

**PREVALENCE AND CORRELATES OF ELECTROCARDIOGRAPHIC
INDICATIONS FOR INVASIVE CARDIAC PROCEDURES AMONG
PATIENTS WITH REDUCED EJECTION FRACTION HEART FAILURE IN
WESTERN KENYA**

BY

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**A THESIS SUBMITTED TO THE SCHOOL OF MEDICINE, COLLEGE OF
HEALTH SCIENCES IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR AN AWARD OF THE DEGREE OF MASTER OF
MEDICINE IN INTERNAL MEDICINE, MOI UNIVERSITY**

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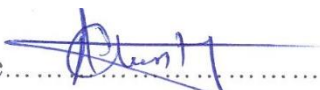
DECLARATION

Declaration by Candidate

This research thesis is my original work and has not been presented for the award of any degree or an academic credit in any university. I attest to the best of my knowledge that it contains no material previously published by another person, except where due acknowledgement has been made in the text.

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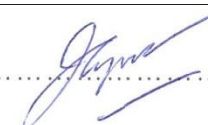
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DEDICATION

I dedicate this work to my mother for being my pillar of strength, my husband for his continuous support and encouragement and my children for their love. I also dedicate this work to my friends for their moral support and encouragement during this entire process.

ABSTRACT

Background: Heart failure is a heterogeneous and life-threatening syndrome that affects more than 26 million individuals globally. The phenotype Heart Failure with reduced Ejection Fraction (HFrEF) contributes to 60% of all diagnosed cases. Despite the use of Guideline Directed Medical Therapy, a number of HFrEF patients remain symptomatic with a high risk of death. Electrocardiographic abnormalities are more prevalent in HFrEF and associated with poorer outcomes. However, improved outcomes following invasive cardiac procedures have been demonstrated in patients with pathological “Q” waves, clinically significant arrhythmias and prolonged QRS duration. These procedures include coronary angiography with or without revascularization, Cardiac Resynchronization Therapy, Implantable Cardioverter Defibrillators and Pacemaker implantation. This study aimed at determining the prevalence and describing the correlates of patients who can potentially benefit from Invasive cardiac procedures.

Objectives: To determine the prevalence and correlates of pathological “Q” waves, prolonged QRS and clinically significant arrhythmias in HFrEF patients.

Methods: A cross-sectional study was conducted between July and November 2023 at MTRH medical wards, CCU and cardiology clinics. Recruitment of 243 participants above eighteen years with current clinical echocardiogram of ≤ 6 months used to identify HFrEF (Left Ventricular Ejection Fraction $\leq 40\%$) were consented and underwent 12 lead electrocardiograms recording. Prevalence of pre-specified electrocardiogram abnormalities was calculated and correlates namely older age, body mass index, documented hypertension, diabetes and renal dysfunction analyzed. Bivariate associations were tested using chi square for categorical variables, one sample t- test for continuous variables and multivariate associations - logistic regression

Results: Participants had a mean age of 60 years and females predominated 137(56.4%). Those with abnormal electrocardiogram were 143(58.8%) with prolonged QRS being the commonest 62(25.5%) and LBBB morphology constituting the most subtype. Clinically significant arrhythmias were 48(19.8%) with atrial fibrillation dominating. The least prevalent indication was pathological Q waves at 33(13.6%). More than a third were overweight 91(37%) and hypertension was the commonest comorbidity 132(54.3%). Using logistic regression, older age and being overweight were associated with studied electrocardiogram abnormalities with p- values <0.001 and 0.035 respectively.

Conclusion Over half of study participants had at least one electrocardiographic indication for invasive cardiac procedures on the basis of prolonged QRS, pathological Q waves or clinically significant arrhythmias. Being elderly and overweight were significantly associated with indications for invasive cardiac procedures.

Recommendation Close monitoring should be done for the elderly and weight management for those with cardiovascular diseases. Secondly, further studies to explore the uptake of invasive cardiac procedures and examine the long-term benefits in view of the quality of life and mortality.

LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitors
ARB	Angiotensin-2 Receptor Blockers
ARNI	Angiotensin-2 Receptor Blocker-Neprilysin Inhibitors
ECG	Electrocardiogram
ECHO	Echocardiogram
CRT	Cardiac Resynchronization Therapy
CABG	Coronary Artery Bypass Grafting
ESC	European Society of Cardiology
GDMT	Guideline Directed Medical Therapy
HIV	Human Immunodeficiency Virus
HF_rEF	Heart Failure with Reduced Ejection Fraction
HF_{mr}EF	Heart Failure with Mildly Reduced Ejection Fraction
HF_pEF	Heart Failure with Preserved Ejection Fraction
ICD	Implantable cardioverter defibrillator
LVAD	Left Ventricular Assist Device
MRA	Mineralocorticoid Receptor Blocker
MTRH	Moi Teaching and Referral Hospital
SGLT-2	Sodium-Glucose Co-Transporter 2

OPERATIONAL DEFINITION OF TERMS

Heart Failure – Refers to a clinical syndrome consisting of cardinal symptoms that may be accompanied by signs due to a structural or functional abnormality of the heart that results in elevated intracardiac pressures and /or inadequate cardiac output at rest and/ or during exercise.

In this study the diagnosis of heart failure with reduced ejection fraction was based on echocardiographic findings of left ventricular systolic dysfunction.

Based on myocardial left ventricular dysfunction, heart failure has one of the 3 phenotypes:

- a. **Heart failure with preserved ejection fraction (HFpEF)** – left ventricular ejection fraction $\geq 50\%$
- b. **Heart failure with mildly reduced ejection fraction (HFmrEF)** – left ventricular ejection of 41 – 49%
- c. **Heart failure with reduced ejection fraction (HFrEF)** – left ventricular ejection fraction $\leq 40\%$

Arrhythmia – Is an irregularity of the heart beat that may affect the rate giving a brady arrhythmia when too slow such as atrioventricular blocks or a tachy arrhythmia when too fast such as supraventricular tachycardias or ventricular tachycardias.

Pathological “Q” wave – is defined as any Q-wave in leads V2–V3 $\geq 0.02s$ or QS complex in leads V2 and V3, or Q-wave $\geq 0.03s$ and $> 0.1mV$ deep or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping.

QRS Interval – a period between P and T waves that correlate with ventricular depolarization, the normal duration is 90 – 120ms.

- **Prolonged QRS** – duration greater than 120ms. It has 3 patterns:

- i. **Left Bundle Branch Block**-wide QRS, monophasic notched “R” waves with “T” wave inversion on lateral leads (I, aVL, v5, v6)
- ii. **Right Bundle Branch Block** – RSR’ in V1/V2 (rabbit ear), slurred ‘S’ wave on lateral leads
- iii. **Non-specific** intraventricular conduction delay (No RBBB or LBBB Pattern).

Invasive cardiac procedure – In this study refers to all procedures done in the catheter/electrophysiology laboratory including right heart catheterization, left heart catheterization, coronary diagnosis and revascularization, mitral clips, pace makers, catheter ablation for unstable arrhythmias and implantable cardioverter defibrillator/ cardiac resynchronization therapy insertions.

Indications for invasive cardiac procedures – a medical condition whose definitive diagnosis and or management warrants an invasive cardiac procedure which in this study include three electrocardiographic abnormalities; pathological “Q” waves, prolonged QRS and Clinically significant arrhythmias.

Body Mass Index in kg/m^2 - definition was adapted from World Health Organization classification where the normal value is considered to be 18.5 to 24.9:

- Underweight is values below 18.5 kg/m^2
- overweight is values between 25 to 29.9 kg/m^2
- obesity is values above 30 kg/m^2

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ACKNOWLEDGEMENT

I would like to thank the almighty God for walking with me through this journey. My sincere gratitude also goes to my supervisors, Dr. Felix A. Barasa and Prof. Paul O. Ayuo for their support, patience and guidance during the entire process right from the beginning to the completion of writing this research project. My colleagues in the department of medicine have also been very instrumental in giving me positive criticism with the aim of improving this thesis. Last but not least, I acknowledge my family for their never-ending moral support and my employer Nyamira County for giving me a paid study leave to pursue my studies.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Heart failure is an increasing public health problem that exerts great stress on patients, care givers and healthcare systems. The current worldwide prevalence of heart failure is 26 million (McDonagh et al., 2021). Heart failure has been divided into distinct phenotypes based on the measurement of left ventricular ejection fraction; in heart failure with preserved ejection fraction, the left ventricular ejection fraction is $\geq 50\%$, heart failure with mildly reduced ejection fraction, has left ventricular ejection fraction of between 41% and 49% and heart failure with reduced ejection fraction has left ventricular ejection fraction of $\leq 40\%$. The phenotype heart failure with reduced ejection fraction contributes to 60% of diagnosed heart failure (ESC 2021).

Transition in ejection fraction over time is common, and patients who progress from heart failure with mildly reduced ejection fraction to heart failure with reduced ejection fraction have a worse prognosis than those who remain stable or transition to a higher ejection fraction category (Dunlay et al., 2012). When compared to heart failure with mildly reduced ejection fraction and heart failure with preserved ejection fraction, heart failure with reduced ejection fraction has a poorer long-term prognosis, with mortality rates of 15% to 20% during the first year of diagnosis rising to 40% to 50% within 5 years (Albakri, 2018b).

Heart failure with reduced ejection fraction phenotype has several etiologies including; pericardial diseases, coronary artery diseases, cardiomyopathies, valvular disease, hypertension, infections, toxins as well as conduction abnormalities. Studies show that Hypertension, cardiomyopathy, rheumatic heart disease and pericardial disease are the

main contributors to the etiology of heart failure in sub-Saharan Africa, accounting for over 90% of cases with coronary artery disease being uncommon, however, the situation is changing due to modifications in lifestyle, risk-prone behavior, diet, cultural attitudes and other consequences of rapid urbanization (Ntusi & Mayosi, 2009).

The three major goals of treatment of heart failure with reduced ejection fraction includes reducing mortality, prevention of recurrent hospitalizations and improvement of quality of life. European Society of Cardiologists 2021 guideline stipulated management to be multidisciplinary beginning from lifestyle modification by maintaining a good diet, salt and water restriction, exercising to maintain a normal body mass index, cessation of alcohol and smoking with consideration of vaccination with influenza and pneumococcal vaccine.

Clinical trials have shown benefit in the use of medical therapy with beta blockers, mineralocorticoid receptor blockers, sodium glucose cotransporter 2 inhibitors and angiotensin receptor/ neprilysin inhibitors all termed as guideline directed medical therapy (McDonagh et al., 2022). Despite the use of guideline directed medical therapy, a significant number of heart failure with reduced ejection fraction patients continue to be symptomatic and face a high risk of death. Some of the reasons why these patients do not respond to guideline directed medical therapy include poor characterization of heart failure with reduced ejection fraction, disease progression through its natural history and failure to address comorbidities such as arrhythmias that occur suddenly and have a potential to cause sudden death. As a result, several randomized clinical trials have looked into the use of invasive cardiac procedures and device therapy that can be of benefit in heart failure with reduced ejection fraction (Bardy et al., 2005).

The invasive cardiac procedures include invasive coronary angiography, insertion of intracardiac devices like permanent pacemakers, cardiac resynchronization therapy and

implantable cardioverter defibrillators which in combination with guideline directed medical therapy have been shown to reduce mortality in heart failure with reduced ejection fraction patients (McDonagh et al., 2021). Moreover, device-based interventions can overcome some of the limitations of drug therapy including intolerance, nonadherence, inconsistent delivery and recurrent and long-term costs.

An electrocardiogram is one of the most commonly used tools in the assessment of cardiovascular disease involving cardiac rhythm, myocardial ischemia/infarction and conduction abnormalities. Electrocardiogram abnormalities are more prevalent in heart failure with reduced ejection fraction as compared to other heart failure phenotypes and associated with poorer outcomes (Ponikowski et al., 2016). Patients with pathological "Q" waves, clinically significant arrhythmias such as atrial fibrillation/ventricular tachycardias and prolonged QRS duration have had the best outcomes following invasive cardiac procedures. In addition, an electrocardiogram has differential predictive abilities of abnormalities to distinguish between heart failure with reduced ejection fraction and other phenotypes. In one study, it was noted that markers of abnormal ventricular depolarization such as QRS duration, axis deviation, abnormal ventricular repolarization (ST/T-wave abnormalities), and conduction disease (left bundle-branch block) were associated with heart failure with reduced ejection fraction (O'Neal et al., 2017).

Age, male sex, higher New York Heart Association grade, advanced secondary valvular heart disease, chronic kidney disease, and pleural effusion were some of the correlates of abnormal electrocardiogram in heart failure with reduced ejection fraction found to indicate poor outcomes in a study conducted in Europe (Tymińska et al 2021).

1.2 Problem statement

The burden of heart failure is high with a worldwide prevalence of 26 million with the phenotype heart failure with reduced ejection fraction accounting for 60% of the cases (McDonagh et al., 2022). Prevalence in Kenya is not well established due to lack of population-based data (Mbau et al., 2021). In MTRH, approximately 250 heart failure with reduced ejection fraction patients attend the cardiology clinic in a month.

Despite the use of Guideline Directed Medical Therapy, heart failure with reduced ejection fraction has been shown to have a poorer long-term prognosis with high mortality rates of 15% to 20% during the first year of diagnosis (Albakri, 2018b).

Electrocardiographic abnormalities are more prevalent in heart failure with reduced ejection fraction and associated with poorer outcomes (Tyminska et al., 2021). Despite an electrocardiogram being readily available and cheap, the abnormalities remain under diagnosed and therefore under treated (Dagdeviren et al., 2005).

1.3 Study justification

An electrocardiogram is a cheap, readily available diagnostic tool for evaluation of specific conduction abnormalities yet local data on prevalence of electrocardiographic abnormalities in heart failure with reduced ejection fraction for invasive cardiac procedures is scarce. This study therefore aimed at providing information on what proportion of heart failure with reduced ejection fraction patients are likely to benefit from invasive cardiac procedures as diagnosed by an electrocardiogram as well as give an insight on the burden of these abnormalities. This will inform on policies towards optimization of advanced care to improve overall outcome in heart failure with reduced ejection fraction patients' population.

The correlates of these electrocardiographic abnormalities will aid in stratification of patients with the aim of identifying high risk patients who can benefit from invasive cardiac procedures hence cue them to perform an electrocardiogram and refer them for close monitoring.

1.4 Research questions

1. What is the prevalence of electrocardiographic indications for invasive cardiac procedures among patients with heart failure with reduced ejection fraction in Moi Teaching and Referral Hospital?
2. What are the correlates of heart failure with reduced ejection fraction patients associated with electrocardiographic indications for invasive cardiac procedures in Moi Teaching and Referral Hospital?

1.5 Objectives

1.5.1 Broad objective

To determine the prevalence and correlates of pathological “Q” waves, prolonged QRS and clinically significant arrhythmias in patients with heart failure with reduced ejection fraction at Moi Teaching and Referral Hospital.

1.5.2 Specific objectives

- i. To determine the prevalence of pathological “Q” waves, prolonged QRS and clinically significant arrhythmias in heart failure with reduced ejection fraction patients.
- ii. To describe the correlates of pathological “Q” waves, prolonged QRS and clinically significant arrhythmias.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Introduction

This chapter, looks at published studies done on heart failure with reduced ejection and entails the following sub sections;

Prevalence of heart failure with reduced ejection fraction and prevalence of electrocardiographic indications for invasive cardiac procedures. In this section, a comparison is done between the developed countries versus Sub Saharan African countries including Kenya.

The chapter then delves into the etiologies of heart failure with reduced ejection fraction, with an overview of some of the conditions contributing to its development.

Further, it analyzes the clinical presentation of heart failure with reduced ejection fraction, focusing on symptomatic manifestations and key findings from clinical examinations.

The diagnostic approach is then discussed in accordance with the latest guidelines, this section also outlines the essential steps required to confirm a diagnosis of heart failure with reduced ejection fraction.

In terms of management, the chapter covers both pharmacological treatment and invasive cardiac procedures that are backed by clinical trials as well as their role in improving patient outcomes.

Finally, it reviews the electrocardiographic interpretation and its significance in the context of invasive cardiac procedures.

2.2 Prevalence of Heart Failure with reduced Ejection Fraction and electrocardiographic abnormalities

Heart failure is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms that may be accompanied by signs due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise (ESC 2021). It is a heterogenous and life-threatening syndrome that affects more than 60 million individuals globally and is characterized by severe morbidity and mortality, poor quality of life and a high burden on the healthcare systems in terms of resource and expenditure, the phenotype Heart Failure with reduced Ejection Fraction contributes to 50% of heart failure (Becher et al., 2022).

The prevalence and etiology of heart failure with reduced ejection fraction vary across regions. In Africa, according to a large prospective study; INTER-CHF showed the prevalence of heart failure with reduced ejection fraction to be the highest at 53.7% with hypertensive heart disease as the leading cause at 35% followed closely by ischemic heart disease at 20% (Karaye et al., 2021). Another study showed the most prevailing causes of heart failure with reduced ejection fraction to be largely ischemic heart disease and dilated cardiomyopathy (Abebe et al., 2016). THESUS-HF study concluded that hypertensive heart disease, dilated and peripartum cardiomyopathies in addition to rheumatic heart disease were all more frequent in their cohort, while ischemic heart disease was more frequent in the INTER-CHF cohort. These differences could be explained by the fact that THESUS-HF recruited patients at an earlier time period (2007-2010) in the African epidemiological transition than the INTER-CHF (2012-2014) (Karaye et al., 2021).

In Kenya Heart failure was noted to have a premature (30-70 years old) mortality rate of 8%, with a total cardiovascular disease rate of 13.8% (Mbau et al., 2021). The Kenya cardiovascular disease management guidelines 2018 estimate 25% of hospital admissions and 13% of deaths in Kenya to be due to cardiovascular diseases. Prevalence of Heart Failure in Kenya's tertiary facilities as per Kenya's Heart Failure Registries were 357(44.9%) in Kenyatta National Hospital, 309(38.9%) in Moi Teaching and Referral Hospital and 129 (16.2%) in Agha Khan University Hospital (Kimeu et al., 2023). There was no local data specifically for heart failure with reduced ejection fraction. Heart failure with reduced ejection fraction has been shown to have a poorer long-term prognosis with high mortality rates of 15% to 20% during the first year of diagnosis and rising to 40 to 50% within 5 years of diagnosis (Albakri, 2018b).

In a study done in Europe by Tyminińska et al 2021, 58.5% of patients with heart failure with reduced ejection fraction had abnormal ECGs compared to 38.2% who had normal electrocardiographs. He further quantified the prevalence of those with wide QRS at 37.3%, pathological "Q" wave at 33% and arrhythmias at 34.1%. In Africa, a study conducted by Rath & Student, (2022) on electrocardiographic abnormalities in heart failure with reduced ejection fraction concluded that 97.2% of these patients with heart failure with reduced ejection fraction had electrocardiographic abnormalities with prolonged QRS having a prevalence of 25.2% and pathological Q waves having a prevalence of 16.8%. In another study in Africa, it was noted that atrial fibrillation had a prevalence of 32.7% and ventricular tachycardia at 32.0% in Heart Failure patients (Albakri, 2018).

2.3 Etiologies of Heart Failure with reduced Ejection Fraction

Identification of the etiology of the underlying cardiac dysfunction is crucial in the evaluation of heart failure with reduced ejection fraction. Heart failure with reduced ejection fraction can occur as a result of conduction system disorders, valvular disease, myocardial dysfunction, coronary arterial disease, hypertensive and toxin induced pathologies.

Hypertension – The European Society of Cardiology defines hypertension as a condition where the blood pressure in the arteries is persistently elevated and is diagnosed when a person's systolic blood pressure is 140mmHg or higher and / or their diastolic blood pressure is 90mmHg or higher, measured on at least two different occasions (ESC 2021). Chronically increased left ventricular workload in hypertensive patients can result in left ventricular hypertrophy, impaired left ventricular relaxation, left atrial enlargement, an increased risk of arrhythmias, especially atrial fibrillation, and an increased risk of heart failure (Ziaieian & Fonarow, 2016). Hypertension is classified as either primary where the underlying cause is indeterminate or secondary which arises due to another disease. It is the most important risk factor for heart failure development with the lifetime risk of heart failure being almost twice as high in people with hypertension as in those with normal blood pressure (Tromp et al., 2021). In Sub Saharan Africa, hypertensive heart disease accounts for 50.34% of all heart failure causes (Germain Mandi et al., 2020). According to STEPs survey, the prevalence of hypertension in Kenya is 28.8% and the prevalence increases with age. An increase by 20mmHg in systolic blood pressure and/ or an increase by 10 mmHg of diastolic blood pressure doubles the risk of cardiovascular mortality. Studies show that reducing blood pressure in hypertensive patients has significant benefits in preventing these cardiovascular events and reducing mortality. Meta-analyses of randomized clinical

trials including several hundred thousand patients have shown that a 10-mmHg reduction in systolic blood pressure or a 5-mmHg reduction in diastolic blood pressure is associated with significant reductions in all major cardiovascular events, all-cause mortality and heart failure (Ettihad et al., 2016). By achieving even modest reductions in blood pressure, there is a significant opportunity to prevent cardiovascular events, reduce mortality, and lower the incidence of heart failure with reduced ejection fraction. Target blood pressure which should be pursued with medical treatment was evaluated in the pivotal SPRINT (Systolic Blood Pressure Intervention Trial), which demonstrated that among patients at high risk for cardiovascular events, targeting a systolic Blood Pressure of less than 120 mmHg decreases the incidence of the primary outcome that included heart failure (Wright et al., 2015). Moreover, drugs like renin angiotensin aldosterone inhibitors and mineralocorticoid receptors blockers not only reduce blood pressure but have also proved effective in Heart failure with reduced ejection fraction (Triposkiadis et al., 2023). The choice of drugs to select varies with race, a study done in the African population, the CREOLE study, concluded that hypertension is more severe among black African patients thus necessitated the use of two or more drugs, three commonly recommended drug combinations; a calcium channel blocker combined with either an angiotensin converting enzyme inhibitor or a thiazide diuretic were reported to be superior (Ojji et al., 2019).

Coronary artery disease – coronary artery disease is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, leading to significant alterations in myocardial perfusion and function. This accumulation of plaques can be either obstructive or non-obstructive, with each form presenting its own set of clinical manifestations and potential complications. The global impact of coronary arterial disease varies, with significant regional differences in prevalence and

outcomes. In Europe, coronary arterial disease is the leading cause of heart failure (ESC 2021). Historically, ischemic heart disease was considered relatively rare in sub-Saharan Africa, where infectious diseases were the predominant health concerns however an epidemiological transition characterized by a shift from infectious diseases to non-communicable diseases such as coronary arterial disease, highlights the growing burden of cardiovascular conditions in the region. This epidemiological transition also reflects on the etiology of heart failure in keeping with the steady increase in cardiovascular risk factors for coronary artery disease with the prevalence in patients with heart failure with reduced ejection fraction shown to be 52.3% (Kimeu R.2023).Furthermore, the prevalence of ischemic heart disease and related morbidity may be increasing as a result of behavioral and lifestyle changes associated with urbanization and the epidemiological transitions (Mensah, 2008). As sub-Saharan Africa undergoes rapid urbanization, there is a noticeable shift in dietary habits, physical activity levels, and overall lifestyle, which contribute to a higher risk of developing coronary arterial disease. An autopsy study evaluating cardiovascular causes of death in a tertiary facility in Kenya reported that myocardial infarction was the leading cause of cardiovascular death, accounting for 18.7% of the cases (Ogeng'o et al., 2011).

Acute ischemia, is typically associated with sudden and severe reductions in blood flow, often due to the rupture of an atherosclerotic plaque and subsequent thrombosis. This acute event can lead to myocardial infarction, which not only causes immediate damage to the heart muscle but also triggers a cascade of inflammatory and repair processes. These processes contribute to further myocardial damage and can complicate recovery and long-term heart function. Chronic ischemia results from a long-standing reduction in blood flow to the myocardial tissue, which leads to a gradual decline in

myocardial function. Over time, the persistent lack of adequate oxygen and nutrients causes cellular damage and death in the affected areas. The damage from both acute and chronic ischemia triggers a series of pathological responses, including myocardial remodeling and scar formation. The remodeling process, while initially an attempt by the heart to compensate for the loss of functional tissue, often exacerbates the dysfunction. This is because the formation of scar tissue replaces healthy myocardial tissue, which impairs the heart's ability to contract and relax effectively, thus leading to reduced cardiac output.

The rise in coronary arterial disease prevalence in this region underscores the need for targeted public health strategies and interventions to address the evolving cardiovascular health challenges in sub-Saharan Africa. Coronary angiography is indicated for patients with suspected coronary arterial disease for diagnosis with or without revascularization. Once a diagnosis is confirmed, the revascularization can be done either by stenting or coronary arterial bypass grafting depending on the severity and anatomy of occluded vessels. A study showed that successful revascularization among patients with heart failure due to ischemic cardiomyopathy may improve left ventricular dysfunction and prognosis by reducing ischemia to viable myocardium (Petrie et al., 2016). On the contrary, a more recent trial, Revascularization for Ischemic Ventricular Dysfunction (REVIVED), concluded that myocardial revascularization in patients with ischemic left ventricular dysfunction was not associated with a reduction in mortality or hospitalizations (Perera et al., 2022). Further studies in our region will therefore be pivotal in informing the best management practices.

Valvular heart disease is characterized by damage and dysfunction in one or more of the four valves of the heart, due to inflammation or myxoid degeneration. Regurgitant

valvular disease - results in dilatation of the ventricular chambers by volume overload while stenotic valvular disease cause pressure overload. These lead to impaired contraction and eventually affect the cardiac output. Rheumatic heart disease is the most common cause of valvular heart disease in young adults worldwide. It is caused by an immune response to group A streptococcus and primarily causes mitral and aortic valve pathologies (Noubiap et al., 2019). In developing countries such as Africa, Pacific Island countries, and Asia, rheumatic heart disease is the most prevalent subtype of valvular heart disease while in most developed countries, degenerative valvular heart disease is mainly the prevalent subtype. A study conducted in Moi Teaching and referral Hospital found that rheumatic heart disease is the most common cardiovascular disease amongst the youth affecting two-thirds of this population (Lumsden et al., 2016). The most common complication of valvular heart disease, heart failure, affects the survival and quality of life in valvular heart disease patients (Marciniak et al., 2017). In addition to its direct cardiac effects, valvular heart disease can lead to secondary complications, including atrial fibrillation that comes as a consequence of atrial remodeling from volume overload, which further exacerbates the risk of cardio embolic events and heart failure with reduced ejection fraction. In the elderly heart valve diseases occur due to degenerative abnormalities associated with severe aortic stenosis, mitral and tricuspid regurgitation (Rostagno, 2019). Recent studies revealed that valvular heart disease is responsible for 5.0%–13.6% of Heart Failure with reduced Ejection Fraction cases (Chioncel et al., 2017). Advances in diagnostic techniques have improved the ability to detect and monitor valvular heart disease, facilitating earlier repairs and better outcomes for patients.

Disorders of rate and rhythm – Disorders of rate and rhythm, encompassing chronic bradyarrhythmia and tachyarrhythmias, significantly impact the rate of ventricular

contractions and consequently affect cardiac output. Chronic bradyarrhythmia, characterized by a slower than normal heart rate of less than 60 beats per minute and tachyarrhythmias, marked by an abnormally fast heart rate of greater than 100 beats per minute. Both pose substantial challenges to maintaining effective cardiac function. Arrhythmia induced cardiomyopathy is a condition in which left ventricular dysfunction is induced or mediated by atrial or ventricular arrhythmias. (Gopinathannair et al., 2015).

The primary mechanisms for initiating and perpetuating tachyarrhythmias according to Harrison's principle of medicine include:

- Abnormal automaticity which refers to the spontaneous and inappropriate initiation of electrical impulses in the heart.
- Increased triggered activity which involves abnormal calcium handling within the cardiac cells leading to premature contractions.
- Re-entry circuits which are pathways of electrical activity that loop back on themselves, causing sustained rapid heart rates.

Atrial fibrillation is one of the most common atrial arrhythmias and is associated with a three-fold increased risk of incident heart failure (Stewart et al., 2002). It is characterized by chaotic and irregular electrical activity in the atria, leading to an irregular and often rapid ventricular response. This irregularity can result in inefficient blood flow and an increased risk of thromboembolic events, such as cerebrovascular accidents. The management of atrial fibrillation involves addressing both the arrhythmia itself and its associated risks, such as anticoagulation therapy to prevent stroke and rate or rhythm control strategies to manage symptoms and improve quality of life. Ventricular arrhythmias, more commonly ventricular fibrillation, has been

presumed to be the cause of a significant proportion of sudden death by causing a sudden and severe loss of effective cardiac output, resulting in collapse and sudden cardiac death if not promptly treated. Sudden cardiac death accounts for approximately 50% of all cardiovascular deaths, with up to 50% being the first manifestation of cardiac disease according to European Society of Cardiologists 2021. Ventricular arrhythmias have also been shown to accelerate the pathological mechanisms of heart failure (Gupta & Figueredo, 2014). Reduced left ventricular ejection fraction is used, often in combination with New York Heart Association class, for primary prevention indication of an Implantable Cardioverter Defibrillator in the setting of chronic coronary arterial disease and dilated cardiomyopathy.

Cardiomyopathy- is defined as ‘a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to cause the observed myocardial abnormality’ (ESC 2023).

It can be classified into primary cardiomyopathy where various genetic abnormalities associated with the cardiomyopathy have been unraveled. The clinical sub types of primary cardiomyopathies according to Kushwaha et al., (1997) include: Hypertrophic cardiomyopathy which is characterized by an abnormal thickening of the heart muscle, particularly the left ventricle accompanied by myofibrillar disarrays and diastolic dysfunction of cardiac ventricles which impairs the heart's ability to relax and fill properly. Hypertrophic cardiomyopathy is notable for being a major cause of sudden cardiac death in young athletes and can also lead to heart failure with reduced ejection fraction. Clinical symptoms often include shortness of breath, chest pain and syncope, particularly during physical exertion, due to the compromised cardiac function and increased risk of arrhythmias. The second type is dilated cardiomyopathy characterized

by dilated ventricular cavity with systolic dysfunction that results in reduced cardiac output and can lead to symptoms of heart failure. It also poses a risk of sudden cardiac death due to the potential for life-threatening arrhythmias.

Thirdly we have Restrictive cardiomyopathy accompanied by increased stiffness of the myocardium with diastolic dysfunction without significant hypertrophy. Restrictive cardiomyopathy is distinguished by increased myocardial stiffness, which leads to impaired ventricular filling during diastole. Unlike hypertrophic cardiomyopathy, restrictive cardiomyopathy does not feature significant hypertrophy but rather a rigidity of the heart muscle that results in reduced diastolic volume. There is arrhythmogenic right ventricular cardiomyopathy which is characterized by a dilated dysfunctional right ventricle that leads to ventricular arrhythmias and fibrofatty replacement of right ventricle. Lastly, we have left ventricular noncompaction characterized by an abnormal spongy appearance of the left ventricle, due to prominent trabeculations and deep intertrabecular recesses. This structural anomaly can be associated with left ventricular hypertrophy and/or dilation and may lead to heart failure, thromboembolic events, and arrhythmias (Maron et al., 2006).

Secondary cardiomyopathies result from external factors that indirectly damage the myocardium. These can include metabolic disorders such as diabetes mellitus and thyroid disease, which can affect cardiac function through various mechanisms. Endocrine diseases, including hyperthyroidism or hypothyroidism, may also impact myocardial performance and contribute to cardiomyopathy. Infiltrative diseases such as amyloidosis or sarcoidosis represent another category of secondary cardiomyopathy. In amyloidosis, abnormal protein deposits infiltrate the myocardium, leading to restrictive cardiomyopathy and heart failure. Sarcoidosis involves granulomatous

inflammation that can affect the heart muscle and conduction system, potentially causing arrhythmias and heart failure

Toxin /drug induced – Anti-cancer medications, such as anthracyclines, are known to cause cardiotoxicity through several mechanisms. These include increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative stress. Oxidative stress, in turn, can cause lipid peroxidation, damaging cell membranes, and proteins, and triggering a cascade of inflammatory responses. This inflammation can lead to cardiomyocyte apoptosis (programmed cell death) and interstitial fibrosis (formation of excess fibrous connective tissue), ultimately resulting in impaired cardiac function. Moreover, abnormal signaling of epidermal growth factor (EGF) and beta-arrestin can disrupt cellular homeostasis, while inhibition of nuclear topoisomerase II β leads to DNA damage and impaired cell division. Additionally, the inhibition of vascular endothelial growth factor signaling can compromise blood vessel formation and repair, exacerbating cardiac damage. Defective mitochondrial biogenesis and calcium overloading further impair cellular energy metabolism and contractility, respectively, contributing to the overall cardiotoxicity of anti-cancer drugs (Gu et al., 2015).

Chronic alcohol consumption is another well-documented cause of cardiotoxicity. Alcohol is considered to be toxic to myocytes and studies show that consuming more than 90–120 g/day of alcohol (approximately 7–15 standard drinks per day) over a 5-to-15-year period is associated with changes in cardiac structure and function (Fauchier et al., 2000). Alcoholic cardiotoxicity was previously thought to arise due to nutritional deficiency, specifically thiamine (vitamin B12). However, when these alcoholic patients received thiamine therapy or other nutritional supplements, myocardial

structural and functional changes were often not reversed. It is possible that certain dietary components and/or deficiencies may increase either the susceptibility or progression of ethanol-induced myocardial changes (Reinke et al., 1987).

Infections – Bacterial infections, viruses and other organisms induce myocarditis, with viruses being the most common cause (Sagar et al., 2012).

Viral Infections, particularly viral myocarditis, are a significant cause of cardiac inflammation and damage. Viruses such as Coxsackie and echoviruses, HIV, adenovirus, hepatitis B and C, Parvovirus B19, poliovirus, and Epstein-Barr virus are common culprits. Bacterial infections, including those caused by *Legionella*, *Staphylococci*, *Salmonella*, *Shigella*, *Streptococci*, and *Clostridium*, as well as parasitic infections like trichinosis and schistosomiasis, and protozoal infections like *Trypanosoma cruzi* and *Toxoplasma gondii*, also contribute to myocarditis. Spirochetes such as *Borrelia burgdorferi*, responsible for Lyme disease, can lead to significant cardiac involvement (Sagar et al., 2012).

Structural and functional damage of the myocardium, caused by these organisms activate the innate and adaptive immune response, which can lead to severe inflammation. The immune response is eventually downregulated; however, myocardial inflammation can also persist. Persistent inflammation is characterized by an ongoing damage to the cardiomyocytes and ultimately results in heart failure (Kindermann et al., 2012). It is estimated that the myocardium is involved in up to 5% of patients who develop an acute viral illness. In patients presenting with angina-like symptoms, mildly elevated Troponin-I, and absence of coronary artery disease, the prevalence of myocarditis by cardiac magnetic resonance imaging is 13% (Patriki et al., 2018).

2.4 Pathophysiology of Heart Failure with Reduced Ejection Fraction

According to Harrison's principle of medicine, the pathophysiology is described in three phases:

Phase 1- Index event

Cardiac output = heart rate * stroke volume

Damage to the heart muscles from the primary etiologies above cause loss of myocytes or impaired function of the living myocyte that disrupts ability of the myocardium to generate force impairing the cardiac output. The primary event may be sudden in onset such as an acute myocardial infarction or more gradual as occurs in chronic pressure or volume overload. Despite an initial reduction in cardiac performance, patients may be asymptomatic or mildly symptomatic for prolonged periods due to activation of compensatory mechanisms that ultimately contribute to disease progression.

Phase 2 - Compensatory mechanism

Reduced cardiac output results in hypo perfusion of vital organs and a drop in systemic blood pressure since blood pressure is a product of cardiac output and total peripheral resistance.

The drop in cardiac output and resultant drop in blood pressure is sensed by baroreceptors in the heart and blood vessels which then send signals to the brainstem vasomotor center in the medulla that immediately causes stimulation of the hypothalamus – pituitary axis to secrete anti diuretic hormone that will re absorb sodium and water thus restoring the cardiac output.

Activation of the sympathetic nervous system also occurs as an immediate response to improve ventricular function by increasing heart rate and myocardial contractility.

Constriction of venous capacitance vessels redistributes flow centrally and the increased venous return to the heart (preload) further augment's ventricular function.

If the above mechanism does not restore the cardiac output, reduced renal blood flow stimulates intrarenal baroreceptors that sense renal afferent arteriolar pressure via granular cells in the juxta glomerular apparatus which are then stimulated to release the enzyme renin. Renin catalyzes the production of angiotensinogen in the liver that is converted into angiotensin 1 which is further catalyzed by angiotensin converting enzyme into angiotensin 2 that has the following effects: Cause direct arteriole vasoconstriction and increase sympathetic activity that further causes vasoconstriction thus increasing the afterload and work of the heart. Secondly, it Stimulates adrenal cortex to release aldosterone that increases collecting ducts epithelial sodium channels for sodium and water re absorption. Lastly, there is stimulation of posterior pituitary to secrete anti diuretic hormone that further causes increased aquaporin deposition in the collecting duct to retain more water.

Natriuretic peptides such as atrial natriuretic peptides (released from the atria), B- type natriuretic peptides (released from the ventricles) and C- type peptide are natural beneficial hormones with the atrial natriuretic peptides being released in response to atrial expansion while B – type natriuretic peptide being released from a failing heart. They result in excretion of sodium and water, vasodilatation, inhibition of renin secretion and antagonism of the effects of angiotensin 2 on aldosterone and vasopressin levels. Although these effects are beneficial to patients with heart failure, they are usually not sufficient to fully counteract the vasoconstriction and volume retaining effects of the other activated hormonal systems. They are inactivated by neprilysin, a membrane bound peptidase.

Among other peptides that are generated in heart failure is endothelin-1, a potent vasoconstrictor derived from endothelial cells lining the vasculature and their plasma concentration in heart failure patients correlate with disease severity and adverse outcomes.

Phase 3 - Left Ventricular Remodeling

The compensatory mechanisms modulate left ventricular function within a physiologic /homeostatic range so that the functional capacity of the patient is preserved / minimally depressed. However, over-activation of the neuro hormonal, adrenergic and cytokine systems lead to a series of adaptive cellular changes including alteration in contractile properties of myocytes, progressive loss of myocytes through apoptosis, abnormal myocardial metabolism and re organization of extracellular matrix with dissolution of organized structural collagen with replacement of interstitial matrix which doesn't provide structural support to myocytes.

The pattern of compensatory hypertrophy and remodeling that develops depends on whether the ventricle is subjected to chronic volume overload giving eccentric hypertrophy where the chambers dilate or chronic pressure overload giving concentric hypertrophy where the chamber walls become thicker without a corresponding increase in chamber size. This hypertrophy and remodeling help to reduce wall stress and maintain contractile force but ultimately, ventricular function may decline further.

Although each of the neurohormonal alterations in heart failure is initially beneficial, continued activation is harmful. Increased circulating volume by salt and water retention cause peripheral congestion with oedema and augmented venous return to the heart may eventually worsen the engorgement of pulmonary vasculature exacerbating congestive pulmonary symptoms such as dyspnea. Elevated arteriolar resistance increases the afterload against which the failing ventricle contracts therefore impairing

stroke volume and reducing cardiac output. Increased heart rate augments metabolic demand and can further reduce performance of the failing heart. Continuous sympathetic activation results in down regulation of cardiac beta-adrenergic receptors contributing to a decrease in the myocardium's sensitivity to circulating catecholamines and a reduced inotropic response (Wallukat, 2002). Chronically elevated levels of angiotensin 2 and aldosterone have additional detrimental effects, they provoke production of cytokines, activate macrophages and stimulate fibroblasts resulting in fibrosis and adverse remodeling of the failing heart.

Because the undesired consequences of chronic neurohormonal activation eventually outweigh the benefits, much of today's pharmacologic therapy of heart failure is designed to moderate these compensatory mechanisms. Studies have shown that left ventricular remodeling can be reversed with medical and device therapy with improved clinical outcomes.

2.5 Stages of heart failure

The American Heart Association developed the staging system for heart failure that classifies heart failure into four stages. This staging emphasizes the importance of prevention and early detection in the early phases and appropriate management in the advanced stages. In view of this classification, heart failure with reduced ejection fraction falls in stage D and trials are centered towards improving the quality of life of patients in this stage and improving their survival.

At Risk (Stage A) – Patient at risk of heart failure without structural cardiac or biochemical changes and no signs and symptoms.

Pre – Heart Failure (Stage B) – Patient with evidence of either structural heart disease, abnormal cardiac function or elevated natriuretic peptide but with no signs and symptoms of heart failure.

Heart Failure (Stage C) - Patients with symptoms and signs of heart failure

Advanced Heart Failure (Stage D) – Severe symptoms and / or signs of heart failure at rest, recurrent hospitalizations despite guideline directed medical therapy refractory or intolerant to guideline directed medical therapy requiring advanced therapies, transplantations, mechanical circulatory support or palliative care.

2.6 Symptoms and signs of Heart Failure with reduced Ejection Fraction

Based on Framingham criteria, heart failure can be diagnosed clinically on the basis of 2 major criteria or 1 major and 2 minor criteria are met.

Major criteria

- Paroxysmal nocturnal dyspnea or orthopnea
- Neck vein distension
- Hepatojugular reflex
- Acute pulmonary oedema
- Rales
- Cardiomegaly on chest radiography
- Third heart sound gallop

Minor criteria

- Nocturnal cough
- Dyspnea on exertion
- Ankle oedema

- Hepatomegaly
- Pleural effusion
- Tachycardia (>120 beats per minute)

The symptoms severity can further be classified based on New York Heart Association

Class 1 – no limitation of physical activity

Class 11 – slight limitation of physical activity

Class 111- marked limitation of physical activity

Class 1V – Symptoms at rest

2.7 Diagnosis of Heart failure with reduced ejection fraction

The diagnosis of Heart failure with reduced ejection fraction requires the presence of symptoms and/or signs of heart failure and a reduced ejection fraction (Left Ventricular Ejection Fraction $\leq 40\%$). This is most usually obtained by echocardiography which gives objective evidence of cardiac dysfunction (ESC 2021). The diagnostic tests recommended are measurements of natriuretic peptides, electrocardiogram, an echocardiogram to determine left ventricular ejection fraction and other tests to determine the etiology.

2.7.1 Natriuretic peptides

When heart failure is suspected, measuring serum B-type natriuretic peptide or its N-terminal component pro B- type natriuretic peptide is an essential diagnostic step according to both the European Society of Cardiology and the National Institute for Health and Care Excellence (NICE) guidelines. These guidelines emphasize the importance of using B-type natriuretic peptide or N-terminal component pro B- type natriuretic peptide levels as a screening tool to identify patients who should be referred

for echocardiography and further specialist assessment. Specifically, the ESC guidelines recommend that patients with a B-type natriuretic peptide level of ≥ 35 pg./mL or an N-terminal component pro B- type natriuretic peptide level of ≥ 125 pg./mL should be referred for echocardiography and specialist evaluation.

The use of B-type natriuretic peptide and N-terminal component pro B- type natriuretic peptide in diagnosing heart failure is supported by their high sensitivity, which is approximately 97%. This high sensitivity means that a normal level of BNP or N-terminal component pro B- type natriuretic peptide effectively excludes the diagnosis of heart failure, making these biomarkers highly useful in clinical practice (Daniels & Maisel, 2007). However, while elevated levels of BNP or N-terminal component pro B- type natriuretic peptide strongly suggest the presence of cardiac disease and indicate the need for further cardiac workup, it is important to note that these biomarkers are not specific to heart failure alone. Elevated levels can also be observed in other cardiac conditions such as right ventricular failure, acute myocardial infarction, congenital heart disease, and valvular disease.

These peptides are primarily expressed by cardiomyocytes in the atrial and ventricular walls. These peptides play crucial roles in regulating blood pressure and maintaining cardiovascular homeostasis. In addition to their natriuretic and diuretic effects, they also inhibit cardiac hypertrophy and remodelling, which are key processes in the progression of heart failure. The B-type natriuretic peptide was initially identified in porcine brain tissue and was thus referred to as the “brain natriuretic peptide.” Subsequent research revealed that BNP is predominantly released from cardiac ventricular cells, especially in response to ventricular stretching forces associated with elevated filling pressures. This release mechanism is crucial for understanding the

clinical utility of B-type natriuretic peptide or its N-terminal component pro B- type natriuretic peptide in diagnosing heart failure (Koratala et al., 2017). When the ventricles are subjected to increased filling pressures, such as in the case of heart failure, they release B-type natriuretic peptide or its N-terminal component pro B- type natriuretic peptide. These peptides then exert various beneficial effects, including promoting natriuresis (the excretion of sodium through urine), diuresis (the increased production of urine), vasodilation (the widening of blood vessels), and suppression of the sympathetic nervous system. These actions collectively help to reduce the workload on the heart and improve cardiac function. The measurement of B-type natriuretic peptide or its N-terminal component pro B- type natriuretic peptide levels thus provide valuable insights into the hemodynamic status of the heart and aids in the diagnosis and management of heart failure.

Despite their high sensitivity, the specificity of B-type natriuretic peptide or its N-terminal component pro B- type natriuretic peptide is relatively low. This means that elevated levels of these peptides can occur in a variety of conditions other than heart failure. For instance, right ventricular failure, acute myocardial infarction, congenital heart disease, and valvular disease can all lead to increased levels of B-type natriuretic peptide or its N-terminal component pro B- type natriuretic peptide. Furthermore, several non-cardiac conditions can also result in elevated levels of these peptides. These conditions include any disease that increases blood volume and wall stress, such as sepsis, anaemia, renal dysfunction, Cushing syndrome, hyperaldosteronism, hypertension with left ventricular hypertrophy, and cirrhosis. Therefore, while elevated B-type natriuretic peptide or its N-terminal component pro B- type natriuretic peptide levels are indicative of an underlying cardiac or systemic disorder, they must be interpreted in the context of the patient's overall clinical picture.

The diagnostic utility of B-type natriuretic peptide or its N-terminal component pro B-type natriuretic peptide extends beyond the initial diagnosis of heart failure. These biomarkers are also valuable in assessing the severity of heart failure, monitoring disease progression, and guiding therapy. For instance, higher levels of B-type natriuretic peptide or its N-terminal component pro B-type natriuretic peptide are associated with worse outcomes and can help identify patients who may benefit from more intensive treatment strategies. Additionally, changes in B-type natriuretic peptide or its N-terminal component pro B-type natriuretic peptide levels over time can provide insights into the effectiveness of therapeutic interventions and help guide adjustments in treatment.

2.7.2 Electrocardiogram

An Electrocardiogram (ECG) is a valuable first-line investigation tool for patients suspected with Heart failure recommended by both the European Society of Cardiology and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines on the diagnosis and management of Heart failure. It was invented in 1902, by a Dutch physician William Einthoven and is a recording of the electrical activity of the heart that is noninvasive and is most useful in the assessment of cardiovascular disease involving cardiac rhythm, myocardial ischemia/infarction and conduction abnormalities. For this reason, the electrocardiogram helps in diagnosing probable etiologies of heart failure with reduced ejection fraction that could be emanating from ischemia and arrhythmias. Its use can also be extended to evaluating disease progression and in guiding on the treatment. The conventional electrocardiogram machine consists of 12 leads divided into two groups, i.e., limb leads and precordial leads. Limb leads are further categorized as standard bipolar limb leads (I, II, and III) and augmented unipolar leads (aVL, aVF, and aVR). The precordial leads

include V1 to V6. The limb leads view the heart in a vertical plane and the precordial leads record the heart's electrical activity in the horizontal plane. For the diagnosis of heart failure with reduced ejection fraction, the 12-lead surface electrocardiogram has high sensitivity (89%) but low specificity. The electrocardiographic utility in heart failure with reduced ejection fraction is therefore mainly to rule it out hence, if the electrocardiograph is normal then heart failure with reduced ejection fraction is unlikely (Khan N.2007). Markers of ventricular repolarization and delayed ventricular activation observed on an electrocardiograph can predict the future risk of heart failure with reduced ejection fraction. These findings suggest a role for electrocardiogram markers in the personalized risk assessment of heart failure subtypes, offering insights into disease progression and potential interventions. This predictive capability underscores the importance of regular electrocardiographic monitoring in patients at risk of heart failure, allowing for timely and targeted therapeutic approaches (O'Neal et al., 2017).

2.7.3 Echocardiogram

An echocardiogram is a non-invasive device that uses high frequency sound waves (ultrasound) to make pictures of the heart used in the clinical setting to provide different kinds of information, including the following, changes in the valves of the heart, congenital birth defects, diseases of the muscle tissue of the heart, disorders affecting the pericardium and problems with the flow or pumping of blood through the heart. In addition, it can be used to show changes in the heart that could be signs of pulmonary embolism, a tumor or aortic aneurysm and giving an idea of which parts of the heart have been damaged in people with coronary arterial disease but can't show the individual coronary arteries.

For patients with heart failure, echocardiography is indispensable. Heart failure, characterized by the heart's inability to pump sufficient blood, can be due to various underlying causes. An echocardiogram provides detailed information about cardiac structure and function, making it a cost-effective and accessible diagnostic tool. It is particularly recommended in the diagnostic workup of patients where heart failure cannot be excluded based on clinical findings alone. In cases of heart failure with reduced ejection fraction, echocardiography is crucial for assessing left ventricular ejection fraction. This measurement indicates how much blood the left ventricle pumps out with each contraction. A left ventricular ejection fraction below normal levels confirms heart failure with reduced ejection fraction and guides evidence-based pharmacological treatments and device therapies. For instance, the implantation of cardioverter defibrillators or cardiac resynchronization therapy can be guided by left ventricular ejection fraction measurements (Ponikowski et al., 2016).

Diagnostic algorithm for heart failure

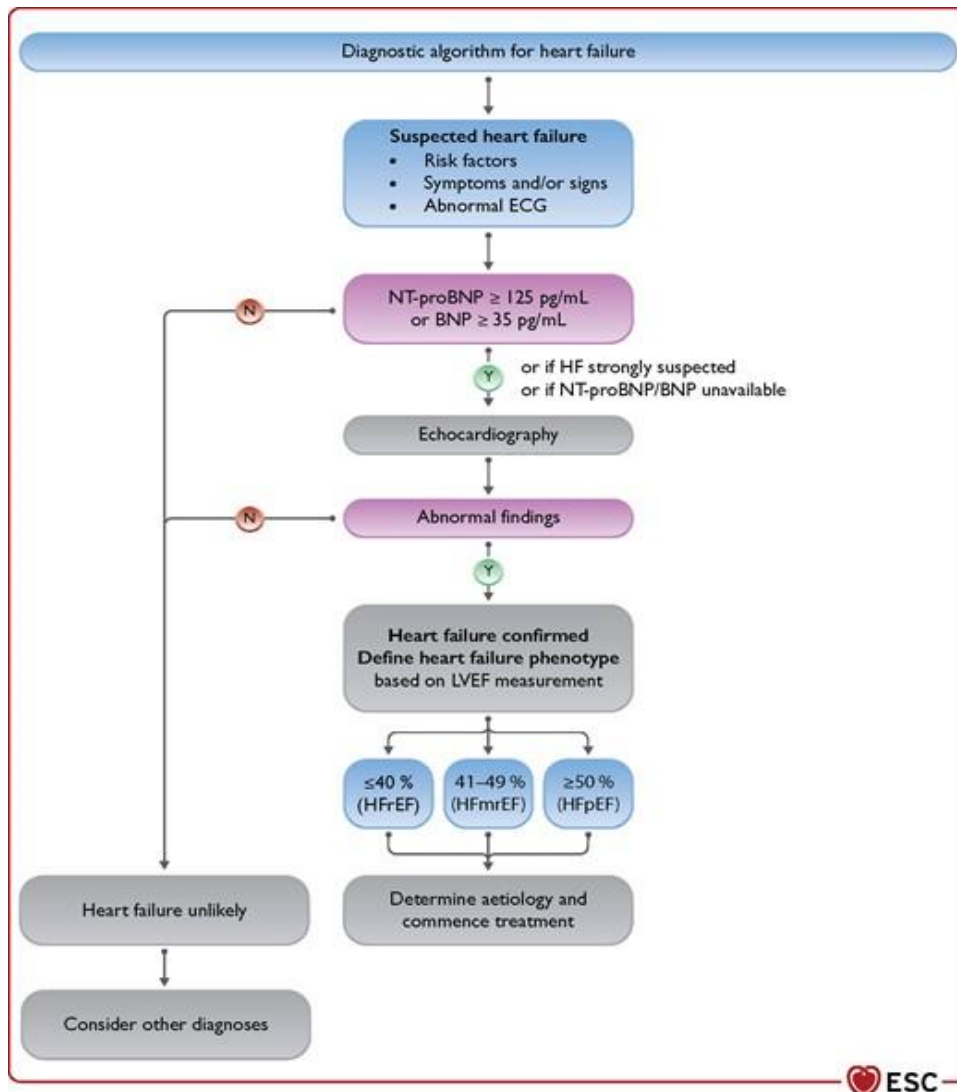


Figure 1: Diagnostic algorithm for heart failure from ESC guidelines 2021

2.8 Pharmacological therapy in Heart Failure with reduced Ejection Fraction

Heart failure is characterized by the overactivation of the neurohormonal axis—particularly of the sympathetic nervous system and the renin–angiotensin–aldosterone system. Initially this is an adaptive response but one that becomes maladaptive and results in salt and water retention and then a cascade of deleterious consequences related to hemodynamic effects and fibrosis. Pharmacological agents targeting these neurohormonal pathways have demonstrated opportunities for improved outcomes in patients with heart failure with reduced ejection fraction (Haydock & Flett, 2022). The three major goals of treatment for patients with heart failure with reduced ejection fraction include: reduction in mortality, prevention of recurrent hospitalizations due to worsening heart failure and improvement in clinical status, functional capacity, and quality of life (McDonagh et al., 2022).

Pharmacological management of heart failure with reduced ejection fraction has seen significant scientific breakthrough in recent decades and ability to alter the natural history gets better.

- In 1980's - angiotensin converting enzyme inhibitors
- In 1990's - beta blockers
- In 2000 – mineralocorticoid receptor antagonist
- In 2015 – angiotensin receptor/neprilysin inhibitor
- In 2020 – sodium glucose cotransporter - 2

Guideline directed medical therapy (GDMT) including a combination of the so called “fantastic four” that includes beta blockers, mineralocorticoid receptor antagonist, angiotensin receptor- neprilysin inhibitor/Renin Angiotensin Aldosterone System blockers and Sodium Glucose cotransporter 2 inhibitors, has been shown to reduce

mortality risk by 75% thus the cornerstone/pillar for heart failure with reduced ejection fraction management (McDonagh et al., 2022).

a) Vasodilators

One of the neurohormonal compensatory mechanisms is excessive vasoconstriction, vasodilator drugs help to reverse this adverse consequence. Renin – angiotensin-aldosterone system inhibitors result in vasodilatation of both venous and arteriolar systems and include angiotensin converting enzyme inhibitors which are the recommended first line, angiotensin receptor blockers are used as second line agents due to less robust mortality data from clinical trials, angiotensin receptor/neprilysin inhibitors should be considered before resorting to angiotensin receptor blockers alone.

Angiotensin converting enzyme-inhibitors such as enalapril and captopril were the first class of drugs shown to reduce mortality and morbidity in patients with heart failure with reduced ejection fraction. They have also been shown to improve symptoms. They competitively inhibit the action of angiotensin converting enzyme thus blocking the conversion of angiotensin I to angiotensin II, which leads to reduced circulating Angiotensin II, a potent vasoconstrictor. The resulting vasodilation leads to reduced preload and reduced ventricular wall stress, and reduced afterload and increased cardiac output (Herman et al., 2022). In addition, improved renal blood flow, drop in aldosterone and antidiuretic hormone lead to sodium elimination resulting in reduced intravascular volume and improvement in systemic and pulmonary vascular congestion, they also augment circulating levels of bradykinin which is a beneficial vasodilator in heart failure. (Gavras et al., 1978). Several large, prospective, randomized, placebo-controlled trials have proved that treatment with angiotensin converting enzyme inhibitors reduces overall mortality of 23%, especially in patients with heart failure with reduced ejection fraction (Yusuf, 1991).

Angiotensin receptor blockers function by blocking the effects of Angiotensin II on its receptors including: vasoconstriction, sympathetic activation, production of aldosterone with sodium and water retention and stimulation of antidiuretic hormone release with water retention and can be used as an alternative in patients who cannot tolerate the side effects of angiotensin converting enzyme inhibitors. Examples include losartan and valsartan. Inhibition of renin angiotensin aldosterone system in Heart Failure patients significantly decreased morbidity and mortality. Angiotensin converting enzyme work the same as angiotensin receptor blockers but the later are better tolerated in view of less bradykinin mediated side effects such as cough and angioedema (Singh & Karnik, 2019).

Angiotensin receptor-Neprilysin inhibitor; Angiotensin receptor-Neprilysin inhibitor; Valsartan/sacubitril (Entresto) has demonstrated superior efficacy over enalapril in managing heart failure with reduced ejection fraction as evidenced by the PARADIGM-HF trial. The trial results revealed that valsartan/sacubitril achieved a significant 16% relative risk reduction in cardiovascular mortality compared to enalapril. This translates to a marked improvement in patient outcomes, particularly in reducing hospitalizations due to worsening heart failure. The benefits of valsartan/sacubitril extend beyond mortality, including improvements in symptoms and overall quality of life for patients suffering from heart failure with reduced ejection fraction.

Sacubitril, a neprilysin inhibitor, plays a crucial role in this therapeutic combination by blocking the enzyme neprilysin. This inhibition prevents the breakdown of natriuretic peptides, which have beneficial effects such as promoting diuresis (increased urine production), natriuresis (increased sodium excretion), and vasodilation (widening of

blood vessels). These effects collectively contribute to a reduction in fluid overload and improved blood flow, essential for managing heart failure symptoms.

The combination of valsartan (an angiotensin II receptor blocker) with sacubitril leads to a comprehensive approach to neurohormonal regulation. While sacubitril enhances the natriuretic peptide system, valsartan inhibits the renin-angiotensin-aldosterone system, particularly the effects of angiotensin II. This dual mechanism provides a synergistic effect, optimizing the management of heart failure by mitigating the adverse effects of renin-angiotensin-aldosterone system activation and enhancing the protective effects of natriuretic peptides (Ekici et al., 2021).

Additionally, the use of sacubitril/valsartan is associated with several benefits over traditional therapies. It has been shown to reduce the rate of hyperkalemia (elevated potassium levels) and slow the decline in estimated glomerular filtration rate, which is a marker of kidney function (McDonagh et al., 2021). These benefits are particularly important because patients with heart failure are at increased risk for both hyperkalemia and renal impairment due to the effects of heart failure and its treatments.

b) Beta-blockers

Beta-adrenergic receptors are G-protein coupled receptors that are activated by norepinephrine and epinephrine and found in the myocardium. Their activation has detrimental effects in patients with chronic heart failure (Wallukat, 2002). The mechanisms of β -blocker effects in heart failure are cardiac protection from β_1 -adrenoceptor overstimulation, antiarrhythmic effects, reduction in heart rate, and positive energetic effects (Böhm & Maack, 2000). Beta-blocker therapy also results in direct antagonism of the cardiotoxic effects of catecholamines, upregulation of myocardial β -receptors with the restoration of their function and consequent increase

in the inotropic reserve of the heart, suppression of elevated cardiotoxic neurohormonal systems (the renin–angiotensin–aldosterone and endothelin systems), and prolongation of the diastolic phase with improvement of coronary flow. All these actions lead to improvement in the structure and function of the left ventricle (Masarone et al., 2021). Clinical trials have shown that long-term beta blocker therapy resulted in augmented cardiac output, reduced hemodynamic deterioration, need for fewer hospitalization and improved survival. Carvedilol, Metoprolol succinate, and Bisoprolol have been shown to improve survival in multiple randomized trials (Packer et al., 1996). They should be initiated in clinically stable, euvolemic patients at a low dose and gradually up titrated to the maximum tolerated dose to a target dose of 60-70 beats per minute, where Heart failure with reduced ejection fraction patients have decompensated on a beta blocker, they should be maintained on the same dose (McDonagh et al., 2022). COPERNICUS (Carvedilol Prospective Randomized Cumulating Survival) and MERIT-HF (Metoprolol Randomized Intervention Trial in Congestive Heart Failure) trials showed overall that first, early in-hospital initiation was well tolerated with minimal side effects and clinical benefit observed within the first weeks of treatment was similar to that observed in long-term trials (Gottlieb et al., 2002; Krum et al., 2003).

c) Mineralocorticoid receptor antagonists

Mineralocorticoid receptor Antagonists such as spironolactone and eplerenone reduce mortality, risk of hospitalization and improve symptoms (McDonagh et al., 2021). They competitively inhibit aldosterone at its binding sites in the distal renal tubules where they activate epithelium sodium channels to reabsorb sodium with water with loss of potassium and hydrogen ions and arteriolar smooth muscle leading to urinary sodium and water loss with a net effect of diuresis, conservation of potassium and vasodilation.

It has also been shown to reduce the degree of inflammation and remodeling in the heart. A sub-analysis of the randomized aldactone evaluation study (RALES) trial assessed the interactions between serum markers of cardiac fibrosis and the effect of spironolactone on outcomes in heart failure with reduced ejection fraction and it concluded that adding spironolactone significantly decreased the levels of these serum markers of cardiac fibrosis (Zannad et al., 2000). The RALES study demonstrated that the heart failure with reduced ejection fraction patients on 25 mg spironolactone once daily had a 30% reduction in the risk of death from all causes, a 32% reduction in the risk of death from cardiovascular causes, 35% lower frequency of hospitalization for worsening heart failure, and a 30% reduction in the risk of hospitalizations from cardiac causes.

OPTIMIZE – HF trial demonstrated that spironolactone use reduced all – cause mortality by 8% and heart failure readmissions by 13% in elderly heart failure with reduced ejection fraction patients ((Bayoumi et al., 2019). The EMPHASIS-HF trial which evaluated the effect of eplerenone in patients with New York Heart Association class II and Ejection Fraction less than 35% concluded that patients treated with eplerenone had a 27% lower risk of hospitalization due to Heart Failure and a 23% lower risk of hospitalization for any cause (Zannad et al., 2011).

d) Sodium Glucose cotransporter -2 inhibitors

Sodium Glucose cotransporter -2 inhibitors – such as dapagliflozin and empagliflozin act by inhibiting sodium – glucose co - transporter 2 in the proximal convoluted tubules of the kidneys resulting in sodium and glucose excretion with accompanying fluid thus diuresis. Sodium Glucose cotransporter – 2 inhibitors also improve blood pressure by sodium and water balance and inhibiting the sympathetic system thus contributing to the improvement of cardiovascular benefits.

In DAPA-HF trial, therapy with dapagliflozin, resulted in a 26% reduction in the worsening heart failure with hospitalization and cardiovascular death. Alleviated Heart Failure symptoms, improved physical function and quality of life in patients with symptomatic heart failure with reduced ejection fraction (Petrie et al., 2020). The EMPEROR-Reduced trial found that empagliflozin reduced the combined primary endpoint of Cardiovascular death or Heart failure hospitalization by 25% (Petrie et al., 2020).

Regardless of etiology, Guideline Directed Medical Therapy remains a cornerstone of heart failure with reduced ejection fraction management, although evidence for its use in the setting of primary valvular heart disease and left ventricular systolic dysfunction is frequently lacking (Gill et al., 2021).

In Heart failure with reduced ejection fraction, the morbidity and mortality still remain high, with a 5-year survival rate of 25% after hospitalization despite the use of guideline directed medical therapy (Murphy et al., 2020). Poor characterization, disease progression and failure to address comorbidities are some of the reasons why these patients do not respond to Guideline Directed Medical Therapy.

For this reason, several randomized clinical trials have investigated the use of invasive cardiac procedures and device therapy which have demonstrated mortality benefits among Heart failure with reduced ejection fraction patients (McDonagh et al., 2022).

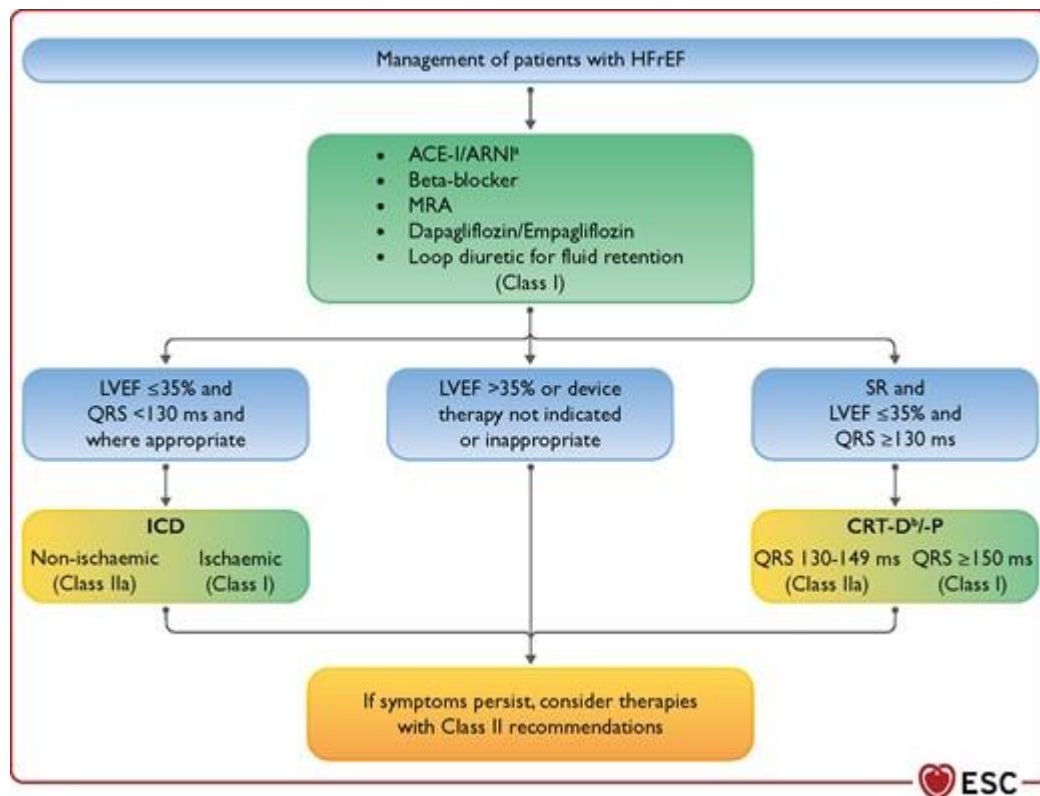


Figure 2: Management of patients with Heart Failure with reduced Ejection Fraction

2.9 Invasive cardiac procedures in Heart Failure with reduced Ejection Fraction

Catheterization involves the passage of a thin flexible tube known as an intra – cardiac catheter through an intravenous line on peripheral vessels like femoral, radial and brachial arteries/ veins into cardiac chambers, the pulmonary artery, coronary arteries and veins which is then manipulated with the guidance of live x- ray images (fluoroscopy).

There are certain cardiac indications according to the European Society of Cardiologists and American Heart Association that require invasive cardiac procedures for diagnosis and /or treatment:

cardiac catheterization laboratory procedures

- Taking measurements of right cardiac chamber, pulmonary artery and left cardiac chamber pressures.
- Valvuloplasty which involves opening of narrowed heart valves by ballooning.
- Thrombectomy where blood clots are removed from the arteries.
- Endomyocardial biopsy procedures for biopsy tissue histology.
- Evaluation of cardiac transplantation pre- and post-surgery.
- Assessment of new onset cardiomyopathy of uncertain etiology coronary artery disease diagnostics through angiography and / or therapeutic like angioplasty and stent insertion.
- It is the gold standard for diagnosing constrictive pericarditis.

Electrophysiology laboratory procedures

- Electrophysiology studies where catheters with electrodes are inserted into the vessels and electrical signals sent to map the electrical pathways and identify arrhythmia sources.
- Radiofrequency catheter ablation or cryoablation.
- Placement of cardiac devices such as permanent pacemakers, implantable cardioverter defibrillators and cardiac resynchronization therapy.

These tests define coronary artery anatomy, conduction system physiology, cardiac anatomy, cardiac function and pulmonary arterial hemodynamics to establish diagnoses and help clinicians select treatment. Invasive cardiac procedures is also the basis for several therapeutic interventions. Two major causes of death in heart failure with

reduced ejection fraction are cardiac pump failure and sudden death from malignant ventricular arrhythmias. Device-based therapy such as cardiac resynchronization therapy and implantable cardioverter defibrillator have been shown to reduce mortality and rehospitalization rates and improve prognosis in selected subsets of heart failure with reduced ejection fraction patients (Moss, Hall, et al., 2009). Those shown to confer benefit to Heart failure with reduced ejection fraction patients include:

Catheter ablation – a technique whereby radiofrequency energy source is introduced via intracardiac catheter to create scar tissue in the regions generating supraventricular tachyarrhythmias such as persistent atrial fibrillations and atrial flutters with the aim of eradicating them. Catheter ablation, particularly radiofrequency ablation has revolutionized treatment for tachyarrhythmia. It has evolved rapidly over the years and has proven to be first-line therapy for many tachyarrhythmias in most of the patients having recurrent symptoms. Catheter ablation was seen as a last resort for people who didn't respond to drug treatments and had severe symptoms. Now, catheter ablation is seen as a first-line treatment for people with different types of atrial fibrillation and different levels of severity. One of the clinical trials concluded that rate control is not inferior to rhythm control for the prevention of death and morbidity from cardiovascular causes and may be appropriate therapy in patients with a recurrence of persistent atrial fibrillation (Van Gelder et al., 2002).

According to European Society of Cardiologist 2014 atrial fibrillation guidelines, catheter ablation is indicated in:

- symptomatic paroxysmal atrial fibrillation refractory to or with intolerance of at least one class 1 or class 111 anti-arrhythmic agent.

- Selected patients with recurrent symptomatic paroxysmal atrial fibrillation prior to trial of anti-arrhythmic agents after weighing risks versus benefits.
- Patients who cannot be anticoagulated.
- Definitive treatment of symptomatic supraventricular tachycardia due to atrioventricular re-entrant tachycardia (AVRT), atrioventricular nodal re-entrant tachycardia (AVNRT), unifocal atrial tachycardia, or atrial flutter;
- Atrial fibrillation with lifestyle-impairing symptoms and failure of antiarrhythmic agents

Current guidelines state that catheter ablation for atrial fibrillation in heart failure with reduced ejection fraction improves symptoms and left ventricular ejection fraction (Hindricks et al., 2021). In addition, it was demonstrated to be effective in reducing recurrence of any atrial fibrillation by 48% and symptomatic atrial fibrillation by 51% compared with drug therapy over 5 years of follow-up with significant reduction of its burden regardless of the baseline atrial fibrillation type (Poole et al., 2020). Patients' quality of life improved as evidenced by a low Minnesota Living with Heart Failure Questionnaire Score (MLHFQ) after a rhythm control with catheter ablation (Parkash et al., 2022). Moreover, CASTLE-AF trial and a meta-analysis showed the catheter ablation to have a mortality benefit in atrial fibrillation with heart failure with reduced ejection fraction compared to the standard pharmacological interventions (Alturki et al., 2019). The mortality benefit was replicated in the AATAC trial where the risk of death and heart failure related unplanned hospitalizations were both significantly lower in the catheter ablation arm as opposed to the standard pharmacological interventions arm (Di Biase et al., 2016).

Implantable cardioverter defibrillator (ICD) - A high proportion of deaths among patients with heart failure with reduced ejection fraction occur suddenly and

unexpectedly due to fatal tachyarrhythmias. An implantable cardioverter defibrillator is an intracardiac device implanted to detect and terminate sustained ventricular tachyarrhythmias like ventricular tachycardia/ fibrillation/ flutter that can cause sudden cardiac death. It is recommended by European Society of Cardiologists and American Heart Association for; primary prevention of sudden cardiac death for ischemic and non- ischemic dilated cardiomyopathy, at least 40 days post myocardial infarction and those with left ventricular ejection fraction $\leq 35\%$ in symptomatic heart failure (New York heart association 2 and 3) despite being on guideline directed medical therapy for 3 months or more and expected to live for more than a year. It is also indicated for secondary prevention in those with hemodynamically unstable ventricular tachycardia or ventricular fibrillation.

The MADIT-I study showed that Implantable Cardioverter Defibrillator saves lives in high-risk patients with coronary heart disease and the MADIT-II trial reported a 6.2% absolute risk reduction in sudden cardiac death with Implantable Cardioverter Defibrillator versus conventional therapy (Moss et al., 2002). Implantable Cardioverter Defibrillator therapy was associated with significantly improved survival in patients with ischemic cardiomyopathy. DANISH trial did not demonstrate a significant benefit of Implantable Cardioverter Defibrillator in preventing primary outcome of all-cause mortality in patients with nonischemic systolic heart failure but did report a significant decrease in risk of sudden cardiac death (Køber et al., 2016). A study conducted to compare the difference in outcome between medical therapy versus device therapy concluded that in patients with New York Heart Association class II or III with heart failure with reduced ejection fraction, the use of amiodarone had no favorable effect on survival, whereas implantable cardioverter defibrillator therapy reduced overall mortality by 23 percent (Bardy et al., 2005). Despite the benefits demonstrated by

clinical trials of these implantable cardioverter defibrillators, the uptake in Kenya is low. A study conducted in a tertiary facility in Kenya showed that out of the eligible patients, only 33.5% had the device implanted and the reason for low uptake was majorly inability to afford it (Oluoch et al., 2024).

Cardiac resynchronization therapy (CRT) is a modality of cardiac pacing used in patients with left ventricular systolic dysfunction and dyssynchronous ventricular activation that provides biventricular pacing that confers more benefit in those with left bundle branch block morphology with $QRS \geq 150\text{ms}$ and in sinus rhythm. Once activated, cardiac resynchronization therapy can reduce cardiac mechanical dyssynchrony coordinated contraction of the ventricles then gives the previously dyssynchronous heart an instant mechanical advantage that augments cardiac output. In addition to the immediate hemodynamic benefits, during a span of months, cardiac resynchronization therapy leads to further improvement in the structure and function of the heart (Gras et al., 2002).

Cardiac Resynchronization Therapy has been shown in trials to improve cardiac function, symptoms and reduce morbidity and mortality in heart failure with reduced ejection fraction patients likely due to reversal of cardiac remodeling and improvement in left ventricular ejection function beyond the use of guideline directed medical therapy. It also improves quality-adjusted life-years among these patients. It is recommended by European Society of Cardiologists/American Heart Association in:

Class 1 indications:

- symptomatic heart failure with reduced ejection fraction of $\leq 35\%$ in sinus rhythm left bundle branch block with $QRS \geq 150\text{ms}$.

- Patients with heart failure with reduced ejection fraction regardless of NYHA class or QRS width who have an indication for ventricular pacing for high degree atrio - ventricular block in order to reduce morbidity, this includes patients with atrial fibrillation.

Class 2 indications:

- It should be considered for symptomatic patients with heart failure with reduced ejection fraction in sinus rhythm with QRS duration $\geq 150\text{ms}$ and non-Left bundle branch block QRS morphology with ejection fraction $\leq 35\%$ to improve symptoms and reduce morbidity and mortality
- Patients with an ejection fraction $\leq 35\%$ who have a conventional pacemaker or an Implantable cardiac device and subsequently develop worsening heart failure should be considered for upgrade to Cardiac Resynchronization Therapy.
- Symptomatic patients in heart failure with reduced ejection fraction in sinus rhythm with a QRS duration of 130 – 149ms and non-left bundle branch block morphology with an ejection fraction $\leq 35\%$ in order to improve symptoms and reduce morbidity and mortality.

Studies have shown that in patients with heart failure with reduced ejection fraction and cardiac desynchrony, cardiac resynchronization improves symptoms and the quality of life and reduces complications and the risk of death (Cleland et al., 2005). In MADIT-CRT, the clinical benefit of cardiac resynchronization therapy was evident. In this study, the use of cardiac resynchronization therapy combined with an implantable cardioverter defibrillator in asymptomatic or mildly symptomatic patients with heart disease and a reduced ejection fraction with wide QRS complex was associated with a 34% reduction in the risk of death or heart-failure events, as compared with the use of an implantable cardioverter defibrillator alone (Moss et al., 2009). This was consistent in the RAFT

trial where patients with reduced ejection fraction, wide QRS and New York Heart Association class II and III, exhibited survival benefit associated with receipt of combined cardiac resynchronization therapy with implantable cardioverter defibrillator (CRT – D) that appeared to be sustained during a median year of nearly fourteen years of follow up. This was replicated in the MIRACLE trial where a decrease in hospitalizations because of heart failure, significant improvements in 6-minute walk distance, New York Heart Association class and quality of life score were noted to have improved. In addition, the trial showed that resynchronization therapy was an effective adjunct to pharmacological therapy in reducing the secondary combined endpoint of heart failure hospitalization or death (Abraham et al., 2002). A meta-analysis of thirty-two studies sought to review the association between QRS narrowing through Cardiac Resynchronization Therapy and clinical, as well as echocardiographic response showed that patients had clinical improvement, exhibited shorter QRS and had echocardiographic improvement through Cardiac Resynchronization Therapy (Bazoukis et al., 2020).

In Kenya, studies have shown that the uptake of cardiac resynchronization therapy is low despite all the studied benefits due to the initial high cost of implantation of the device. However, in comparison, the cost related to repeat hospitalization, disease progression, morbidity and mortality is much greater hence more patients should benefit from this procedure (Gikonyo et al., 2021).

Permanent pace maker – A pacemaker is an electronic device that stimulates the heart with electrical impulses to maintain or restore a normal heartbeat. It is implanted primarily for treatment of node dysfunction with bradyarrhythmia, certain fascicular blocks and sick sinus syndrome that causes a combination of bradycardia, tachycardia or sinus pauses. A single chamber pacemaker is used when there is a sinoatrial node

dysfunction or an atrioventricular block. It stimulates either the right atrium or the right ventricle. On the other hand, a dual chamber pacemaker is needed where both the atrium and ventricle need stimulation. It coordinates the timing between atrial and ventricular contractions mimicking the natural sequence of the heart's electrical activity. Common indications in American Heart Association/European Society of Cardiologist guidelines include:

Sinus node dysfunction:

class I indications

- Documented symptomatic sinus bradycardia including frequent sinus pauses which produce symptoms and symptomatic sinus bradycardia that results from required drug therapy for medical condition.
- Symptomatic chronotropic incompetence.

Class II indications

- Sinus bradycardia with heart rate less than 40 beats per minute, but no clear association between the symptoms and bradycardia.
- Unexplained syncope when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiological studies.
- Minimally symptomatic patients with chronic heart rate less than 40 beats per minute while awake.

Acquired high-grade to complete Atrio Ventricular block

Class I indications

- Complete third-degree Atrio Ventricular block with or without symptoms.
- Symptomatic second-degree Atrio Ventricular block, Mobitz type I and II

- Exercise-induced second- or third-degree Atrio Ventricular block in the absence of myocardial infarction
- Mobitz II with widened QRS complex

Class II indications

- Asymptomatic Mobitz type II with the narrow QRS complex.
- First degree Atrio Ventricular block when there is a hemodynamic compromise.
- Asymptomatic second-degree Atrio Ventricular block at Intra or Infra-His levels found in electrophysiology studies

A study conducted showed that Kenya had only 0.2/1000000 pacemaker implant centers with only 7/1000000 pacemaker implants done per annum despite having several patients in need of the permanent pacemakers making it a healthcare concern as conservatively treated patients with high-degree atrio ventricular blocks have notably poorer survival compared with pacemaker-treated patients (Egas et al., 2023).

Invasive coronary angiography – Is an imaging modality for assessment of coronary arterial disease under fluoroscopy with the aim of stenting for those with significant epicardial coronary narrowing. Indications for coronary angiography in heart failure according to American society of cardiologists include:

- Those with angina or significant ischemia unless the patient is not eligible for revascularization of any kind.
- Those who have chest pain that may or may not be of cardiac origin who have not had evaluation of their coronary anatomy and who have no contraindications to coronary revascularization.

- Those known or suspected to have coronary artery disease but who do not have angina unless the patient is not eligible for revascularization of any kind.
- Those with new onset heart failure with suspicion of ischemic etiology or suspicion of progressive ischemia in those with worsening heart failure.
- Pre surgical assessment for before major cardiac surgeries or those with significant risk factors for coronary arterial disease planning for a non-cardiac major surgery.
- Inconclusive non-invasive tests like stress test or computer tomography angiogram

Cardiovascular disease remains the most common cause of death in the general population in European countries accounting for under 2.2 million deaths in females and just under 1.9 million deaths in males (Byrne et al., 2023). The European journal of preventive cardiology 2021, also ranks Ischemic heart disease as the commonest cause of heart failure at 26.5%.

In Kenya, a study conducted at the Agha khan hospital Nairobi showed the prevalence of coronary arterial disease to be at 52.3% in African patients with heart failure with reduced ejection fraction. In patients with ischemic cardiomyopathy, 88% had coronary atherosclerosis on conventional coronary angiography (Kimeu et al., 2023). This epidemiological transition may have been as a result in lifestyle changes that emulate the Western world. For this reason, it can be deduced that the prevalence of coronary arteriole disease is high but under estimated in our population due to limited access to invasive coronary angiography.

2.10 Electrocardiogram interpretation and indications for invasive cardiac procedures

The fundamental principle behind recording an electrocardiogram is an electromagnetic force, current, or vector with both magnitude and direction. In clinical practice, the goal of the electrocardiogram interpretation is to determine whether the waves and intervals are normal or pathological (Sattar et al., 2022). In clinical settings, an electrocardiogram is routinely performed on most patients with heart failure as part of their diagnostic workup. However, it is not uncommon for the results of these electrocardiograms to be overlooked or not given the necessary attention they warrant (Khan et al., 2007). This can lead to missed opportunities for early detection and intervention in cardiac abnormalities that could be critical for patient care.

The waves and intervals observed on an electrocardiogram are systematically labeled alphabetically, starting with the P wave. The P wave represents the electrical activity associated with atrial depolarization. Following the P wave is the QRS complex, which indicates ventricular depolarization and is typically the most prominent feature on the electrocardiogram. Lastly, the ST-T-U complex includes the ST segment, T wave, and occasionally a U wave. The ST segment reflects the period between ventricular depolarization and repolarization, the T wave corresponds to ventricular repolarization, and the U wave, if present, is thought to be related to the repolarization of the Purkinje fibers or other late repolarization events (Jordan M Prutkin, 2023).

Given the detailed information an electrocardiogram provides, its interpretation is crucial for diagnosing various cardiac conditions, such as arrhythmias, myocardial infarction and other forms of heart disease. Ensuring that the waves and intervals are properly analyzed can significantly influence the clinical management and outcomes

for heart failure patients. Thus, greater emphasis should be placed on the thorough examination of electrocardiogram results to enhance patient care and treatment efficacy.

P wave — The P wave represents atrial depolarization. The normal sinus P wave represents depolarization from the right to left atrium through Bachmann bundle and is an initial low amplitude deflection preceding the QRS complex that is positive in most leads. The duration is generally <0.12 sec (three small boxes) and the amplitude <0.25 mv (2.5 small boxes). The shape and size of the P wave can provide valuable information about atrial health and function. Variations in the P wave's morphology can indicate atrial enlargement, atrial conduction abnormalities, or other atrial pathologies.

PR interval — is measured from the beginning of the P wave to the first part of the QRS complex. It includes time for atrial depolarization (the P wave) and conduction through the Atrio Ventricular node and the His-Purkinje system (which constitute the PR segment). The length of the PR interval changes with heart rate but is normally 0.12 to 0.20 sec (three to five small boxes). Deviations from this range can indicate various cardiac conditions. A prolonged PR interval, known as first-degree heart block, may suggest delayed conduction through the atrio ventricular node. Conversely, a shortened PR interval can be associated with pre-excitation syndromes like Wolf Parkinson White syndrome.

Normal Rhythm — refers to the pattern of electrical activity that controls the heartbeat. The normal electrical activity originates from the sinoatrial node, which is often referred to as the heart's natural pacemaker. When the heart's rhythm is controlled by the Sino atrial node, it is termed sinus rhythm. Sinus rhythm is identified on an electrocardiogram by the presence of a P wave that is upright in leads II, III, and aVF,

and inverted in lead aVR. This P wave is followed by the QRS complex, which represents the depolarization of the ventricles. In sinus rhythm, the electrical impulses are conducted in a regular and consistent manner, ensuring that the heart beats in a coordinated and efficient way.

Arrhythmias

Deviations from sinus rhythm denoted as an arrhythmia can indicate various cardiac conditions that may require medical attention. These arrhythmias can be categorized as brady arrhythmias where the heartbeat is slow at a rate less than 60 beats per minute or tachy arrhythmia with a heart rate above 100 beats per minute. Arrhythmias result from abnormalities of impulse initiation that results from either automaticity, triggered activity or impulse conduction. Abnormal impulse conduction results in reentrant excitation; a combination of slowed conduction and unidirectional conduction block provides the conditions necessary for reentry to occur. Other arrhythmias may arise due to a combination of both abnormal impulse initiation and conduction (Wit & Rosen, 1983) .

Brady arrhythmias which manifest as slow conduction in the mildest form and failure to conduct either intermittently or persistently. They are further sub - classified as:

First degree atrioventricular block where there is slowing of conduction through the atrioventricular junction and manifest as prolonged PR interval ($> 200\text{ms}$). Second degree atrioventricular block where there is intermittent failure of electrical impulse conduction from the atrium to the ventricles that can be morbitz 1 (Wenckebach) demonstrate by a progressive lengthening of PR interval and a dropped beat or morbitz 11 where there is intermittent failure to conduct P wave without changes in PR interval. Third degree atrioventricular block results when there is complete failure of conduction

from the atrium to ventricles. Permanent pacemakers are implanted in any patients with symptomatic bradycardia and irreversible second- and third-degree atrioventricular block.

Tachy arrhythmias which can be supraventricular such as atrial fibrillation and flutter, junctional rhythm or ventricular arrhythmias like sustained ventricular tachycardia, ventricular fibrillation.

In supraventricular arrhythmias, atrial fibrillation has been shown to be the most common arrhythmia in heart failure with reduced ejection fraction and can be a cause as well as a complication of heart failure with reduced ejection fraction. It is characterized by disorganized electrical impulses originating from the atria leading to an irregular atrioventricular node response and subsequent irregular ventricular rhythm. P waves are absent and QRS complex is narrow.

Heart Failure with reduced Ejection Fraction and Atrial Fibrillation share common risk factors and pathophysiological pathways. Neurohormonal imbalance and activation of the renin–angiotensin–aldosterone system leads to inappropriate physiological changes: increased filling pressures and afterload, increased left atrial strain and fibrosis, proarrhythmic remodeling and conduction abnormalities with development and maintenance of atrial fibrillation. These patients also demonstrate dysregulated calcium handling and calcium overload, which can result in after-depolarizations and arrhythmias (Koniari et al., 2021)

Heart failure with reduced ejection fraction complicated by atrial fibrillation is associated with a worse prognosis and is a major contributor to cardiovascular morbidity and mortality. Atrial fibrillation predisposes to thrombus formation in the left atrial appendage which may lead to a stroke or other cardio-embolic complications. In

contrast, heart failure with reduced ejection fraction caused by atrial fibrillation has a favorable prognosis especially if the arrhythmia is diagnosed and treated (Santhanakrishnan et al., 2016). Heart failure with reduced ejection fraction may improve or resolve with treatment through electrical cardioversion or more invasive radiofrequency ablation of Atrial Fibrillation (McDonagh et al., 2021).

In Ventricular arrhythmias, Ventricular tachycardia can occur when three or more consecutive beats with a rate > 100 beats /minute originate from the ventricles and ventricular fibrillation is a chaotic rhythm with undulations that are irregular in timing and morphology without discrete QRS (McDonagh et al., 2021).

ADHERE study which provided important insights into the clinical characteristics and patterns of care of heart failure patients showed that among ventricular arrhythmias, ventricular tachycardia was the most prevalent reported in heart failure patients in heart failure registries (Adams et al., 2005).

Ventricular arrhythmias are a common manifestation of Heart Failure with reduced Ejection Fraction with ischemic heart disease being the most common underlying etiology. Sudden cardiac death accounts for approximately 45% of all deaths in these patients (Agesen et al., 2021). Randomized control trials have shown that in heart failure with reduced ejection fraction patients, this can be mitigated by insertion of implantable cardioverter defibrillator. **Clinically significant arrhythmias** signify abnormality in the cardiac rhythm that may impair contractility and eventually compromise the cardiac output thus giving clinical manifestations.

Normal QRS complex — The QRS complex represents the time for ventricular depolarization. The entire QRS duration normally lasts for 0.04 to 0.12 sec (1 to 3 small boxes). If the initial deflection is negative, it is termed a Q wave. Small Q

waves are often seen in lateral leads that includes lead I, aVL, and V4-V6 as a result of initial septal depolarization. The first positive deflection of the QRS complex is called the R wave. It represents depolarization of the left ventricular myocardium. Right ventricular depolarization is obscured because the left ventricular myocardial mass is much greater. The negative deflection following the R wave is the S wave, which represents terminal depolarization of the high lateral wall. Normal ventricular depolarization represented by QRS interval occurs after an impulse traverse the atrioventricular node and HIS bundle which is a specialized conducting tissue that splits into right and left bundles resulting in synchronized depolarization of the ventricles.

Prolonged QRS interval

In diseased hearts, altered electrochemical substrate and impaired conduction fibers can change the velocity and uniformity of electrical propagation, resulting in areas of activation delay. If the delay is significant enough, it manifests as lengthening of the QRS complex on the surface 12-lead electrocardiogram. It can manifest as right bundle branch block with an RSR' pattern on electrocardiogram where impulse is delayed or blocked along the right bundle branch; left bundle branch block where impulse is delayed or blocked in the left bundle branch causing the left ventricle to depolarize later and has notched R waves on left lateral electrocardiograph leads or non-specific intraventricular conduction delay if the pattern does not conform to left nor right bundle branch block patterns (Jaffe L 2014).

In a large Veteran's Administration study of more than 45 000 patients, investigators found that every 10-ms prolongation of the QRS duration was associated with an 18% increase in risk for cardiovascular death in the general population (Aro et al., 2011). In

most patients with systolic left ventricular dysfunction, increased QRS duration is associated with a worse prognosis (Wang et al., 2008).

Pathological Q wave is defined according to European Society of Physicians as Pathological Q waves are defined as (1) any Q-wave in leads V2–V3 $\geq 0.02s$ or QS complex in leads V2 and V3, or (2) Q-wave $\geq 0.03s$ and $> 0.1mV$ deep or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping, or (3) R wave $\geq 0.04s$ in V1–V2 and R/S ratio ≥ 1 with a concordant positive T-wave in the absence of a conduction defect.

A study done at Agha khan Hospital Nairobi showed that coronary arterial disease was a major etiology in Heart Failure with reduced Ejection Fraction among the African population and one of the most powerful predictors of coronary arterial disease was the presence of pathological Q waves (Kimeu et al., 2023).

Their presence on electrocardiogram is specific for a prior transmural Myocardial Infarction with 85% specificity, however, the sensitivity is low at 66% (Nadour et al., 2014).

ST segment — The ST segment occurs after ventricular depolarization and before repolarization has begun. The intersection of the end of the QRS complex and the initial part of the ST segment is termed the J point. Abnormalities in the ST segment, such as elevation or depression, can indicate issues like myocardial ischemia or infarction.

T wave — The T wave represents the period of ventricular repolarization. Since the rate of repolarization is slower than depolarization, the T wave is broad, has a slow upstroke, and a more rapid downslope to the isoelectric line following its peak.

Abnormalities in the T wave may indicate various cardiac conditions, such as ischemia, electrolyte imbalances, or the effects of medications.

QT interval — The QT interval consists of the QRS complex, the ST segment, and T wave. Thus, the QT interval is primarily a measure of ventricular repolarization. Normal in males is < 440ms; females < 460ms (11.5 small boxes); > 350ms. Abnormalities in the QT interval, such as prolongation or shortening, can indicate an increased risk of arrhythmias or other cardiac conditions.

U wave — may be seen in some leads, especially the precordial leads V2 to V4. Data suggest it may be from late repolarization of the mid-myocardial M cells, due to a longer action potential duration compared with the endocardium or epicardium.

Other values that may be interpreted from an electrocardiogram include rate and axis:

Rate - If the cardiac rhythm is

regular, the interval between successive QRS complexes can be used to determine heart rate by division of 300 by the number of large boxes. If the rhythm is irregular, the rate is calculated by counting the number of complexes on the electrocardiogram and multiplying by six, since the standard electrocardiogram displays 10 sec of time. A rate of 60 to 100 bpm is considered normal. A rate less than 60 bpm is bradycardia while a rate over 100 bpm is tachycardia.

Axis - The electrical signal recorded on the electrocardiogram contains information relative to direction and magnitude of the various complexes. The average direction of any of the complexes can be determined:

- If the QRS complex is positive (upright) in both leads I and II, then the axis falls between -30 and 90°, and the axis is normal.

- If the QRS complex is positive in lead I but negative in lead II, then the axis is leftward (-30 to -90°).
- If the complexes are negative in lead I and positive in aVF, then the axis is rightward (90 to 180°).
- If the complexes are negative in both I and aVF, then the axis is extreme (180 to -90°).

The following electrocardiographic abnormalities which form the element of my study are indications for invasive cardiac procedures:

- Clinically significant arrhythmias including:
 - i. Significant bradyarrhythmia – permanent pacemakers
 - ii. Supraventricular tachyarrhythmias – catheter ablation
 - iii. Malignant ventricular tachyarrhythmias – Implantable Cardioverter Defibrillators
- Prolonged QRS duration – Cardiac Resynchronization therapy
- Pathological “Q” waves– angiography with catheterization and stenting

Electrocardiogram abnormalities are more prevalent in Heart Failure with reduced Ejection Fraction compared to the other phenotypes of heart failure and are associated with poorer outcomes. In the ATTRaCT study, the percentage of abnormal electrocardiogram was higher in Heart Failure with reduced Ejection Fraction than Heart Failure with Preserved Ejection Fraction (76% vs 57%; $P < .001$). The presence of electrocardiogram abnormalities is a marker of patients in a worse clinical condition and with a worse one-year prognosis(Tymińska et al., 2021).

The presence of electrocardiographic abnormalities was more commonly associated with a history of advanced heart valve disease, atrial fibrillation, chronic kidney disease, signs of heart failure decompensation (higher natriuretic peptides, pleural effusion, higher New York Heart Association class), use of diuretics and anticoagulants (Tymińska et al., 2021).

Several studies have been conducted comparing outcomes in Heart Failure with reduced Ejection Fraction with other phenotypes. One such study showed that mortality at one year was 8.8% for Heart Failure with reduced Ejection Fraction compared with 6.3% for Heart Failure with preserved Ejection Fraction (Chioncel et al., 2017). Another study showed that Heart Failure with reduced Ejection Fraction patients had a higher mortality and higher all cause readmission risk compared to other phenotypes (Cheng et al., 2014).

Furthermore, studies done in the European countries indicate a high prevalence of electrocardiographic abnormalities in Heart Failure with reduced Ejection Fraction compared to other phenotypes and poor outcomes associated with the presence of these electrocardiographic abnormalities. In African countries, the findings were more or less similar. However, there is a notable gap in the paucity of local data on electrocardiographic abnormality studies in the Heart Failure with reduced Ejection Fraction phenotype.

Several studies on Heart failure with reduced ejection Fraction show improved outcomes on optimization of guideline directed medical therapy and invasive cardiac procedures for those with the electrocardiogram indications, however, this phenotype still remains poorly characterized. This study, aims at finding the prevalence of electrocardiogram abnormalities and outlining the correlates with the aim of better

characterizing this phenotype thus improving the outcomes of Heart Failure with reduced Ejection Fraction patients.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study site and setting

This study was conducted in the outpatient cardiology clinic, medical wards and cardiac care unit at Moi Teaching and Referral Hospital Eldoret (MTRH) which is a level six facility and one of the four tertiary referral hospitals in Kenya. It serves patients from all over the country but majority of the patients come from Western, Nyanza and Rift valley regions. It plays a key role as a training institution for various health cadres including medicine, nursing, dentistry, pharmacy and public health.

The hospital has a bed capacity of 1000 and serves a catchment population of more than 20 million people. It is also home to the Chandaria Cancer and Chronic Diseases Centre where patients with chronic diseases such as cardiovascular diseases are attended to. The cardiac clinic is run twice a week by cardiologists. On average 500 heart failure patients attend the clinics in a month, half of them being heart failure with reduced ejection fraction patients. In a 5-month period, an average of 136 patients are admitted in the general medical wards for heart failure management with the cardiac care unit having approximately 148 heart failure patients (December 2020 – April 2021).

3.2 Study population

The study population was patients with heart failure with reduced ejection fraction attending cardiology clinic or admitted to the male and female medical wards and cardiac care unit at Moi Teaching and Referral Hospital.

3.3 Study design

This was an analytical cross-sectional study.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

- Adults 18 years and older. This selection was based on the fact that electrocardiograph variables are age dependent up to 18 years. Electrocardiograph in those who are below 18 years is amenable to false interpretation if not done in the context of the age.
- Those with echocardiographic reports with an ejection fraction $\leq 40\%$
- Those who gave consent

3.4.2 Exclusion criteria

- Those with echocardiographic reports older than 6 months. According to the European Society of Cardiologists Guidelines, patients start getting an improvement in their ejection fraction from month 6 of good compliance to guideline directed medical therapy. For this reason, using an echocardiogram report that is older than 6 months may have given a false classification of participants into Heart failure with reduced Ejection Fraction when their current Ejection Fraction may have improved to above 40%.
- Patients with primary valvular disease or prosthetic valves in situ. These patients' primary pathology is mechanical and once valve repair is done there is improvement seen in their ejection fraction thus may not be candidates for invasive cardiac procedures.
- Pregnant women. This is due to hemodynamic changes that occur in pregnancy such as increased blood volume and heart rate with subsequent increase in cardiac output. The heart may also enlarge slightly due to increased workload. These changes may give confounding results in this study.

3.5 Sample size

There was paucity of relevant data from Kenya on the prevalence of abnormal electrocardiographic findings in heart failure with reduced ejection fraction phenotype however, from a study done in the European countries by Tyminińska et al., 2021:

- Pathological “Q” waves contributed to 33%
- Prolonged “QRS” interval contributed 37.3%
- Arrhythmias 35%

Going by this data, the highest prevalence was used in the above three which was 37.3% for prolonged “QRS” rounded to 37% to estimate the sample size in objective one which encompassed the other two abnormalities.

Objective 1. we used the Cochranes formular

$$n = \frac{(Z\alpha/2)^2 \times P(1 - P)}{d^2}$$

Where:

n is the desired sample size

$Z\alpha/2$ is the standardized score corresponding to a two-sided 95% confidence interval and is equivalent to 1.96

P is the estimated proportion and corresponds to 0.37(37%)

d is the margin of error (precision) and corresponds to 0.05 (5%)

Substituting in the above equation gives:

$$n = \frac{(1.96^2 \times 0.37(1 - 0.37))}{0.05^2} = 358$$

Given that the heart failure with reduced ejection fraction population in MTRH is finite, the appropriate adjustment was made to determine the final sample size using the formula:

$$N = \frac{F \times n}{n + F - 1}$$

In one cardiology clinic day, an average of 25 Heart failure with reduced ejection fraction patients are attended to, giving a total of 200 when multiplied by 8 clinic days conducted in a month. In addition, monthly average of 33 heart failure with reduced ejection fraction patients are admitted to the general inpatient medical wards and 15 to the cardiac care unit. Adding the 200 patients seen monthly in the clinics to the 50 inpatients gives a summation of 250 patients in a month (month of January 2022). In a 3-month cycle after which the majority are then seen as revisits at the clinic, it translates to 750 (250 *3) giving a finite population over the period (< 10,000). The sample size adjustment was therefore made as follows:

$$N = \frac{F \times n}{n + F - 1}$$

Where:

N is the adjusted sample size

n is the originally calculated sample size corresponding to 358

F is the finite population corresponding to 750

Substituting in the above equation gives:

$$N = \frac{750 * 358}{358 + 750 - 1} = 243$$

The target sample size for the study was therefore 243 participants.

Objective 2

For objective two Peduzzi et al 1996 formula of $10K/P$ was used

Where 10 is a constant

Independent variables in this study were 6

And estimated prevalence was 0.37

$$N = 10 * 6 / 0.37 = 162.$$

Given that objective one had a bigger sample size of 243, this was the figure used for both objectives.

3.6 Sampling technique

Participants meeting eligibility criteria were recruited one after another consecutively based on their arrival to the clinic/ inpatient until the last patient for the day. This was done twice a week in the cardiology clinic where an average of 15 heart failure with reduced ejection fraction patients would be seen and daily in the wards for four months until a sample size of 243 cases was reached.

3.7 Study procedure

Screening

The principal investigator or trained research assistant screened the files of heart failure patients during cardiology clinic days and daily for admitted patients in medical wards and cardiac care unit. Echocardiographic recruitment criteria for Heart Failure with Reduced Ejection Fraction was based on real world experience and retrieved from patient files if the study was less than six months and done by clinical study echo technicians. Those files were labelled and set aside to avoid repeat screening. Those whose echocardiogram reports were more than six months old or reported a primary

valvular lesion/prosthetic valve were exempted from the study. The female participants in this study were already postmenopausal, however, those in their reproductive age group who reported of a period of amenorrhea were requested to have a urine test to screen for pregnancy before recruitment.

Recruitment and consenting

For patients meeting the eligibility criteria, the aim and procedure of the study and what was expected of them was explained and a written consent form issued for them to read and sign, if they desired to proceed with the study procedure without coercion or inducement. The consent forms were read and interpreted for those who were illiterate after which they appended their signatures. Questionnaires were then administered by the research assistant that captured socio demographic data, history of comorbidities and the medication the participants were on. On completion of the first participant's interview, the participant would be requested to wait on the queue until their turn to be attended to by the primary clinician reached. The next eligible participant in the clinic was identified in a consecutive pattern based on their arrival until all participants were identified, the in-patients' recruitment was done daily based on the number that were admitted on that day once the patients were stabilized and settled in their beds.

Study procedure

The ambulant participants who met the inclusion criteria were escorted by the principal investigator /research assistant who had undergone training on how to conduct the study procedure, to a private room. A brief history was taken after which the participant was requested to empty his/her bladder. The participant was then requested to remove extra clothing like jackets/shawls/caps and empty the pockets before stepping on an automated weighing machine for weight measurement, height was then measured and

body mass index calculated by dividing weight (in kilograms) with height (in meters squared).The principal investigator/ research assistant took blood pressure measurements using a digital Omron blood pressure machine with the patient seated upright on a comfortable seat with the legs not crossed and a second reading done with the patient lying supine on the examining coach, the value was then documented on a form. Those whose readings were above 140/90 and not previously known to be hypertensive were allowed to rest on the coach for an hour before a repeat measurement was done. The pulse was located on the radial artery of the forearm and counted manually up to one minute then recorded, temperature was taken with an armpit mercury thermometer and saturations recorded from a pulse oximeter. The patient's chest was then exposed and a focused physical exam done with the patient still in supine position with the head elevated at 45 degrees, taking note of obvious physical findings like thyroid swelling.

After the anthropometric measurements and physical exam were done an electrocardiogram was recorded by the principal investigator/ research assistant with the assistance of a certified electrocardiogram technician using the technique of Jevon P.2010 as follows:

- Procedure was explained to the patient and consent obtained
- Biodata was entered on a standard Philips ECG machine
- The 12 leads comprising the chest and limb leads were then connected as per the anatomical landmarks
- The machine was switched on to record the heart's electrical activities.

The electrocardiogram print outs were read and the findings interpreted to the participants by the principal researcher. Those found to have indications for invasive cardiac procedures (QRS > 120, pathological "Q" waves, clinically significant

arrythmias) were then counselled on their condition and a copy of the electrocardiogram print outs made to be interpreted later with the assistance of a certified cardiologist for the findings to be recorded on a form.

The patients' blood samples for estimating the urea, creatinine, electrolyte levels were obtained using aseptic venipuncture technique of the cubital vein as follows:

- The principal investigator/research assistant wore clean gloves
- Circumferential tourniquet was applied above the area of the cubital vein
- The area was then cleaned with a swab and a small needle connected to a 2cc syringe used to draw blood
- The tourniquet was slowly released as the needle was withdrawn from the vessel and pressure with a dry cotton wool applied on the area to achieve hemostasis.
- The samples were then emptied into a red top vacutainer and taken to the laboratory.

Each participant was then escorted to the consultation room to be seen by their primary clinician. The urea, creatinine and electrolyte levels took a few hours to be analyzed so the results were communicated to the participants on phone. Those participants whose values were deranged requiring urgent attention were requested to come back to the facility or a facility close to them soonest possible.

For the in patients all the procedures were done by the patients' bed side. Previously measured weight was retrieved from the records of the few who could not stand and height estimated with a tape measure with the patient lying supine.

3.8 Data management plan and variables

3.8.1 Data collection and cleaning

A pre-designed Data form was used in collecting socio demographic and clinical data which also captured laboratory results and electrocardiogram readings as follows:

- I. QRS intervals of more than 120ms
- II. pathological Q waves
- III. clinically significant arrhythmias.

Data collection tool was pre – tested in a pilot among 5 patients with heart failure with reduced ejection fraction who were subsequently excluded from the main study. The form was filled by the principal investigator or the research assistant and variables counter checked by both to ensure completeness and accuracy.

Quality Assurance and Data Entry

Echocardiograms in Moi Teaching and Referral Hospital were done by highly trained ISO-Certified echocardiogram technologists and reports read by a senior cardiology fellow who was in his final year of training and certified in performing and reading echos hence considered as of high quality. Electrocardiograms were done by the principal investigator with the assistance of certified technologists, the interpretation was done with the assistance of an experienced cardiologist thus ensuring good quality reports. All laboratory results that were used were done at the Moi Teaching and Referral Hospital ISO certified laboratory. Data was entered into redcap data base. Confidentiality was maintained by excluding identifiable information from the keyed set and errors in data entry was assessed using frequencies to identify outliers.

Data Storage and Back Up

Data was coded, cleaned and stored in a computer then backed up in a flash disk and google drive for recovery. Stored data was encrypted with the password only known to the principal investigator. The signed consent forms, filled questionnaires and other data collection forms were kept locked under the custody of principal investigator.

Independent variables

- Age in years
- Sex, male or female
- Hypertension
- Chronic kidney disease
- Diabetes
- Body mass index

Dependent variables

Abnormal electrocardiogram; composite of prolonged QRS, Pathological Q wave, clinically significant arrhythmias.

3.8.2 Data analysis plan

Objective 1:

In analyzing data, descriptive statistics was used; means and standard deviations for continuous outcomes if they met normal distribution: median and interquartile range if they did not meet normal distribution, while categorical data was described using counts and percentage.

Prevalence of electrocardiographic indications for cardiac intervention was calculated as frequency of QRS prolongation, pathological “Q” waves, clinically significant

arrhythmias divided by the total heart failure with reduced ejection fraction cases and multiplied by 100 to give proportion in percentage.

Objective 2

Analysis of correlates, bivariate associations was tested using Chi square for categorical variables, t- test for continuous variables and multivariate associations - logistic regression analysis. Statistical significance was assessed using 5% level of significance and 95% confidence intervals.

R statistical software was used for all analysis.

3.9 Ethical considerations

Ethical clearance was sought and obtained from Moi University/Moi Teaching and Referral Hospital, Institutional Research Ethics Committee IREC number 505/2023, Moi Teaching and Referral Hospital management and National Commission for Science Technology and Innovation NACOSTI number - 177696 before the conduction of research. Informed written consent was filled by the participants before recruitment into the study and there was no monetary inducement to the participants nor coercion. Confidentiality was ensured by using codes to identify patients and study files instead of their names and those who declined to consent were not victimized but continued getting usual standard care.

This study involved no invasive procedures or administration of drugs to the participants. It did not introduce anything new as the patient underwent the usual procedures used routinely in their care thus posed minimal risk if at all. The risks that may were anticipated were psychological and prolonged time spent in the clinic.

Participants were allowed to pull out of the study at their discretion. Results generated from this study will guide on patient care.

CHAPTER FOUR

RESULTS

4.0 Introduction

This section contains the recruitment schema of the study giving details of how participants were included or excluded from the study. It also captures the baseline characteristics organized into socio demographic, clinical as well as the main categories of guideline directed medical therapy the patients received. The section also contains the study findings starting with objective one on prevalence of electrocardiographic indications for invasive cardiac procedures and second objective on the correlates of these electrocardiographic indications for invasive cardiac procedures.

4.1 Recruitment schema

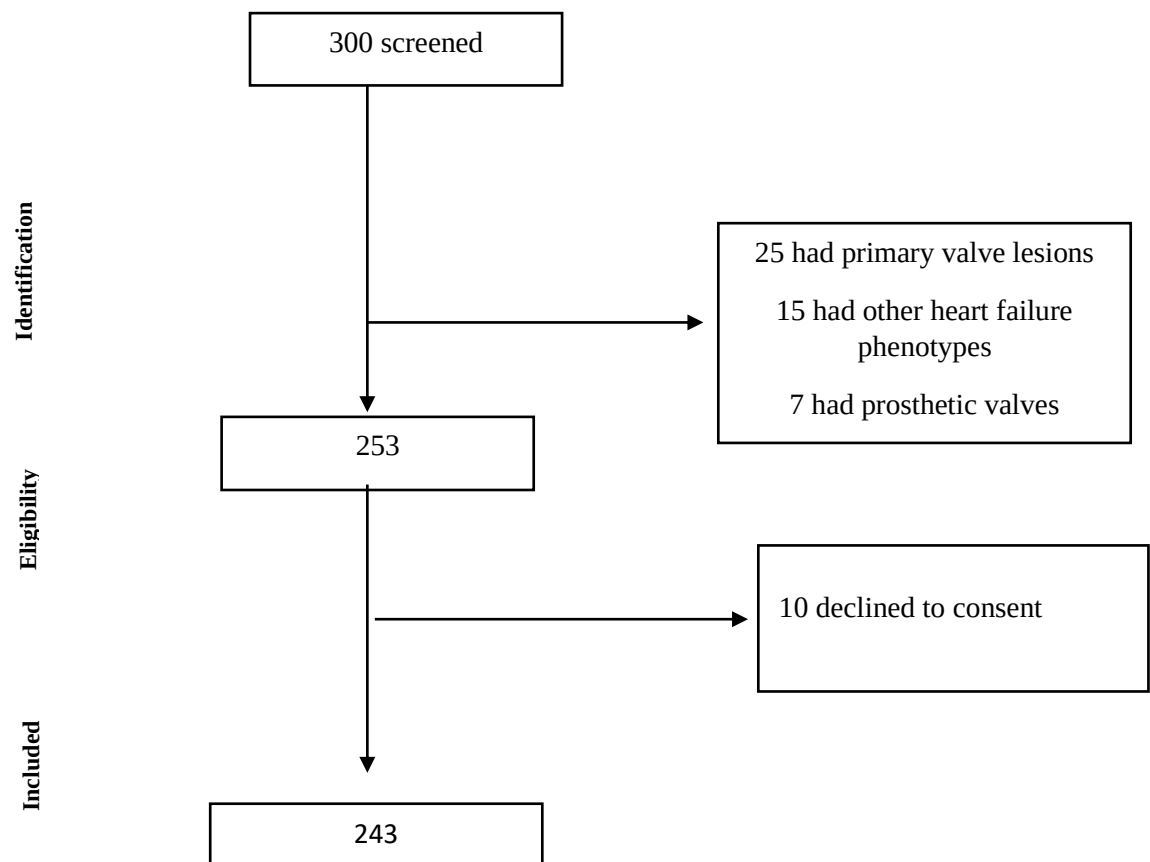


Figure 3: Recruitment Schema of the Study

4.2 Baseline characteristics

Out of a total of 243 participants, 164 (67.5%) were from cardiology clinic, 69 (28.4%) from internal medicine wards and 10 (4.1%) participants from cardiac care unit. Majority of the participants had moderately reduced ejection fraction 165 (67.9%) while 78 (32.1%) had severely reduced ejection fraction of less than 30%.

In the baseline characteristics table below, the mean age of the participants with heart failure with reduced ejection fraction was 60 SD years with the majority being females 137 (56.4%). Most of the participants had a normal BMI 112 (46.1%) with more than a third being overweight 91 (37.4%). Hypertension was the commonest comorbidity seen in 132 (54.3%) participants followed by chronic renal disease (16.9%) and diabetes (16.9%). More than half of the participants had deranged renal function test with those with elevated urea being the majority 164 (67.5%) and creatinine accounting for 132 (54.3%). Table 1 below gives a summary of the baseline characteristics.

Table 1: Baseline characteristics table (N-243)

CHARACTERISTICS	
AGE	
Mean/SD	60 (19)
SEX	
Female	137 (56.4%)
BODY MASS INDEX	
Underweight	9 (3.7%)
Normal	112 (46.1%)
Overweight	91 (37.4%)
Obese	31 (12.8%)
CORMOBIDITIES	
Hypertension	132 (54.3%)
Diabetes mellitus	41 (16.9%)
Chronic Renal Dysfunction	41 (16.9%)
Coronary artery disease	19 (7.8%)
Thyroid disease	12 (4.9%)
MEDICATION	
Mineralocorticoid receptor antagonists	153 (63%)
ACEIs ¹ /ARBs ² /ARNIs ³	150 (61.7%)
Beta blockers	134 (55.1%)
Sodium Glucose cotransporter-2 inhibitors	117 (48.1%)
ABNORMAL LABORATORY FINDINGS	
Urea	164 (67.5%)
Creatinine	132 (54.3%)
Sodium	103 (57.6%)
Potassium	57 (23.5%)
EJECTION FRACTION	
30 - 40%	165(67.9%)
< 30%	78(32.1%)

¹ ACEIs- Angiotensin Converting Enzyme Inhibitors² ARBs- Angiotensin Receptor Blockers³ ARNIs- Angiotensin Receptor Neprilysin Inhibitors

4.3 Prevalence of ECG indications for invasive cardiac procedures in HFrEF patients.

Majority of the participants 143 (58.8%) had abnormal ECG tracings. Prolonged QRS was the commonest 62 (25.5%) with the left bundle branch block morphology constituting the most subtype. The other indication for invasive cardiac procedures in this population were clinically significant arrhythmias 48 (19.8%) of which atrial fibrillation predominated and only 1 participant having a high degree atrio-ventricular block. The least prevalent indication was pathological Q waves 33 (13.6%).

Table 2: Prevalence of ECG indications for invasive cardiac procedures in HFrEF patients

VARIABLE	FREQUENCY
Prolonged QRS	62 (25.5%)
Left Bundle Branch Block	50 (80.64%)
Right Bundle Branch Block	11 (17.74%)
Nonspecific intraventricular conduction delay	1 (1.61%)
Clinically Significant Arrhythmias	48 (19.8%)
Atrial fibrillation	47 (97.9%)
Ventricular tachycardia	0
3 rd degree heart block	1 (2.08%)
Pathological Q waves	33 (13.6%)

4.4 Correlates of ECG indications for invasive cardiac procedures and selected independent variables.

Table 3: Bivariate Analysis (Chi square for categorical variables, t-test for continuous variables)

Variable	Abnormal ECG		p value
	No (N=111)	Yes (N=132)	
Age (years)			< 0.001
Mean (SD)	54.860 (21.805)	64.000 (15.938)	
Sex			0.251
Female	67 (60.4%)	70 (53.0%)	
Male	44 (39.6%)	62 (47.0%)	
Body Mass Index			0.357
Underweight	4 (3.6%)	5 (3.8%)	
Normal	58 (52.3%)	54 (40.9%)	
Overweight	36 (32.4%)	55 (41.7%)	
Obese	13 (11.7%)	18 (13.6%)	
Hypertension			0.046
No	43 (38.7%)	68 (51.5%)	
Yes	68 (61.3%)	64 (48.5%)	
Diabetes			0.200
No	96 (86.5%)	106 (80.3%)	
Yes	15 (13.5%)	26 (19.7%)	
Renal Disease			0.435
No	90 (81.1%)	112 (84.8%)	
Yes	21 (18.9%)	20 (15.2%)	

Table 4: Multivariate logistic regression model

Characteristic	UOR	95% CI	P-value	AOR	95% CI	P-value
Age	1.03	1.01, 1.04	<0.001	1.03	1.01, 1.05	<0.001
Sex						
Female	1			1		
Male	1.35	0.81, 2.26	0.300	1.27	0.69, 2.34	0.400
BMI						
Normal	1			1		
Underweight	1.34	0.34, 5.67	0.700	1.79	0.39, 8.79	0.500
Overweight	1.64	0.94, 2.89	0.083	1.93	1.05, 3.59	0.035
obese	1.49	0.67, 3.38	0.3	1.85	0.75, 4.66	0.200
Hypertension						
No	1			1		
Yes	0.6	0.36, 0.99	0.047	0.44	0.25, 0.78	0.005
DM						
No	1			1		
Yes	1.57	0.79, 3.20	0.200	1.62	0.75, 3.57	0.200
Renal disease						
No	1			1		
Yes	0.77	0.39, 1.50	0.400	0.71	0.33, 1.53	0.400

Based on the multivariate logistic regression above, an increase in age and being overweight are associated with abnormal ECG with a p value of < 0.001 and 0.035 respectively. Those with hypertension were less likely to have ECG indications for invasive cardiac procedures evidenced by a p value of 0.005 with an adjusted odds ratio of 0.44.

CHAPTER FIVE

5.0 DISCUSSION, STUDY STRENGTHS AND STUDY LIMITATIONS

5.1 Discussion

Participants were mostly middle aged with a mean age of 59.8 years with a female predominance of 137(56.4%). Majority had a normal body mass index 112(46.1%) but more than a third were overweight 91(37.4%), the obese accounted for only 12.8% of the participants. Guideline directed medical therapy was fairly well prescribed in this study, those on mineralocorticoid receptor antagonist were 153(63%), angiotensin receptor blockers/angiotensin converting enzyme inhibitors/Angiotensin receptor neprilysin inhibitors 150(61.7%) and beta blockers 134(55.1%) prescription of Sodium glucose cotransporter – 2 inhibitors was unsatisfactory with only 117(48.1%) participants being on it.

A meta-analysis done in 9 Sub Saharan Africa countries showed that in heart failure patients, the most common comorbidity was hypertension at 45% while ischemic heart disease accounted for a lower percentage 8% (Agbor et al., 2018). Eldoret has a similar pattern to the rest of the sub-Saharan countries with hypertension being the commonest comorbidity at 54.3% and ischemic heart disease accounting for 7.8% of the comorbidities. In European countries, heart failure with reduced ejection fraction mostly affects the elderly population as evidenced by a study done by Tyminińska et al., 2021 which showed a preponderance of the elderly participants. This age difference in heart failure with reduced ejection fraction patients between African and European countries could be due to the judicious utilization of the invasive cardiac procedures which are readily accessible by Europeans for early diagnostics and interventions with device therapy that have been shown to reduce mortality hence increasing longevity of the patients. In addition, North American ADHERE study (Adams et al., 2005) and

European EHFS II study (Nieminen et al., 2006) showed that ischemic heart disease was the commonest comorbidity of heart failure in 57% and 54% respectively.

This study demonstrated that the commonest abnormality was prolonged QRS complex 62(25.5%) with the most common variant being left bundle branch block 50(80.64%). Prolonged QRS complex implies intraventricular conduction delay which may be due to myocardial fibrosis, cardiomyopathies, amyloidosis or hypertrophy. Our cohort may have had myocardial fibrosis from myocyte repair after different forms of injuries from the insulting agents such as ischemic injuries/drugs/alcohol, some also had ventricular hypertrophy from pressure overload largely due to hypertension among others. An increase in QRS duration has been found to be proportionately related with a reduction of left ventricular ejection fraction (Murkofsky et al., 1998) and is independently associated with increased mortality (Lund et al., 2013).

Patients with this abnormality have been reported to benefit from device therapy in the MADIT CRT trial, primarily driven by a reduction in heart failure events (Moss et al., 2009) therefore majority of this study's participants were potential candidates for such therapy. European cardiac society guidelines on heart failure give a class 1 indication for those with a QRS > 150ms with left ventricular ejection fraction of < 35% with left bundle branch block morphology. Cardiac resynchronization therapy has not been accessible for most of the patients in Moi Teaching and Referral Hospital due to previously unavailable catheter/electrophysiology laboratory prompting them to go to expensive private facilities which the majority could not afford. This could explain this study's findings where we see younger heart failure with reduced ejection fraction patients with a mean age of 60 years compared to the age profile of other European countries where the majority of the patients were first diagnosed at the age of 65 years (Bellanca et al., 2023) and those with Cardiac Resynchronization Therapy device

insertion showed to have a mean survival of up to ten years from the time of insertion (Leitz et al., 2021) thus showing its benefit in increasing the life expectancy of this cohort of patients. With the opening of a cardiac catheter/electrophysiology laboratory in tertiary government facilities including Moi Teaching and Referral Hospital and the procedure being covered by insurance, the prognosis and heart failure outcomes are likely to improve as most patients will be able to afford.

The prevalence of prolonged QRS complex also appears to be related to race which could be as a result of higher prevalence of ischemic heart disease in the white population. In a retrospective study in South Africa, participants with QRS prolongation were 27(25.2%) and those with left bundle branch block were noted to be the majority (Rath.M 2022) whereas European registry records showed a prevalence of 37.3% (Tymińska et al., 2021). Further, CARDIA study in the United States concluded that being white was associated with prolonged QRS when compared to the black population (Ilkhanoff et al., 2012).

This study demonstrated that atrial fibrillation is the commonest in the clinically significant arrhythmias. Atrial fibrillation and heart failure are the two significant epidemics in cardiovascular medicine leading to increased morbidity and mortality (Schnabel et al., 2015). Atrial fibrillation can contribute to heart failure by loss of atrial transport, increase in heart rate with shortening of diastolic filling time and irregular ventricular response all which cause a reduction in cardiac output (Clark et al., 1997). Conversely, heart failure also contributes to atrial fibrillation by increasing atrial filling pressure with atrial dilatation leading to atrial scarring and fibrosis, all which promote ionic remodeling. Atrial tissue stretching in heart failure also promotes atrial fibrillation by inducing triggered activity (Li et al., 1999). For this reason, when atrial fibrillation

is detected in a heart failure patient, one can or cannot discern which one came first due to this vicious cycle.

Atrial fibrillation is a common cardiac co-morbidity in heart failure with reduced ejection fraction patients and remarkably increases the risk of systemic embolization and mortality (Santhanakrishnan et al., 2016). In the latest American Heart Association/European Society of Cardiologists guidelines (2022/2023) cardioversion of patients in atrial fibrillation back to sinus rhythm has received a strong recommendation as it has been shown to impact positively in terms of symptoms and mortality. There is therefore a window of opportunity for these participants to undergo catheter ablation which is an intervention that cardioverts the atrial fibrillation and reverts them back to sinus rhythm. Additionally, patients with concomitant atrial fibrillation and prolonged QRS tend to benefit more from Cardiac Resynchronization Therapy if they are in sinus rhythm (McDonagh et al., 2022), meaning that there is an added advantage for patients in atrial fibrillation with prolonged QRS complex to undergo both catheter ablation of the rhythm disturbance followed by Cardiac Resynchronization Therapy device implantation for optimum benefit.

In concordance with this study, a cross-sectional study conducted in a tertiary facility in Nigeria to differentiate electrocardiogram abnormalities in heart failure with preserved ejection fraction versus heart failure with reduced ejection fraction showed that the commonest arrhythmia in heart failure with reduced ejection fraction was atrial fibrillation accounting for 15 out of 79 heart failure with reduced ejection fraction patients thus a prevalence of 18.9% (Karaye & Sani, 2008). In Europe, several registry analysis studies have been done on the prevalence of atrial fibrillation in heart failure with reduced ejection fraction as opposed to cross sectional studies. One of these studies analyzed data from an observational prospective heart failure long-term registry of the

European Society of Cardiology that showed the prevalence of atrial fibrillation in 7930 heart failure with reduced ejection fraction patients to be 27% (Zafir et al., 2018).

The variation in prevalence between the two populations that is, the African versus European populations, can be attributable to the difference in their race. Many studies have reported a lower prevalence of atrial fibrillation in black versus white individuals despite higher risk factor burden in the blacks considering it a paradox, genetics may play a role in atrial fibrillation prevalence according to race (Norby et al., 2021). The prevalence of ventricular arrhythmias in heart failure patients is difficult to assess given their spontaneous nature and association with sudden cardiac death; however, ventricular arrhythmias have been noted to be particularly prevalent in patients with reduced ventricular ejection fraction and underlying cardiac ischemia (Gupta & Figueredo, 2014).

The presence of pathological Q wave indicates a possible prior transmural Myocardial Infarction with 85% specificity; however, the sensitivity is low at 66% (Nadour et al., 2014). Myocardial infarction is one of the most powerful predictors of coronary arterial disease (Kimeu et al., 2023). Heart failure from prior myocardial infarction is a consequence of cardiomyocyte death and scar formation occurring alongside ventricular remodeling. The prevalence of pathological “Q” wave in this study was 33(13.6%).

A large cohort study involving patients with heart failure with reduced ejection fraction found the presence of these contiguous pathological Q waves to be associated with a 1.4-fold increased risk of sudden cardiac death (Yoga Sundaram et al., 2023). This sudden cardiac death could explain its low prevalence as some of the patients die before its clinically detected.

According to World Health Organization, introduction of coronary angiography in tertiary facilities will avert morbidity and mortality from ischemic heart disease by improving diagnosis and allowing stenting procedures in those patients who meet the criteria. European Study of Cardiologists guidelines 2022 also recommend use of diagnostic angiography in patients with ischemic heart disease which when followed up with revascularization either through stenting or coronary arterial bypass grafting has been shown to not only improve myocardial perfusion but also improve the left ventricular ejection fraction thus improving the symptoms and mortality. For this reason, the participants with pathological Q waves on electrocardiogram are potential beneficiaries of these interventions to improve their survival.

Similar to this study, a cross sectional study done in cardiology unit in three tertiary hospitals in Cameroon comparing electrocardiographic abnormalities between heart failure with reduced ejection fraction and heart failure with preserved ejection fraction showed that amongst heart failure with reduced ejection Fraction patients, the prevalence of pathological Q waves was 11.6% (Boombhi et al., 2020), on the contrary, a European study by Tymińska et al., 2021 showed the prevalence to be higher at 33%, the difference in these findings is in keeping with the high prevalence of coronary artery disease with ischemic cardiomyopathy being the leading cause of heart failure with reduced ejection fraction in western countries as opposed to African countries.

This study's findings demonstrated that among our study cohort, older age is associated with abnormal electrocardiogram, these findings were consistent with several other studies indicating the association of age with major electrocardiographic abnormalities. One such study was a cross-sectional study of differences in electrocardiogram abnormalities among three cohorts and longitudinal changes observed over fifteen years which showed that electrocardiographic abnormalities were frequent in the elderly and

associated with increased mortality (Molander et al., 2003). Similarly, a cross-sectional study done in China to assess the factors associated with electrocardiogram abnormalities showed that independent of other factors, older age significantly increased the odds of having an abnormal electrocardiogram (Yu et al., 2020). This finding was also replicated in a study done in Iran which showed that the odds of having major electrocardiographic changes significantly increased with aging (Ahmadi et al., 2023). These findings go to prove the fact that there are physiological changes that occur in aging such as fibrosis of the conduction system, a decline in pacemaker cells and reduced responsiveness to beta adrenergic receptor stimulation which lead to increased electrocardiographic abnormalities in the elderly (Cheitlin, 2003).

Being overweight is associated with having electrocardiographic abnormalities. Being overweight has been known for years to carry a high cardiovascular risk in several studies, one such study by Kenchaiah et al demonstrated that there was an increase in the risk of heart failure of 5% for men and 7% for women for each increment of 1 in body mass index (Kenchaiah et al., 2002.) In addition, being overweight/obese has been demonstrated to carry an independent risk for abnormal electrocardiogram in the absence of heart failure. The association of overweight with various electrocardiographic abnormalities is mediated by a complex array of structural and electrical remodeling. High metabolic requirements of body fat along with local and systemic inflammatory factors act to increase the stroke volume and cardiac wall stress, which result in compensatory remodeling of the cardiac chambers and consequently, electrical conduction (Ahmad et al., 2019). In this study, the number of participants with obesity were few accounting for 31% of the total participants hence not well powered to show any statistically significant associations, this could be attributable to

the fact that heart failure is known to cause wasting thus few obese patients in heart failure.

Participants with hypertension were less likely to have electrocardiographic indications for invasive cardiac procedures. A cross-sectional study done in Hong Kong China showed that the duration of hypertension correlated with the risk of Left Ventricular Hypertrophy on electrocardiogram but no other significant associations were found between electrocardiographic abnormalities and blood pressure levels (Tin et al., 2022). In addition, Siri Sjöberg et al 2015 showed no correlation between QRS duration and left ventricular mass therefore concluded that QRS prolongation was not just a product of anatomical remodeling but electrical remodeling component has to be present. Moreover, left ventricular hypertrophy in hypertension was associated with increased risk of myocardial ischemia but the left ventricular hypertrophy may mask pathological Q waves (Bauml & Underwood, 2010).

Contrary to these findings, a study concluded that atrial fibrillation and ventricular arrhythmias were more commonly observed in hypertensive patients (Lip et al., 2017). This was attributed to hemodynamic changes, neuroendocrine factors, atrial and ventricular structural remodeling and the proarrhythmic electrophysiologic phenotype of a hypertrophied left ventricle, and prolonged QTc interval. The difference between these study findings may have been due to the varying definitions of “abnormal electrocardiogram”. In our study an abnormal electrocardiogram includes indications for invasive cardiac procedures which is a composite of prolonged QRS, pathological “Q” wave and clinically significant arrhythmias. However, more studies need to be done in the hypertensive population to evaluate the associations of left ventricular hypertrophy with electrocardiographic indications for invasive cardiac procedures.

5.2 Study Strengths

This study was a cross-sectional design, thus the challenge of non-responders, loss to follow up and missing data was not encountered. In addition, the electrocardiograms were done real time and current echocardiograms were used so reflected the status at the time of recruitment.

5.3 Study Limitations

This study had its limitations, first, the prevalence of atrial fibrillation could have been under estimated as patients were not on a 24-hour Holter monitor to detect the paroxysmal arrhythmias. In addition, no participant was noted to have ventricular arrhythmias which may have been as a result of the study set up that was in the cardiac clinic and inpatient wards as opposed to an emergency room where such patients present.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Over half of the study participants exhibited at least one electrocardiographic indication for invasive cardiac procedures on the basis of prolonged QRS, pathological Q waves or clinically significant arrhythmias. Being elderly and overweight are significantly associated with indications for invasive cardiac procedures.

6.2 Recommendations

1. Elderly patients with heart failure with reduced ejection fraction should be closely monitored and those who are overweight be enrolled on intensive weight management strategies.
2. Further studies to explore the uptake of invasive cardiac procedures and examine the long-term benefits in view of the quality of life and mortality.

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APPENDICES

Appendix 1: Consent Form

Study Title: PREVALENCE AND CORRELATES OF ELECTROCARDIOGRAPHIC INDICATIONS FOR INVASIVE CARDIAC PROCEDURES AMONG HEART FAILURE WITH REDUCED EJECTION FRACTION IN WESTERN KENYA.

Name of Principal Investigator(s): DR. GATHIGIA CHARITY ANNE

Name of Sponsor/Funding Agency: Self-funded

Informed Consent Form for:

Adult patients on management for Heart failure with reduced ejection fraction admitted to inpatient ward and cardiac care unit and those on follow up at cardiology clinic.

This Informed Consent Form has two parts:

- Part I: Information Sheet [to share information about the study with you]
- Part II: Certificate of Consent [for signatures if you choose to participate]

PART I: INFORMATION SHEET

Introduction:

You are being requested to take part in a research study. This information is provided to give you details about the study. Please read this form carefully. You will be given a chance to ask questions.

Taking part in this research study is voluntary and declining to participate will not affect your rights to health care or any other services. Your treatment/payment or enrollment in any health plans or eligibility for benefits will not be affected if you decide not to take part. You are also free to withdraw from this study at any time. If after data collection you choose to quit, you can request that information provided by you be destroyed under supervision. This would be before data is de-identified and aggregated. You will be notified if new information becomes available about the risks or benefits of this research. You will receive a copy of this form after it is signed.

Purpose of the study: To determine the prevalence and correlates of electrocardiographic indications for invasive cardiac procedures among Heart failure patients with reduced ejection fraction in western Kenya.

Study site: The study will be conducted at MTRH, Cardiology Outpatient Clinic, inpatient and cardiac care unit.

Study population: The study will include adult patients on management for Heart Failure with Reduced Ejection Fraction.

Study procedures: The principal investigator will seek approval from IREC which will assess ethical aspects of the study. Permission to conduct the study will also be sought from Moi Teaching and Referral Hospital. Upon giving consent, the ambulant participants will be escorted by the principal investigator /research assistant to be triaged; blood pressure will be measured, pulse recorded, temperature taken and saturations recorded. Weight and height will also be measured and body mass index calculated by dividing weight in kilograms with height in meters squared.

Each participant will then be guided from the triage area by the primary investigator/research assistant to a private room one at a time and a focused physical exam carried out with evident comorbidities noted and filled in a questionnaire. An ECG will then be done on the participant using the standard technique:

- Patient biodata is entered on the ECG machine
- Patient then lies in supine position and the chest is exposed
- The 12 leads comprising the chest and limb leads are then connected and the machine switched on to record the cardiac activities.

Findings will be recorded and a copy of the ECG print out will be made to be interpreted later with the assistance of a cardiologist. A blood sample will then be drawn for analysis of creatinine, electrolytes and random blood sugars.

Those participants with documented HFrEF on ECHOs => 6 months will be sent to the ECHO room with an ECHO request form for it to be done by the ECHO technician.

As each participant waits for the laboratory results and ECHO reports to be ready, questionnaires that were issued to them will be filled to capture socio demographic data, history of comorbidities and current medication they are on. Those who are unable to read will be assisted in this process by the research assistant.

Each participant will be escorted to the consultation room to be seen by their primary caregiver as soon as the ECHO reports and Laboratory work ups are ready.

The results will be interpreted to the participants and those found to have indications for invasive cardiac procedures (QRS > 120, pathological “Q” waves, hemodynamically significant arrhythmias) will then be counselled on their condition for further evaluation and follow up by the cardiologist.

For the sick patients who are not ambulant and those admitted in the wards and CCU all the procedures will be done by the patients’ bed side and questionnaires filled with the assistance of the principal researcher/research assistant after stabilization of the patient.

If you agree you will do the following:

You will be required to answer some structured questions in form of questionnaires that will ask personal questions that you will be required to answer, should you wish not to answer some of the questions you can skip a particular section and you may or may not provide a reason. I will be asking you questions on demographics and assess your clinical and laboratory information. I will do this by checking your medical file. In addition, I might need to collect blood samples from a vein on your arm, which will be analyzed at the lab to find out your Creatinine levels and random blood sugar levels. A sterile 5cc capacity syringe and an 18gauge needle will be used to draw sample from a cleaned and sterilized anterior cubital vein on your body. A tourniquet will be used to facilitate the collection of blood samples, and this may be associated with some feeling of pain. You may also experience some pain when your skin is punctured and blood samples are drawn; which we do not expect to last for long. Approximately 4 cc of whole blood will be drawn. I will then request you to uncover your chest while ensuring utmost privacy in order to record your ECG findings, after which you may need a repeat echo if the one in the file is more than 6 months old.

Benefits: This is a research project and the findings will be used by the MTRH management, Government's policy makers and health providers to design appropriate policies and plans to provide better health services for patients with Heart Failure with Reduced Ejection Fraction.

Risks/Discomforts: some of the questions may be uncomfortable for you to answer, the sample collection may trigger pain that will last for a few minutes and you may be required to stay for longer compared with the other patients.

Payments and Reimbursements:

There is no payment or reimbursement for participating in the study

Confidentiality: All efforts will be made to keep your information private and confidential. Using or sharing of such information will follow National privacy guidelines. By signing the consent document for this study, you are giving permission for the use and disclosure of your study information. We may need to share your protected information with the community advisory board, MTRH//MU-IREC, NACOSTI or the healthcare team. We will retain your research records for at least six years after the study is completed. At that time, the research information is destroyed. If you decide to withdraw your permission for use of your personal data, contact the principal investigator in writing and let them know your decision. At that time, we will stop further collection of any information about you. However, the health information collected before this withdrawal may continue to be used for the purposes of reporting and research quality.

Compensation for injury: The procedures undertaken in this study are routine and no harm or injury is anticipated.

PART II: CONSENT OF PATICIPANT:

I have read or have had someone read to me the description of the research study. The investigator or his/her representative has explained the study to me and has answered all the questions I have at this time. I have been told of the potential risks, discomfort, and possible benefits (if any) of the study. I freely volunteer to take part in this study. [This section must be written in person. If the participant is illiterate, or for some reason is unable to write, they should provide a thumbprint and a competent witness must be engaged during the consent process]

Name of Participant Signature of participant/Thumbprint Date & Time

Name of Witness [Optional] Signature of Witness Date & Time

Name of the person obtaining consent Signature of person Date & Time

obtaining consent

Printed name of the investigator Signature of Investigator Date

Contacts for questions about the study

Questions about the study: Contact Information

[Dr. **Gathigia Charity Anne**, 0720 622422, charitygathigia@gmail.com]

Questions about your rights as a participant: You may contact the Institutional Ethics and Research Committee (MTRH//MU-IREC) 0787723677 or email irec@mtrh.go.ke or irecoffice@gmail.com. The MTRH//MU-IREC is a group of people that review studies for safety and to protect the rights of participants.

Appendix 2: Questionnaire

HFrEF Study

1. Date of enrollment: __ __ / __ __ __ / __ __ __ __ (example:
26/MARCH/2021)
d d m m m y y y y

Demographics

1. Date of Birth: __ __ / __ __ __ __
d d y y y y
2. Gender: ☐ Male ☐ Female

Physical Measurements & Current Vital Signs

Weight (in Kgs): __ __ Height (in cm): __ __
Systolic BP: __ __ mm/Hg Diastolic BP: __ __ mm/Hg
Saturation: __ __ % Respiratory Rate: __ breaths/min

Medical History & Clinical Information

1. Hospitalization in the last year: ☐ Yes ☐ No ☐
Unknown
2. History of coronary artery disease: ☐ Yes ☐ No ☐
Unknown
3. History of hypertension: ☐ Yes ☐ No ☐
Unknown
4. History of diabetes mellitus: ☐ Yes ☐ No ☐
Unknown
5. History of or current use of an implantable cardiac electronic device:
☐ Yes ☐
No ☐ Unknown
- a. If Yes, check as appropriate: ☐ Pacemaker ☐ ICD ☐ CRT-D
6. Currently, does participant have any of the following:
- a. ESRD patient on dialysis: ☐ Yes ☐ No ☐
Unknown
- b. CKD patient not on dialysis: ☐ Yes ☐ No ☐
Unknown

Laboratory evaluations (Insert the most recent results)**UECs:**

Cr (mmol/L)	Urea (mmol/L)	K ⁺ (mmol/L)	Na ⁺ (mmol/L)
_____	_____	_____	_____

Medication Prescription Data

Drug (s) prescribed at current clinic visit (<i>Check current prescription</i>)	Drug (s) prescribed at last prior clinic visit (<i>Check last prior clinic notes</i>)	Maximum doses of drug (s) prescribed over last 12 months (<i>Check clinic notes over last 12 months</i>)
ACE-Is / ARNIs / ARBs ☐ Enalapril: ____ mg ☐ OD ☐ BD ☐ Lisinopril: ____ mg ☐ OD ☐ Sacubitril-Valsartan: ____/____ mg ☐ BD ☐ Candesartan: ____ mg ☐ OD ☐ Losartan: ____ mg ☐ OD ☐ BD ☐ Valsartan: ____ mg ☐ OD ☐ BD ☐ Other ACEI/ARB/ARNI (indicate dose & frequency): _____	ACE-Is / ARNIs / ARBs ☐ Enalapril: ____ mg ☐ OD ☐ BD ☐ Lisinopril: ____ mg ☐ OD ☐ Sacubitril-Valsartan: ____/____ mg ☐ BD ☐ Candesartan: ____ mg ☐ OD ☐ Losartan: ____ mg ☐ OD ☐ BD ☐ Valsartan: ____ mg ☐ OD ☐ BD ☐ Other ACEI/ARB/ARNI (indicate dose & frequency): _____	ACE-Is / ARNIs / ARBs ☐ Enalapril: ____ mg ☐ OD ☐ BD ☐ Lisinopril: ____ mg ☐ OD ☐ Sacubitril-Valsartan: ____/____ mg ☐ BD ☐ Candesartan: ____ mg ☐ OD ☐ Losartan: ____ mg ☐ OD ☐ BD ☐ Valsartan: ____ mg ☐ OD ☐ BD ☐ Other ACEI/ARB/ARNI (indicate dose & frequency): _____
Beta-Blockers ☐ Metoprolol XL: ____ mg ☐ OD	Beta-Blockers ☐ Metoprolol XL: ____ mg ☐ OD	Beta-Blockers ☐ Metoprolol XL: ____ mg ☐ OD

☐ Carvedilol: ____ mg ☐ OD ☐ BD ☐ Bisoprolol: ____ mg ☐ OD ☐ Other Beta-Blocker (indicate dose & frequency): _____	☐ Carvedilol: ____ mg ☐ OD ☐ BD ☐ Bisoprolol: ____ mg ☐ OD ☐ Other Beta-Blocker (indicate dose & frequency):_____ _____	☐ Carvedilol: ____ mg ☐ OD ☐ BD ☐ Bisoprolol: ____ mg ☐ OD ☐ Other Beta-Blocker (indicate dose & frequency): _____
MRAs ☐ Spironolactone: ____ mg ☐ OD ☐ Eplerenone: ____ mg ☐ OD Other MRA (indicate dose & frequency): _____	MRAs ☐ Spironolactone: ____ mg ☐ OD ☐ Eplerenone: ____ mg ☐ OD Other MRA (indicate dose & frequency): _____	MRAs ☐ Spironolactone: ____ mg ☐ OD ☐ Eplerenone: ____ mg ☐ OD Other MRA (indicate dose & frequency): _____
SGLT-2 Inhibitors ☐ Empagliflozin: ____ mg ☐ OD ☐ Dapagliflozin: ____ mg ☐ OD Other SGLT-2 Inhibitor (indicate dose & frequency): _____	SGLT-2 Inhibitors ☐ Empagliflozin: ____ mg ☐ OD ☐ Dapagliflozin: ____ mg ☐ OD Other SGLT-2 Inhibitor (indicate dose & frequency): _____	SGLT-2 Inhibitors ☐ Empagliflozin: ____ mg ☐ OD ☐ Dapagliflozin: ____ mg ☐ OD Other SGLT-2 Inhibitor (indicate dose & frequency): _____

Appendix 3: IREC Approval



MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/1/2/3

MTRH/MU-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

Reference: IREC/505/2023
Approval Number: 0004458



MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3
29th June, 2023

Dr. Gathigia Charity Anne,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Gathigia,

PREVALENCE AND CORRELATES OF ELECTROCARDIOGRAPHIC INDICATIONS FOR CARDIAC CATHETERIZATION AMONG HEART FAILURE PATIENTS WITH REDUCED EJECTION FRACTION IN WESTERN KENYA

This is to inform you that **MTRH/MU-IREC** has reviewed and approved the above referenced research proposal. Your application approval number is **FAN: 0004458**. The approval period is **29th June, 2023- 28th June, 2024**. This approval is subject to compliance with the following requirements;

- i. Only approved documents including (informed consents, study instruments, Material Transfer Agreements (MTA) will be used.
- ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by **MTRH/MU-IREC**.
- iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to **MTRH/MU-IREC** within 72 hours of notification.
- iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to **MTRH/MU-IREC** within 72 hours.
- v. Clearance for export of biological specimens must be obtained from **MOH at the recommendation of NACOSTI** for each batch of shipment.
- vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
- vii. Submission of an executive summary report within 90 days upon completion of the study to **MTRH/ MU-IREC**.

Prior to commencing your study; you will be required to obtain a research license from the National Commission for Science, Technology and Innovation (NACOSTI) <https://oris.nacosti.go.ke> and other relevant clearances from study sites including a written approval from the CEO-MTRH which is mandatory for studies to be undertaken within the jurisdiction of Moi Teaching & Referral Hospital (MTRH) and its satellites sites.

Sincerely,

PROF. E. WERE
CHAIRMAN

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE



cc	CEO	-	MTRH	Dean	-	SOP
	Principal	-	CHS	Dean	-	SON

Dean	-	SOM
Dean	-	SOD

Appendix 4: Hospital Approval (MTRH)



MOI TEACHING AND REFERRAL HOSPITAL

Telephone: (+254)-0532033471/2/3/4
 Fax: 0532061749
 Email: ceo@mtrh.go.ke/ceosoffice@mtrh.go.ke

NANDI ROAD
 P.O. BOX 3-30100
 ELDOR ET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

17th July, 2023

Dr. Gathigia Charity Anne,
 Moi University,
 School of Medicine,
 P.O. Box 4606-30100,
 ELDOR ET-KENYA.

PREVALENCE AND CORRELATES OF ELECTROCARDIOGRAPHIC INDICATIONS FOR CARDIAC CATHETERIZATION AMONG HEART FAILURE PATIENTS WITH REDUCED EJECTION FRACTION IN WESTERN KENYA

You have been authorised to conduct research within the jurisdiction of Moi Teaching and Referral Hospital (MTRH) and its satellites sites. You are required to strictly adhere to the regulations stated below in order to safeguard the safety and well-being of staff, patients and study participants seen at MTRH.

- 1 The study shall be under Moi Teaching and Referral Hospital regulation.
- 2 A copy of MTRH/MU-IREC approval shall be a prerequisite to conducting the study.
- 3 Studies intending to export human bio-specimens must provide a permit from MOH at the recommendation of NACOSTI for each shipment.
- 4 No data collection will be allowed without an approved consent form(s) to participants unless waiver of written consent has been granted by MTRH/MU-IREC.
- 5 Take note that data collected must be treated with due confidentiality and anonymity.

The continued permission to conduct research shall only be sustained subject to fulfilling all the requirements stated above.

The approval period is 17th July, 2023 – 16th July, 2024.

Signature 17/07/2023
 DR. WILSON K. ARUASA, MBS, EBS
 CHIEF EXECUTIVE OFFICER

c.c. - Senior Director, Clinical Services
 - Director, Nursing Services
 - HOD, HRISM



*All correspondences should be addressed to the Chief Executive Officer
 Visit our Website: www.mtrh.go.ke*

TO BE A GLOBAL LEADER IN THE PROVISION OF EXCEPTIONAL MULTI-SPECIALTY HEALTH CARE, TRAINING AND RESEARCH

Appendix 5: Nacosti Approval

 REPUBLIC OF KENYA	 NATIONAL COMMISSION FOR SCIENCE, TECHNOLOGY & INNOVATION
Ref No: 177696	Date of Issue: 10/November/2023
RESEARCH LICENSE	
	
This is to Certify that Dr.. GATHIGIA CHARITY ANNE of Moi University, has been licensed to conduct research as per the provision of the Science, Technology and Innovation Act, 2013 (Rev.2014) in Uasin-Gishu on the topic: PREVALENCE AND CORRELATES OF ELECTROCARDIOGRAPHIC INDICATIONS FOR CARDIAC CATHETERIZATION AMONG HEART FAILURE PATIENTS WITH REDUCED EJECTION FRACTION IN WESTERN KENYA. for the period ending : 10/November/2024.	
License No: NACOSTI/P/23/31382	
177696 Applicant Identification Number	 Director General NATIONAL COMMISSION FOR SCIENCE, TECHNOLOGY & INNOVATION
Verification QR Code	
	
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