa	50132817	43.1	41.4	42.2
46.	South Sudan	43551941	–	–	–
47.	Sudan	43551941	–	–	–
48.	Swaziland	1186056	–	–	–
49.	Togo	6027798	–	–	–
50.	Tunisia	10480934	39.0	38.1	38.5
51.	Uganda	33424683	–	–	–
52.	Tanzania	44841226	40.0	38.3	39.2
53.	Zambia	13088570	41.3	39.0	40.1
54.	Zimbabwe	12571454	38.2	39.9	39.0

Source WHO, NCD Country profile 2011.[11]

Table 2 Recent studies on awareness treatment and control of hypertension in sub-Saharan Africa

Serial number	Author	Year	Country	Awareness (%)	Treatment (%)	Control (%)
1	Addo[12]	2008	Ghana (urban)	39	18	4
2	Damasceno[13]	2009	Mozambique (national)	10.6 (men) 18.4 (women)	3.5 (men) 11.2 (women)	1.0 (men) 4.8 (women)
3	Oladapo[14]	2010	Nigeria (rural)	14.2	18.6	NA
4	Ekwunife[15]	2010	Nigeria (semi-urban)	30 (all) 40.3 (men) 24.7 (women)	21 (all) 23.7 (men) 17.5 (women)	9 (all) 5.0 (men) 17.5 (women)
5	Dzudie[16]	2012	Cameroon (urban)	31.7	59.9	24.6

What the recent Global Burden of Disease study reveals about the burden of hypertension in Africa

In the 2012 comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk clusters in 21 regions of the world, high BP was reported as the leading risk factor for global disease burden (7.0%, 95% uncertainty interval 6.2% to 7.7% of global disability-adjusted life years (DALYs)).[3]

A recent systematic analysis of data from 199 countries with 786 country-years and 5.4 million participants indicates that the mean systolic BP as well as the burden of hypertension has fallen between 1980 and 2008 in both men and women globally.[3]

However, regional analysis of the same data indicates that in the last 10 years the mean systolic BP has risen in men and women from west, central and east Africa, and the highest mean rise in systolic BP was recorded in several SSA countries.[3]

What is new on the pathogenesis of hypertension in Africa?

The Biafra study and developmental origins of hypertension in Africans

The impact of the Nigeria–Biafra civil war on the burden of cardiovascular disease (CVD) risk factors was recently studied by Hult *et al*.[19] It was noted that children born during this period of starvation and famine were found to be more likely to have metabolic syndrome compared to those born before or after this period. Thus the civil strife and starvation/famine occurring in many places in Africa poses great danger for the region in the coming years.

New insights on the genetics of hypertension in SSA

Epithelial sodium channel

Suppression of plasma renin activity is one of the major features of hypertension in black individuals and may be a surrogate of salt sensitivity. The epithelial sodium channel (ENaC), which is the final regulator of sodium balance in the kidney, is an attractive gene in the genetics of hypertension. There is an association of the T594M variant of the β-chain with hypertension in black patients in the UK, but this was not confirmed in a South African study.[20]

A unique mutation called R563Q was, however, reported from South Africa and it is an active site for the degradation of ENaC (three amino acids from the original description of Liddle's syndrome mutation). This mutation has been associated with low renin, low aldosterone hypertension, and hypertension within families,[20] as well as early pre-eclampsia in black and coloured hypertensive populations of South Africa[20 21]; 5.9% and 1.7% of hypertensive black and coloured South Africans, respectively, have this mutation ($p<0.0005$ for association with hypertension). It is often associated with resistant hypertension which responds dramatically to amiloride, a specific inhibitor of ENaC. It is also present in 20% of unselected Khoi-San (the original inhabitants of southern Africa), who are the presumed origin of the mutation as it is not present in other African diaspora. It not associated with hypertension in the Khoi-San due to lower salt intake and may have had a survival advantage in the extremes of salt and water present in the arid regions of southern Africa.

Bochud *et al*[22] showed that black South Africans had enhanced sodium absorption in the proximal convoluted tubules compared to whites. Single nucleotide polymorphisms (SNPs) of the G-protein receptor kinase-4 are linked to low renin hypertension and impaired sodium excretion on the proximal tubule.[23] Rayner *et al*[23] demonstrated that these SNPs have a significantly higher prevalence in the black population of South Africa and are linked to natriuresis and BP response to salt restriction.

Cytochrome P450, subfamily IIIA, polypeptide 5 genotypes

Cytochrome P450, subfamily IIIA, polypeptide 5 (CYP3A5) polymorphism was found to be associated with ambulatory BP (ABP) in Africans from the Seychelles Island,[24] CYP3A5*1 carriers showing a higher age and sodium related increase in ABP than non-carriers.

Is there any new information on the impact of HIV infection on BP in Africans?

At least two studies have looked at the impact of HIV status on the prevalence of hypertension in SSA at the community level.

In 2003–2004, Barnighausen and his co-workers[25] studied the effect of HIV on body mass and BP in a large general population in a rural area in South Africa before antiretroviral treatment (ART) became widely available.

In a multiple regression analysis, after controlling for confounders such as age, gender, educational attainment, household wealth, marital status, and place of residence (urban or rural), HIV infection reduced systolic BP (SBP) by 3.0 mm Hg ($p=0.005$). The authors proposed that the possible reason for this finding may be due to HIV related hypoadrenalism or side effects of traditional medicines against HIV/AIDS.

In another related survey in 2010, Malaza *et al*[26] conducted a health survey based on the WHO STEPwise approach in 14 198 rural adult participants in South Africa to determine factors associated with hypertension and excess weight, including HIV infection and ART status. They reported that the prevalence of hypertension differed between HIV infected and HIV uninfected individuals (19.5% vs 27.9%, $p=0.001$). HIV uninfected women were significantly more likely to be hypertensive than HIV infected women (31.4% vs 20.1%, $p=0.001$), while there was no association of hypertension with HIV status among men ($p=0.099$).

Furthermore, it was observed that in a univariate analysis, all explanatory variables (sex, age, HIV/ART status, wealth, place of residence area, educational attainment, and body mass index (BMI)) were significantly associated with hypertension.

However, in a multivariable analysis, sex, age, HIV and ART status, BMI, place of residence, and educational attainment remained significantly associated with hypertension, but not sex and wealth. "The adjusted odds ratio of hypertension increased by 5.3% (95% CI 5.0% to 5.7%) per age year. HIV infected persons on ART treatment had a reduced adjusted odds ratio of hypertension (aOR 0.60, 95% CI 0.49 to 0.75), compared to HIV negative persons. The adjusted odds ratio in HIV infected persons not on ART did not differ from HIV negative persons (p=0. 0.158)."[26]

With the advent of highly active ART, long term survival of HIV infected persons has been noted to be associated with cardiovascular and metabolic complications. HIV vasculopathy (occlusive and aneurysmal involvement of visceral, cerebral, and peripheral vessels) is well documented. Nel and Rayner recently reported "the unusual involvement of the renal artery by HIV vasculopathy resulting in severe hypertension with target organ damage requiring multiple antihypertensive drugs" in a young woman in South Africa.[27]

Other new studies on the pathogenesis of hypertension

Recent evidence for the effects of salt intake on BP in SSA

There are emerging data which show that the lack of relationship between urinary indices of salt consumption and BP in Africans enrolled in the INTERSALT study may be because of the inability of these measures to fully reflect salt consumption[28] The African programme on Genes in Hypertension (APOGH) study recently reported that in a black community in South Africa urinary index of salt intake was strongly and independently related to central (aortic) SBP and pulse pressure but not to diastolic BP (DBP) or brachial artery BP.[29]

The authors concluded that the effect of salt intake on BP may have been previously underestimated in the region. They suggested that "salt intake will increase aortic SBP 1.45 times more than it will brachial BP. Hence if we assume that a reduction in Na^+ intake of 100 mmol/day (3.7 g Na^+ per day which equates to 9.2 g or about four teaspoons of table salt per day) reduces brachial SBP by −8.1 mm Hg in groups of African descent as suggested by the DASH study, then presumably aortic SBP may decrease by as much as −11.8 mm Hg in response to a decrease in Na^+ intake".

Their finding is consistent with the increasing evidence that central BP predicts cardiovascular events beyond brachial artery BP.

Effect of increased adiposity on BP

The APOGH study has also reported on the size effect of excess body fat on conventional BP and ABP. After adjusting for potential confounders, they showed that every 15 cm increase in waist circumference was associated with a 4.04 mm Hg increase in 24 h SBP and a 4.33 mm Hg increase in 24 h DBP. Every 15 cm increase in waist circumference was also associated with a 3.35 mm Hg increase in conventional SBP and a 3.27 mm Hg increase in DBP.[30]

The implication of this finding according to the authors is that "even with a significant study sample for an ABP study, at least the independent impact of adiposity on BP in groups of African descent is remarkably small".

The group has also previously demonstrated that the impact of excessive body fat on BP may be genetically predetermined.[31]

The additive effect of obesity on cardiovascular injury has been explored in Africans.[32–34] The deleterious effect of obesity has been shown to work in synergy with elevated BP. The APOGH study has reported that pronounced synergy between indices of obesity and BP (conventional, aortic and 24 h SBP or pulse pressure) is independently associated with left ventricular (LV) mass and LV wall thickness.[35] This finding was also tested in an animal model of hypertension.[36]

What is new on the outcome of hypertension in Africa?

What can be learnt from the national mortality studies in South Africa?

In a recent review on health in South Africa, Mayosi *et al*[37] reported on the quadruple burden of disease in the country and also showed the interaction of infectious diseases with chronic non-communicable diseases (NCDs), especially in rural and poor urban communities. According to the report, statistics on cause of death indicate that there has not been a change in the overall mortality from NCDs.

Hypertensive heart disease and other chronic conditions such as diabetes mellitus and renal diseases increased in all age groups. Interestingly, stroke did not increase after a peak in 2003 in people aged 65 years and above, but decreased in the younger age group.

What is new on hypertensive target organ damage in SSA?

Recent studies (table 3) on hypertensive target organ damage (TOD) show that hypertensive heart disease, hypertensive nephropathy, hypertensive retinopathy, stroke, and ischaemic heart disease are common, even at the first contact in healthcare facilities in SSA.[38–42]

Studies using conventional and newer modalities for assessing LV diastolic dysfunction (tissue Doppler imaging (TDI)) have shown that abnormalities of LV and right ventricular (RV) diastolic function are common in African hypertensive subjects.[43–47]

Ogah *et al*[48] studied 832 consecutive and unselected hypertensives in Abeokuta, Nigeria. They found LV systolic dysfunction (LVSD) to be present in 18.1% (mild LVSD in 9.6%, moderate LVSD in 3.7%, and severe LVSD in 4.8%). Male gender, BMI, and LV mass were reported as the predictors of LVSD.

Karaye *et al*[45] detected RV diastolic dysfunction (RVDD) and RV systolic dysfunction (RVSD) in, respectively, 61.7% and 32% of 128 hypertensives in Kano, Nigeria. Subjects with eccentric LV hypertrophy (LVH) had the highest RVSD. LV ejection fraction (LVEF) was the only determinant of RVSD while age was the only determinant of RVDD after controlling for confounders. Akintunde *et al*[49] documented RV morphological and functional abnormalities in a similar study and concluded that RVDD may be an early clue to hypertensive heart disease in Africans.

Akintunde *et al*[46] demonstrated that the combined index of global myocardial performance (Tei index) is significantly higher in hypertensive individuals with HF compared to normal controls. The Tei index also increased with the severity of hypertensive HF and is inversely related to LVEF, but is directly related to the E/A ratio and deceleration time.

Some workers have studied the prevalence and patterns of LVH and LV geometry in the SSA population. In a large population of hypertensive individuals, Adebiyi *et al*[47] reported the prevalence of LVH in hypertensives to range from 30.9–56.0%, depending on the partition values used in the definition.

Table 3 Recent studies on hypertensive target organ damage in sub-Saharan Africa (SSA)

Serial number	First author	Country	Year	Sample size	LVH	CCF	Microalbuminuria	Overt proteinuria/ CKD	Retinopathy	Stroke	IHD
1.	Peer[38]	South Africa	2008	403	35	–	–	26	–	–	49
2.	Ekore[39]	Nigeria	2009	124	17.7	2.4	–	26.1	4.0	0.8	–
3.	Addo[40]	Ghana	2009	219	33.3	–	–	13.4	Grade 1=56.5 Grade 2=12.9 Grade 3=1.0	2.8	–
4.	Stewart[41]	South Africa	2009	761	39	5.4	–	24	–	–	16.2
5.	Oladapo[42]	Nigeria	2010	415	27.9	4.6	12.3	15.2	2.2	6.3	1.7

CCF, congestive heart failure; CKD, chronic kidney disease; IHD, ischaemic heart disease; LVH, left ventricular hypertrophy.

Abnormal geometry was present in 61.1–74.0% and this was more common in women.

Ogah *et al*[40] showed that LV wall tensions, LV wall stress, left atrial size, DBP, alcohol consumption, and family history of hypertension were independent predictors of LVM.

What is new on the management of hypertension in Africa?

Insight from the NOAAH trial

The Newer versus Older Antihypertensive Agents in African Hypertensive patients (NOAAH) trial[51] was initiated to compare, in native African patients, a fixed combination of newer antihypertensive drugs not involving diuretics with a combination of older drugs including a diuretic in subjects aged 30–69 years with uncomplicated hypertension. The study has been conducted in six centres in four SSA countries since 1 September 2010 and is probably the first randomised multicentre trial of antihypertensive medications in hypertensive patients born and living in SSA.

An early report from this trial[52] shows that BP control can be achieved rapidly in native Africans by using a simple regimen comprising a single pill combining two antihypertensive drugs. The study has also demonstrated that randomised clinical trials of cardiovascular drugs can be conducted among the indigenous populations of SSA by African investigators.

Trials of salt reduction and their implications in SSA

In South Africa up to 46% of the salt that is consumed is added during preparation of food or at the table. Thus, much of the salt consumed is found in processed foods produced by industry.[53] In a landmark collaboration between the Medical Research Council of South Africa and three food industry partners, the cation content of five commonly consumed foods—brown bread, brick margarine, soup mix, stock cubes, and a flavour enhancer—was altered by lowering the sodium content and increasing the potassium, magnesium, and calcium content. Black subjects with mild to moderate hypertension were randomised in a double blind controlled clinical trial to either a standard diet or to an identical but cation altered diet. Over an 8 week period there was a highly significant reduction in 24 h ambulatory SBP (−6.2 mm Hg) in subjects on the altered diet. The trial diet was also found to be palatable. If this BP response was sustained, it would result in a 20% reduction in the number of deaths attributed to high BP, preventing more than 9000 deaths per year in South Africa. These findings suggest that appropriate policy interventions that will encourage or regulate the food industry to produce foods such as bread with reduced sodium content could have a major impact on the control of high BP in South Africa (and the rest of Africa). This is in line with the United Nations High Level resolution on non-communicable disease that was adopted by all countries in September 2012.

The UK was the first country to set voluntary sodium reduction targets for categories of foods through its Food Standards Agency, closely followed by Australia, the USA, and Canada. South Africa is the first country to adopt mandatory regulation for maximum sodium concentrations in food categories that are major contributors to salt intake in its population, namely bread, margarine and spreads, savoury snacks, processed meats, soup powders, and stock cubes.[53 54] It is estimated that reducing the sodium content of bread by 50%, along with other proposed reductions in margarine, soups and gravies, would decrease salt intake by 0.85 g per day; this would result in 7000 fewer deaths due to CVD and 4000 fewer non-fatal strokes in the country per year, saving about US$40 million each year in healthcare costs associated with non-fatal strokes alone.[55] It is important that other governments in SSA adopt similar legislation or standards for processed foods as recommended by the UN resolution.

The South African 2011 guideline and the International Forum for Hypertension control and prevention in Africa guideline for the management of hypertension and their relevance to the continent

The recent publication of the South African hypertension guideline 2011[56] forms an important basis for the development of a new Pan-African hypertension guideline for SSA. The South African guideline reflects important changes in perspectives and advances in the management of hypertension compared to the International Forum for Hypertension control and prevention in Africa (IFHA) guideline published by Lemogoum *et al*.[57] There are several key recommendations that may improve BP control in SSA if adopted by a Pan-African guideline. In the IFHA guideline, initial therapy outside the compelling indications was hydrochlorothiazide 12.5 mg daily. Recent evidence suggests that hydrochlorothiazide at this dose has a weak antihypertensive effect. In contrast the South African guideline recommends either a thiazide diuretic, ACE inhibitor (or angiotensin receptor blocker) or calcium channel blocker (CCB) as first line therapy; more importantly, if BP is >20/10 mm Hg above goal the guideline recommends starting with a fixed drug combination of two of the first line therapies. Diuretics and CCBs are also preferred in black patients. Another key difference is that the IFHA guideline recommends increasing the dose of the initial agent (eg, hydrochlorothiazide) if target BP is not achieved. It is well established that escalating monotherapy results in a small increment in BP lowering, but with more side effects, while the adoption of combination therapy even in low doses is five times more effective in lowering BP. In the ASTRAL study involving patients with essential hypertension from 36 centres in five SSA countries, treatment with a fixed drug

combination of ramipril and hydrochlorothiazide resulted in a highly significant reduction in both SBP and DBP from baseline at 4 and 8 weeks (−24.7/−14.2 mm Hg, p<0.001 and −31.7/−17.9 mm Hg, p<0.001), respectively.[58] The South African guideline also recommends spironolactone for the management of resistant hypertension, a strategy that has been shown to be effective in large studies such as the Anglo-Scandinavian Cardiac Outcomes Trial,[59] but which lacks any definitive data from SSA.

What is the implications of the new information for prevention, treatment and research?

The National High Blood Pressure Programme adopted in the USA is a remarkable success story. Despite concerted efforts to persuade the population to adopt more healthy lifestyles, there has been a substantial increase in diabetes and obesity. However, there has been a dramatic decline in heart and stroke disease in both black and white patients through better BP control by more effective use of antihypertensive drugs, focusing on both patient and physician education.[60] This is particularly evident in the south east region of the USA where there was the highest mortality for stroke. This means the campaigns to improve lifestyle changes in the USA have not had a major impact on the prevention and treatment of hypertension, and holds lessons for policies in Africa.

The initial results of the NOAAH study point to a similar outcome.[52] Effective treatment with cheap generic fixed drug combinations leads to better and timely BP control. Guidelines need to reflect this reality, and policymakers need to focus their resources on improving access to primary care clinics, developing simple protocols for the pharmacological management of hypertension, and making available fixed drug combinations that are effective in black populations. Physicians and patients need to be educated, and where resources are limited nurse practitioners can be trained to implement these policies. In South Africa, for example, nurses were successfully trained to implement the 2006 guideline. However, there are considerable hurdles to overcoming these problems. Hypertension remains low on the agenda of most SAA countries. Furthermore in South Africa there are no fixed drug combinations for the treatment of hypertension on the essential drug list, despite the widespread availability of affordable generics. There are no indications that there will be a change of strategy despite the success of combination antiretroviral drugs in controlling HIV.

Another strategy to improve patient adherence is the use of cell (mobile) phone technology through the use of short message service alerts for patients to take their medication, attend clinics, and collect their medication. Most people in Africa carry cell phones and are the primary method of communication. This strategy is currently under investigation in clinics in Cape Town.

The study by Charlton *et al*[53] is an important exception in the battle to implement healthy lifestyles in the population. Their study showed that changes in the cation content of commonly used foodstuffs results in significant reductions in BP in black patients with mild to moderate hypertension, thus providing a basis for the prevention and treatment of hypertension at a population level. Most intake of dietary sodium is involuntary in the form of processed foods and can be modified by regulating the content in commonly used foodstuffs. The lead has been set by the South African government and may form a blueprint for the rest of SSA. The cost is minimal and the strategy is more feasible than trying to change attitudes to the types of food eaten to reduce obesity and blood lipids, which is far more difficult and controversial.

Another important implication of the new information is the possibility of developing a more physiological approach to the treatment of hypertension, especially in those with BP that is more difficult to control. It is well established that patients of African descent have low renin hypertension, and this may be related to SNPs of genes regulating sodium balance in the kidney like the ENaC. This provides a pharmacogenetic approach to treatment in a higher resourced area such as Cape Town. However, the SNPs may be diverse and involve many of the pathways regulating sodium balance, so that identifying these genes is not feasible in the wider context of Africa. Thus, the screening of patients with difficult to control hypertension using aldosterone and plasma renin activity (especially if this is the point of care) may provide a physiological approach to treatment. For example, those with low renin and low aldosterone (the Liddle's phenotype, suggesting an ENaC mutation) are treated with amiloride and those with low renin and higher aldosterone receive spironolactone. This approach will be tested in four centres in Africa in a prospective study.

CONCLUSION

This overview of hypertension in SSA suggests that hypertension is a dominant risk factor for CVD, and the prevalence is anticipated to rise dramatically. Unless decisive action is taken by governments and policymakers the negative health effects of uncontrolled hypertension will be severe. It is recommended that governments adopt the UN resolution on NCDs and in particular start regulating the sodium content of processed foods. In addition, resources need to be made available for effective pharmacological treatment of hypertension with cheap generic fixed combination drugs. An updated but simplified Pan-African guideline is also recommended.

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REVIEW

Blood pressure, prevalence of hypertension and hypertension related complications in Nigerian Africans: A review

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Abstract

To review studies on hypertension in Nigeria over the past five decades in terms of prevalence, awareness and treatment and complications. Following our search on Pubmed, African Journals Online and the World Health Organization Global cardiovascular infobase, 1060 related references were identified out of which 43 were found to be relevant for this review. The overall prevalence of hypertension in Nigeria ranges from 8%-46.4% depending on the study target population, type of measurement and cut-off value used for defining hypertension. The prevalence is similar in men and women (7.9%-50.2% *vs* 3.5%-68.8%, respectively) and in the urban (8.1%-42.0%) and rural setting (13.5%-46.4%). The pooled prevalence increased from 8.6% from the only study during the period from 1970-1979 to 22.5% (2000-2011). Awareness, treatment and control of hypertension were generally low with attendant high burden of hypertension related complications. In order to improve outcomes of cardiovascular disease in Africans, public health education to improve awareness of hypertension is required. Further epidemiological studies on hypertension are required to adequately understand and characterize the impact of hypertension in society.

Key words: Blood pressure; Hypertension; Prevalence; Non-communicable disease; Nigeria

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INTRODUCTION

Hypertension is a common, important and major global public health problem[1].

Its prevalence has been found to be 44% in Western Europe and 28% in North America. It has been documented as a threat to the health of people in sub-Saharan Africa and a major contributor to morbidity and mortality in the sub-region[2-4]. There is emerging evidence to show that the pattern of diseases in sub-Saharan Africa is changing, with non-communicable diseases (NCD) responsible for about 22% of the total deaths in the region in 2000, cardiovascular disease alone accounting for 9.2% of the total mortality [World Health Organization (WHO) 2002]. According to Kearney *et al*[5], by 2025 about 75% of the world hypertensive population will be in developing countries. In Nigeria for example, it is the number one risk factor for stroke, heart failure, ischemic heart disease, and kidney failure. With an increasing adult population as well as rising prevalence of hypertension, Nigeria will experience economic and health challenges due to the disease if the tide is not arrested. As far back as the early 60s a lot of interest has been shown by workers on the blood pressure of Nigerian Africans. The essence of this work is to review studies on hypertension as well as hypertension research in the country.

COUNTRY PROFILE

Nigeria is classified as a low-middle income country with a Gini Index of 43.7 and income per capita of $1490. 49% of the population is living in urban areas, the gross national income per capita is $2070. Life expectancy at birth is 51 years for both sexes (53 for men and 54 for women).The probability of dying between 15 and 60 years for men and women (per 1000 population) is 377 and 365 respectively. The mortality rate for under 5s is 138/1000 and the maternal mortality ratio is 840/10^5 live births. Non-communicable diseases contribute about 14% of the number of years of life lost. The number of doctors/10 000 population is about 4. Five point one percents of men and 9.0% of women aged 20 years and above are obese; 11.9% of men and 1.0% of women aged 15 years and above smoke cigarettes.

The prevalence of HIV (per 1000 adults aged 15-49 years) is 36 while the prevalence of tuberculosis (per 100 000 population) is 497[6-8].

METHODS

The Pubmed scientific database was searched from 1950-2011 for studies of blood pressure and hypertension in the country. The search criteria were "Hypertension", "High Blood Pressure" and "Nigeria". Studies conducted mainly on adult subjects were included.

Additional references were sought from retrieved publications. The African index medicus, African Journal Online and WHO Global cardiovascular infobase were also searched.

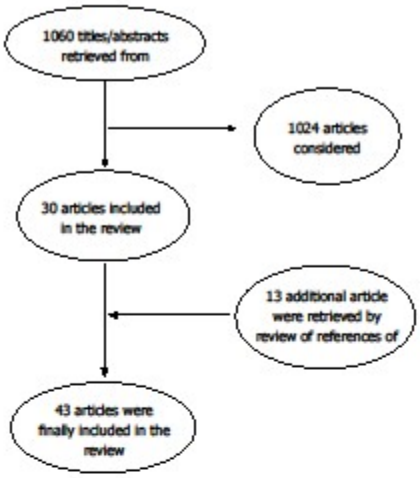

Figure 1 Selection process.

All the data collected were entered into an excel spreadsheet. Information collected include: first author's name, year of publication, place of study, study design, population, sample size, mean age range, proportion of women enrolled, mean age, and prevalence of hypertension in the sample population as well as in men and women.

The pooled prevalence rate of hypertension was computed for the period 1970-1979, 1990-1999, and 2000-2011 from community-based studies.

RESULTS

Our search yielded a total of 1060 references. However 30 publications were found to be useful for this review. An additional 13 articles were retrieved through the review of the bibliography of the earlier obtained articles. Figure 1 is a summary of the selection process. These cross-sectional studies were published between 1960 and 2012 in 12 of the 36 states of Nigeria: Oyo[9-22], Enugu[23-27], Lagos[28,29], Osun[30,31], Edo[32-35], Cross-River[36,37], Akwa-Ibom[37], Rivers[38], Kastina[39], Sokoto[40], Borno[41] and Abia[42]. Three of the studies involved more than one state[37,43].

In terms of geopolitical spread, the majority of studies were conducted in the Southwestern part of the country, some of the studies were conducted before 1990 while the majority were after 1990.

Historical vignette

Many years ago it was generally believed that high blood pressure was rare in native Africans. This was based on reports mainly by workers on the eastern coast of the continent such as Cooke[44], Donnison[45], Jex-Blake[46] and Vint[47].

The earliest report of hypertension in Nigerian Africans was probably by Callander[48]. He commented on the blood pressure of army recruits and Nigerian soldiers at routine medical examination. He noted that in 100 healthy soldiers, 52 had a systolic blood pressure > 140 mmHg, and 23 had a diastolic blood pressure (BP) > 90 mmHg.

His observations from the army recruits were more remarkable. In 400 recruits aged between 19-24 years, 42.5% were rejected on account of elevated blood pressure and "this after an hour's rest and amytal sedation before the pressure was recorded".

In two reports in 1956, hypertension was documented as a cause of cardiovascular disease in Nigerians.

Beet *et al*[49] noted that it was responsible for 34% of cases of heart failure in Northern Nigeria while Nwokolo *et al*[50] also documented some cases in Enugu in the Eastern part of the country. Also Lambo *et al*[51] reported on the association of high blood pressure and mental disorder in elderly psychiatric patients in the Western region.

The earliest and first large scale study of blood pressure in Nigerians was by Abrahams *et al*[11]. The study was conducted in a rural town of Ilora which is about 50 km north of Ibadan. They noted, like most other studies conducted during that period, in Caucasians and American Blacks that blood pressure rose with age in both men and women. However, they did not document any clear relationship between blood pressure, weight climate and diet. This was followed by studies by Smith[52] in Lagos, Akinkugbe *et al*[9] in Ibadan, Johnson[53] in Lagos, Oviasu *et al*[54-55] in Benin city and Oyediran in Epe near Lagos.

Akinkugbe is generally regarded as the father and doyen of blood pressure and hypertension research in Nigeria because of his seminal work in this field in the late 60s and 70s[9,10,53-62]. He documented that: (1) Systolic blood pressure rose with age in both sexes and in all age groups from 12-70 years. This trend was less marked in diastolic blood pressure; (2) Blood pressure levels were similar in women from rural and urban areas but seemed much higher in urban than in rural men; (3) The rate of rise of pressure was more rapid in earlier decades than subsequently; (4) There was little correlation with weight and much less so with height after 40 years of age; (5) The incidence of proteinuria was highest in the early teenage group years, but did not relate to blood pressure trends; and (6) Casual systolic and diastolic pressure differed in no important respects from those in Negro populations in the Caribbean, but systolic and diastolic values are marginally higher in United States Negroes than in West Indian or West African Negroes".

Cole *et al*[63] was the first to conduct a drug trial on hypertensive patients and this was followed by a series of work by Salako *et al*[64-69]. Falase *et al*[70-72] demonstrated the lack of effect of low doses of prazosin in the treatment of hypertension in Nigeria.

A series of studies by Salako and Falase showed that Nigerians responded well to thiazide diuretics and calcium channel antagonists when these drugs were used as monotherapy. Other classes of drugs, such as beta adrenergic blockers, require the use of high doses before they are effective in Nigerian hypertensives. The use of high doses of these drugs often causes unacceptable side effects. These classes of antihypertensive drugs are, however, effective in low doses when they are combined with either thiazide diuretics or calcium channel antagonists or both. Effective management of hypertension in Nigerians therefore requires the use of thiazide diuretics or calcium channel antagonists as monotherapy or in combination with other classes of antihypertensive agents.

Osuntokun *et al*[73-76] first studied hypertension in diabetic subjects in the country and showed in many seminal research studies the contribution of hypertension as a risk factor for stroke in hospital based and population based studies. Akerele documented hypertension in Nigerian children in 1974. The relation of renal disease, hypertension and schistosomiasis was explored by Soyannwo *et al*[77-81].

Table 1 shows the hypertension research from 1961-1981.

Diagnosis of hypertension

Earlier studies used 160/95 mmHg as the benchmark for the diagnosis of hypertension. The vast majority of studies which were conducted in the last 20 years used 140/90 mmHg as the cut off.

Twenty of the studies were carried out in urban populations, 11 in rural communities, while the remaining 6 were conducted both in urban and rural populations. The majority of the population based studies used multistage cluster sampling.

Sampling in five of the studies was by convenience (during free medical programmes).

The sample size in the studies ranged from 132 to 4930 subjects. The proportion of women who participated ranged from 24.9% to 71.2% while the mean age of the population ranged from 31.6 years to 61.2 years.

Prevalence of hypertension

The prevalence of hypertension in both men and women ranged from 8% to 46.4%; with regards to gender, the prevalence of hypertension ranged from 7.9% to 50.2% and 3.5% to 6.8.8% in men and women, respectively. The reported prevalence in rural areas ranged from 13.5%-46.4% in both sexes, 14.7%-49.5% in men and 14.3-68.8% in women. Data from urban studies revealed a range of 8.1%-42.0% in both men and women, 7.9%-46.3% for men and 3.5%-37.7% for women. In general hypertension prevalence was higher in urban than rural areas (Table 2).

Pooled prevalence and trend: A prevalence of 8.9% was estimated from the only community-based study available for 1970-1979. For 1990-1999, the pooled prevalence of hypertension was 15.0% (CI 13.7-16.3). The pooled prevalence increased significantly to 22.5% (CI 21.8-23.2) from 2000 to 2009.

Table 1 Events in the first 21 years of blood pressure and hypertension research in Nigeria (1961-1981)

No.	Author	Year	Comments
1	Abrahams *et al*[22]	1961	First population based study of blood pressure in the country. Studied the systemic blood pressure of rural Nigerians resident in Ilora
2	Monekosso[32]	1964	Reported some cases in a clinical survey of a village in South West Nigeria
3	Smith[29]	1966	Studied blood pressure of urban inhabitants in Lagos
4	Akinkugbe[34]	1968	Documented the rarity of hypertensive retinopathy in Nigerians
5	Akinkugbe *et al*[27]	1968	Reported on the rarer causes of hypertension in Nigeria
6	Akinkugbe *et al*[5]	1968	Wrote on arterial blood pressure in rural Nigerians in Eruwa
7	Akinkugbe[35]	1969	Reported on the hypertensives diseases in Ibadan, Nigeria
8	Akinkugbe[30]	1969	Wrote on antihypertensive therapy in the African context
9	Ojo *et al*[36]	1969	Studied hypertension in pregnancy
10	Akinkugbe[28]	1969	Reported on the result of his survey of blood pressures in school children
11	Cole *et al*[37]	1970	First documented drug trial (Declinax) in hypertensive Nigerians
12	Brockington[24]	1971	Reported on postpartum hypertensive heart failure
13	Johnson[33]	1971	Reported on his study of blood pressure in rural areas around Lagos
14	Carlisle[38]	1971	Reported on the remission of hypertension in some Nigerians
15	Salako[24]	1971	First trial of oral thiazides
16	Salako[39]	1971	Reported on serum electrolytes in hypertensive Nigerians
17	Salako[24]	1972	Reported on electrolyte changes following thiazide therapy in hypertensive Nigerians
18	Osuntokun *et al*[25,74]	1972	Seminal work on hypertension in diabetic Nigerians
19	Salako *et al*[40]	1973	Evaluated the usefulness of Moduretic in the treatment of hypertension in Nigerians
20	Akinkugbe *et al*[41]	1974	Reported on the experience with beta blockers in hypertension management
21	Adeyele[26]	1974	Documented on hypertension in Nigerian children
22	Akinkugbe[42]	1976	Studied blood pressure in non-pregnant women
23	Falase *et al*[75]	1976	Demonstrated lack of effect of low dose prazosin in hypertensive Nigerians
24	Etta *et al*[43]	1976	Assessed the relation of blood pressure to indices of obesity
25	Olatunbosun *et al*[44]	1976	Evaluated the relation of blood pressure to heavy metals
26	Jain *et al*[45]	1977	Reported on the incidence of hypertension in Abuth Zaria
27	Akinkugbe *et al*[23]	1977	Conducted a biracial study of blood pressure in school children
28	Olatunde *et al*[46]	1977	Trial of beta blockers in hypertensive Nigerians
29	Osuntokun *et al*[25,74]	1977	Demonstrated through hospital registry and population based studies that hypertension is a major risk factor for stroke in Nigeria
30	Abdurrahman *et al*[47]	1978	Studied blood pressure in school children in Northern Nigeria
31	Mabadeje[48]	1979	Conducted a trial of chlorthalidone in hypertensive Nigerians
32	Falase *et al*[71,72]	1979	Documented poor response of hypertensive Nigerians to Beta blockers monotherapy
33	Alakija[76]	1979	Pilot study of hypertension in Benin City
34	Abengowe *et al*[49]	1980	Reported on the pattern of hypertension in Northern Savannah
35	Oviasu *et al*[50,59]	1980	Document on blood pressure and hypertension in urban city of Benin/ Occupational factors in hypertension
36	Ladipo[56]	1981	Carried out a study on hypertensive retinopathy in Ile-Ife

Impact of blood pressure cut-off threshold on the prevalence of hypertension: In a study of the prevalence and patterns of hypertension in a semi-urban community in South Western Nigeria, Adedoyin *et al*[31] demonstrated that with a cut-off value of ≥ 140/90 mmHg for the diagnosis of hypertension, the prevalence was 36.6% (isolated systolic hypertension (ISH) in 22.1% and isolated diastolic hypertension (IDH) in 14.5%).

On the other hand when the threshold was increased to 160/95 mmHg, only 13.35% were found to be hypertensive (6.63% had both ISH and IDH).

A male:female ratio of 1.7:1 and 1:5 was documented for blood pressure of ≥ 140/90 mmHg and ≥ 160/90 mmHg, respectively.

Impact of age: In all the studies, the most likely determinant of blood pressure and presence of high blood pressure was age. BP was shown to increase steadily with age from the youngest to the oldest age brackets, irrespective of gender.

It appears that population mean blood pressure has increased over the years since the first survey by Abrahams *et al*[11]. This may be due to an increase in detection rather than a temporal increase as the observation is limited by a lack of serially conducted studies in any of the populations.

Comparison of prevalence of hypertension in Nigeria with some other parts of Sub-Saharan Africa: Figure 2 shows the comparison of prevalence of hypertension in different parts of Sub-Saharan Africa, including Nigeria, as estimated for 2008 by Twagirumukiza *et al*[77]. The overall prevalence of hypertension was put at 18.4% for Nigeria compared with a prevalence of 10.35% for Ethiopia and 23.0% for Ghana (Figure 3).

Hypertension awareness, treatment and control

As in many populations of the world, the awareness of hypertension is low in Nigeria. In four of the studies, the reported awareness rates were 14.2% in rural areas by Oladapo *et al*[22], 18.5% in Edo State[78], and 29.4% and 30.0% in semi-urban and urban populations in Enugu State[25,26].

The proportion of hypertensives on treatment was reported to be 21% (23.7% men, 17.5% women) by Ekwunife *et al*[79] and 18.6% (19.0% men, 18.4% women) by Oladapo *et al*[22].

Table 2 Prevalence of hypertension in 38 studies in Nigeria (1960-2011)

No.	First author	Year	Study location	State	Region	BP cut off	Target population	Setting	Sample size	% all	% men	% women
1	Abrahams *et al*[21]	1960	Ilora	Oyo	SW	160/90	Community based	Rural	457	13.3	NA	NA
2	Smith[28]	1961	Lagos	Lagos	SW	160/95	Hospital based	Urban	207	8.8	9.5	7.9
3	Akinkugbe *et al*[9,10]	1968	Eruwa	Oyo	SW	140/90	Community based	Rural	3602	10.1	9.1	11.2
4	Johnson[29]	1971	Lagos	Lagos	SW	160/95	Community based	Urban	1592	8.9	7.9	9.9
5	Jain *et al*[30]	1977	Kaduna	Kaduna	NW	160/95	Hospital based	Urban	2950	3.8	2.9	4.9
6	Oviasu *et al*[31,32]	1978	Isi-uwa	Edo	SS	160/100	Community based	Rural	1482	2.1	2.8	0.5
7	Oviasu *et al*[34,35]	1980	Benin city	Edo	SS	140/90	Civil servants	Urban	1265	13.3	14	10
8	Idahosa[110]	1987	Benin city	Edo	SS	140/90	Civil servants	Urban	1450	15.1	NA	NA
9	Ogunlesi *et al*[111]	1991	Ibadan	Oyo	SW	160/95	Male factory workers	Urban	541	8		
10	Ekpo *et al*[36]	1992	Calabar	Cross river	SS	160/95	Civil servants, factory workers, plantain workers	Urban	4382	8.1	8.9	3.5
11	Bunker *et al*[112]	1992	Benin city	Edo	SS	140/90	Civil servants	Urban	559	20-43	21.6	12.5
12	Kaufman *et al*[16]	1996	Ibadan	Eyo	SW	140/90	Community based	Urban	205	11		
13	Kaufman *et al*[17]	1996	Ibadan	Oyo	SW	140/90 (160/95)	Rural farmers/urban poor/retired railway workers	Rural/urban	598	14,25,29 (3,11,14)	-	-
14	Cooper *et al*[113]	1997	National	National	National	140/90	Community based	Rural	2509	14.5	14.7	14.3
15	Akinkugbe[113]	1997	National	National	National	160/95	Community based	Rural/urban	4930	10.7		
16	Owoaje *et al*[24]	1997	Ibadan	Oyo	SW	140/90	Community based	Urban	247	23.4	22.2	24.3
17	Kadiri *et al*[114]	1999	Ibadan	Oyo	SW	160/95	Civil servants	Urban	917	9.3	9.8	8
18	Olatunbosun *et al*[25]	2000	Ibadan	Oyo	SW	160/95	Civil servants	Urban	998	10.3	13.9	5.3
19	Lawoyin *et al*[26]	2002	Ibadan	Oyo	SW	140/90	Community cohort	Urban	2144	12.4	12.1	12.7
20	Onyemelukwe[115]	2003	Lagos	Lagos	SW	140/90	Community based	Rural/urban	1082	SHT 22.5, DHT 24.7	NA	NA
21	Akinkugbe[116]	2003	Lagos	Lagos	SW	140/90	Community based	Rural/urban	1018	34.8	36.2	33.5
22	Erhun *et al*[117]	2005	Ile-ife	Osun	SW	140/90	University community	Urban	1000	21	23.3	16.4
23	Oghagbon *et al*[118]	2008	Ilorin	Kwara	NC	140/90	Factory workers	Urban	281	27.1	28.4	22.9
24	Omuemu *et al*[98]	2007	Udo	Edo	SS	140/90	Community based	Rural	590	20.2	26.2	13.2
25	Ukoh[119]	2007	Benin city	Edo	SS	140/90	Hospital based	Urban	2852	20.2	NA	NA
26	Nwankwo *et al*[40]	2008	Maiduguri	Borno	NE	140/90	Community based	Rural/urban	224	40 (urban), 27.8 (rural)		
27	Adedoyin *et al*[41]	2008	Ile-ife	Osun	SW	140/90	Community based	Rural	2250	18.7	15.5	21
28	Ekore *et al*[211]	2009	Ibadan	Oyo	SW	140/90	Hospital based	Urban	405	30.6	34.4	28.2
29	Ulasi *et al*[42]	2010	Njodo Nike, Enugu	Enugu	SE	140/90	Community based	Semi-urban/rural	1939	35.4 (urban), 25.1 (rural)	NA	NA
30	Ekwunife *et al*[99]	2010	Nsukka	Enugu	SE	140/90	Community based	Urban	756	30	40.3	24.7
31	Sani *et al*[99]	2010	Katsina	Katsina	NW	140/90	Hospital based	Urban	300	25.7	27.9	24
32	Adegoke *et al*[43]	2010	Ile-ife	Osun	SW	140/90	Community based	Rural	132			
33	Oladapo *et al*[212]	2010	Egbeda	Oyo	SW	140/90	Community based	Rural	2000	20.8	21.1	20.5
34	Ahaneku *et al*[27]	2011	NA	Enugu	SE	140/90	Community based	Rural	218	44.5	49.5	42.3
35	Onwubere *et al*[44]	2011	Ezeagu	Enugu	SE	140/90	Community based	Rural	858	46.4	31.2	68.8
36	Ejim *et al*[213]	2011	Imezi owa,	Enugu	SE	140/90	Community based	Rural (middle age/elderly)	858		50.2	44.8
37	Ulasi *et al*[45]	2011	Enugu	Enugu	SE	140/90	Traders	Urban	731	42	46.3	37.7
38	Hendriks *et al*[214]	2011	Afon and Ajasse Ipo	Kwara	NC	140/90	Community based	Rural	2678	19.3	NA	NA
39	Isezuo *et al*[46]	2011	Sokoto	Sokoto	NW	140/90	Community based	Rural	782	24.8	25.9	23.6
40	Andy *et al*[47]	2012	CRS/AK	CRS/AK	SS	140/90	Community Based	Rural	3869	23.6	31.2	18.1
41	Onwuchekwa *et al*[48]	2012	Kegbara-Dere	Rivers	SS	140/90	Community based	Rural	1078	18.3	-	-
42	Odugbemi *et al*[215]	2012	Lagos	Lagos	SW	140/90	Traders	Urban	400	34.8	-	-
43	Ogah *et al*[49]	2012	Abia	Abia	SE	140/90	Community	Rural/urban	2983	SHT 31.4, DHT 22.5	Rural: SHT 33.5, DHT 23.4; Urban: SHT 33.6, DHT 20.6	Rural: SHT 30.5, DHT 25.4; Urban: SHT 26.4, DHT 18.4

SW: South west; SE: South east; SS: South south; NW: North west; NE: North east; NC: North central; NA: Not available; SHT: Systolic hypertension; DHT: Diastolic hypertension; BP: Blood pressure.

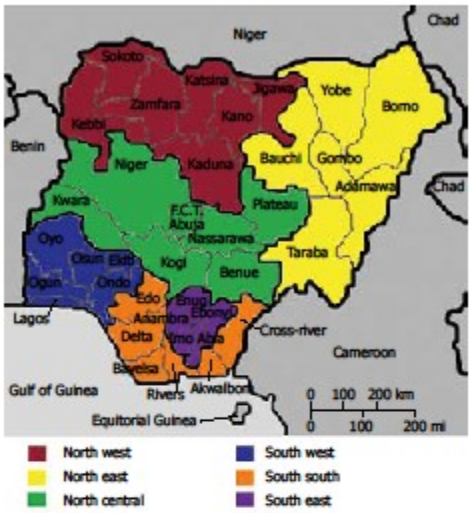

Figure 2 Map of Nigeria showing the 36 states and federal capital territory as well as the 6 geopolitical zones.

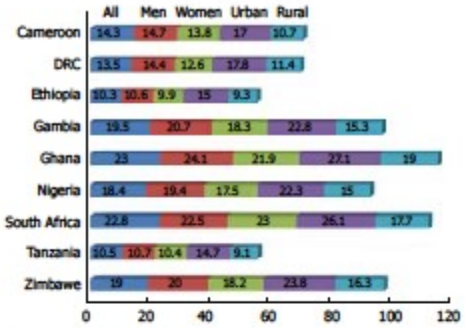

Figure 3 Comparision with other countries.

Blood pressure control was poor, it was reported as 9% (5% in men and 17.5% in women) by Ekwunife *et al*[99].

Studies on pathophysiology of hypertension in Nigeria

Osotimehin *et al*[100] estimated plasma Na^+-K^+ ATPase inhibitor by a technique in which it competes with ouabain for binding on red cells in normotensives without a family history of hypertension, normotensives with a family history of hypertension and hypertensive individuals. They observed that plasma levels of the inhibitor were significantly higher in the last two groups and that this correlated positively with urinary sodium excretion in the three groups.

In another study, the author demonstrated low renin activity in hypertensive Nigerians[101].

Ogunlesi *et al*[102] and Aderounmu *et al*[103] studied intracellular sodium and blood pressure and showed that erythrocyte sodium (ENa) was higher in hypertensives compared with normal controls. ENa also correlated with systolic and diastolic blood pressure. Obasohan *et al*[104] went further to demonstrate higher sodium-lithium counter-transport (SLC) activity and ENa levels both in hypertensive subjects and their offspring.

In a more recent study, Adebiyi *et al*[105] showed that plasma noradrenaline level was higher in hypertensive subjects compared to control subjects. Hypertensive Nigerians also have lower levels of plasma renin, angiotensin converting enzyme (ACE) and atrial natriuretic peptide (ANP). Systolic blood pressure positively correlated with plasma noradrenaline but negatively with renin, ACE and ANP. This finding of high noradrenaline levels in hypertensive Nigerians supports the hypothesis that activation of the sympatho-adrenergic system might play a dominant role in the pathophysiology of hypertension in Nigerians.

Several workers have also demonstrated higher salt taste and salt taste threshold in hypertensive individuals as well as their offspring compared to their normotensive counterparts[106-108].

However such a relationship was not demonstrated in adolescent school children[109].

Hypertension related admissions in Nigeria

In a review of the prevalence of hypertension and its complications among medical admissions in Enugu, South Eastern Nigeria, 18% (1360 subjects out of the 7399 admissions in the period between December 1998 and November 2003) had hypertension related diseases. Hypertensive congestive cardiac failure accounted for 26.5% of cases and 46.1% of hypertension related complications. Hypertension with its complications accounted for more than two-thirds (69.6%) of the cardiovascular system admissions[122,123].

In a three year review of adult hypertensive admissions in Benin city (South-South Nigeria), Ukoh[119] reported that 575 out of the total of 2852 adult medical admissions in Benin were as a result of high blood pressure related morbidities. The most common hypertensive complications were stroke, congestive cardiac failure and chronic kidney failure.

In another report from the same region, stroke was the commonest cause of death at the medical emergency room of the University of Portharcourt teaching hospital[124].

In a review of 424 hypertension related admissions in the same hospital (173 males and 251 females, aged 18-100 years with a mean of 56.5 ± 16.2); stroke was responsible for 169 (39.9%) hypertensive complications. "Heart failure occurred in 97 (22%) cases while renal failure and encephalopathy accounted for 40 (9.4%) and 7 (1.7%) hypertensive complications, respectively. There were 99 deaths out of which 51 (51.5%) were due to stroke, 14 (14.12%) were due to heart failure, and 12 (12.1%) were due to renal failure"[125].

During the same period, 191 of the hypertension

related admissions died giving a case fatality of 42.9%. Eighty six (45%) of the deaths occurred during acute hypertensive crises such as stroke, hypertensive encephalopathy and acute renal failure. Other important complications leading to death included heart failure (17.3%) and renal failure (16.8%)[125].

High blood pressure also contributed to the burden of adult medical admissions in Uyo (Southern Nigeria): hypertension related heart failure, stroke or severe uncontrolled hypertension. This was shown to be commoner in the wet seasons of the year[126].

In Sokoto (Northwestern Nigeria), Isezuo *et al*[127] documented hypertension related admissions in 440 subjects admitted in a tertiary centre between 1995 and 2000. Hypertension related morbidities included heart failure (36.4%), stroke (34.8%) and chronic renal failure in 7.1% and other conditions in 21.7%. Hospital admissions for hypertension related morbidities were more generally higher in the rainy season than the dry season.

Kolo *et al*[128] studied hypertension related admissions and outcomes in a tertiary hospital in Bauchi (North Eastern Nigeria). They documented that out of the 3108 admissions into the medical ward of the hospital, 735 (23.7% were related to hypertension with an excess mortality of 42.9%. Stroke was the commonest complication, accounting for 44.4% of cases and had the highest mortality (39.3%). This was followed by chronic kidney disease (36.6%), hypertensive emergencies (30.9%) and heart failure which had the least intrahospital mortality of 27.5%.

Hypertensive target organ damage in Nigeria

Hypertensive target organ damage (TOD) is common in Nigeria. Because of low awareness of hypertension in the country, hypertensive TOD is often what brings patients to healthcare facilities.

Oladapo *et al*[129] recently reported the results of the study of the prevalence and pattern of TOD and associated clinical conditions in 415 hypertensive individuals in a rural community in Southwestern Nigeria. 179 (43.1%) of the participants had evidence of TOD and 45 (10.8%) had established cardiovascular disease. Left ventricular hypertrophy (LVH) was present in 27.9%, atrial fibrillation in 16.4%, microalbuminuria in 12.3% and overt proteinuria in 15.3%.

Furthermore stroke was present in 6.3%, heart failure in 4.6%, retinopathy in 2.2%, ischaemic heart disease in 1.7% and peripheral vascular disease in 3.6%. TOD was significantly higher in those with severe hypertension and diabetes mellitus. In a related study but in younger subjects aged 18-44 years, Ekore *et al*[21] examined 124 individuals for TOD. LVH was present in 22 (17.7%), chronic cardiac failure in 3 (2.4%), retinopathy in 5 (4.0%), nephropathy in 12 (26.1%) and transient ischaemic attacks in one patient (0.8%)

Ayodele *et al*[130] examined 203 patients in an outpatient clinic in Abeokuta and documented LVH in 31%, heart failure in 10.8%, chronic kidney disease (CKD) in 18.2% and stroke in 8.9%.

Hypertensive heart disease

Various aspects of hypertensive heart disease (HHD) have been studied in the country - such as LVH, LV geometry, left atrial structure, function and dysfunction, LV diastolic function and dysfunction, LV systolic function and right ventricular function. The burden of arrhythmias and conduction abnormalities has also been reported in compensated and asymptomatic hypertensives in the country.

Left ventricular hypertrophy: The prevalence of ECG LVH in hypertensive subjects varies from 18%-56% depending on the criteria used. Sokolow-Lyon-Rappaport voltage criteria have the best sensitivity (80%) and area under the receiver operating characteristic curve. Romhilt-Estes score was reported to have the best specificity[131].

In another Nkado *et al*[132] noted a significant correlation of ECG voltage with echocardiographically determined LV mass.

ECG LVH with strain pattern has also been shown to have a worse LV structure and systolic function in hypertensive Nigerians[133].

Left ventricular diastolic dysfunction: LV diastolic dysfunction has been demonstrated in hypertensive Nigerians by various workers[134-138]. Furthermore it has also been demonstrated in offspring of hypertensive individuals. Adamu *et al*[137] reported LV diastolic dysfunction in 62% of hypertensive subjects compared to 11.3% in age and sex-matched controls. Impaired relaxation was the commonest LV filling pattern.

Adebayo *et al*[139] demonstrated early diastolic dysfunction in hypertensives using a newer method of evaluation (tissue doppler imaging). In another study, the authors evaluated left atrial structural and functional alterations in hypertension which was found to be statistically different compared to age and sex-matched apparently normal individuals[140].

LV systolic dysfunction: In a study of 832 unselected hypertensive subjects, Ogah *et al*[141] documented LV systolic dysfunction (LVSD) in 18.1% of the participants (mild LVSD = 9.6%, moderate LVSD = 3.7% and severe LVSD = 4.8%).

LV mass, body mass index and male gender were found to be independent predictors of LVSD in the study.

The Tei index (index of global myocardial performance) was found to be significantly higher in hypertensives compared to controls. This index also increased with severity of hypertensive heart failure. It was found to be inversely related to LV ejection fraction and directly related to some indexes of diastolic function such as E/A ratio and deceleration time[142].

Echocardiographic LVH and LV geometric patterns: Adebiyi *et al*[143] studied the prevalence and pattern

of LVH in a large population of hypertensive Nigerians seen at the University College Hospital, Ibadan. The prevalence of LVH ranged from 30.9%-56.0% depending on the method of indexation employed.

Abnormal LV geometry was documented in 61.1%-74.0% and was commoner in the female gender.

Correlates of LV mass in hypertensive Nigerians: Ogah *et al*[144] assessed the correlates and determinants of LV mass in 285 hypertensive individuals. The authors found that diastolic blood pressure, family history of hypertension, alcohol consumption, left atrial size; LV wall stress and tension were the independent predictors of LV mass (LVM) in these hypertensive subjects.

Right ventricular function and dysfunction: Karaye *et al*[145] reported right ventricular diastolic dysfunction (RVDD) and right ventricular systolic dysfunction (RVSD) in 61.7% and 32%, respectively, of 128 individuals with high blood pressure in Kano. RVSD was highest in those with eccentric LVH. Age was found to be the only determinant of RVDD while LV ejection fraction was a predictor of RVSD after adjusting for confounding variables. In a similar study, Akintunde *et al*[146] reported RV structural and functional alteration in hypertension and concluded that RVDD may be an early precursor of HHD in Nigerians.

The burden of arrhythmias in hypertensive Nigerians: Hypertension and LVH are both risk factors for atrial fibrillation and ventricular arrhythmias.

Okeahialam *et al*[147] studied 1547 ECG tracings obtained from well compensated hypertensive patients over a 5-year period in Jos to determine the burden of arrhythmias. About 10% of patients had one form of arrhythmia or another. The common arrhythmias were ventricular ectopic (133, 86.9%) atrial ectopic (21, 13.7%) and atrial fibrillation (10, 6.5%). Others included sinus arrhythmia in 3 (1.9%), sinus escape beats in 3 (1.9%), wandering pacemaker in 3 (1.9%) and Wolf Parkinson White in 1 (0.7%). Factors associated with the presence of arrhythmias include: age, presence of ECG LVH and left atrial enlargement.

Conduction abnormalities: In the same study, Okeahialam *et al*[147] noted the following conduction abnormalities in 1547 well compensated hypertensive patients. First degree AV block was present in 7 while 6 subjects had right bundle branch block and left bundle branch block.

Hypertension as a risk factor for heart failure in Nigeria: Hypertension is by far the commonest risk factor for congestive heart failure in Nigeria. In the Abeokuta heart failure (HF) registry, hypertension was responsible for 78.7% of HF in the city. It was also responsible for 62.6%, 56.3%, 57% and 44.1% of heart failure cases in Abuja[148], Port Harcourt[149], Jos[150] and Uyo[126] respectively. In the recently published transnational study of HF in sub-Saharan Africa, hypertension was clearly shown as the predominant cause of HF in the region, especially in Nigeria. Ogah *et al*[151] recently described the characteristics of 197 subjects with hypertensive HF in the Abeokuta HF registry. The mean age of the subjects was 58.4 years which is 15-20 years younger than the mean age of patients with HF in the developed world. The male to female ratio was 1.4:1. HF in hypertensive Nigerians was characterized by severe LV systolic dysfunction (65.5%) and abnormal LV geometry (concentric and eccentric LVH). Intrahospital mortality was 3.6%.

It has also been noted that most of the patients diagnosed as having dilated cardiomyopathy in Nigeria are cases of hypertensive heart failure with poor myocardial failure because of poor or no control[152,153].

Hypertension as a major risk factor for stroke in Nigeria

Stroke is currently a major public health problem in Nigeria. As in many developing countries of the world it has some peculiarities. It occurs at a younger age with associated high mortality and disability adjusted life years.

Available hospital based studies in Nigeria suggest there are rising rates of stroke in the country[154].

Available data, at least from hospital based studies, show that stroke accounts for 0.23%-4.0% of all hospital admissions, 0.5%-45% neurological admissions and 5%-17% of deaths on medical wards. It is the commonest cause of neurological admission in Lagos, the largest city and the commercial nerve centre of Nigeria. Cerebral infarction, intracerebral hemorrhage and subarachnoid haemorrhage, respectively, are responsible for 64%, 19% and 6% of strokes in the country[154].

In a community based study in Lagos[155], stroke prevalence was estimated as 1.14 per 1000 (1.51/1000 in men, 0.69/1000 in women and 24.1/1000 in those older than 65 years.

The mortality associated with stroke in Nigeria is high with 30 d case fatality ranging from 28% to 40%[154].

In a 10-year review of stroke in Sagamu, Ogun State, stroke accounted for 2.4% of all emergency admissions. Forty nine percent had cerebral infarction, 45% intracerebral haemorrhage and 6% SAH. The studies further showed that 1.8% of all deaths at the emergency room were due to stroke. Case fatality at 24 h, 7 d, 30 d and 6 mo were 9%, 28%, 40% and 46%, respectively[154]. In the year 2007, mortality from stroke in the country was put at 126/100 000 population[156].

In Nigeria, as in most developing countries, hypertension is the most important modifiable risk factor for stroke. It is present in almost 80% of cases. Unfortunately most victims are unaware of their blood pressure status prior to the event[157].

Hypertension as a risk factor for chronic kidney disease in Nigeria

Hypertension is a major cause of CKD and chronic renal failure (CRF) in Nigeria. In Enugu (South East) and Benin City (South South), hypertension is the commonest

cause of CKD and CRF[158,159]. It is only second to chronic glomerulonephritis in the South West[160-163]. Hypertension induced CRF in Nigeria is four times commoner in men than women with a male: female ratio of 4.3:1. Severe throbbing frontal headache and nocturia are common. The duration of hypertension is usually between 2-15 years. It is associated with a history of cigarette smoking, poor compliance to anti-hypertensive medications, family history of hypertension, severe/accelerated hypertension and severe uraemia. The presence of other hypertension related TOD, such as heart failure and retinopathy, is common. Mortality is high, 51% within the first 12 mo of diagnosis. Renal histological findings include glomerular sclerosis, malignant arteriolar changes and absence of glomerular cellular proliferation[164,165].

Hypertension and coronary artery disease in Nigeria

Hypertension is a major risk factor for coronary artery disease (CAD) in Nigeria. Anjorin *et al*[166] recently reviewed 87 patients with CAD seen over a period of 22 years (1983-2004) at the University of Maiduguri teaching hospital. Hypertension was identified as a risk factor in 53%, diabetes in 41%, cigarette smoking in 39%, hypercholesterolemia in 29% and obesity in 20%.

Hypertensive retinopathy in Nigeria

In a review of 407 patients with retinal diseases in Ile-Ife (Southwest) by Onakpoya *et al*[167], hypertensive retinopathy was responsible for 12% of cases. In Ibadan, hypertensive retinopathy is the 9th commonest cause of retinal diseases and responsible for 4.6% of cases[168]. It is also responsible for 7.7% of all retinal/optic nerve disorders and 0.1% of ocular disorders in a rural community in northern Nigeria. In Enugu (South East), hypertensive retinopathy is responsible for 13% of vitreoretinal diseases in a tertiary healthcare facility[169].

DISCUSSION

Since the creation of the Nigerian state in 1960, a lot of studies have been undertaken to provide information on the burden of hypertension in the country. This includes a national survey which was conducted in 1997[113]. It is pertinent, however, to note that most studies provided crude prevalence of the condition in the country. In addition, there are a lot of variations in the studies in terms of target population as well as criteria for diagnosis. Earlier studies used 160/95 mmHg (occasionally 160/90 mmHg) while the most recent ones used 140/90 mmHg as a cut off mark for the diagnosis of hypertension. The age structure in most of the studies is essentially middle age and represents the age structure of the Nigerian population, except in few studies that purely targeted middle age or elderly populations[15,25]. In many of the studies, the prevalence of hypertension was higher in men than in women at least up to the age of 40 years when the prevalence equalized[9,10,26,32]. This picture is similar to findings in other Africans, African Americans and in Blacks in the Caribbean[112].

The higher prevalence in the urban population may indicate differences in lifestyle. Urban populations are more likely to eat processed foods which are high in salt and fat content. Obesity which is a risk factor for hypertension is also higher in urban areas than in rural areas because of reduced physical activity.

In a few of the studies, especially in the Eastern part of the country, hypertension was found to be as high in the rural population as it is in the urban population[27]. This picture has been documented in some United States and European studies[170-173]. It is likely that those rural populations may be older as most old people move to rural areas after retirement from active service.

Hypertension awareness range from 3.5% in Sokoto to 30% in Nsukka[22,25,26,40,99]. There was no remarkable gender difference. Treatment ranged from 11.9%-21%[40,99]. In two studies the treatment rate was slightly higher in men than in women; however the control rate was significantly higher in women than in men (17.5% and 5%, respectively).

The higher detection rate in men than women is at variance with data from most parts of Africa and other parts of the world. Women are more likely to be detected during antenatal visits and are also more likely to accept the diagnosis of hypertension.

On the other hand, the blood pressure control rate is better in women than in men. Women are more likely to attend clinics for follow-up.

In general, hypertension and other chronic diseases awareness, treatment and control is generally low in the country as in most developing countries. These diseases are often asymptomatic and in most cases presentation is when complications have set in.

Emerging data from hospital studies show that hypertension or its complications is the commonest NCD in Nigeria. In 1961, hypertension related illnesses contributed to 8.8% of all medical admission in Lagos[28]. Abengowe *et al*[95] reported 9.3% in Kaduna in 1980. Recent data from the country indicated a rate of 28% in Port-Harcourt[124] and 21% in Benin City[119]. This is comparable to a rate of 30% from Tanzania[174].

In conclusion, hypertension in Nigeria today is the commonest risk factor for stroke, heart failure, ischemic heart disease and chronic kidney disease[175].

There is, therefore, a need to encourage health promotion in the population as means of primary prevention. There is also a need for increased public health education to increase the awareness of hypertension and the sequelae. Hypertension control programmes need to be established in communities in the country and more community based screening programmes for cardiovascular disease risk factors and NCDs need to be carried out. There is also a need to carry out research on the reasons for regional differences in prevalence of hypertension as well as reasons for lack of urban-rural differences in some areas in the country. The lack of scientific data to measure trends in the country should also be addressed.

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Review Articles

Cardiomyopathies and myocardial disorders in Africa: present status and the way forward

AYODELE O FALASE, OKECHUKWU S OGAH

Abstract

A review of heart diseases in Africa shows that the cardiomyopathies continue to be important causes of morbidity and mortality in the population. Hypertension remains the commonest cause of myocardial disease, followed by the cardiomyopathies. Ischaemic heart disease continues to be rare. Of the cardiomyopathies, dilated cardiomyopathy (DCM) is still the commonest. A large proportion of patients diagnosed with DCM in Africa have been shown to be cases of hypertensive heart failure, with varying degrees of myocardial dysfunction. Hypertrophic cardiomyopathy, which in the past was thought to be rare among Africans, has been shown to have the same prevalence as in other parts of the world. Moreover it is now known to be a genetic disorder. Endomyocardial fibrosis has become rare in communities where it used to be common. Its aetiology continues to be elusive. Arrhythmogenic right ventricular cardiomyopathy has been reported among Africans but there are no reports of left ventricular non-compaction or the ion channelopathies from Africa. Lenegre disease and the long-QT syndromes are well-known entities in clinical practice in Africa although long-QT in Africa is associated with potassium deficiency arising from prolonged treatment with diuretics. Left ventricular non-ischaemic aneurysms still occur but are rare. In view of these, a new classification of myocardial disorders was proposed for Africa.

Keywords: cardiomyopathy, Africa, sub-Saharan Africa

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For the past 60 years, reports from all parts of Africa have shown a remarkable unanimity in the pattern of heart diseases among black Africans.[1,2] While ischaemic heart disease is the dominant cardiovascular disease in the Western world, it is rare in black Africans.

The typical pattern of heart failure in the sixties in a black African hospital is shown in Fig. 1A.[1] From this figure, it is obvious that the commonest cause of heart failure was hypertension. This was followed by diseases that primarily affected the myocardium (labelled myocardial disease in the illustration), then rheumatic heart disease, followed by endomyocardial fibrosis. Recent data (Fig. 1B) among the same ethnic group show that the prevalence of hypertension has doubled, there is no difference in the prevalence of dilated cardiomyopathy, the prevalence of

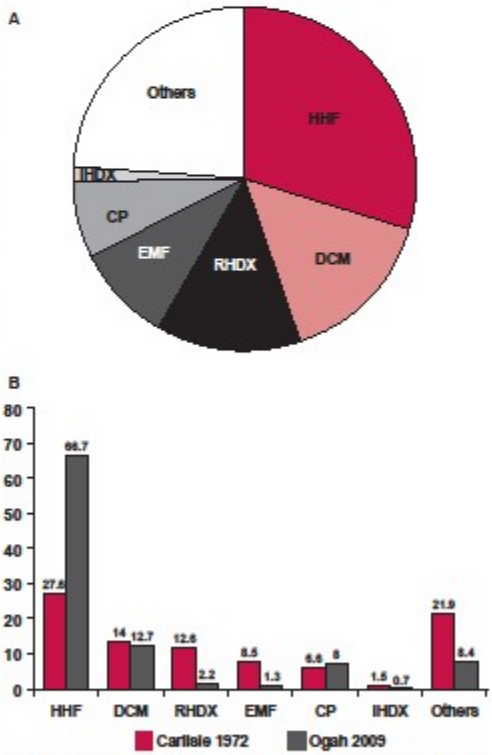

Fig. 1A. Causes of heart failure in Nigerians at the University College Hospital, Ibadan between 1968 and 1969 (Carlisle and Ogunlesi 1972). B. Causes of heart failure in the same ethnic group in the year 2010 compared with the 1972 data.[3] HHF – hypertensive heart failure; RHDX – rheumatic heart disease; DCM – dilated cardiomyopathy; EMF – endomyocardial fibrosis; CP – cor pulmonale; IHDX – ischaemic heart disease.

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ischaemic heart disease remains low, while that of rheumatic heart disease has decreased considerably.[3]

We are primarily concerned with myocardial diseases and endomyocardial fibrosis in this discourse. We performed a systematic search of Pubmed for published data on cardiomyopathies in sub-Saharan Africa from January 1960 to December 2009. This was supplemented with parallel searches of references of identified journals, as well as a search of specific data sets such as African Index Medicus, African Journals Online (AJOL) and the World Bank database. The search strategy was Africa or sub-Saharan Africa and cardiomyopathy, dilated cardiomyopathy, endomyocardial fibrosis, and peripartum cardiomyopathy.

Prior to 1980 there were several descriptions from many geographical areas of the world but mainly from Africa of obscure forms of heart disease that primarily affected the heart muscle. These descriptions were published under several names such as idiopathic cardiomegaly,[4] nutritional heart disease,[5] cardiovascular collagenosis with parietal endocardial thrombosis,[6] and cardiomyopathy.[7] The common features of these descriptions were that affected patients presented in congestive cardiac failure with cardiomegaly, the cause of which was not readily apparent. The disease was particularly common in the tropical and sub-tropical countries of the world where it constituted one of the major clinical and health problems.[8]

Similarly, there were several descriptions from many parts of the world, of another group of myocardial diseases that was characterised by inappropriate massive hypertrophy of the cardiac muscle (HCM). It was first described by Teare in 1958.[9] Prior to 1980, it appeared to have a worldwide distribution although initial reports suggested that it was rare in black people. The reason for this might have been due to a high prevalence of hypertensive heart disease, which interfered with the correct diagnosis of the disease.[10] HCM too had been described in the past under several names, including idiopathic hypertrophic sub-aortic stenosis, muscular sub-aortic stenosis, obstructive cardiomyopathy and asymmetrical hypertrophy.[11]

Thirdly, there were before 1980 several descriptions of another group of myocardial disorders of unknown origin, which was characterised by fibrosis of the endomyocardium, particularly the inflow tract, apex and part of the outflow tract of either or both ventricles. The mitral/tricuspid valve apparatus, depending on which ventricular chamber was affected was commonly enmeshed in fibrous tissue, which very often involved the posterior valve leaflet. The anterior valve leaflet was rarely involved. It was called endomyocardial fibrosis (EMF) in those tropical countries that first reported it.[12]

Prior to the description of the tropical forms of EMF, there were also reports of a similar disease that was characterised by the presence of hypereosinophilia. It was first described by Löffler in 1936,[13] and was known as Löffler's endocarditis parietalis fibroplastica. This disease was initially believed to be confined to only the temperate zones of the world and was considered to be a separate illness from the tropical forms of EMF. However several reports have now confirmed its presence in Africa and other countries of the world where the tropical forms of EMF is prevalent.[14] Some have even suggested that it is the early form of tropical EMF (Fig. 2).[14]

Classification of the cardiomyopathies

Because of the initial confusion arising from the names given to all these diseases, the inadequacy of previous classifications,[15] and to ensure unanimity in their descriptions, a task force was set up by the World Health Organisation and the International Society and Federation of Cardiology (WHO/ISFC) to harmonise the features of the diseases, adopt uniform names for them, and design an acceptable classification. The report of the task force was published in 1980,[11] while the full description of each disease was published by the WHO as a report of an expert committee in 1984.[10]

At the 1980 meeting, it was agreed to adopt the name 'cardiomyopathy' for all diseases of the heart muscle of unknown cause. For a disease to qualify as a cardiomyopathy therefore, the patient must have been extensively investigated and no cause found for the malady. Diseases whose causes were known were simply identified by their causative factors, such as alcohol heart disease, myocarditis or viral heart disease. Such diseases were grouped under a separate heading called 'specific heart muscle diseases' which was defined as 'heart muscle diseases of known cause or associated with disorders of other systems'.

Since it was considered inappropriate to slot well-known disorders of the myocardium caused by systemic or pulmonary hypertension, coronary artery disease and congenital heart diseases under this group, they were excluded from the classification. It was felt that all diseases of the myocardium would have had to be listed under specific heart muscle diseases if this was not done. In summary, cardiomyopathy was regarded as a disease of exclusion.

The meeting further agreed to group the cardiomyopathies into three types. The first two were named to highlight the changes in their structures (hypertrophic and dilated) while the third, unfortunately, in our view, was named to reflect its restrictive haemodynamic features (restrictive). This classification was

Fig 2.A. Hypertrophic cardiomyopathy; B. dilated cardiomyopathy; C. endomyocardial fibrosis.

made before arrhythmogenic right ventricular dysplasia was characterised and identified as a separate disease in the literature, hence its omission in the classification.

The reaction of clinicians/researchers to this classification was mixed. While everyone agreed with the designation of these diseases as cardiomyopathies, not everyone agreed with its classification. Several classifications followed thereafter but, in so doing, many of them again extended the definition of cardiomyopathies to include any disorder of the myocardium.

The report of another task force, set up by the WHO in 1995[16] to update the 1980 classification, defined the cardiomyopathies as any disease of the myocardium with cardiac dysfunction, although it retained the original three types of cardiomyopathies: hypertrophic, dilated and restrictive. It added a fourth one, arrhythmogenic right ventricular cardiomyopathy (formerly known as arrhythmogenic right ventricular dysplasia). But while it recognised that dilated cardiomyopathy may derive its origin from conditions such as viral myocarditis, it created, under specific cardiomyopathies, an entity known as inflammatory cardiomyopathy, which it defined as 'myocarditis in association with cardiac dysfunction'.

Similarly it also created another entity, known as alcoholic cardiomyopathy, under specific cardiomyopathies after it had agreed that dilated cardiomyopathy may be caused by the consumption of alcohol. Moreover, ischaemic cardiomyopathy was recognised in the report as a separate entity under specific cardiomyopathies, although the same disease was earlier said to be a variety of dilated cardiomyopathy. Finally, the document introduced new names for well-recognised diseases. For example, hypertensive cardiomyopathy was substituted for the well-known and more specific terms, hypertensive heart disease/hypertensive heart failure.

The latest classification, sponsored by the American Heart Association,[17] agreed to classify the cardiomyopathies in line with 'the molecular era of cardiovascular disease'. It also agreed that cardiomyopathies should include any disorder of the myocardium and therefore defined them as 'a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that are frequently genetic. Cardiomyopathies either are confined to the heart or are part of generalised systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability'.

The panel made a case for inclusion of the ion channelopathies in the classification of the cardiomyopathies, although it agreed that they are primary electrical diseases with no gross or histopathological abnormalities. As in the 1980 classification, it excluded from the list of cardiomyopathies 'pathological myocardial processes and dysfunction that are a direct consequence of other cardiovascular abnormalities, such as that which occurs with valvular heart disease, systemic hypertension, congenital heart disease, and atherosclerotic coronary artery disease producing damage secondary to impairment in coronary flow'.

The report went further to classify the cardiomyopathies into two major groups 'based on predominant organ involvement'. These were primary and secondary cardiomyopathies. Primary cardiomyopathies, which may be genetic, non-genetic or acquired, were defined as 'those solely or predominantly confined to heart muscle and are relatively few in number'. The genetic forms included hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular non-compaction, conduction system disease, glycogen storage disorders, mitochondrial myopathies, and ion-channel disorders. The mixed forms were dilated cardiomyopathies and the restrictive (non-hypertrophied and non-dilated) types.

In the report, secondary cardiomyopathies were diseases that were associated with systemic illnesses. These were similar to those listed under specific heart muscle disease and specific cardiomyopathies by the 1980 and 1996 reports, respectively.

Classification of the cardiomyopathies in Africa

For clinicians working in Africa where the cardiomyopathies are most prevalent, the question that follows is which of these classifications is appropriate for Africa? Before we answer this question, let us briefly review what is currently known about the cardiomyopathies in Africa.

Hypertrophic cardiomyopathy

In the pre-echocardiography era, hypertrophic cardiomyopathy (HCM) was hardly diagnosed in Africa. All abnormal electrocardiographs (ECGs) suggestive of left ventricular hypertrophy (LVH) were attributed by clinicians to hypertensive heart disease since hypertension was the dominant cardiovascular disease among Africans and was extremely common in African populations. The widespread use of echocardiographic examination all over Africa changed all this as it showed that HCM indeed occurs among Africans.

For instance, HCM was found in 0.2% of 6 680 unselected echocardiograms in Tanzania[18] and in 2% of 712 echocardiograms in Lagos, Nigeria.[19] Similar reports have also come from South Africa where extensively genetic investigations have confirmed similar findings with other parts of the world.[20] In Ghana,[21] 1.15% of 572 patients referred for echocardiography at the Ghana National Cardiac reference centre had HCM, while Abegaz in Ethiopia discovered that 53 out of 1 240 abnormal echocardiograms performed at the Armed Forces General Hospital had HCM.[22] The prevalence rate among populations outside Africa ranged from 0.2 to 0.5%. Interestingly, Maron *et al.*[17] found in their CARDIA study that the prevalence of HCM in blacks was twice that of whites, while more African-Americans performing competitive sports died suddenly compared with their white counterparts.

The aetiology of HCM has similarly been sorted out. Investigations all over the world have conclusively shown that HCM is inherited as an autosomal dominant genetic disorder that is caused by mutations in at least 10 different genes that code for sarcomeric proteins.[3,15] Mutations in the β-myosin heavy chain gene, myosin-binding protein C and troponin T account for 70 to 80% of all the cases. The total number of mutations is well over 100, and new mutations are being discovered. HCM is therefore no longer a heart muscle disease of unknown cause and this implies that the 1980 report on the cardiomyopathies is no longer valid.

Arrythmogenic right ventricular cardiomyopathy (ARVC)

Reports from Africa about this disease have come from only South Africa.[20,23] There are familial cases of ARVC as well as

non-familial ones. Although the disease has been associated with enteroviral and adenoviral myocarditis, it is not considered to be primarily caused by myocarditis. Lately it has been shown that the disease is not confined to the right ventricle as the name suggests, because the left ventricle may be affected in up to 75% of the patients.[12]

Other genetic disorders of the myocardium

Familial and non-familial cases have been described in patients with the recently discovered myocardial disorder known as left ventricular non-compaction (LV non-compaction).[12] Characteristic morphological changes of this disease are often found in the left ventricle of those with the disease. There are no reports of LV non-compaction from Africa, possibly because African cardiologists are not yet familiar with its echocardiographic changes.

Genetic disorders of the electrical system of the myocardium with or without morphological changes have also been described. They include Lenegre disease,[13] a progressive disease of the conduction system of the heart and the ion channelopathies. Among the ion channelopathies are the long-QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, short-QT syndrome and idiopathic ventricular fibrillation, all of which can cause sudden death. Lenegre disease and the long-QT syndromes are well-known entities in clinical practice in Africa although long-QT is only associated in Africa with metabolic problems, particularly potassium deficiency following prolonged treatment with diuretics. It is however interesting to note the recent report from South Africa,[14] which concluded that the genetic forms of long-QT syndrome (LQTS) occurred most commonly among the white Caucasian population of South Africa, with fewer cases from those of mixed ancestry and none from those of black African descent.[3] The other ion channelopathies have not been reported from Africa, probably because of lack of sophisticated cardiac electrophysiological studies and a dearth of well-trained personnel required to make the diagnosis.

Dilated cardiomyopathy

Next to hypertension, this is the commonest cause of heart failure in black Africans.[1,2] In some communities in Africa, DCM is the commonest cause of heart failure. Before the advent of echocardiography, the diagnosis was made on the basis of clinical presentation, chest X-ray, ECG, and sometimes in the large teaching hospitals, cardiac catheterisation and angiography. Echocardiography has made the diagnosis easier and is presently the preferred investigation for making a diagnosis.

Affected patients often presented in congestive cardiac failure with functional mitral and tricuspid regurgitation due to myocardial failure, the cause of which was not apparent. ECG changes were variable. Some had low-voltage complexes while others presented with left ventricular hypertrophy. Abnormal intraventricular conduction defects were common, especially left bundle branch block. Chest X-ray usually showed cardiomegaly with failure, while angiography confirmed a dilated left ventricle with poor myocardial contraction and functional mitral regurgitation.

DCM is widely regarded as an end-stage myocardial disease from a wide variety of adverse factors. The most common of these insults are briefly considered below.

Hypertension

For a long time, several workers in Africa had suspected that many patients who were labelled as having DCM were really hypertensives. And there had been several debates at world conferences where this assertion was actively advanced by many workers. Mokhobo,[15] from South Africa advised caution in making a diagnosis of cardiomyopathy since 'cardiomyopathy and hypertension are both common in black patients and confusion may arise between them'. Lowenthal,[16] also from South Africa wrote as follows: 'these cases are regarded as evidence in favour of the hypothesis that many cases of cryptogenic heart disease (cardiomyopathy, congestive cardiomyopathy, idiopathic cardiomegaly) are in fact hypertensives presenting with normotensive cardiac failure'.

From Nigeria, Brockington,[16] after extensive studies, came to the conclusion that hypertension and what he called heart muscle disease at the time were similar and that the latter was 'the late stage of untreated chronic hypertensive heart failure'. Brockington's view was supported by Celia Oakley at a debate during a conference on cardiomyopathies held in London in 1971 but John Goodwin at the same conference disagreed, asserting that hypertensive heart disease was structurally different from heart muscle disease.

The contentious problem in the past had always been the presenting blood pressure. Some patients had a normal blood pressure at presentation but in others the blood pressure was mildly raised, although out of proportion with the degree of the patient's heart failure. Very often, the hypertension was transient, the blood pressure becoming normal with treatment of the heart failure and staying normal without sustained treatment

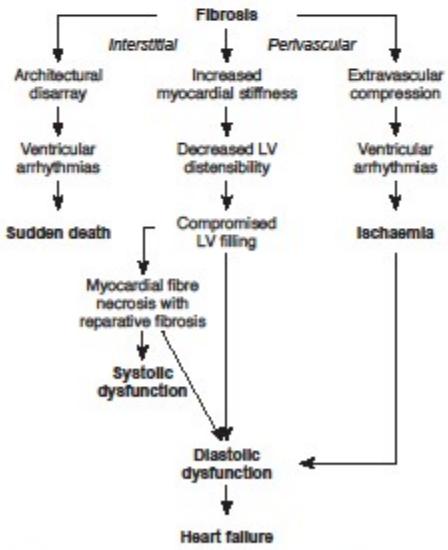

Fig. 3. The consequences of myocardial fibrosis on the heart of patients with arterial hypertension, modified from Diez *et al. Nature Clin Pract Cardiovasc Med* 2005; 2(4): 209–216.

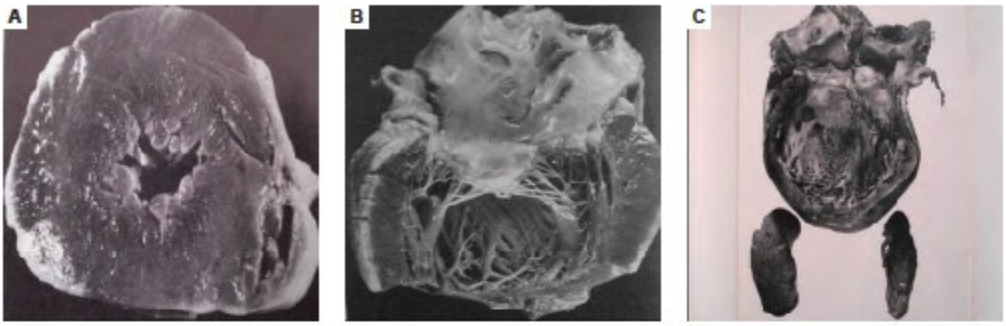

Fig. 4. Representation of progression of the left ventricle in hypertensive patients, from concentric hypertrophy with a small cavity, to concentric hypertrophy with a large cavity, to a destroyed myocardium unable to sustain a high blood pressure.

with diuretics or hypotensive agents. Some investigators had referred to this phenomenon as 'reactive hypertension' or 'Sahli's Hochdruckstauung'[27] because it was thought to be due to intense peripheral vasoconstriction, which occurred in heart failure.

Studies from Nigeria in the seventies have however shown that what was called heart muscle disease in the past was not caused by a single disease process.[28-33] Over 75% of patients were hypertensives whose hearts had become damaged over time because of poor or lack of control of high blood pressure.[34] Progression from a hypertrophied heart (concentric or asymmetric) in Nigerian hypertensives to the stage of flabby heart has been discussed in an earlier publication (Figs 3, 4).[34]

Alcohol

Early reports from Nigeria showed that alcohol consumption played a significant part in the genesis of myocardial damage of patients diagnosed with cardiomyopathies. The authors also suggested that excessive consumption contributed to the heart failure of some of their hypertensives.[29,33] This is in agreement with Rees *et al*.[35] who in 1974 suggested from Nairobi that some of their patients with cardiomyopathies were suffering from the combined effects of excessive alcohol consumption and hypertension, and this combination led to congestive cardiac failure.

Some of the patients studied in Nigeria had thiamine deficiency and these were linked with protein malnutrition and excess consumption of alcohol. All but one had low-output cardiac failure and they did not respond to thiamine administration.[30] By contrast, high-output and low-output cardiac failure caused by thiamine deficiency was shown to have equal prevalence in South African alcoholics.[27]

Generally, it is now estimated that alcohol is a contributory factor in a significant number (up to 45%) of patients with heart failure of unknown cause in Africa,[23] and alcohol also contributes to the heart failure of a significant number of hypertensives.

Myocarditis

Studies in the seventies also showed that myocarditis was the cause of a significant number of patients diagnosed at the time as heart muscle disease of unknown cause, especially among young people below the age of 30 years. At that time, it was only possible to investigate the role of Coxsackie B virus and *Toxoplasma gondii* in the patients studied, but higher antibody levels were found in the patients compared with control subjects. About 45% of the patients eventually turned out to be hypertensive, implying that myocarditis was playing some part in the genesis of their myocardial damage.[28-30,32]

A few cases of acute myocarditis caused by Coxsackie B_3 virus and *Toxoplasma gondii* were documented during the four years the patients were followed up. Sub-clinical infection by *Toxoplasma gondii* is common in Nigeria and several studies have found that virtually everyone living in this community has seroconverted to the organism.[32,33]

Since then, several studies have confirmed the role of myocarditis in the genesis of myocardial failure all over the world and many more organisms [viruses including the human immunodeficiency virus (HIV), bacteria including mycobacteria, parasites such as *Trypanosoma, Toxoplasma gondii* and *Schistostoma*] have been identified as culprits.[2] In Africa, many patients with myocardial failure and a positive HIV test have been shown to have not only viral myocarditis (HIV, Epstein-Barr virus, cytomegalovirus, parvovirus, adenovirus and human simplex virus) but also infections from other organisms such as toxoplasmosis and cryptococcus.

Endomyocardial biopsies and detection of viral genomes have been crucial in the identification of these agents in the myocardium of the patient.[37,38] In an excellent study by Shaboodien,[39] a prevalence of 100% infectivity (enterovirus, Epstein-Barr virus, parvovirus, human simplex virus and adenovirus) was found in the hearts of the patients with 'idiopathic dilated cardiomyopathy' she biopsied. Unfortunately these advanced techniques are not widely available in Africa outside South Africa.

The role of excessive immune activation in the pathogenesis of the disease has also been studied in Africa. A study found that HLA-DR1 and HLA-DRw10 were commoner in patients with DCM.[40] Elevated plasma levels of inflammatory cytokine tumour necrosis factor (TNF)-α, C-reactive protein and a plasma marker of apoptosis have also been found in DCM patients,[41-43] and those with peripartum cardiomyopathy.[44] Leucocyte cytokines were also found to be elevated in these patients. In those with peripartum cardiomyopathy, the level of Fas/Apo-1 was also elevated.

These findings had led to studies on the immunomodulatory effect of pentoxifylline in the management of the DCM patients,

with promising results.[45] The process of progression from acute myocarditis to dilated cardiomyopathy was recently elucidated by Kawai.[46]

Peripartum cardiomyopathy (PCM)

PCM commonly occurs during the last trimester of pregnancy and the first six months after delivery. Risk factors that have been reported in the literature are:[47,48,50]

- black race
- advanced maternal age
- twin pregnancies
- gestational hypertension
- long-term tocolysis.

Reports from Haiti have shown that partial improvement of systolic function occurred in the first year of follow up.[50] In fact a third of their women with PCM recovered fully within five years. Mortality rates were 15% in the first six months and 42% during 25 years of follow up. The Hausas in the northern part of Nigeria have the highest known incidence of PCM in the world – about 13% of all female admissions at the Ahmadu Bello University Teaching Hospital, Zaria.[51-54]

A wide range of diseases has been advanced as the cause of myocardial damage of these women. They include myocarditis, hypertension, abnormal immune response to pregnancy, impaired cardiac (systemic) microvasculature, increased myocyte apoptosis, cytokine-mediated inflammation, selenium deficiency (Keshan disease), lying on heated mud beds after taking two hot baths in addition to excessive consumption of a special porridge to which as much as 30 g/day of potash (kanwa) has been added (Zaria cases), genetic predisposition, increased adrenergic tone leading to myocardial stunning, and excessive production of prolactin.[55]

Recent studies have also shown that unbalanced peri/post partum is linked to proteolytic cleavage of prolactin, which turns it into a potent anti-angiogenic, pro-apoptotic and pro-inflammatory factor. These observations tend to suggest that prolactin cleavage could operate as a specific pathomechanism for the development of PCM.[55,56] Bromocriptine has been shown to be beneficial in reducing the raised levels of prolactin found in some of the women, improving their left ventricular function.[57]

The plasma marker of apoptosis, Fas/Apo-1 has also been shown to be elevated in patients with PCM,[42,43] while troponin T levels have been found to be useful in predicting the presence of persistent left ventricular dysfunction in patients.[58] Baseline Fas/Apo-1 levels and higher NHYA at presentation were found to be the only predictors of mortality, while MRI using late gadolinium enhancement can be useful in evaluating the extent of myocardial damage and predict the outcome of the disease.[46,58,60]

With molecular studies, viral genomic materials of enterovirus, parvovirus B_{19}, human herpes virus 6, Epstein-Barr virus and cytomegalovirus have been identified in the heart muscle of some women with PCM.[61-63] On the contrary, Cenac *et al.*[64] found no evidence of viral myocarditis in Niger, West Africa. Sanderson *et al.*,[37] O'Connell *et al.*[65] and Midei *et al.*[66] on the other hand found evidence of myocarditis in biopsy materials of the women they studied. In fact, Midei *et al.*[66] reported that as many as 78% of newly diagnosed patients with PCM seen by his group had myocarditis and resolution was associated with improvement of left ventricular function.

Familial dilated cardiomyopathy

Familial forms of dilated cardiomyopathies have been well summarised by Maron *et al.*[17] It is estimated that they constitute 20 to 35% of cases of DCM. They are genetically heterogenous but the predominant mode of inheritance is autosomal dominant, with X-linked autosomal recessive and mitochondrial inheritance occurring less frequently. Many of the mutant genes that are linked to autosomal dominant DCM also encode the same contractile sarcomeric proteins that are responsible for hypertrophic cardiomyopathy.

According to Maron *et al.*,[17] DCM is also caused by a number of mutations in other genes encoding cytoskeletal/sarcolemmal, nuclear envelope, sarcomere and transcriptional co-activator proteins. The most common of these is the lamin A/C gene, which is also associated with conduction system disease, and encodes a nuclear envelope intermediate filament protein.

In Africa, the first report of familial DCM was from Uganda where a set of twin brothers was reported to have had the disease.[67] Reports of familial cases have also come from South Africa. A case of familial DCM with prominent ventricular arrhythmias was reported by Brink *et al.*[68] while Przybojewski *et al.*[69] described two brothers of Afrikaner ancestry with unexplained DCM. Cases of DCM have been linked with progressive familial heart block types I and II.[70-72] There were also reports of DCM in two brothers,[68] and a case of microcephaly associated with DCM.[72]

Mayosi *et al.*[73] has also shown that actin mutations do not play a major role in DCM but a mitochondrial DNA susceptibility gene increases the risk of DCM in the general population. Other studies from South Africa evaluated the role of mutations in signaling pathway proteins, in particular, polymorphisms in the angiotensin-converting enzyme and beta-adrenoreceptor subtypes in the progression of DCM.[74]

Malnutrition

Initial reports of DCM from South Africa suggested that the disease was caused by malnutrition. The patients whom Gillanders[9] and Higginson *et al.*[75,76] studied improved when their diet was changed to what was described as a 'balanced' one. This view has been discarded as Gillanders' experiments could not be reproduced.

In our study, we found that patients with DCM had significantly lower serum albumin levels compared with controls, irrespective of whether they consumed alcohol or not. This was attributed to hepatic dysfunction caused by congestive cardiac failure.[29]

Haemosiderosis

Consumption of iron in excess from iron-containing beer (Bantu haemosiderosis) has been suggested as a potentially reversible causative factor of DCM.[75] It has also been found that the 'poor correlation of cardiac and hepatic iron deposits with heart disease' might have led to the under-recognition of dietary iron overload as an important factor in the pathogenesis of DCM.[77] High levels of serum ferritin have been found in patients with DCM compared with patients with heart failure from other causes, and about 50% of the patients had ferritin levels above 500 ng/ml.[80]

Hb genotype

No association was found between Hb genotype and DCM in the patients we studied and there are no reports linking different types of Hb genotypes with DCM.

Summary of studies on DCM in Africa

From all these studies, we can conclude as follows:

- Hypertension contributes to some of the cases diagnosed clinically as DCM in Africa. Such patients should be identified and reclassified as having hypertensive heart failure with varying degrees of myocardial dysfunction.
- Chronic alcohol consumption and myocarditis have also been identified as the causes of myocardial damage in some of the patients clinically diagnosed as cardiomyopathy in Africa and even worldwide.
- Familial cases of DCM have been described in Africa but limited research has been done on the continent.
- Lack of facilities and technical know-how have also made the routine diagnosis of myocarditis in Africa impossible. Many are therefore missed.
- Estimation of markers of inflammation such as C-reactive protein, inflammatory markers such as the tumour necrosis factor α, and the plasma marker of apoptosis (Fas/Apo-1) may perhaps help in making a preliminary diagnosis of myocarditis. This needs to be further explored.
- In patients with PCM, abnormal immune response to pregnancy, increased myocyte apoptosis, selenium deficiency, cultural practices such as those of the Zaria women, and prolactin excess/cleavage are other causes that have been advanced by workers in the field. In those with excess prolactin production/cleavage, bromocriptine has been found to improve the cardiac status of these women.
- Thiamine deficiency is common among Africans with DCM and it is related to excessive alcohol consumption and/or malnutrition. By itself, it is not an important cause of DCM.
- Haemosiderosis has been found in many patients with DCM and is probably due to excessive consumption of alcohol stored in iron containers. Haemosiderosis is reversible.

Implication

For a patient's heart failure to qualify to be labelled as dilated cardiomyopathy according to the 1980 classification of the cardiomyopathies,[11] a patient must have been extensively investigated and no cause for his/her disease found. Under this classification, diseases whose causes are known should be named appropriately.

From the above, therefore, we can assert that some of the patients diagnosed with DCM in Africa have hypertensive heart disease/failure. Others have alcohol heart disease, viral heart disease or myocarditis, peripartal heart disease and familial dilated heart muscle disease. There are other cases of DCM whose aetiology does not fall into these categories. The prevalence of such cases varies among the different communities of Africa.

Restrictive cardiomyopathy

Under the 1980 classification,[11] the term restrictive cardiomyopathy was in our view out of place. While hypertrophic and dilated cardiomyopathies referred to structural changes within the heart, restrictive cardiomyopathy referred to haemodynamic changes. It would have been more consistent if a term such as fibrotic/obliterative cardiomyopathy was used to describe endomyocardial fibrosis (EMF) and Löeffler's endomyocardial disease, the two diseases the report had in mind. Moreover, with the advent of echocardiography, it is now known that diastolic problems of the heart are not limited to endomyocardial fibrosis and its variants. They occur in several other diseases, including hypertension and hypertrophic cardiomyopathy, and indeed in infiltrative disorders such as amyloidosis.

Under the 1980 classification,[11] it was recommended that Löffler's cardiomyopathy be relabelled eosinophilic endomyocardial disease (EED). Both EED and EMF are characterised by scarring of the endomyocardium of either or both ventricles, which creates cavity obliteration and restriction of filling of the ventricles with blood. While the outflow tract of the affected ventricle is spared, the atrio-ventricular valve becomes enmeshed with scar tissue, which consequently binds down the posterior valve leaflet and leaves the valve perpetually open. Free regurgitation of blood occurs because of this, resulting in an enormously dilated atrium.

EED was first described in Europe by Löffler[13] in 1936, while EMF was first described by Bedford and Konstam[12] in 1946 among Nigerian soldiers who served in the second world war. EMF was similarly reported by Davies[14] in East Africa in 1947, although observations had been made about the disease by Arthur Williams[14] as far back as 1938. Despite a myriad publications on the two diseases in the world literature, there is still no agreement on their aetiology.

In an excellent review, Bukhman *et al.*[15] summarised the causes of EMF, which had been proposed by several authors in the literature as follows:

- infection – toxoplasmosis, rheumatic fever, malaria, helminth parasites
- allergy – eosinophilia, auto-immunity
- malnutrition – protein deficiency, magnesium deficiency
- toxic agents – cerium, cassava, thorium, serotonin, plant toxin, vitamin D.

In addition to these, the following were considered as probable causes from Ibadan, Nigeria:

- vitamin E (tocopherol) deficiency
- obstruction of cardiac lymphatics
- *Schistosoma* infestation: *Schistosoma* ova had been found in EMF lesions of some Nigerian patients.

Of all these, only the hypereosinophilic syndrome of Löffler has been shown to be definitely associated with fibrosis and obliteration of the cardiac apex, similar to tropical EMF. The cause of tropical EMF still remains largely unknown. However Löffler's endomyocardial disease and the tropical forms of EMF, although similar, do not appear to be the same disease, as there are important differences between them. These can be summarised as shown in Table 1.

The questions that arise from all these studies are as follows:

1. What causes eosinophils to degranulate and attack the patient's own tissues? In our view this has not been adequately addressed. It is known that eosinophils are normally deployed by the body to fight parasites and are often elevated in those with allergies, including drug reactions, collagen disorders such as polyarteritis nodosa and some malignancies. But these eosinophils do not harm the patient's tissues. What therefore

TABLE 1. DIFFERENCES BETWEEN TROPICAL EMF AND EED

Parameter	*Tropical EMF*	*EED (Loeffler's)*
Constitutional symptoms	Absent	Present
Hypereosinophilic syndrome	Absent	Present
Degranulated and vacuolated eosinophils	Few cases	Invariably present
Cationic proteins	Not elevated	Elevated
Location of lesions	RV, LV or BV	Invariably BV
Geographical distribution	Mainly rainforest regions	Worldwide
Age group	Usually children	No specific age group
Eosinophilic infiltration of other organs	Absent	Present

EMF = endomyocardial fibrosis; EED = eosinophilic endomyocardial disease; RV = right ventricular; LV = left ventricular; BV = biventricular.

programmes/induces them to attack the patient's tissues and organs and cause the fibrotic reactions seen in the hypereosinophilia of Löffler's disease?

2. Can filaria worms induce eosinophils to proliferate on a massive scale (i.e. hypereosinophilia), infiltrate major organs of the body, degranulate and attack patients' tissues and organs during the process of eliminating the invading organisms?
3. Are there other agents – toxins, infections such as *Toxoplasma gondii* and *Schistosoma manzoni* – that are capable of damaging the endomyocardium like hypereosinophilia?
4. Can parasites such as filaria worms, ova of common parasites such as *Schistosoma*, or other organisms such as *Toxoplasma gondii* get caught within the endomyocardium, cause chronic inflammation and subsequently fibrotic reactions? These parasites are known to lodge in various organs of the body such as the liver and lungs, where they induce fibrotic reactions, and it is often forgotten that they can also lodge within the myocardium of the heart. There may be an eosinophilic reaction to the parasite in such a situation but this will be mild and transient, and not on the same scale as Löffler's endomyocardial disease.
5. Is the peculiar location of the lesions in EMF and EED due to the mode of blood flow through the ventricles? Studies have shown that there is relative stasis of blood flow within the apices of the ventricles and for this reason most clots congregate at the apices of the ventricles.
6. Is there a consensus with the pathogenesis proposed by Olsen,[81] of fibrotic lesions within the endomyocardium of patients with EMF/EED? His studies showed that the process of development of EMF/EED goes through the following phases:
   - necrotic phase with active myocarditis, inflammatory infiltrates and eosinophils
   - thrombotic phase with endocardial thickening, thrombosis and decrease in the number of inflammatory cells
   - fibrotic phase involving the endocardium, replacement of tissues by collagen and superficial thrombosis.
7. What is the implication of the recent observations in Uganda by Freers *et al.*,[83,84] which showed that fibrosis in patients with EMF is not confined to the endomyocardium but also occurs in other tissues such as the peritoneum, pleura, liver and pericardium. Does it conform to the parasitic theory put forward in (4) above?
8. Are there others markers specific for Löffler's endomyocardial disease that could make the diagnosis of the disease easier in Africa?

Answers to these questions will help researchers in Africa make significant progress in finding the cause(s) of EMF. The greatest problem we have with the disease at present is that we do not know how the illness begins. Several investigators have described what they believe are the early illnesses of the disease but these are not convincing. Yet, it is during the early stages of the disease that we can find its cause and define its pathogenesis.

The EMF cases seen in our wards in Africa are already in the chronic stages of the disease, when the cause is difficult or impossible to find. By going to the villages where there is poverty and a high incidence of EMF, and by using an echocardiogram to aid their study, the research team presently working in Mozambique[85] has a unique opportunity to help us find the cause of the disease (Fig. 5).

Left ventricular non-ischaemic ventricular aneurysms

These are ventricular aneurysms that occur in black people living in the tropics, particularly those who live in the equatorial rainforest belt of Africa, and are not due to or associated with coronary artery occlusion.[86,87] They belong to the group of forgotten tropical cardiomyopathies. Although they are now rare, they still occur. Sporadic cases of such aneurysms have been described in the past from the United States of America, France, Sweden, South Africa and the West Indies, mainly among black people living in those countries. It was first reported in 1813 by Corvisart, in a black man who died of the disease in France in 1796.

The aneurysms are often sub-valvular in location, more commonly affecting the mitral and aortic valve rings. Sub-mitral aneurysms tend to be very large, often creating mitral regurgitation; sub-aortic aneurysms on the other hand tend to be smaller and may cause left and right ventricular outflow

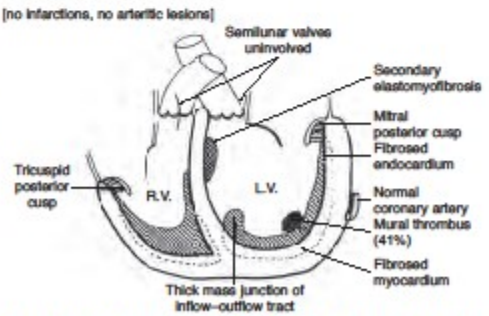

Fig. 5. Davies' representation of endomyocardial fibrosis.

obstruction with aortic and pulmonary regurgitation. Sometimes the aneurysms are annular, extending in a circular direction around the heart and may extend laterally, superiorly and anteriorly. Left atrial aneurysms may be found in some patients.

Atrio-ventricular conduction abnormalities, including complete heart block are common. The cause of the aneurysms is unknown, although the pathological findings and the presence of fibrinous pericarditis support the theory that the out-pouchings are initiated by myocarditis.

Proposed new classification

Earlier, we posed this question 'which of the several classifications of myocardial disorders is suitable for Africa?' The problem is that there is no agreement at present on the definition of cardiomyopathy. While some regard it as 'any disorder of the myocardium', others believe that it should be defined as heart muscle disease of unknown cause. Yet others believe that it should be defined as 'any disease of the myocardium with cardiac dysfunction'. This last definition implies that patients with hypertensive heart disease/failure will be described as hypertensive cardiomyopathy and those with aortic valve disease for example, aortic valve cardiomyopathy.

While waiting for another consensus meeting to resolve this difficulty, we wish to propose the following classification (Table 2). It is our view that this could stimulate the continental society (PASCAR) to set up an expert committee to look into this subject.

TABLE 2. PROPOSED CLASSIFICATION OF MYOCARDIAL DISORDERS FOR AFRICA

1. DISEASES THAT ARISE WITHIN THE CARDIOVASCULAR SYSTEM

GENETIC

A. DISORDERS OF THE MYOCYTES
- (i) Non-dilated types:
  - Hypertrophic cardiomyopathy
  - LV non-compaction
- (ii) Dilated types:
  - Arrhythmogenic right ventricular cardiomyopathy
  - Familial dilated cardiomyopathy

B. DISORDERS OFTHE ELECTRICAL STRUCTURES
- (i) Conduction system disease

Structural types: Lenegre disease

Non-structural types: ion channelopathies
- Long-QT syndrome
- Brugada syndrome
- Catecholaminergic polymorphic ventricular tachycardia
- Short-QT syndrome
- Idiopathic ventricular fibrillation

NON-GENETIC

(i) Hypertrophic
- Hypertensive heart disease (concentric, asymmetric)
- Chronic rheumatic heart diseases (obstructive forms such as aortic/pulmonary stenosis
- Chronic lung disease, pulmonary embolism, primary pulmonary hypertension. These affect only the right ventricle and can dilate in untreated cases
- Congenital heart diseases – obstructive types

(ii) Dilated
- Hypertensive heart disease/failure (of different grades and severity)
- Alcohol heart disease
- Myocarditis e.g. viral, bacterial, protozoal, rickettsial
- Chronic rheumatic heart diseases (regurgitant forms such as mitral/aortic/tricuspid/pulmonary regurgitation
- Ischaemic cardiomyopathy

(iii) Associated with pregnancy
- Peripartum heart disease

(iv) Fibrotic/obliterative
- Löeffler's endomyocardial disease
- Endomyocardial fibrosis

(v) Unknown cause
- Dilated cardiomyopathy
- Left ventricular non-ischaemic ventricular aneurysms

2. DISEASES THAT ARISE OUTSIDE THE CARDIOVASCULAR SYSTEM

INFILTRATIVE
- Amyloidosis (primary, familial autosomal dominant, senile, secondary forms)
- Gaucher disease
- Hurler's disease
- Hunter's disease

STORAGE
- Haemochromatosis
- Fabry's disease
- Glycogen storage disease (type II, Pompe)
- Niemann-Pick disease

TOXICITY
- Drugs
- Heavy metals
- Chemical agents

GRANULOMA
- Sarcoidosis

ENDOCRINE
- Diabetes mellitus
- Hyperthyroidism
- Hypothyroidism
- Hyperparathyroidism
- Phaeochromocytoma
- Acromegaly

CARDIOFACIAL
- Noonan syndrome
- Lentiginosis

NEUROMUSCULAR/NEUROLOGICAL
- Friedreich's ataxia
- Duchenne-Becker muscular dystrophy
- Emery-Dreifuss muscular dystrophy
- Myotonic dystrophy
- Neurofibromatosis
- Tuberous sclerosis

NUTRITIONAL DEFICIENCIES
- Beri beri (thiamine)
- Pellagra
- Scurvy
- Selenium
- Carnitine
- Kwashiorkor

AUTOIMMUNE/COLLAGEN
- Systemic lupus erythematosus
- Dermatomyositis
- Rheumatoid arthritis
- Scleroderma
- Polyarteritis nodosa

ELECTROLYTE IMBALANCE

CONSEQUENCE OF CANCER THERAPY
- Anthracyclines: doxorubicin (adriamycin), daunorubicin
- Cyclophosphamide
- Radiation

The classification we are proposing is a modification of that of Maron *et al.*[19] but we believe that the diseases should be named according to what caused them. All myocardial disorders are included under the classification we are proposing, while less emphasis was placed on the term cardiomyopathy, which, as observed earlier, has now acquired several meanings. It was, however, retained for only those diseases for which the term has become part of the general usage, for example hypertrophic cardiomyopathy. The name dilated cardiomyopathy was used for only those diseases that are characterised by dilatation of the left ventricle with systolic dysfunction, whose cause could not be determined after all the necessary investigations had been performed.

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Appendix II (Other recent publications)

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Appendix III: Participant information leaflet and informed consent

UNIVERSITY OF THE WITWATERSRAND

HUMAN RESEARCH ETHICS COMMITTEE

INFORMED CONSENT

PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT

Each participant must receive, read and understand this document before any study-related procedure!

STUDY NUMBER:

STUDY TITLE: A study of the natural history of heart failure in two African populations

SPONSOR: None (PhD Thesis)

INVESTIGATORS: Dr O.S Ogah/ Prof. K Sliwa / Prof S Stewart/ Prof A.O Falase

INSTITUTION/s: Soweto Cardiovascular Research Unit, Chris Hani Baragwanath Hospital, University of Witwatersrand, Johannesburg, South Africa / and Cardiology Unit, Department of Medicine, Federal Medical Centre, Idi-Aba, Abeokuta, Nigeria

TELEPHONE NUMBERS: Prof. K. Sliwa - 083 457 4823 (for South Africa)

(24-hour contact) Dr. O.S Ogah - +234 (0) 8067747121(for Nigeria)

Time and date of first informed consent discussion:

Date (dd/mm/yyyy):

Time:

To the Participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.*

INTRODUCTION:

Good day, my name is Dr Okechukwu Ogah. I am a postgraduate student at the Department of Cardiology, University of Witwatersrand. I would like to invite you to consider participating in a research study, entitled " A study of the natural history of heart failure in two African populations".

Before agreeing to participate, it is important that you read and understand the following explanation of the purpose of the study, the study procedures, benefits, risks, discomforts, and precautions as well as the alternative procedures that are available to you, and your right to withdraw from the study at any

time. This information leaflet is to help you to decide if you would like to participate. You should fully understand what is involved before you agree to take part in this study.

If you have any questions, do not hesitate to ask me.

You should not agree to take part unless you are satisfied about all the procedures involved.

Please be completely truthful with me regarding your health history.

If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.

If you have a personal doctor, please discuss with or inform him/her of your possible participation in this study. If you wish, I can also notify your personal doctor in this regard.

PURPOSE OF THE STUDY:

You have been admitted to hospital with the diagnosis of heart failure.

The information surrounding the characteristics, causes, treatment and short term outcome of acute heart failure in Africa is largely unknown.

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

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

LENGTH OF THE STUDY AND NUMBER OF PARTICIPANTS:

The study will be performed in two centres in Africa

Approximately 400 participants will participate in this study in these two centres

The participant will be above 18 years of age

The total amount of time required for your participation in this study will be a maximum of six months

You will be asked to visit me one month after discharge and on three monthly intervals thereafter

PROCEDURES:

If you agree to take part in this study, you will first be asked questions and examined to see if you qualify for this study. Upon your cardiac clinic visit or on admission in coronary care unit (CCU) you will be evaluated for heart failure and the standard treatments administered.

Baseline information, including your age, sex and race will be recorded. A thorough cardiovascular examination will be done, including vital sign measurements.

Present and prior medication details will be obtained and/or previous hospitalization due to heart failure.

Any medical tests that may be indicated will be performed, echocardiogram, electrocardiogram, blood tests.

You will be followed-up for this condition as part of the study for six months.

WILL ANY OF THESE STUDY PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

No discomfort or inconvenience will be caused as it is an observational study.

BENEFITS:

While there may be no direct benefit to you by participating in this study, your participation may yield information that could benefit other patients in Africa having Heart failure. It may help to improve our understanding of patients with heart failure at the time of presentation and during the following six months of follow-up as well as insight into its treatment.

ALTERNATIVE TREATMENT:

Standard treatment will be used to treat heart failure.

If you decide not to take part in this study you will still receive the same care from your usual doctor, but without us recording your responses as described in this sheet.

ARE THERE ANY WARNINGS OR RESTRICTIONS CONCERNING MY PARTICIPATION IN THIS STUDY?

You should not participate in the study if you are already participating in another heart failure study.

RIGHTS AS A PARTICIPANT IN THIS STUDY:

Voluntary: Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating any reason. Your withdrawal will not affect your access to other medical care.

Discontinuation of study participation: You may discontinue at any time, you only need to say. I will supervise any discontinuation with your health as the first priority.

WITHDRAWAL FROM THIS STUDY:

Your withdrawal will not affect your access to other medical care.

I retain the right to withdraw you from the study if it is considered to be in your best interest.

If you did not give an accurate history or did not follow the guidelines of the study and the regulations of the study facility, you may be withdrawn from the study.

REIMBURSEMENT FOR STUDY PARTICIPATION:

You will not be paid to participate in this study.

ETHICAL APPROVAL:

This clinical study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC)

The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2000), which deals with the recommendations guiding doctors in biomedical research involving human subjects. A copy may be obtained from me should you wish to review it.

This study is not sponsored by any organization

SOURCE OF ADDITIONAL INFORMATION:

For the duration of the study, you will be under the care of Dr. Ogah (Nigeria patients). If at any time you feel that any of your symptoms are causing you any problems, or you have any questions during the study, please do not hesitate to contact me.

Doctors from the Department of Cardiology who are working on this study are:

Dr. O.S Ogah and Dr J.O Adesina

They can be contacted at the above 24 hour telephone numbers.

If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Dr. A.D Eni-Olorunda, Chairman of the Federal Medical Centre, Human Research Ethics Committee, which is an independent committee established to help protect the rights of research participants at the following number: +234(0) 8033196560

For further information relates to queries relevant to the study conducted in Nigeria you can contact: Dr. O.S Ogah (08067747121) OR Dr. J.O Adesina (0805842948)

CONFIDENTIALITY:

All information obtained during the course of this study, including hospital records, personal data and research data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.

This information will be reviewed by Prof. Sliwa, Prof. Stewart, and Dr. Ogah. You have the right to privacy, and all information obtained in the survey that identifies you will remain confidential as much as possible within state laws.

The information might also be inspected by the University of the Witwatersrand, Human Research Ethics Committee (HREC), as well as your personal doctor. Therefore, you hereby authorize me to release your medical records to the University of the Witwatersrand, Human Research Ethics Committee (HREC). These reviewers may learn of your identity but are required by law to keep it confidential. These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study.

Any information uncovered regarding your state of health as a result of your participation in this study will be held in strict confidence. You will be informed of any finding of importance to your health in this study but this information will not be disclosed to any third party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the Department of Health exists. In this case, you will be informed of my intent to disclose such information to the authorised state agency.

PERSONAL DOCTOR / SPECIALIST NOTIFICATION OPTION:

Please indicate below, whether you want me to notify your personal doctor or your specialist of your participation in this study:

( ) Yes, I want you to inform my personal doctor / specialist of my participation in this study.

( ) No, I do not want you to inform my personal doctor / specialist of my participation in this study

( ) I do not have a personal doctor / specialist

INFORMED CONSENT:

I hereby confirm that I have been informed by the study doctor, Dr Okechukwu Ogah/ Prof Karen Sliwa about the nature, conduct, benefits and risks of the clinical study A study of the natural history of heart failure in two African populations I have also received, read and understood the above written information (Patient Information leaflet and Informed Consent) regarding this clinical study.

I am aware that the results of the study, including personal details regarding my sex, age, date of birth, and diagnosis will be anonymously processed into a study report.

In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the Department of Cardiology, Chris Hani Baragwaneth Hospital or on its behalf.

I may, at any stage, without prejudice, withdraw my consent and participation in the study.

I have had sufficient opportunity to ask questions and of my own free will declare myself prepared to participate in the study.

Participant:

_____

Printed Name Signature/Mark/Thumbprint Date and Time

I, Dr O.S Ogah/ Prof. Karen Sliwa, herewith confirm that the above patient has been fully informed about the nature, conduct, benefits and risks of the above study.

Study Doctor:

_____

Printed Name Signature Date and Time

Study nurse/translator/other person explaining Informed Consent (Designation):

_____

Printed Name Signature Date and Time

Witness (if applicable):

_____

Printed Name Signature Date and Time

VERBAL PATIENT INFORMED CONSENT:

(Applicable when patients cannot read or write or are incapable of giving consent)

I, the undersigned, Dr Okechukwu Ogah/ Prof. Karen Sliwa / have read and have explained fully to the patient, named _____ and/or his/her relative/friend/legal representative, _____ the participant information leaflet.

The account I have given has explained both the possible risks and benefits of the study as well as the alternative treatments available for his/her illness. The patient and/or his/her relative/friend/legal representative understand these.

The patient and/or his/her relative/friend/legal representative indicated that he/she understands that the patient will be free to withdraw from the study at any time for any reason and without jeopardising his/her subsequent treatment.

I hereby certify that, the patient and/or his/her relative/friend/legal representative acting on his/her behalf have agreed to participate in this study.

Participant:

_____

Printed Name Signature/Mark/Thumbprint Date and Time

Study Doctor:

_____

Printed Name Signature Date and Time

Research nurse/translator/other person explaining Informed Consent (Designation):

_____

Printed Name Signature Date and Time

Legal Representative/Friend:

_____

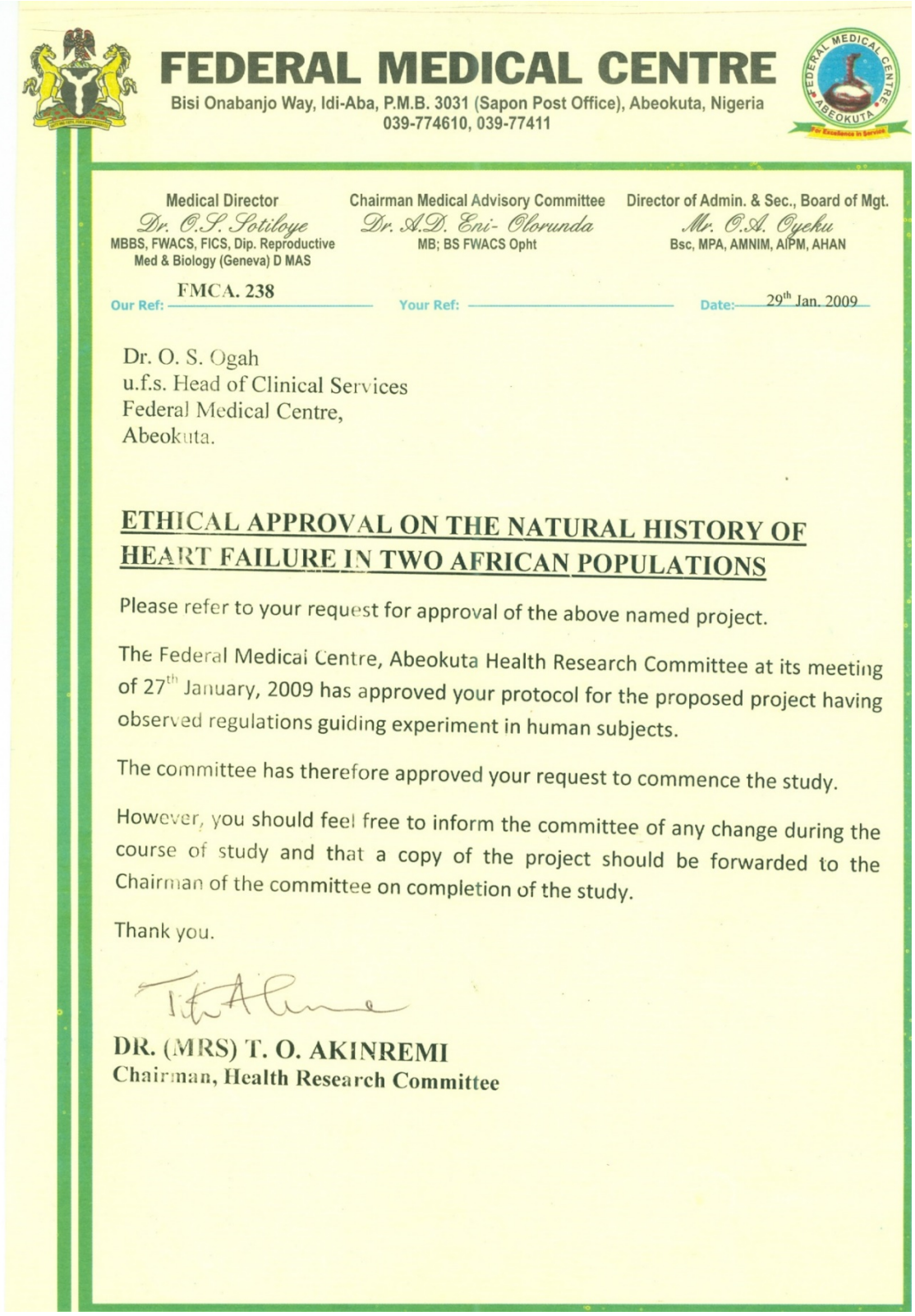
Printed Name Signature/Mark/Thumbprint Date and Time

Witness (if applicable):

_____

Printed Name Signature Date and Time

Appendix IV: Ethics approvals



FEDERAL MEDICAL CENTRE

Bisi Onabanjo Way, Idi-Aba, P.M.B. 3031 (Sapon Post Office), Abeokuta, Nigeria
039-774610, 039-77411

Medical Director	Chairman Medical Advisory Committee	Director of Admin. & Sec., Board of Mgt.
Dr. O.S. Sotiloye	*Dr. A.D. Eni- Olorunda*	*Mr. O.A. Oyeku*
MBBS, FWACS, FICS, Dip. Reproductive Med & Biology (Geneva) D MAS	MB; BS FWACS Opht	Bsc, MPA, AMNIM, AIPM, AHAN

Our Ref: FMCA. 238 Your Ref: Date: 29th Jan. 2009

Dr. O. S. Ogah
u.f.s. Head of Clinical Services
Federal Medical Centre,
Abeokuta.

ETHICAL APPROVAL ON THE NATURAL HISTORY OF HEART FAILURE IN TWO AFRICAN POPULATIONS

Please refer to your request for approval of the above named project.

The Federal Medical Centre, Abeokuta Health Research Committee at its meeting of 27th January, 2009 has approved your protocol for the proposed project having observed regulations guiding experiment in human subjects.

The committee has therefore approved your request to commence the study.

However, you should feel free to inform the committee of any change during the course of study and that a copy of the project should be forwarded to the Chairman of the committee on completion of the study.

Thank you.

DR. (MRS) T. O. AKINREMI
Chairman, Health Research Committee

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Okechukwu S Ogah

CLEARANCE CERTIFICATE	**M090521**
PROJECT	A Study of the natural History of Heart Failure in two african Populations
INVESTIGATORS	Dr Okechukwu S Ogah.
DEPARTMENT	Department of Cardiology
DATE CONSIDERED	09.05.29
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 09.07.30 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof K Sliwa-Hahnle

DECLARATION OF INVESTIGATOR(S)

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

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

.....