PRESCRIBING PATTERNS AND POTENTIAL DRUG INTERACTIONS AMONG PATIENTS WITH HEART FAILURE AT KENYATTA NATIONAL HOSPITAL

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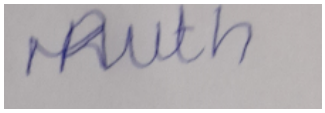
Signature: 

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SUPERVISORS APPROVAL

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DEDICATION

I dedicate this work to my two daughters Amariah Soipan and Adah Silantoi and my loving parents Charles and Elizabeth Marita for their unwavering support, encouragement and love.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS AND ACRONYMS

ACE-I	-	Angiotensin-Converting Enzyme Inhibitors
ADEs	-	Adverse Drug Events
AHA	-	American Heart Association
AMI	-	Acute Myocardial Infarction
ARBs	-	Angiotensin Receptor Blockers
ARNIs	-	Angiotensin-Receptor Neprilysin Inhibitors
BMI	-	Body Mass Index
CCBs	-	Calcium Channel Blockers
CHF	-	Chronic Heart Failure
CVD	-	Cardiovascular Disease
DCM	-	Dilated Cardiomyopathy
DIs	-	Drug Interactions
ESC	-	European Society of Cardiology
HF	-	Heart Failure
HTN	-	Hypertension
KNH	-	Kenyatta National Hospital
LMWHs	-	Low Molecular Weight Heparins
LV	-	Left Ventricle
LVEF	-	Left Ventricle Ejection Fraction
NCDs	-	Non-Communicable Diseases
NHIF	-	National Health Insurance Fund
NSAIDs	-	Nonsteroidal Anti-Inflammatory Drugs
NYHA	-	New York Heart Association
pDDIs	-	Potential Drug-Drug Interactions
QDRS	-	The Quick Dementia Rating Scale
US	-	United States
VT	-	Ventricular tachycardia

OPERATIONAL DEFINITION OF TERMS

Potential drug-drug interactions - are characteristically adverse drug events (ADEs) which can result from the effect of one medication being altered by another when both are administered concurrently.

Potential targets of minimization – these are safe and cost-effective practices for heart failure management which are meant to be achieved as an outcome of the study.

Prescribing patterns – these explain the extent and profile of drug use, trends, quality of drugs, and compliance with regional, state, or national guidelines like standard treatment guidelines, usage of drugs from essential medicine list and use of generic drugs.

Severity of HF – are the stages used to assess the level of heart failure disease progression. The New York Heart Association (NYHA) is the most utilized.

ABSTRACT

Background: Heart failure contributes significantly to the global disease burden. Patients with heart failure require multiple drugs, which predisposes them to potential drug-drug interactions. Therefore, improved prescription patterns and characterization of the potential drug-drug interactions are essential.

Objective: To characterize the prescribing patterns and potential drug-drug interactions (pDDIs) for patients with heart failure at Kenyatta National Hospital (KNH).

Methods: This was a cross-sectional study based at the KNH cardiac clinic. One hundred and twenty-four patients with heart failure were selected consecutively. Data collection started from 1st August 2021, which involved interviewing the patients and collecting data from their files during the clinic visit. The pDDIs were checked using the IBM Micromedex Drug interaction checker 2018 version. Data was analysed using STATA Version 13.0. Fischer's or Pearson's tests were done to identify an association between the independent variables such as the sociodemographic characteristics and pDDIs at $p \leq 0.05$. Predictor variables of pDDIs were determined using bivariate and multivariate logistic regression model.

Results: Most patients were female (n=68, 58.1%), married (n=97, 82.9%), Christians (n=115, 74.4%) and residing in the urban areas (n=65, 55.6%). The most widely prescribed drugs were beta-blockers (n = 81,76.9%), diuretics (n = 70, 71.8%), and mineralocorticoid receptor antagonists (n = 66, 56.4%). Each patient experienced an average of 2.05 pDDIs, with 156 (65.0%) being classified as major interactions. Possible outcomes of pDDIs included hyperkalaemia (n=57, 23.8%) and complete heart block (n=33, 13.8%). Having diabetes was associated with the development of a pDDI (p=0.040). Patients receiving an angiotensin converting enzyme inhibitors (p=0.012) or a beta-blocker (p=0.042) had a significant risk of developing a pDDI. The use of spironolactone was an independent predictor of the occurrence of a pDDI (AOR=26.0 (95% CI:5.2-135.4); p<0.001).

Conclusion: Patients with heart failure and comorbid diabetes and those receiving a beta-blocker or an angiotensin-converting enzyme blocker or a mineralocorticoid receptor are predisposed to pDDIs.

Recommendation: Regular monitoring of electrolytes and cardiovascular system functionality should be regularly done to patients with heart failure. A study investigating the clinical outcomes of various doses of spironolactone in heart failure could inform the optimal doses for patients and improve their management.

CHAPTER ONE: INTRODUCTION

1.1 Background of the Study

Heart failure (HF), sometimes referred to as congestive heart failure, is an ailment that occurs when the heart fails to pump blood at a rate analogous to the needs of the metabolizing tissues within the body or is able to supply blood to these tissues only under an elevated diastolic filling pressure (1). The classic symptoms of this condition include tachycardia, fatigue, shortness of breath and swollen legs, among others. Heart failure contributes significantly to the global disease burden; an estimated 40 million people worldwide were affected by heart failure in 2015 (2). The prevalence of heart failure is 2% among adults and the rates increase to 6 -10% among those aged 65 years and above in the US and Western Europe (3). In Africa, changes brought about by lifestyles and urbanization have resulted in a growing cardiovascular disease burden with HF showing high prevalence rates at 3-7%. The rates are projected to rise owing to the increase of lifespan and risk factors, such as obesity, insulin-related disorders such as diabetes mellitus, obesity, hypertension and pre-existing cardiovascular diseases (4). Heart failure has a mortality risk of 35% within the first year after diagnosis that degrades to 10% in the second year among those who survive (5).

Heart failure is, however, a manageable condition if it can be accurately diagnosed according to its severity and aetiology, and the appropriate interventions taken. The widely used New York Heart Association (NYHA) categorizes the condition into four classes depending on the severity. The categories include Class I, Class II, Class III and Class IV. The key objectives of treatment are improving the clinical outcomes, the functional capacity and the quality of life of the patients, prevention of subsequent hospital admissions or re-admissions, and minimizing mortality associated with the condition (6–8). However, avoiding hospitalization of HF patients and improving functional capacity are being increasingly prioritized to reduce overall morbidity. According to the European Society of Cardiology (ESC), there is enough evidence to suggest that HF could be delayed or prevented through interventions designed to modify HF risk factors or treat asymptomatic left ventricle (LV) systolic dysfunction (3).

In the US, results from several trials indicate that controlling hypertension has the effect of delaying the early onset of the condition, while some studies indicate that it could prolong (9–13). Different antihypertensive medications [diuretics, Angiotensin II Converting Enzyme Inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and beta-blockers] have yielded better clinical outcomes, especially in geriatric populations, both in individuals with and without a pre-existing history of myocardial infarction (9,10,12). In South Africa, Hitzeroth et al., (14) demonstrated that complete resolution of congestion coupled with effective diuresis is crucial in the improvement of functional capacity and symptoms, which eliminates the need for recurrent hospital re-admissions, increases the probability of putting the patients on recommended doses of disease-modifying medications, and ultimately enhancing clinical outcomes.

ACEIs and ARBs are used in many African countries with good results (15). Beta-blockers are not readily available in several African countries, despite their proven efficacy elsewhere, hence contributing to their low usage and increased mortality. For instance, a study in Egypt showed low rates of use of beta-blockers, and intravenous vasodilators, coupled with high usage of inotropes, was associated with a significant increase in mortality for HF patients (16). Similarly, in Nigeria, the use of β blocker was low. The most common cause for the diminished utilization of β blockers includes poverty (since a good number of the patients pay out of pocket), oedema, condition severity at presentation, and low BP on admission (17).

The current Kenyan guidelines (18) recommend the utilization of ARBs, β blockers, ACEIs, and aldosterone antagonists. These drugs have been shown in various clinical trials as having better outcomes on the morbidity and mortality of these patients (3). Recent studies have shown there is still a gap between clinical practice and guidelines in heart failure treatment (19). Additionally, drug compliance and physician's adherence to guidelines have been demonstrated to be independent predictors of better outcomes in heart failure (1).

While pharmacological interventions have largely showed positive results in the management of HF over the years in many trials as well as surveys of patients, their

efficacy is being threatened by the risk of potential drug-drug interactions (pDDIs), which could attenuate their effect or prove harmful to the patient. Studies show that there is indeed a high prevalence of pDDIs among HF and cardiovascular disease (CVD) patients. For example, in a study done in Switzerland involving 400 HF patients, 863 pDDIs were detected in 68% of the patients at hospital admission, which significantly increased to 1171 pDDIs in 88.8% of the patients at discharge (20). A recent study in Nepal among cardiac patients, however, recognized at least one interacting drug combination in a cohort of 32 patients and a pDDI incidence of 21.3%. Approximately 48 prospectively perilous drug interactions were also identified (21).

In Ethiopia, Diksis et al., (22) illustrated a high prevalence of pDDIs (74.41%) in a group of hospitalized patients suffering from cardiac diseases in medical wards attributable to the convolution of pharmacotherapy. The prevalence rate depends on a number of factors that include the number of prescribed drugs, age and length of hospital stay. A very recent study by Lati et al., (23) among diabetic hypertensive adult outpatients at the Kenyatta National Hospital (KNH) revealed a high prevalence of pDDIs at 57.7%. On average, the number of drug interactions was one interacting pair per patient, with a majority of the prescriptions (81.0%) having moderate drug-drug interactions. Patients receiving more than two drugs were almost three times more likely to have drug-drug interactions compared to those using less than two drugs.

Potential DDIs have varying levels of severity depending on the drug combinations, and this affects the treatment outcomes. The levels of severity of pDDIs range from use with caution, modify treatment/monitor, avoid combination/use alternative and contraindicated. For instance, the study by Straubbar et al., (20) found 'major' potential adverse effect in 25.7% of the HF patients, with hyperkalemia being the most ubiquitous inherent adverse effects of key ferocity and the combination of a potassium-sparing diuretic and an ACEIs recorded in 16.0% of the patients. The pDDIs can also have adverse drug effects that cannot be tolerated by the patients. A case in point is the simultaneous use of the NSAID and cortico-steroid that has been found to elevate the risk of gastrointestinal bleeding and perforation among patients with low molecular weight heparins (LMWHs) (24–27).

Farooqui et al., (28) study in Pakistan revealed that the regularly occurring combination of drug-drug interaction among CVD patients were diclofenac-methotrexate, losartan-diclofenac, gabapentin-acetaminophen, and omeprazole-losartan. In the combination of losartan and omeprazole, omeprazole inhibits hepatic drug-metabolizing enzymes leading to an increase in the serum levels of losartan. Surveys have also revealed that gabapentin induces the reduction of the blood levels of acetaminophen by inducing its breakdown, while diclofenac may lead to the elevation of the levels of methotrexate through reduction of its elimination in the kidneys (29). Noor et al., (30) found that adverse drug events were more frequent in patients taking higher doses of interacting drugs. Management of drug interactions in the elderly may pose difficult due to frailty, inter-individual variation, and disturbed homeostasis (31).

Lubinga and Uwiduhaye (32) found that pDDIs had adverse effects on patients' management in Mbarara Hospital in Uganda. The combinations of oral corticosteroids and NSAIDS led to increased bleeding in 30.6% of the patients, followed by loop diuretics and ACEIs, which increased the risk of hypotension among 22.7% of the CVD patients. Moreover, both groups had the highest number of patients hospitalized. Magot et al., (33) study at the KNH established that enalapril and furosemide was the most prevalent interacting drug combination, and it was associated with hyperkalemia among hypertensive patients. Similarly, Lati et al., (23) found that the most common potential clinical outcome of the drug-drug interaction was hyperkalemic lactic acidosis induced by combining enalapril with metformin and hypoglycemia on concomitant use of antidiabetics and a beta-blocker. Therefore, better prescribing practices among patients can reduce adverse drug reactions to a great extent.

1.2 Statement of the Problem

The burden of non-communicable diseases (NCDs) and particularly heart failure is on the rise in Kenya, where heart diseases cause 25% of hospital admissions and 13% of deaths (34). With increasing life expectancies and survival rates of other NCDs that commonly present among HF patients, the prevalence of HF is expected to increase in the country and, even more importantly, the rates of pDDIs, thus, necessitating better management approaches for these patients. Poor management will mean higher mortalities and lower

quality of life resulting from HF. As such, more attention should be paid to pharmacological modalities, particularly prescription patterns, given that a substantial number of diagnosed HF cases end up in hospitalizations. This goes against the aim of HF management and, moreover, could increase the level of pDDIs among the patients. There are no clear-cut prescriptions for clinicians and as a result, most patients end up with polypharmacy (35) to manage the HF state and other comorbidities. With polypharmacy, pDDIs are inevitable.

Literature available indicate that generally, there are several drug therapy problems (DTPs) among patients with CVD (23,36). Available literature also points to numerous pDDIs among patients with CVD such as HTN (23,33,36). However, there are few published studies focusing on HF locally. The present study will, therefore, focus on the nation's largest referral hospital – Kenyatta National Hospital (KNH) – that handles numerous HF cases in the country and seek to document the prescribing patterns and potential drug-drug interactions among patients diagnosed with heart failure. Reports show that re-hospitalizations rates arising from chronic heart failure at the hospital are at 38% within a 4 to 6-month period, while mortalities range between 25% and 38% within the same period (37). However, presently data is unavailable on the prescription patterns and pDDIs among these patients at KNH and their implications on the severity of the HF.

1.3 Research Questions

1. What are the patterns of drug use among heart failure patient at Kenyatta National Hospital?
2. What are the potential drug-drug interactions among individuals being managed for heart failure at Kenyatta National Hospital?
3. What are the potential targets of minimizing potential drug-drug interactions for heart failure patients at Kenyatta National Hospital?

1.4 Study Justification

Heart failure is increasingly adding to the global disease burden of non-communicable diseases in both developed and developing countries. Its impact is largely felt in terms of growing hospitalizations, deteriorating quality of life, high mortality, and economic

strain. Further, the impaired earnings owing to morbidity together with other non-hospitalization costs could be higher. Hence, there is a need to provide highly effective treatment to HF patients with reduced chances of re-hospitalizations and mortality. Sub-optimal use of recommended drugs (15) and potentially harmful drug-drug interactions arising from prescriptions in the hospital could significantly increase the duration of hospitalization and result in higher mortality, which could increase the severity of HF when not adequately addressed (20).

Therefore, establishing the prescription patterns and pDDIs among heart failure patients is important in knowing which regimens give the best outcomes or have few interactions and, therefore, can be used to improve the management of HF patients. Knowing the pDDIs is instrumental in developing strategies for mitigating them among medical practitioners. Finally, knowing the potential targets of minimization of potential drug interactions in HF at KNH could enable the researcher to identify the most suitable and cost-effective method of minimizing the pDDIs

1.5 General Objective

1.5.1 Main Objective

To characterize the drug use pattern and potential drug-drug interactions among patients diagnosed with heart failure at Kenyatta National Hospital.

1.5.2 Specific Objectives

The specific objectives of the study were to:

1. Document the pattern of drug use among patients with heart failure at Kenyatta National Hospital.
2. Analyse the potential drug-drug interactions among patients with heart failure at Kenyatta National Hospital.
3. Assess the potential targets of minimizing potential drug-drug interactions for heart failure patients at Kenyatta National Hospital.

1.6 Significance of the Study

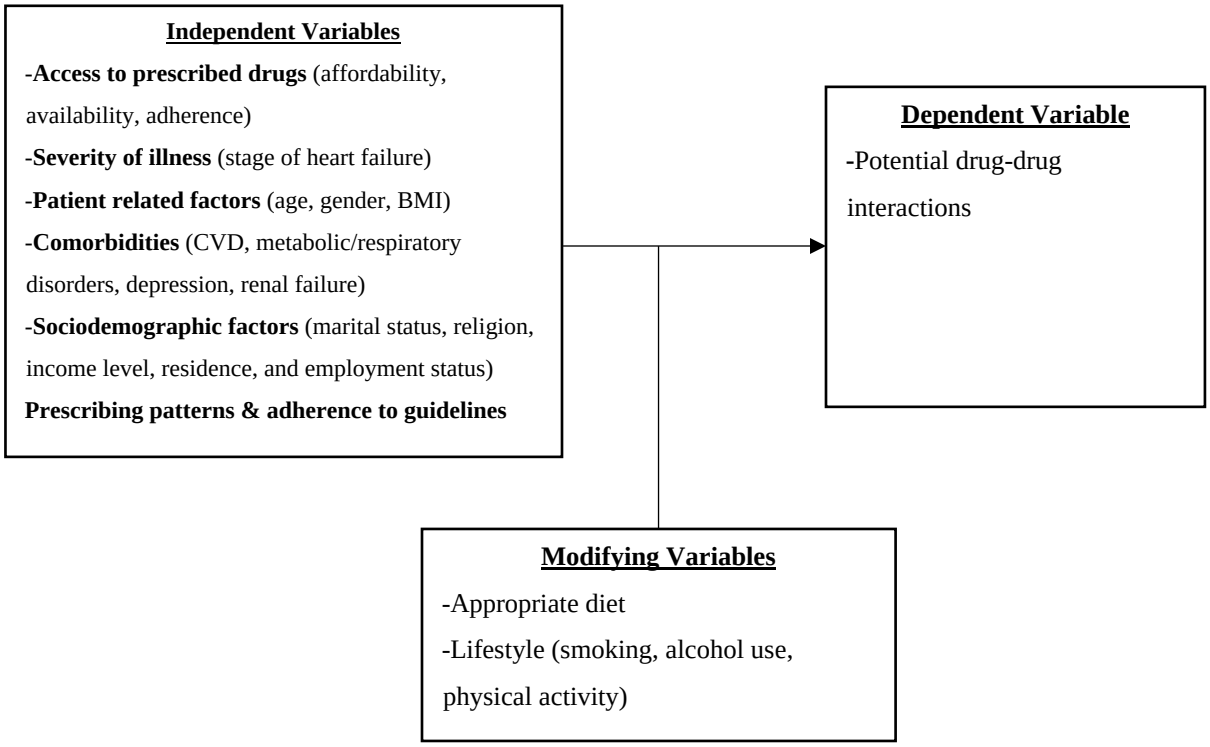
The outcome of this survey will inform the health providers, especially clinicians and pharmaceutical service providers in the facility, about the current prescribing trends and possible ways of improving them and aligning them with the recommended guidelines. The findings will be useful for a referral hospital setting to inform the clinicians and pharmacists whether prescriptions are in line with the Kenyan National Guidelines for Cardiovascular Disease Management, and whether there is need for corrective action to address any discrepancy.

The findings will also highlight the common drug-drug interactions and any missed opportunities to prevent harm to the patients. This will offer the healthcare practitioners an opportunity to reflect on the common pitfalls and improve their prescribing practices. Additionally, the quality assurance team could pick on the findings to address any systematic weaknesses such as the need for additional sensitization or training of the healthcare providers to seal the knowledge gap.

Finally, the study will seal a gap in the field of literature by providing information on the prescribing patterns and potential drug-drug interactions in Kenya. This information could be useful for scholars and researchers who are keen on non-communicable diseases to conduct further studies on a specific area of HF.

1.7 Conceptual Framework

Figure 1: Conceptual Framework



Independent Variables:

-*Access to prescribed drugs*: Having access to drugs by affording them, buying them with ease, and adhering to the prescribed regimen improves the patient's outcome, ameliorates the heart's function, improves overall survival time, and reduces the symptoms, providing a better quality of life. The resolution or worsening of the patient's symptoms will influence the clinician's prescription decision and probability of drug-drug interactions.

-*Severity of illness*: the severity of heart functions determines the pharmacotherapeutic approaches, which affects the number of drugs, the type of drugs, and potential drug-drug interactions.

-*Sociodemographic factors*: Marital status, residence, and religious factors determine whether a patient will be adherent to medication through the presence of a social support system. Income, education level, and employment status influence the health-seeking

behaviours of an individual, their understanding of the disease, and access to the regimen. These factors indirectly or directly affect a patient's adherence to medication and could translate to better control of the heart functions, which influences the decision of the prescriber.

-*Patient-related factors*: The age of the patient, weight (or body mass index), and gender has a role to play in the kind of drugs prescribed. Females are likely to be on contraceptives, which could potentially interact with prescribed drug unlike males. Elderly patients (above 65 years) are likely to receive a different regimen compared to younger patient. An overweight patient is also likely to receive more drugs to improve the lipid profile compared to a patient with a normal body mass index.

-*Comorbidities:* The presence of comorbidities could translate to a patient having more drugs prescribed to manage the illness. The comorbidities such as COPD could also worsen heart failure, hence affect the prescriber's choice of drugs. The presence of asthma could restrict the prescriber's choice of a beta-blocker, so such patients will essentially have a different prescription from other patients with no comorbidity.

-*Prescribing patterns and adherence to clinical guidelines*: The choice of drugs for a particular indication and the combinations used determine whether the patient experiences any potential drug-drug interactions. Most of the clinical guidelines factor in the aspects of combining particular drugs, and they may advice against use of certain combinations that are likely to be harmful. The level of adherence to the prescribed drugs is likely to influence the occurrence of a potential drug-drug interaction.

Modifying Variables

-*Appropriate diet*: Reducing salt intake, consuming more vegetables and fruits, and low-fat content (commonly known as a DASH diet) is likely to reduce blood pressure and assist one in reaching a targeted weight. This is likely to improve heart functions, reduce heart failure symptoms, and affect the prescribing decision.

-*Lifestyle*: Quitting smoking and moderating alcohol consumption could improve heart failure symptoms and reduce chances of developing other comorbidities. Participating in guided exercises boosts the immune system, improves myocardial strength, maintains joint flexibility, improves circulation, and reduced chances of developing other

comorbidities such as obesity and diabetes mellitus. An appropriate lifestyle will improve the symptoms of the patient and play a role in improving the heart failure symptoms or decreasing the chances of developing other comorbidities.

Dependent Variables:

-*Potential drug-drug interactions*: A prescription will be considered appropriate if it has no potential for drug-drug interactions, which will be confirmed using the Micromedex drug interaction checker. Potential drug-drug interactions will be classified into serious, moderate, and minor, and any appropriate monitoring parameters will be noted as well.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter takes note of the fact that heart failure, like other non-communicable diseases, is increasing owing to the changing lifestyle of the people. The disease burden caused by heart failure, even in developing countries, is a clear indication of that. Therefore, successful management of the disease which often requires or ends up in pharmacological interventions, is important. Consequently, establishing challenges arising in pharmacological modalities like pDDIs could be instrumental in improving the future outcomes of the treatments and the associated costs.

2.2 Severity of Heart Failure

Heart failure (HF) is a clinical state, which presents with typical symptoms (ankle oedema, fatigue and breathlessness) that may present concurrently with signs (pulmonary crackles, peripheral oedema and elevated pressure in the jugular veins) caused by a functional and/or structural abnormality of the heart. This abnormality results in reduced cardiac output and/ or increased intra-cardiac pressures during stress or at rest (38, 39). It is a serious global health concern, particularly in developing nations. The condition has significant mortality and morbidity rates and lowers the quality of life for the victims despite recent advances in medicine-based therapy. For instance, a longitudinal study reported diminishing survival rates of victims in the Netherlands, ranging from 86% in the initial diagnosis to 35% by the fifth year (40). In Tanzania, high mortality rates of up to 5.4% per month have been recorded (41) while in Kenya, mortality rates range between 25% and 38% (37, 42).

The patients need frequent hospitalizations depending on the severity of their condition, leading to increased costs both for the healthcare system and the individuals. The financial burden is high even despite NHIF and other private health insurance coverage. Costs of treating hospitalized cases of HF range from $1,026.07 in public hospitals up to $2,160.51 in a private healthcare facility (43). With an average annual income of $6,108.11 annually among the working class (44), the costs are already more than double the annual healthcare expenditure per household which stands at $412.80.

The NYHA functional classification offers the description of the symptom's severity and exercises intolerance. The NYHA classification is based on the patient's limitations experienced during physical activities and there are four classes in general. the symptoms and limitations are based on the varying degrees of angina pain, shortness of breath or normal breathing (45). According to the NYHA Classification – There are four Stages or Classes of Heart Failure: the first class (Class I) is characterized by; No symptoms or impediment in typical exercises or physical activities, e.g. dyspnoea when climbing stairs or walking among others. The second class (Class II) presents with mild symptoms that include mild angina or mild shortness of breath and imperceptible limitation during ordinary activities. The third class (Class III) presents with marked impediment in activity due to symptoms, even during normal activities such as walking short distances (20 to 100 meters). The patients are comfortable only at rest. The fourth class (Class IV) manifests with grievous limitations. The symptoms manifest even when at rest and these patients are bedbound most of the time. These classes are widely used to determine the severity of heart failure. However, there is a poor correlation between the severity of the symptoms and many measures of the LV function, although there exists a correlation between survival and symptom severity whereby patients presenting with mild symptoms may experience reduced risk of hospital admission and death (46,47). In some instances, the term advanced HF 'is utilized to refer to patients that have recurrent decompensation, severe symptoms and worsening cardiac dysfunction (48).

Identification and illustration of the fundamental cardiac cause is key to the diagnosis of the condition. The cardiac cause is primarily a myocardial abnormality that causes systolic and/or diastolic ventricular dysfunction (49). However, abnormalities affecting the heart conduction and rhythm, endocardium, pericardium and valves can lead to heart failure (and two or more abnormalities are often present). Recognition of the cardinal cardiac problem is vital for therapeutic reasons, as the specific pathology dictates the right management to be used (e.g., valve replacement or repair for valvular disease, the specific pharmacological treatment for HF presenting with decreased EF, and depletion of heart rate in tachycardiomyopathy among others). In contexts where the diagnosis is a challenge, the severity of the HF could be higher. Lesyuk et al. (50) explain that the

likelihood of other underlying diseases accompanying HF makes it challenging to accurately identify HF based on the diagnostic codes advanced by the International Classification of Diseases (ICD). For instance, it has been demonstrated by Lee et al. (51), defining HF only as the primary diagnosis results in a 46% decrease in diagnosed HF cases as opposed to when defining HF cases as primary and secondary diagnosis (utilizing similar ICD-codes). Additional analysis revealed that 75% of individuals with HF defined as a secondary diagnosis had an initial primary diagnosis that had a correlation with HF, such as angina pectoris or hypertension. There might be an under-specification of HF when defining HF as the primary diagnosis.

According to the American heart association (AHA) guidelines (52), a patient who has never shown the classic signs and/or symptoms of HF and with a decreased LVEF is detailed as having asymptomatic LV systolic dysfunction. Patients presenting with signs and symptoms of the condition and had a diagnosis of HF made a while back is often identified as having chronic HF. A managed patient with signs and symptoms that have remained unchanged generally for a period of at least one month is referred to as being stable. If a chronic stable HF patient worsens, the patient may be categorized as decompensated and the onset of this may be slow or sudden, often resulting in hospitalization, an event of substantial prognostic significance.

New-onset (de novo) HF may occur acutely due to key predisposing factors such as acute myocardial infarction (AMI), or in a circumspect fashion, like in cases of patients presenting with dilated cardiomyopathies (DCM), whose symptoms often persist for longer periods before a definitive diagnosis is arrived at. Although symptoms and signs of HF may resolve, the underlying cardiac dysfunction may persist despite the signs and symptoms resolving, making the patients carry a risk of experiencing recurrent decompensation.

Tzou et al., (53) carried out a study on Ventricular tachycardia (VT) ablation in severe cases of HF. The mortality, VT recurrence and Clinical variables analysis was conducted in accordance with the NYHA IV status utilizing the Cox proportional hazard and Kaplan–Meier analysis models. The study found out that there existed consequential

dissimilarities between NYHA IV and NYHA II and III patients, though NYHA IV patients were much fewer compared to NYHA II patients. NYHA IV presented with decreased left ventricular ejection fraction; a sizeable number had co-morbidities that included kidney disease and diabetes mellitus while others had VT storm and cardiac resynchronization implantable cardioverter–defibrillator despite using antiarrhythmic drugs ($P<0.01$). NYHA IV patients were less likely to undergo final programmed stimulation, were inducible for more and slower VTs, and needed additional hemodynamic support. There existed no marked difference in those presenting with acute complications. In deaths recorded within health facilities, the 1-year mortality and recurrent VT were slightly elevated in the NYHA IV group, under the circumstances of greater criterion comorbidities. Primarily, NYHA IV patients not having recurrent VT had indistinguishable survival compared with NYHA II and III patients with repetitive VT (68% vs 73%). Mortality in NYHA IV patients was linked significantly with early VT recurrence (≤30 days).

Darze et al, (54) study on incidence and clinical predictors of pulmonary embolism in severe HF patients hospitalized to a coronary care unit found that PE is remarkably elevated despite sufficient preventive treatment. Køber et al., (55) study on increased death rates after dronedarone therapy for patients with worsening HF revealed after a 2-month follow-up that 25 cases in the cohort (8.1%) and 12 cases in the placebo cohort (3.8%) passed away (hazard ratio in the dronedarone cohort). The mortality was predominately linked to the worsening of heart failure — 10 deaths in the dronedarone cohort and 2 deaths in the placebo cohort. In patients presenting with cases of left ventricular systolic dysfunction and severe HF, management with dronedarone was linked to an increased likelihood of early death due to the deterioration of the condition.

Mainar et al., (56) study on the economic impact of heart failure in Spain established that up to 36.1% of the patients had developed heart failure exacerbation while 11.7% of patients had ischemic heart disease. The study concluded that comorbidities associated with heart failure were high. In Kenya, recent studies have shown that rheumatic heart disease is prevalent in the country, accounting for up to 32% of heart failure cases in adult populations. Although CHF is still primarily non-ischemic, coronary disease of the

heart has become prominent in the past 15 years. A study by Ogeng'o et al., (57) found that CHF constituted 14.6% of heart failure. A recent study by Muregi (58) also found that congenital heart disease was the most prevalent (34%), followed by cardiomyopathies (15.1%) and rheumatic heart disease (13.1%). However, local studies did not refer to the established scales such as NYHA to establish the severity of heart failure.

2.3 Drugs used to Treat Heart Failure

The aims of management for patients presenting with HF are to reduce mortality, improve the quality of life, their functional capacity, clinical status and reduce hospital admissions. As a result, several drugs are being used in the management of the condition. Most of these medications operate by attenuating the maladaptive compensatory mechanisms activated in heart failure (59). There are several drug classes currently available for heart failure patients: Angiotensin II Receptor Blockers (ARBs), Angiotensin-Converting Enzyme Inhibitors (ACE-I),

Angiotensin-Receptor Neprilysin Inhibitors (ARNIs) which is a new drug combination of an ARB and neprilysin inhibitor, If channel blocker (or inhibitor), beta-blockers, aldosterone antagonists, isosorbide dinitrate and hydralazine (60). These are usually prescribed for first-line therapy. Diuretics are also used when fluid overload is a problem; loop diuretics are preferred, and in resistance cases, a thiazide diuretic is added (61). Other medications that are usually used in these patients include Anticoagulants, Cholesterol-lowering drugs and Digoxin, which is highly toxic, possesses a narrow therapeutic window, and multiple trials done have revealed that the mortality benefit of the drug has significantly decreased thus, reducing its role in the management of patients with HF (59).

Medicine accessibility is a vital factor in the determination of adherence, and it is imperative to ensure all patients who need the drugs have access to them. Drug availability more so in the developing world context, is still a key issue. The WHO set a goal of ensuring that medicines for cardiovascular conditions are available 80% of communities globally and that at least 50% of the individuals eligible to use these drugs

have access to them by 2025 (62). However, a recent study on drug accessibility of four mainstay cardiovascular drugs: beta-blockers, statin, aspirin and angiotensin-converting enzyme (ACE) inhibitor (63). The results showed that the four drugs were available in approximately 62 % of urban areas and 37 % of rural communities in lower-middle-income nations and in 25 % of urban and 3 % of rural communities in developing nations.

For example, in Cameroon, the availability of the drugs ranged from 25.3% (public health outlets) to 49.2% (community pharmacies) for every category of drugs (64). This represented a higher figure in semi-urban and urban outlets in comparison to the rural ones. A similar study drug availability in Uganda revealed approximately that 22.2 % of health premises overall had ACE inhibitors, differing from 75 % of hospitals to remarkably less in health centres (0–75 % based on the location) and private health facilities (36.5 %) ($p<0.001$) (65). A neoteric survey by Carlson et al., (66) revealed that of the health institutions studied, 49% of Kenyan and 77% of Ugandan ones indicated that they had stocks of heart failure medications. The study also revealed 51% of Kenyan reported having stocks of ACE inhibitors while 79% of Ugandan hospitals reported having stocks of the ACE inhibitors. Additionally, approximately a third of the health facilities in each nation reported having had experienced stock-outs of at least one of the categories of drugs in the previous quarter.

Cardiovascular drugs are available in only 3% of rural communities and 25% of the urban ones in low-income nations. 60% of individuals in these countries cannot afford these drugs (62). The four cardiovascular disease drugs, that is, beta-blockers, statin, aspirin and ACEIs are unaffordable potentially for 0.14 % of households in high-income nations (14 of 9,934 households) but inaccessible due to unaffordability in approximately 60 % of low-income nations studied. Dzudie et al. (64) in Cameroon further found that community pharmacies sold the drugs at the highest price compared to public facility outlets that sold the drugs at a relatively cheaper cost. Nifedipine, hydrochlorothiazide, furosemide and digoxin were affordable in these facilities as they cost a day’s wage or less. Drugs for dyslipidaemia and heart failure (beta-blockers, statins and ACEIs) required 2–5 days and 6–13 days wages respectively for a 30-day chronic treatment dose.

In contrast, a study in Kenya on chronic heart patients at the KNH revealed that 81.9% of the respondents had access to the prescribed medications and only 18.1% found it hard to obtain the medicines (35).

To optimize the benefits, it is vital for individuals with heart failure to take their medications precisely as instructed by their healthcare provider. The utilization of these drugs has positive outcomes that include saving lives, prolonging life and improving the function of the heart. Kimani et al., (35) study in Kenya revealed that medicine's adherence among individuals with Chronic Heart Failure was high at KNH despite the fact that the patients were having little mastery about the condition. The most common adverse effects recorded in this study were nausea and vomiting, tachycardia and rash while hyponatremia presented as the most common electrolyte disturbance disorder; on the other hand, valvular heart disease was the most prevalent comorbidity. In their study, Kimani et al. (35) also established that most of the patients (85.2%) adhered to medication as prescribed. Patients who reported adherence to healthy lifestyle behaviours in addition to improved medication adherence were more likely to experience lower blood pressure compared to the ones who did not observe healthy lifestyle behaviours but took medications.

According to Kimani et al., (35), poor medication adherence arises due to several factors that include inadequate communication between the patient and the healthcare practitioner, forgetfulness, adverse drug effects, occupation, emotional factors, poor accessibility to the prescribed drugs and cost of the drugs. These factors that affect adherence could lead to the failure of the healthcare practitioner to explain adequately the adverse effects and benefits of the drugs, complex regimens, as well as failure to review and consider the patient's occupation or the price of the medications and a penurious therapeutic correlation between the patient and practitioner. Failure to adhere to the therapeutic regimens prescribed may lead to undesirable outcomes and these may be made worse with numerous comorbidities that require different drug therapies in these patients (67).

2.4 Prescribing Patterns

Prescribing patterns elaborate the profile and extent of drug use, the quality of the medications, trends and compliance with state, national or regional guidelines like the use of generic drugs, usage of drugs from essential medicines list and standard treatment guidelines (68). The core prescribing indicators include the standard quantity of medications per encounter; prescribed injections per percentage encounter; percentage encounter prescribed antibiotics; percentage of drugs prescribed with the generic name; percentage of drugs prescribed that are available in the essential medicine's formulary or list. In practice, there are also incidences of unjustifiable prescribing which refers to prescription practices that fail to adhere to good treatment standards (69). This practice may be evident in five different ways that include over-prescribing, under prescribing, extravagant prescribing, incorrect prescribing, and numerous prescribing incidences of irrational patterns of prescribing that may lead to adverse treatment outcomes (59).

Prescription-wise, the European Society of Cardiology guidelines (3) for the management of chronic heart failure (CHF) related to left ventricular (LV) systolic dysfunction are regularly streamlined and validated by national societies (70)**.** These recommendations highlight the advantageous effects of beta-blockers, ARBs, aldosterone antagonists and ACEIs on morbidity and mortality based on large outcome trials (71–73). The first-line treatment for individuals presenting with heart failure that has diminished systolic function should include ARBs or ACEIs inhibitors if the individual develops a lasting cough as an undesired effect of the ACE-I (74).

Conventionally, most guidelines recommend ARBs and ACEIs. These drugs have demonstrated improved mortality and morbidity outcomes such as improved survival, reduced hospital admissions for exacerbations of heart failure, and enhanced life status in individuals with heart failure (75). Beta-blockers are among the mainstay treatment (first line), contributing additional benefits to the improvement in mortality and symptoms provided by ACEIs/ARBs (76,77).

Second-line medications used in the management of CHF do not have a potential mortality advantage. Digoxin is an example of the second-line drugs. It is highly toxic,

possesses a narrow therapeutic window, and the failure in a number of trials has revealed a reduction in its mortality benefit leading to reduced use in managing patients with the condition (21). Diuretics such as loop diuretics have been vital in the management of fluid accumulation and retention in the tissues (78). Generally, the prescribed medications significantly improve health and therapy outcomes and reduce mortality risk. For example, first-line therapy drugs present an advantage of fewer hospital admissions for heart failure exacerbations, enhanced survival and enhanced status of life in individuals with the condition. However, morbidity and mortality have remained high despite the progress and efforts made in the management of the condition (1,79– 81)**.**

Diuretics such as potassium-sparing diuretics, thiazide-like diuretics and loop diuretics have contributed significantly to the management of the conditions as they are used as the mainstay therapy in the management of fluid accumulation and retention. The evidence of safety and efficacy remains limited despite the high reliance on them. Only mineralocorticoid antagonists have evidence of safety and efficacy (82,83). Mineralocorticoid antagonists appear to reduce mortality cases in patients that are 75 years and below (84). A recent Cochrane analysis revealed that in small studies, the utilization of diuretics by patients with HF reduced the risk of death (83). However, the same cannot be correlated to the general population due to the limited number of respondents in the cited reviews (84).

Vasopressin receptor antagonists can also be utilized to manage heart failure in patients. Conivaptan is the first drug approved by the US Food and Drug Administration (FDA) for the management of euvolemic hyponatremia in individuals with heart failure (85). In rare circumstances, diuretics may be used together with hypertonic 3% saline to correct hyponatremia in HF (86). Ivabradine is also approved for individuals presenting with symptomatic heart failure that has reduced left ventricular ejection fraction and are under-optimized guideline-directed therapy (as above) that includes the maximum tolerable dose of beta-blocker, have a continuous resting heart rate above 70 beats per minute and have a normal heart rhythm (87). Ivabradine, in studies carried out, has shown a beneficial effect of reducing the risk of hospital admission due to HF exacerbations in this cohort of individuals with HF (88).

In individuals, who cannot tolerate ARBs and ACE-I, whose kidney function is impaired significantly, then the use of a combined long-acting nitrate such as isosorbide dinitrate and hydralazine, is an efficacious substitute treatment plan of action. This regimen is beneficial as it decreases mortality in individuals with mild HF (89). It is principally advantageous in African Americans populations (AA) (90). In AAs who show signs and symptoms, isosorbide dinitrate (H+I) and hydralazine can be added to ARBs or ACE-Is. In patients with symptomatic HF with significantly reduced ejection fraction (ejection fraction of 40% or below), the utilization of eplerenone or spironolactone (mineralocorticoid antagonists), in addition to ACE-I (once titrated to the target dose or maximum tolerated dose) and beta-blockers, can enhance clinical outcomes (symptoms) and decrease the risk of death (91,92). Sacubitril/valsartan should be utilized together with a mineralocorticoid antagonist and a beta-blocker in those individuals who present with symptoms while taking an ARB or ACEI, to reduce the risk of cardiovascular hospitalization and mortality for heart failure by a further 4.7% (absolute risk reduction). However, the utilization of this therapy or regimen needs the patient to cease using of ARB or ACE-I therapy 48 hours before its initial use (93).

Essential drugs listed for the management HF include enalapril, digoxin, hydrochlorothiazide and furosemide in Kenya and only digoxin in Uganda (66). The national clinical guidelines by MOH lists furosemide, beta-blockers and ACEI/ARB as first-line therapy, while digoxin is reserved for individuals presenting with atrial fibrillation (18). The national clinical guidelines in Uganda for managing HF advocate first-line therapy with ACE inhibitors and furosemide. Some beta-blockers (atenolol and propranolol), ACE inhibitors (captopril and lisinopril) and diuretics (furosemide) are among the listed key medications in one or both of these nations (94).

2.5 Potential Drug-Drug Interactions

Drug-drug interactions (DDIs) are characteristically adverse drug events (ADEs) that can result from the reverberations of one medication being modified by another when both are administered concurrently. Often, it results in a qualitative and/or quantitative alteration in drug action (95). This could significantly alter the preventive, diagnostic, and therapeutic activity of any medication, thereby altering drug efficacy, occasioning

treatment failure, and resulting in the toxicity of medications (96). The categorization of DDIs can be on the basis of their severity and the processes of interactions of the drugs (97). Based on their severity, DDIs can be classified as either mild, moderate, or severe. Mild DDIs seldom require changes in therapy while moderate DDIs could demand changes in therapy regimen. Major DDIs are potentially hazardous or may cause sustained or indefinite damage. Irrespective of the severity of the DDI, there is a need to monitor the patient for possible signs of the interaction (98) In terms of mechanisms of interactions with each other, DDIs can also be classified as pharmacodynamics, pharmacokinetic and pharmaceutical (96).

DDIs are common in patients suffering from chronic conditions such as those with cardiovascular, psychiatric, Human Immuno-deficiency Virus, renal and hepatic ailments. These patients often require several classes of medications, and their liver and kidney functions may be compromised leading to decreased excretion and metabolism. Therefore, the occurrence of DDIs in these types of patients may be consequential (22,99-102). The pDDIs affect both non-hospitalized and hospitalized HF patients. Studies suggest that the prevalence of pDDIs among non-hospitalized HF, for example, India (47.83%) (103), South India (69.33%) (105), Pakistan (48%) (105), and Nepal (78.7%) (21). However, non-hospitalizations rates are higher for younger HF patients. DDIs occur more frequently in hospitalized patients, the ones who remain admitted in health facilities for an extended period, and/or receive more medications per day (106). Hospitalization of patients has been highly linked to pDDIs.

HF patients have an increased likelihood of being affected by pDDIs due to the severity of the illness, chronic therapeutic regimens, comorbid conditions, frequent therapy modification and polypharmacy (107). Polypharmacy plays a crucial role in pDDIs: the higher the number of medications per prescription, the higher the chances of pDDIs occurrence. The likelihood of a patient taking multiple drugs rises with prolonged hospital stays, and this, in turn, increases the pDDIs risk (108). A study by Straubhaar et al., (20) revealed that hospital admission of individuals with heart failure led to an increase in the number of medications prescribed per individual and the likelihood of potentially interacting drug combinations per patient. The prevalence of pDDIs among

HF patients was 36.9% at admission and 63.1% resulting from a change of drugs during hospitalization. In Ethiopia, the prevalence rate of potential drug interactions was 74.41% among cardiac patients (108). This was directly attributed to factors such as the number of prescribed medications and the age of the patient. The high prevalence of prospective DDIs among patients with cardiac conditions in medical wards was mainly due to the complexities of pharmacotherapies administered. Pharmacodynamic drug–drug interaction was the leading mechanism of drug–drug interactions.

DDIs may possess harmful or undesirable outcomes in addition to their advantageous end results (99). Clinically relevant DDIs may lead to inherent harm to patients and these effects cost more than $1 billion per year to governmental health care system expenditure (11). The costs are high owing to the high percentage of major and moderate pDDIs especially among patients with CVD and HF. The study by Straubaar et al., (20) observed that the major potential adverse effect rated at 25.7% of the patients, while 'moderate' was at 65.2%. Hyperkalemia was the most common inherent adverse effect of significant intensity and the combination of a potassium-sparing diuretic with an ACE inhibitor was noted in 16.0% of the HF patients. Fettah (109) reported that interactions with major ferocity accounted for approximately 11.11% of the total DDIs, while those with average and inconsequential severity accounted for 37.22% and 51.66%, respectively among hospitalized cardiac patients in Morocco.

In Nepal., Sharma et al, (21) study among cardiac patients established the incidence of potential DDI to be at 21.3%. Forty-eight inherently severe drug interactions were pinpointed. Enalapril/metformin (10.4%), atorvastatin/azithromycin (10.4%), enalapril/potassium chloride (10.4%), atorvastatin/clarithromycin (8.3%) and furosemide/gentamicin (6.3%) were identified as the most frequent interacting pairs. Medications involved mostly included digoxin, atorvastatin, warfarin, clopidogrel, enalapril and furosemide. Most of the interactions were of moderate ferocity (62.5%) and pharmacokinetic (58.3%) in nature.

PDDIs can also have a synergistic interaction that could prove beneficial to the patient. The term synergy is derived from the Greek word συνεργόδ that means working together.

In pharmacological terms, it possesses a precise meaning, which is definite from the interaction between two or more active substances where the interaction may be on the distribution, absorption, excretion or metabolism of one or more of the substances. For a synergistic therapeutic consequence to happen, there need not certainly be an interaction of this nature, but the consequence should be to the patient's therapeutic benefit (110). For instance, a study by Sundström et al., (111) found that the aggregated relative consequences of blood pressure-lowering medications and statins on cardiovascular events were multiplicative. Al-Amin (112) observed that the most common interacting pair was aspirin and clopidogrel (54%). Drug interaction between aspirin and clopidogrel is a pharmacodynamic one, i.e., aspirin inhibits platelet activation through TXA2 pathway, whereas clopidogrel acts by inhibiting P2Y12 receptor leading to a synergistic anti-haemostatic effect (113). Although this combination therapy may offer additional benefit over monotherapy, the physician should monitor for the risk of bleeding as it belongs to risk category C. Theoretically, it has been postulated that aspirin may cause a reduction in the advantageous effects of ACE inhibitors in individuals presenting with heart failure. However, the information is limited by the retroactive essence of the analyses and does not accurately determine the relationship. Interaction between anti platelet and anticoagulant is well known and may predispose to bleeding. The presence of an enzyme inducer or inhibitor in the treatment regimen may increase the chances of drug toxicity or reduced effect (114),

Potential DDIs may be indicated or contraindicated. An "indication" for a medication refers to the utilization of that pharmacological agent for managing a particular ailment (115). An indication is a justifiable rationale to utilize a certain medication, test, surgery, or procedure. There can be several indications to use a drug or a procedure. The indication identifies the ailment the drug can treat, and some cases mandates which age group is meant to receive the drug. Medication-indication information is a key component of the information required to determine relevant use of drugs (116). Contraindication, on the other hand, is the converse of indication that is a basis not to use a given therapy. A contraindication is a factor or condition that serves to hold back a certain medical therapy due to the severity of the effects it would cause the patient (117).

In the treatment of HF, indications and contraindications are important. Drugs that can worsen heart failure should be avoided and they include most antiarrhythmic drugs (except class III), calcium channel blockers (CCBs) and nonsteroidal anti-inflammatory drugs (NSAIDs) (118). However, Beta-blockers, such as metoprolol (Lopressor), carvedilol (Coreg) and bisoprolol (Zabeta) are usually indicated. These drugs diminish the risk of some abnormal cardiac rhythms and decrease the chances of sudden death. Beta-blockers improve the functions of the heart, decrease signs and symptoms associated with the condition, improve and prolong the life of the patient (119).

A study by Girouard et al., (120) found that when compared to nonusers, users of NSAIDs, and CCBs experienced an elevated risk of all-cause hospital admission, but not the patients taking nifedipine. Old people with HF exposed to an inherently unsuitable class of drugs are at a higher risk of experiencing unwanted health outcomes. Treatment alternatives should be considered, as they are available. In a study from Denmark, 34 % of patients were put on at least one nonsteroidal anti-inflammatory drug or cyclooxygenase-2 inhibitor after discharge for first hospitalization for HF (121). Utilization of some of these medications may be on the rise. For example, an analysis of Medicare beneficiaries admitted with the diagnoses of diabetes mellitus and HF revealed that the percentage taking metformin and/or a thiazolidinedione increased from 13.5% in 1998 to 1999 to 24.4% in 2000 to 2001 (117).

However, with the event of polypharmacy, prescribing HF drugs with other drugs increases the incidences of pDDIs. In a review on the Potential Drug-Drug Interactions in heart failure patients in Bulgaria, Georgiev et al., (122) found that the standard quantity of prescription drugs at hospital discharge was over seven medications per patient and the major pDDIs were 7.28 %. Concerning the risk rating, significant amounts of categories D (Consider therapy modification) and X (Avoid combination) were detected. In India, Devarashetty et al., (123) study among ischemic heart disease patients established that 94% of the patients had pDDIs. The average quantity of medications prescribed per patient was eight, and most prescribed drugs were aspirin, atorvastatin, clopidogrel, metoprolol and ramipril. Aspirin and clopidogrel, aspirin and ramipril were the most commonly interacting pairs. The majority of the interactions were of category C, i.e.,

which requires monitoring of therapy. The number of medications prescribed, and hypertension were discovered to be the factors significantly influencing clinically relevant pDDIs.

Shanbhag et al., (124) study among hospitalized cardiac patients identified a total of 38 potentially interacting drug pairs, among which the majority were of significant grade while only 3 were serious. The majority of interactions were pharmacodynamic in nature. Aspirin/clopidogrel and pantoprazole/clopidogrel were the most common interacting pairs. Drugs most involved were aspirin, clopidogrel, heparin, pantoprazole and ramipril. Fettah (109) also found that two-thirds of the patients had a prevalence of DDIs, the most common of which concerned Kardegic/Plavix, Kardegic/Heparin and Lasilix/Spironolactone. Among the prescribed drugs, more than half were drugs of the cardiovascular system, followed by blood and hematopoietic organ drugs.

2.6 Gaps in the Literature

The preceding discussions have highlighted heart failure and the medication challenges associated with heart failure. Prescribing drugs for HF can be very involving for both non-hospitalized patients and hospitalized patients alike owing to the pDDIs. Therefore, the review examined empirical literature associated with recommended HF drugs, the prescribing patterns for HF drugs and the pDDIs in HF drug prescription. However, despite considerable research in HF pharmacological modalities, little empirical research exists in the Kenyan setup about the prescribing pattern and the drug-drug interactions among patients with HF, the correlates of the prescribing pattern, and the possible areas of intervention to minimize the adverse effects of drug-drug interactions. The prevalence of pDDIs among non-hospitalized patients with HF is usually lower than those in hospitalized cases and, hence, their manifestations and severity are often overlooked in most studies. This study, therefore, seeks to examine non-hospitalized cases in detail as it seeks to fill the gap.

CHAPTER THREE: METHODOLOGY

3.1 Introduction

In this chapter, the details of the methodology to be utilized to carry out the study were discussed. These included the research design, location of the study, target and study populations, inclusion and exclusion criteria, sample, research instruments, pretesting, reliability, validity, data collection procedures, data analysis, logistical and ethical deliberations.

3.2 Research Design

This was a descriptive cross-sectional study (125). This design was appropriate since the study sought to describe the effect of prescribing patterns and potential drug-drug interactions on a cross-section of patients with heart failure at the Kenyatta National Hospital. Cross-sectional studies scrutinize the association between ailments (or other health-related characteristics) and other variables of interest as they subsist in a defined population at a particular period (126). While cross-sectional studies do not necessarily show the cause-effect relationship between variables, the design can allow for the examination of several factors as they present at a given point in time in the population of interest.

3.3 Location of the Study

The study was carried out at Kenyatta National Hospital in Nairobi County. The facility is the largest public referral hospital in the nation and has a capacity of 1800 beds, 22 out-patient clinics, 50 wards, an Accident & Emergency Department and 24 theatres (16 specialized). Among the outpatient clinics is the cardiac clinic where 20 to 25 patients are attended once a week (127). Owing to its location, equipment and personnel, KNH cardiac clinic attracts patients from all over the country who have a range of cardiovascular diseases including heart failure.

The clinic is operated by a team of six cardiologists who attend to all the patients.

3.4 Target Population and Study Population

The study targeted adult patients with heart failure who attend the cardiac clinic and were already on medication for heart failure. The study population comprised of those who met this criterion.

3.5 Inclusion and Exclusion Criteria

3.5.1 Inclusion Criteria

1. Adult patients (at least 18 years of age).
2. Patients diagnosed with heart failure.
3. Patients already on medication for heart failure.
4. Patients who consented to take part in the study.

3.5.2 Exclusion Criteria

1. Patients diagnosed with heart failure but were not able to participate in the study due to cognitive challenges making it difficult for them to recall their experiences
2. Patients who were unwilling to take part in the study.

3.6 Sample

3.6.1 Sample Size Determination

According to the health information department of the KNH, there were 4198 outpatients who attended the cardiac clinic in the year 2020. Of these 753 were new cases while 3445 were old cases. A recent survey by Magot et al., (33) revealed a pDDIs prevalence rate of 92.7% among hypertensive patients at the KNH. The study used this prevalence rate to compute the sample size using the Cochrane formula as shown below:

$$n_0 = \frac{Z^2 P(1-P)}{d^2}$$

Where;

n_0 was the computed sample size for the study

Z was the standard normal deviate which was taken as 1.96 for 95% confidence level.

P was the (estimated) pDDIs rate of the population which in this study was taken as 92.7% or 0.927 based on a recent study undertaken at KNH (33).

d was the desired level of precision, that was, the margin of error taken as 0.05 in this study.

Substituting into the formula we obtained $n_0 = 103$ patients. To this sample size, 20% was added to cater for the non-response rate bringing the total sample size to 124 HF patients.

3.6.2 Sampling Technique

Total enumerative sampling method was utilized whereby every participant that met the inclusion criteria was chosen until the ideal sample size was attained (128) and used to select the patients for the study sample. This was determined through the patients' files which were first sorted to ensure the patients met the inclusion criteria and then their attendance was used to confirm their presence and to these, the research instrument was administered.

3.7 Research Instruments

The study used a questionnaire for primary data collection (Appendix III). The questionnaire was semi-structured and was used to collect information from the patients regarding their sociodemographic characteristics and their response to the drugs. It was also be used to collect data on the comorbidities of the patients and the severity of their HF condition. The questionnaires were used owing to their advantages of quick response and accuracy in capturing data and ease of analysis of the data captured through their format.

For secondary data, the study used an eligibility screening form (Appendix I) and a patient clinic data sheet (Appendix IV) where all the diagnostic and drug prescription data were recorded from the medical records. The study also required the patients to fill in an informed consent form to take part in the study (Appendix II).

3.8 Pretesting

Before administering the instruments on the actual study, the instruments were first to be pre-tested to determine their accuracy, ease of use and dependability for the study. Therefore, the instruments were first pretested on 12 non-participatory respondent sample comprising of in-patients with heart failure.

3.9 Validity

The study considered both internal and external validity to ensure the rationality of its outcome. Internal validity refers to the degree of confidence that the causal relationship being tested is trustworthy and not influenced by other factors or variables (129). The internal validity was improved by ensuring that the constructs used in the measurements of the variables were independent and also reduced the likelihood of confounding factors in the study instruments. The choice of the sample was also carefully done to reduce bias by not sampling extensively from a subset of the sample. The maturation effect was overcome by the use of the cross-sectional design, where the respondents were required to participate once in the study. Using the cross-sectional design took care of testing, attrition, and regression towards the mean. Social interaction was taken care of by ensuring the participants were interviewed separately in a different room. External validity, on the other hand, refers to the scope to which outcomes from a survey can be applied (generalized) to other circumstances, events or groups (130). The study ensured external validity by using validated tools, which were standard across all participants.

3.10 Reliability

Bless and Higson-Smith (131) underscores that authenticity is ―concerned with the consistency of measures‖; thus, the level of reliability of an instrument depends solely on its ability to generate a similar score when utilized frequently. The researcher utilized the intramural consistency method to ascertain the reliability of the research instruments. This was done by calculating the Cronbach's alpha coefficient for all the sections of the questionnaire from the results of the pilot study. According to Cronbach and Azuma, a value of 0.7 or higher of the Cronbach's alpha coefficient revealed high internal consistency (132). The items that were found to lower the Cronbach's alpha below this value were addressed.

3.11 Data Collection Techniques

After obtaining all the relevant authorizations and permits, the principal investigator recruited two research assistants, trained them on approaching the patients, briefing them on the study, taking patients through the consenting process, and how to assess the patient's cognitive functions using the quick dementia rating scale. The assistants

assessed the eligibility of the participants and interviewed them. The principal investigator collected data from the patient's file. The assistants were university of Nairobi, school of pharmacy students. These assistants were assumed to have gained the requisite knowledge in clerking patients, understanding clinical information recorded in patients' files, and interpreting pharmacotherapy approach in heart failure.

The patients were approached by the research assistant in the waiting area and briefly informed of the research and asked to participate on a voluntary basis. Care was taken to ensure that patients were not selected from one population group but rather from a cross-section of the study population.

The willing participant was then requested to accompany the researcher assistants to a private space, where the assistant explained the study briefly to the participant and asked them whether they wish to proceed or not. Thereafter, the participant was taken through the consent form and asked to voluntarily sign the consent declaration form. The research assistant assessed the cognitive functions of the participant using the Quick Dementia Rating System (QDRS) (Appendix 5). Only patients who scored Normal (a score of 0-1 points in the scale) in the QDRS proceeded to the researcher-administered interview that was conducted by the principal investigator. Where a patient was deemed to have cognitive impairment, he or she was informed of failing in the eligibility criteria and appreciated verbally for the willingness to participant in the study. For all other participants, after the face-to-face interview, the patient's clinical data including the severity of heart failure, duration of illness, and aetiology of the heart failure from the files was abstracted from the patient's file and entered into the predesigned questionnaire. Data collection was done in such a way that the patients did not lose their position in the queue.

3.12 Data Analysis

Data collected from the questionnaires was first assessed logically and cleaned. The drugs prescribed and administered were checked for compliance with the Kenyan National Guidelines for Cardiovascular Disease Management (18) and the pDDIs were checked using the IBM Micromedex Drug interaction checker 2018 version and the data entered

into Microsoft Excel 2016, which was used for descriptive analysis and exported to STATA Version 13.0 for statistical analysis. Descriptive statistical analysis was carried out using percentages, standard deviations, frequencies and means to describe the primary attributes of the data. Inferential analysis of data was carried out using the bivariate and multivariate logistic regression model to determine if the relationships between the dependent variables and the independent variables were statistically significant at $p<0.05$.

The independent variables for the study were the clinical and sociodemographic characteristics of the patients, adherence to prescribed regimens, and prescribing patterns. The dependent variable was the occurrence of a potential drug interaction. The modifying variables were the consumption of an appropriate diet and the lifestyle of a participant.

Fischer's exact or Pearson's Chi-square tests were used to identify any correlation between the independent variables and pDDIs. A manual backward stepwise logistic regression was utilized to come up with a parsimonious model with the significant dependent variables.

3.13 Logistical and Ethical Considerations

It is important to think about ethical scope in every preparation stage to conduct an inquest. Kombo and Tromp (133) note that researchers whose participants are animals or people must consider the conduct of their research and give recognition to the ethical issues related to carrying out their research. This study dealt with humans as respondents. Ethical issues to consider were sensitivity, confidentiality and privacy to a medical condition, gender and anonymity (134). Ethical research does lead to harm; it acquires informed consent from participants and respects their rights. Therefore, the researcher ensured that the confidentiality of the participants was assured.

The researcher considered the fact that involvement in research was volitional. Therefore, the researcher took time to explain to the participants the significance of the survey and then made an appeal to the individuals to participate in the study by submitting information applicable to the study. To cultivate a satisfactory working association with

the respondents, the researcher strived to create a bond with them. A clear and requisite explanation of the intention of the research was given to all the participants. The researcher revealed the key intention of the research, told the truth and availed every fact concerning the study so that participants were able to make an enlightened choice regarding participation. The participants in the study were assured of confidentiality and anonymity throughout the entire process.

A letter of authorization from the director of KNH for consent to conduct the research within the hospital was obtained. Every patient was briefed on the intentions of the research, risks and benefits and taken through the consenting process as shown in Appendix II.

CHAPTER 4: RESULTS

4.1 Introduction

This chapter describes the sociodemographic and clinical characteristics of the participants. It also described the aetiology of heart failure, the prescription patterns in heart failure, the potential drug-drug interactions that occurred and their possible outcomes, the comorbidities among patients with heart failure and the drugs used for comorbidities. Additionally, the various covariates of the number of pDDIs and the predictors of the occurrence of pDDIs have been described.

4.2 Sociodemographic Characteristics

Most of the participants were female (n=68, 58.1%), with a normal age distribution (Table 1). Fifty- three (45.3%) participants were not formally educated and most of them were married (n=97, 82.9%). Fifty-six (47.9%) respondents had one to three dependents while majority (n=94, 80.3%) were in the income bracket of 0 to 20,000 Kenya shillings. Most (n=65, 55.6%) resided in the urban area and 115 (98.3%) were Christians. One hundred and one (86.3%) participants had no history of smoking or alcohol use while, 74 (63.3%) exercised occasionally.

Table 1: Sociodemographic Characteristics of the Participants

Variable	Frequency, n (%)
Gender	
Male	49 (41.9%)
Female	**68 (58.1%)**
Age (Years)	
<31	11 (9.4%)
31-45	28 (23.9%)
46-60	**42 (35.9%)**
>60	36 (30.8%)
Median (IQR)	52 (40, 65)
Mean ± SD	52.8 ± 16.9
Education	
Informal	**49 (41.9%)**
Secondary	43 (36.8%)
Tertiary	25 (21.4%)
Marriage Status	
Not married	20 (17.1%)
Married	**97 (82.9%)**
Number of dependents	
None	9 (7.7%)
1-3	**56 (47.9%)**
>3	61 (52.1%)
Monthly Income	
0 - 20,000	**94 (80.3%)**
21,000 – 50,0000	20 (17.1%)
51,000 – 100,000	3 (2.6%)
Above 100,000	0 (0%)
Residence	
Rural	52 (44.4%)
Urban	**65 (55.6%)**
Religion	
Christian	**115 (98.3%)**
Muslim/Other	2 (1.7%)
Employment status	
Unemployed	**87 (74.4%)**
Employed	30 (25.6%)
Smoking status	
Never	**101 (86.3%)**
Past smoker	13 (11.1%)
Current smoker	3 (2.6%)
Alcohol use	
Never	**101 (86.3%)**
Occasionally	11 (9.4%)
Frequent (>6 drinks per week)	5 (4.3%)
Exercise	
Never	23 (19.7%)
Occasionally	**74 (63.3%)**
Actively (>3 times a week)	20 (17.1%)

4.3 Clinical Characteristics of Participants (n=117)

Majority of the patients (n=58, 53.7%) had been ailing for more than three years (Table 2). Majority of the patients exercised a restriction for salt (n=66, 55.6%), red meat (n=77, 65.8%), and saturated fats (n=69, 59.0%), while 81 (69.2%) were not consuming a DASH diet. Majority of the patients had a previous history of admission related to heart failure (n=62, 53.0%), and 63(53.9%) had comorbidities. Sixty- one (52.1%) had preserved ejection fraction.

Table 2: Clinical Characteristics of Participants

Variable	Frequency, n (%)
Duration of illness	
<3years	**58 (53.7%)**
3-5.9 years	21 (19.4%)
6-10 years	12 (11.1%)
>10years	17 (15.7%)
Mean ± SD	5.1 ± 6.2
Median (IQR)	3.2 (1.3, 5.8)
Salt restriction	
No	52 (44.4%)
Yes	**65 (55.6%)**
Read meat restriction	
No	**77 (65.8%)**
Yes	40 (34.2%)
DASH diet	
No	**81 (69.2%)**
Yes	36 (30.8%)
Saturated fats restriction	
No	**69 (59.0%)**
Yes	48 (41.0%)
NYHA Class (based on symptoms)	
I	16 (13.7%)
II	40 (34.2%)
III	32 (27.4%)
IV	29 (24.8%)
History of previous admission	
None	55 (47.0%)
Present	**62 (53.0%)**
Comorbidities	
None	54 (46.2%)
Present	**63 (53.9%)**
Type of heart failure	
HFrEF (≤ 40%)	56 (47.9%)
HRpEF (>40%)	**61 (52.1%)**

4.4 Aetiology of Heart Failure

The most prevalent aetiologies of heart failure were dilated cardiomyopathy (n=44, 37.9%), hypertension (n =31, 26.7%), and rheumatic heart disease (n = 17, 14.7%) as shown in Figure 1.

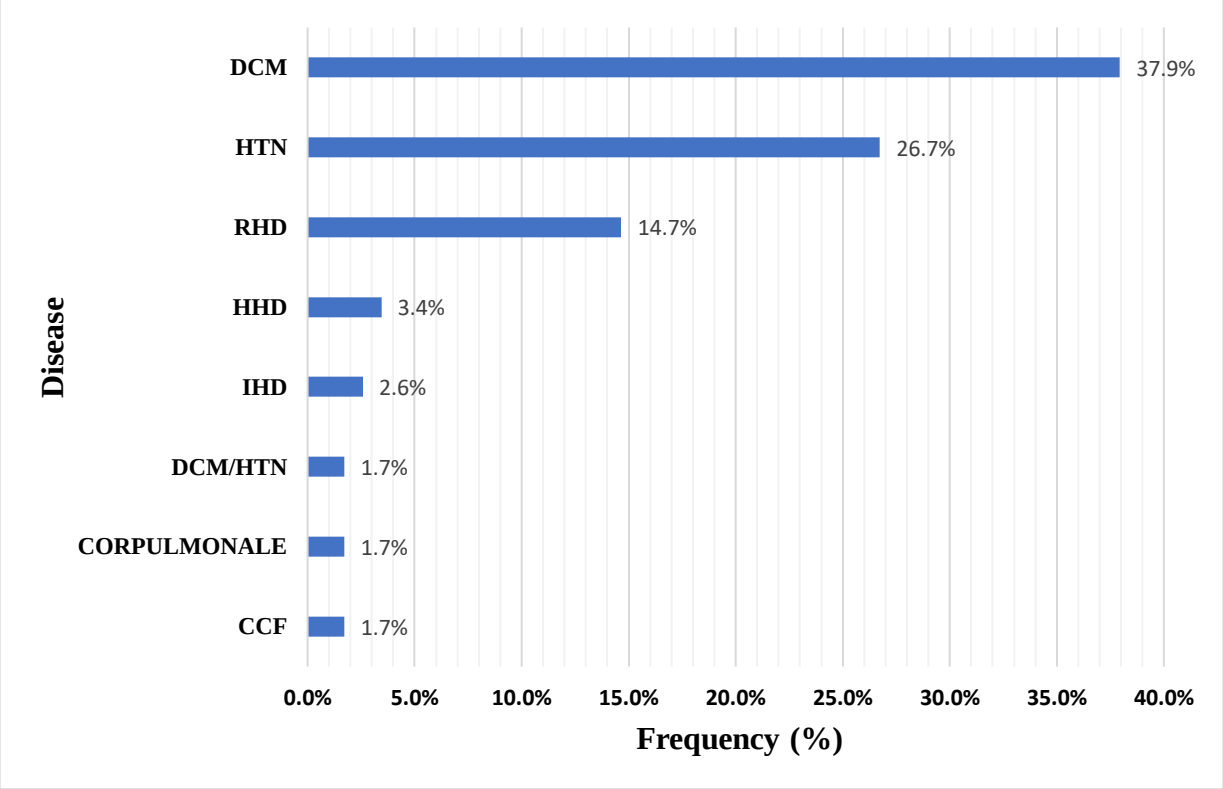


Figure 1: Aetiology of Heart Failure

KEY: DCM – Dilated cardiomyopathy, HTN – Hypertension, RHD – Rheumatic heart disease, HHD – Hypertensive heart disease, IHD – Ischaemic heart disease, CCF – Congestive cardiac failure

4.5 Prescription Patterns among patients with Heart Failure

The most commonly prescribed classes of drugs were beta-blockers (n = 81,76.9%), diuretics (n = 70, 71.8%), mineralocorticoid receptor antagonists (n = 66, 56.4%), angiotensin-converting enzyme inhibitors (n=53, 45.3%), cardiac glycosides (n = 44,

37.6%), and angiotensin receptor blocker (n = 53, 35.9%) as shown in Figure 2.

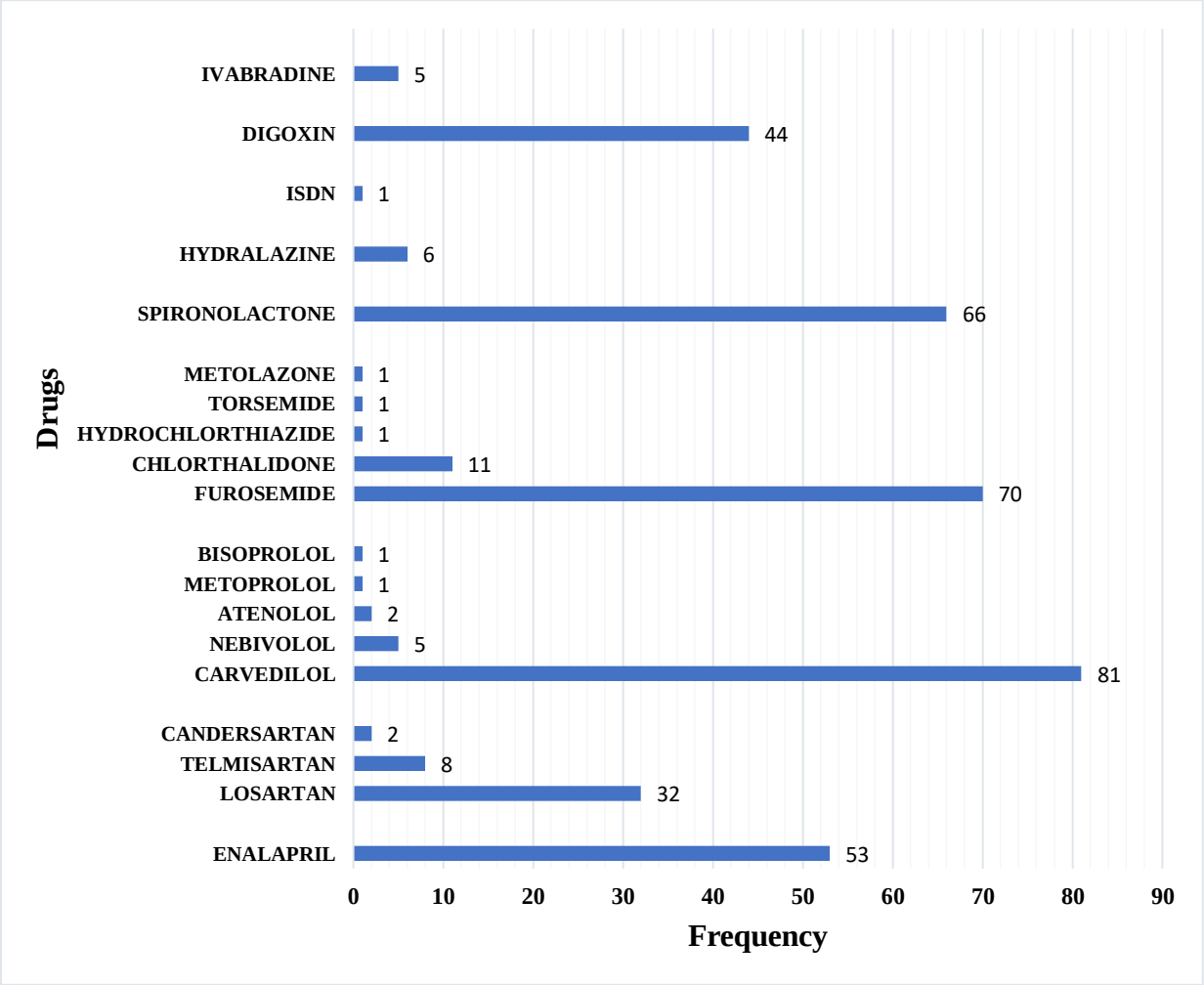


Figure 2: Commonly Prescribed Drugs for Heart Failure

KEY: ISDN – Isosorbide dinitrate

4.5.0 Clinician's Prescription Review Pattern

Thirty-eight (32.5%) participants had their prescriptions changed in their last visit. Changes in prescriptions were mostly due to worsening symptoms or the occurrence of a side effect from the drug. Only a few patients (n=5, 13.2%) initiated a change in their prescription. A change in a prescription mostly resulted in improvement or resolution of symptoms (n=10, 76.9%) and increased expenditure.

Table 3: Pattern of Prescriptions Review

Query	**Frequency, n (%)**
Patients whose prescriptions were changed in the last visit	**38 (32.5%)**
Frequency of change of prescriptions (n=38)	
Once	20 (52.6%)
More than once	18 (47.4%)
Common reasons for the change of prescriptions (n=27)	
Worsening of symptoms (oedema, difficulty in breathing, tachycardia)	**10 (37.0%)**
Drug side effects (coughing, bradycardia, reduced lactation, myalgia, heart burn)	5 (18.5%)
Resolution/Improvement of symptoms	4(14.8%)
Lack of improvement	3 (11.1%)
Prior to surgery	2 (7.4%)
Number of patients who initiated/requested for a prescription change (n=38)	5 (13.2%)
Patients who reported an impact after the change of a prescription (n=38)	13 (34.2%)
Commonly reported consequences from the change of a prescription (n=13)	**10 (76.9%)**
Improved/Resolved symptoms	1 (7.7%)
Onset of fatigue	1 (7.7%)
Onset of tachycardia	1 (7.7%)
Onset of headache	1 (7.7%)
Increased expenditure	
Patients whose expenditure increased after a prescription change (n=38)	22 (11.8%)

4.6 Potential Drug-drug Interactions

Out of the 117 prescriptions 80 (68.4%) had pDDIs. There were 240 pDDIs, out which 156 (65%) were major, 83 (35%) were moderate, and 1 (0.42%) was minor. The specific drugs involved in most interactions included digoxin (n=105, 43.8%), spironolactone (n=101, 42.1%), carvedilol (n=54, 22.5%), and enalapril (n=51, 21.3%) among others.

4.6.1 Possible Outcomes of pDDIs

The most common possible outcomes from the pDDIs are summarized in table 4. They were increased risk of hyperkalaemia (n=57, 23.75%), complete heart block (n=33, 13.75%) and an increased risk of digoxin toxicity symptoms (n= 32, 13.33%).

Table 4: Summary of interacting drugs, potential outcomes and severity of interactions

Possible Outcome	Interacting Drugs	Severity
Increased risk of hyperkalaemia (n=57, 23.75%)	Enalapril/Spironolactone Losartan/Spironolactone Candesartan/Spironolactone Telmisartan/Spironolactone Digoxin/Spironolactone/Metformin	Major
Increased risk of digoxin toxicity and increased risk of complete heart block	Digoxin/Carvedilol	Major
	Digoxin/Atenolol	Moderate
Increased risk of digoxin toxicity (nausea, vomiting, and cardiac arrhythmias) (n=32, 13.33%)	Digoxin/Furosemide	Moderate
	Digoxin/Atorvastatin/Furosemide Digoxin/Telmisartan/Furosemide Digoxin/Spironolactone/Atorvastatin Digoxin/Metoclopramide	Major
Increased risk of digoxin exposure and possibly digoxin toxicity (n=31, 12.92%)	Digoxin/Spironolactone Digoxin/Spironolactone/Metformin Digoxin/Spironolactone/Omeprazole Digoxin/Furosemide Digoxin/Spironolactone/Aspirin Digoxin/Carvedilol Digoxin/Spironolactone/Atorvastatin	Major
Fluctuation in sugars and reduced hypoglycaemia symptoms (n=9, 3.75%)	Carvedilol/Empagliflozin Carvedilol/Glibenclamide Carvedilol/Metformin Carvedilol/Empagliflozin/Insulin Glibenclamide/Nebivolol/Metformin	Moderate
Increased risk of bleeding (n=9, 3.75%)	Aspirin/Clopidogrel Benzathine Penicillin/Warfarin/Atenolol Warfarin/Benzathine Penicillin Warfarin/Valproic Acid Clopidogrel/Warfarin Aspirin/Clopidogrel Levothyroxine/Warfarin Benzathine Penicillin/Warfarin	Major
Increased risk of hypoglycaemia (n=9, 3.75%)	Aspirin/Glimepiride Aspirin/Metformin	Major
	Enalapril/Metformin Furosemide/Insulin/Empagliflozin Telmisartan/Insulin Enalapril/Empagliflozin	Moderate

4.7 Comorbidities

The most common comorbidities included hypertension (n = 34, 29.8%), diabetes mellitus (n = 17, 14.9%), hyperlipidaemia (n = 12, 10.5%), peptic ulcers disease (n = 11, 9.6%), osteoarthritis (n = 6, 5.3%), asthma (n = 4, 3.5%), and chronic obstructive pulmonary disease (n = 4, 3.5%) among others (Figure 3).

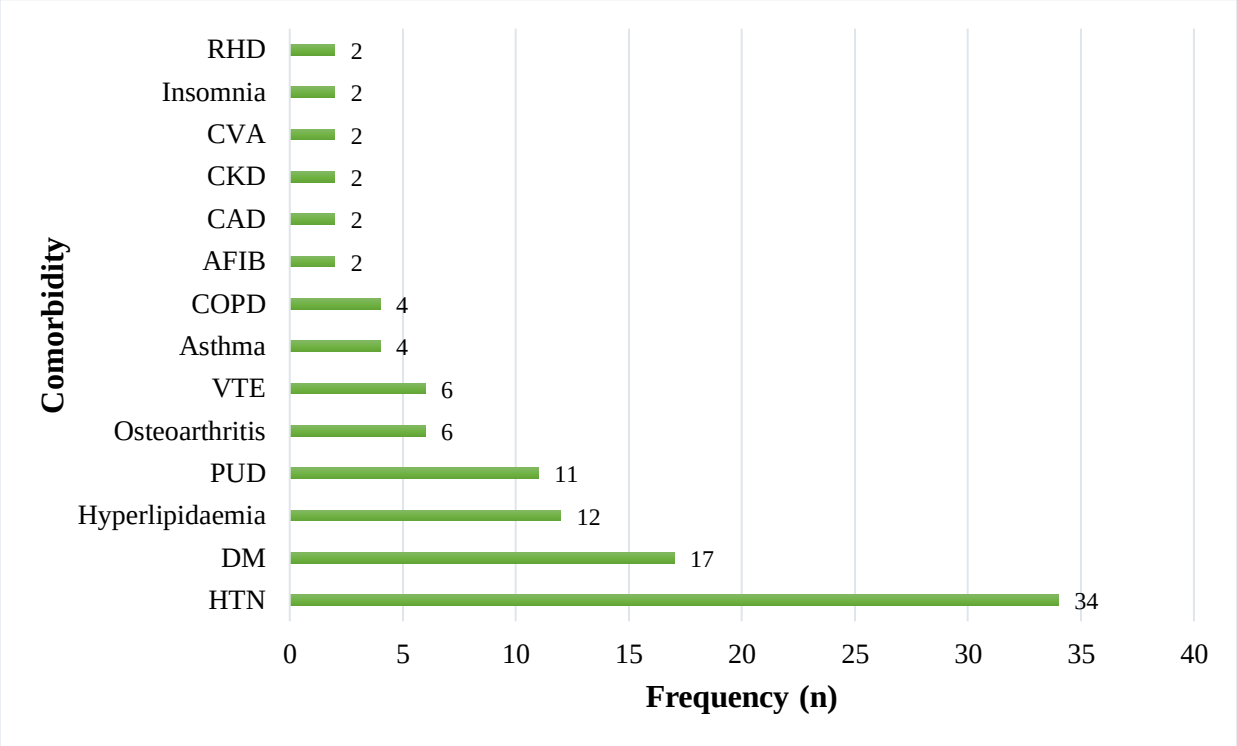


Figure 3: Frequency of comorbidities

KEY: RHD – Rheumatic heart disease, CVA – Cerebrovascular accident, CKD – Chronic kidney disease, CAD – Coronary artery disease, AFIB – Atrial fibrillation, COPD – Chronic obstructive pulmonary disease, VTE – Venous thrombo-embolism, PUD – Peptic ulcers disease, DM – Diabetes mellitus, HTN – Hypertension.

4.7.1 Drugs Used for managing Comorbidities

The most commonly used drugs for comorbidities were amlodipine (n =22,13.3%), atorvastatin (n =22,13.3%), warfarin (n =16, 9.6%), esomeprazole (n = 12, 4.8%), and metformin (n = 8, 4.8%) among others (Figure 4).

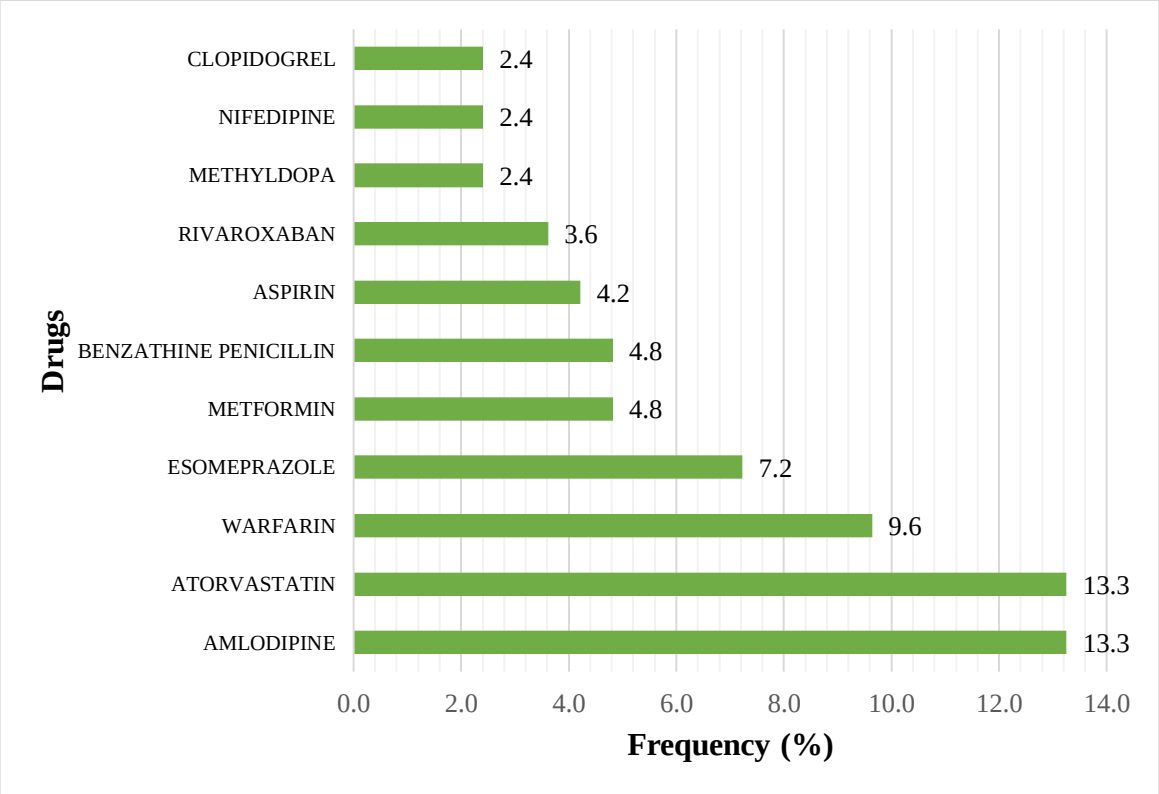


Figure 4: Drugs used to Treat Comorbidities

4.8 Adherence to Drugs

Table 5: Attributes to Adherence

Attribute	**Frequency, n (%)**
Patients who took the drug(s) regularly prescribed by the doctor (n = 117)	111 (94.9%)
Number of days missed taking the heart failure drug(s) in a week (n=117)	
None	**73 (62.4%)**
Whole week	7 (6.0%)
Mean	1.0
Median (IQR)	0 (0,1)
Ability to access prescribed drug(s) without changing over a long time	100 (85.5%)
Ability to access/purchase drugs easily from patient's location	93 (79.5%)
Ability to conveniently afford drugs without budgetary strain	24 (20.5%)
Prevalence of side effects from the prescribed drugs	32 (27.8%)
Most common side effects from the drugs (n=30)	
Polydipsia	5 (16.7%)
Fatigue	3 (6.7%)
Dizziness	3 (6.7%)
Malaise	3 (10.0%)
Loss of appetite	2 (3.3%)
Monthly cost of drugs (reported by the patient) [Ksh.]	
Mean ± SD	3362 ± 2150
Median (IQR)	3000 (2000, 45000)

One hundred and eleven (94.9%) participants were adherent to the prescribed drugs (Table 5). All patients were able to purchase the drugs without changing them for a long time. Only 24 (20.5%) of them were able to afford their drugs conveniently without a budgetary strain. The common side effects were polydipsia, fatigue, dizziness and malaise. The monthly cost of drugs for most patients averaged Ksh. 3362 ± 2150.

Test for Normality

A Shapiro-wilk test for the age, frequency of exercising, and the NYHA class showed a normal distribution. However, the duration of illness, reported monthly cost of drugs, income level and the total number of pDDIs were not normally distributed.

Table 6: Test for Normality

Variable	Statistic	df	Significance (P)
Age	0.985	117	0.258
Duration of illness	0.684	117	<0.001
Income level	0.857	117	<0.001
Exercise level	0.985	117	0.249
NYHA classes	0.996	117	0.996
Ejection fraction	0.931	117	<0.001
Monthly cost of drugs	0.931	117	<0.001
Total number of pDDIs	0.940	117	<0.001

4.9 Covariates of Potential Drug Interactions

4.9.1 Sociodemographic Factors Associated with the Occurrence of a pDDI

A Pearson's Chi-square or Fischer's test was done to establish whether there was an association between the patient's profile and the occurrence of a pDDI at $P \leq 0.05$. None of the variables showed any significant association with the occurrence of a pDDI (Table 7)

Table 7: Sociodemographic Factors Associated with the Occurrence of a pDDI

Variable (Sociodemographic)	Occurrence of a Potential Drug-drug Interaction		
	No (n, %)	Yes (n, %)	P-value
Gender			
Male	21 (18.0)	10 (8.6)	0.205
Female	47 (40.2)	39 (33.3)	
Age (Years)			
≤52	14 (12.0)	17 (14.5)	0.364
>52	47 (40.2)	39 (33.3)	
Education			
Informal	16 (13.7)	15 (12.8)	0.410
Secondary and above	37 (31.6)	49 (41.8)	
Marriage Status			
Not married	5 (4.3)	26 (22.2)	1.000
Married	15 (12.8)	71 (60.7)	
Number of dependents			
0-2	6 (5.1)	25 (21.4)	0.172
More than 2	29 (24.8)	57 (48.7)	
Income			
0 - 20,000	24 (20.5)	7 (6.0)	0.609
21,000 and above	70 (59.8)	16 (13.7)	
Residence			
Rural	14 (12.0)	17 (14.5)	0.925
Urban	38 (32.5)	48 (41.0)	
Religion			
Christian	30 (25.6)	1 (0.85)	0.447
Muslim/Other	85 (72.7)	1 (0.85)	
Employment status			
Unemployed	23 (19.7)	8 (6.8)	0.980
Employed	64 (54.7)	22 (18.8)	
Smoker			
No	30 (25.6)	1 (0.85)	0.066
Yes	71 (60.7)	15 (12.8)	
Alcohol use			
No	30 (25.6)	1 (0.85)	0.066
Yes	71 (60.7)	15 (12.8)	
Exercise			
No	5 (4.3)	26 (22.2)	0.564
Yes	18 (15.4)	68 (58.1)	
Adherent			
No	23 (19.7)	8 (6.8)	0.114
Yes	50 (42.7)	36 (30.8)	
Duration of illness			
Three years or less	14 (12.0)	17 (14.5)	0.567
More than 3 years	44 (37.6)	42 (35.9)	
Comorbidities			
None	12 (10.3)	19 (16.2)	0.332
Present	42 (35.9)	44 (37.6)	
Severity of illness			
NYHA I and II	16 (13.7)	15 (12.8)	0.626
NYHA III and IV	40 (34.2)	46 (39.3)	
Affords Drugs			
No	7 (6.0)	24 (20.5)	0.739
Yes	17 (14.5)	69 (59.0)	

4.9.2 Prescribing Factors Associated with the Occurrence of a pDDI

A Pearson's Chi-square or Fischer's test was done to find out whether there was an association between the prescribing pattern and the occurrence of a pDDI at $P \leq 0.05$. There was a significant association between the occurrence of a pDDI and the use of an ACEIs ($P = 0.011$), the use of a beta blocker ($P = 0.038$), the use of MRAs ($P < 0.001$), and the use of digoxin ($P < 0.001$) (Table 8).

Table 8: Prescribing Factors Associated with the Occurrence of a pDDI

Variables (Prescription pattern)	Occurrence of a Potential Drug-drug Interaction		
	No (n, %)	Yes (n, %)	P-value
ARBs use			
No	17 (14.5)	60 (51.3)	0.133
Yes	14 (12.0)	26 (22.2)	
ACEIs use			
No	22 (18.8)	38 (32.5)	**0.011**
Yes	9 (7.7)	48 (41.0)	
B-blockers use			
No	11 (9.4)	15 (12.8)	**0.038**
Yes	20 (17.1)	71 (60.7)	
Diuretics use			
No	11 (9.4)	27 (23.1)	0.677
Yes	20 (17.1)	59 (50.4)	
MRAs use			
No	29 (24.8)	22 (18.8)	**<0.001**
Yes	2 (1.7)	64 (54.7)	
Vasodilators use			
No	28 (23.9)	83 (70.9)	0.189
Yes	3 (2.6)	3 (2.6)	
Nitrates use			
No	31 (26.5)	85 (72.7)	1.000
Yes	0 (0)	1 (0.9)	
Digoxin use			
No	31 (26.5)	42 (35.9)	**<0.001**
Yes	0 (0)	44 (37.6)	
Ivabradine use			
No	30 (25.6)	82 (70.1)	1.000
Yes	1 (0.9)	4 (3.4)	
Prescription change in the last visit	21(18.0)	58 (49.6)	0.976
No	10 (8.6)	28 (23.9)	
Yes			

KEY: ACEIs – Angiotensin converting enzyme inhibitor, ARB – Angiotensin receptor blocker, MRA – Mineralocorticoid receptor antagonist.

4.9.3 Comorbidities Associated with the Occurrence of a pDDI

A Pearson's Chi-square or Fischer's test was done to find out whether there was an association between the comorbidities and the occurrence of a pDDI at P ≤0.05. There

was a significant association between the occurrence of a pDDI and having type 2 diabetes mellitus (P =0.04) (Table 9).

Table 9: Comorbidities Associated with the Occurrence of a pDDI

Variables (Comorbidities)	Occurrence of a Potential Drug-drug Interaction		
	No (n, %)	Yes (n, %)	P-value
Hypertension			
No	18 (15.4%)	13 (11.1%)	0.066
Yes	65 (55.6%)	21 (18.0%)	
Diabetes			
No	30 (25.6%)	1 (0.9%)	**0.040**
Yes	70 (59.8%)	16 (13.7%)	
Hyperlipidaemia			
No	27 (23.1%)	4 (3.4%)	0.730
Yes	78 (66.7%)	8 (6.8%)	
Peptic ulcer disease			
No	29 (24.8%)	2 (1.7%)	0.725
Yes	77 (65.8%)	9 (7.7%)	
Osteoarthritis			
No	28 (23.9%)	3 (2.6%)	0.189
Yes	83 (70.9%)	3 (2.6%)	
Venous thromboembolism			
No	30 (25.6%)	1 (0.9%)	0.575
Yes	81 (69.2%)	5 (4.3%)	

4.9.4 Covariates of Potential Drug Interactions

A bivariate and multivariate logistic regression was done to identify the predictors of pDDIs at P≤0.05. The bivariate analysis exposed a significant association between the occurrence of a pDDI and the use of MRAs (OR=42.2, P<0.001), the use of ACEIs (OR = 3.1, P=0.012) and the use of beta blockers (OR = 2.6, P=0.042). The multivariable

analysis revealed only one significant association between the occurrence of a pDDI and the use of MRA (AOR = 26.0, P <0.01).

Table 10: Covariates of Potential Drug Interactions

Variable	Bivariate Analysis		Multivariate Analysis	
	Crude Odds Ratio	**P-Value**	**Adjusted Odds Ratio**	**P-Value**
MRAs use No Yes	42.2 (9.3 – 191.4)	**<0.001**	26.0 (5.2 – 135.4)	**<0.001**
ACEIs use No Yes	3.1 (1.2 -7.5)	**0.012**	2.2 (0.5-9.1)	0.277
Beta blockers use No Yes	2.6 (1.0-6.6)	**0.042**	3.9 (0.7-22.1)	0.124
Diabetes No Yes	6.9 (0.9-54.1)	0.068	4.6 (0.4-53.7)	0.227

CHAPTER 5: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

This chapter discusses the research findings. The conclusions and recommendations are also outlined

5.1 Discussion

The study had a female predominance which was a deviation from a previous study done in KNH in 2012 on heart failure where both genders were equally represented (57). A global study on heart failure in 2017 observed that females were more than males. Heart failure has age-dependent progression that is different between males and females. At a younger age, heart failure is more prevalent in males, but females tend to close the gap with advancing age, and the prevalence equalize at 80 years (135,136). The mean age of the participants was 52.8 years, which is close to a similar study done in the same hospital (57).

Majority of the participants had post-primary education. A study investigating cardiovascular diseases in Kenya in 2014 had contrary findings with more than half of the study participants having primary education only (57). The completion rate of primary school education has been increasing in Kenya. It could probably have explained why the level of education was higher among the participants after a span of 7 years. Most patients were non-smokers, and they were not using alcohol. The prevalence of smoking in Kenya is about 11.6% and that of alcohol use is 11-12%, which was a closer reflection of the smoking and alcohol use levels among the study participants (137-140).

Most of the participants exercised regularly. Exercise improves tolerance, endurance of ventilator muscles, quality of life, and blood flow in the coronary artery among others (141). A study done on physical activity level in Kenya identified that those aged 50-69 years were more likely to be active as well as those with lower education levels (142). The high level of physical activity in this group could be because most participants were doing informal jobs and they could have been counselled on the importance of physical activity during the clinic visits.

Majority of the participants had a duration the illness for less than 3 years. Heart failure is associated with high mortality, and the life expectancy averages 5.5 years (143). High risk group includes patients with more than three comorbidities (143) The short duration of illness can be explained by the short lifespan of patients with heart failure and the presence of comorbidities as well.

Patients with heart failure are advised to restrict sodium intake to manage their symptoms. Excess intake of sodium cause fluid retention which is a predictor of acute exacerbation of symptoms and hospitalization (144). Most patients observed restricted use of salt. During the regular clinic visits, patients are advised to reduce salt intake as part of nutritional counselling. Patients who are most adherent to a DASH diet have a 37% lower chance of developing heart failure (145). A DASH diet reduces LDL cholesterol and blood pressure. The diet incorporates high intake of vegetables and fruits and whole grains. It also involves low intake of saturated fats and high-fat dairy (145). Most patients were non-adherent to the DASH diet, which takes high levels of motivation to achieve. Taking a DASH diet is determined by the kind of food that the patient's family takes daily. Most of the patients may not have the required resources, motivation, and family support to adhere to a DASH diet on a daily basis (145). This is probably the reason most patients were not able to use unsaturated fats, which are more expensive than the saturated fats.

Most participants had comorbidities, which contributes to poor functional status, reduced quality of life, and higher rates of mortality. Some of most common non-cardiovascular comorbidities were diabetes mellitus, poor vision, and COPD (146). Medications for patients with heart failure should be chosen carefully, particularly using a multi-disciplinary approach, since most of them are likely to be on other to treat the comorbidities. Most patients had a history of previous hospital admission. These patients have a greater risk of all-cause readmission and readmission due to exacerbations (147). The management of heart failure should be strategic and optimal to improve outcomes.

The aetiologies of heart failure were dilated cardiomyopathy, hypertension, and rheumatic heart disease. A previous study in heart failure in Kenya revealed similar

pattern(57). This finding was slightly different from a study done in Tanzania that showed that hypertension as the commonest aetiology (148). Prudent control of blood pressure and treatment of upper respiratory tract infections are important prevent cardiovascular complications.

The usage of beta blockers was much higher compared to other studies (149,150). However, the utilization of MRAs was similar to other studies (151). The use of ARBs and ACEIs was also slightly higher compared to other studies (151). Most patients were not optimized on carvedilol. Optimizing treatment to the maximum tolerable dose of beta-blockers is important in reducing morbidity and mortality (151). The use of enalapril was not optimized for about a third of the patients. Heart failure medications should be optimized to ensure maximal benefit to the patients.

The overall prevalence of pDDIs was 68.4%, and two thirds were major. A study in Ethiopia reported a higher prevalence of pDDIs and the same trend was observed in Pakistan (22, 152). Though number of pDDIs per patient in our study was lower, there was a relatively higher number of major pDDIs compared to other studies. This points to the need for pharmaceutical intervention, which calls for integrated professional interaction to optimize patient safety.

Most patients were potentially exposed to hyperkalaemia from an interaction between ACEIs/ARBs with spironolactone. Co-administering ACEIs or ARBs together with potassium sparing diuretics is a significant predictor of developing hyperkalaemia (153). On the other hand, the addition of spironolactone to ACEIs or ARBs has clear benefits to patients including reducing mortality and hospitalizations (153). Therefore, whenever spironolactone is added, it should be monitored closely especially when the patient has other comorbidities such as diabetes mellitus and chronic kidney disease. The elderly and dehydrated patients are also at risk of developing hyperkalaemia (153).

Several other interactions were attributable to digoxin use. Cardiac glycosides are substrates of P-glycoprotein (P-gp), which is located on the enterocytes, blood brain barrier, tubular cells and hepatocytes. The P-gp influx pump is responsible for absorbing,

distributing and clearing digoxin, and its inhibition could cause elevated levels of digoxin to toxic levels. Loop diuretics reduces the levels of potassium and magnesium, which increases the risk of cardiotoxicity (154). Digoxin use with potassium-sparing diuretics such as spironolactone increases the digoxin serum concentration by 25%, which increases the chance of toxicity (154). Therefore, the inclusion of digoxin in any regimen should come with increased caution and monitoring plan for the potential electrolyte levels and signs of toxicity. Digoxin should also be initiated at lowest doses possible and any electrolyte derangement particularly potassium should be corrected promptly (154).

5.2 Strengths and Weakness

5.2.1 Strengths

This was the first study in Kenya to investigate the occurrence of potential drug interactions and the factors associated with the interactions.

Interviewing the patients helped to reduce inaccuracies in data collection as it offered an opportunity to reconcile what was recorded in the files with the patient's statements. Since the prescriber was also present in the facility, it was also possible to clarify any inconsistent entries.

5.2.2 Weaknesses

The study had a small sample size of 124 participants, which limits the generalizability of the study to other public hospitals in Kenya. Additionally, the hospital setting has a high number of specialists, which may not reflect the general situation of most public hospitals. However, the findings of this study could be triangulated with similar studies in Kenya to inform the general prescribing practices in the country.

KNH being a referral hospital receives a greater proportion of the severe medical cases. Therefore, the participant's population in KNH could be skewed to the patients with the advanced category of heart failure.

Being a cross-sectional study there were inherent self-reporting bias from patients and inaccuracies. The data collected was dependent on the patient's ability to accurately recall and report certain elements of the data required. Additionally, the data extracted from the medical files was prone to erroneous entries, which were transferred into the

study. The principal investigator tried all possible means to verify whether the information reported by the patient coincides with the clinical records.

5.3 Conclusion

Most patients were not optimized on the recommended therapy for heart failure. The prevalence of potential drug interactions among heart failure patients indicates an unmet need in the medications therapy management. Having diabetes, receiving a beta blocker, receiving an angiotensin converting enzyme blocker was associated with having a potential drug interaction. The use of mineralocorticoid receptor antagonists was a significant predictor of having a potential interaction.

5.4 Recommendations

5.4.1 Recommendations for practice and policy

1. The inclusion of a beta-blocker, angiotensin converting enzyme inhibitor and mineralocorticoid receptor antagonist to the regimen of patients with heart failure should be accompanied with regular monitoring of electrolytes as well as the cardiovascular system functionality.
2. Patients with heart failure should have their regimen reviewed by a multidisciplinary team, where possible including a clinical pharmacist, to optimize treatment
3. Patient education that includes their care givers and family could help encourage patients to adhere to a DASH diet to reduce morbidity and mortality

5.4.2 Recommendation for further research

1. A study investigating the clinical outcomes of various doses of spironolactone in heart failure could inform the optimal doses for patients and improve their management.

2. A local study profiling the beta blockers with the least potential for drug-drug interactions among heart failure patients would inform better management practices.

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APPENDICES

APPENDIX I: ELIGIBILITY SCREENING FORM

All participants to be enrolled in the study must meet the eligibility criteria based on the inclusion/exclusion criteria in this form.

1. Study information

Title	**Prescribing Patterns and Potential Drug-drug Interactions in Heart Failure Patients at KNH**
KNH/UoN/ERC Protocol Number	
Principal Investigator	**RUTH MARITA**

2. Participant information

Participant's Unique ID
Gender: Male Female

3. Inclusion/Exclusion Criteria

INCLUSION CRITERIA	**YES**	**NO**
Is the patient an adult patient of at least 18 years of age?		
Is the patient medically diagnosed with heart failure?		
Is the patient already on medication for heart failure?		
Has the patient consented to take part in the study?		
EXCLUSION CRITERIA		
Does the patient have cognitive challenges making it difficult for them to recall their HF experiences?		
Is the patient unwilling to take part in the study?		

Statement of Eligibility

The participant is eligible ☐ Not eligible ☐ for participation in this study

Signature:	Date:
Researcher's Name:	

APPENDIX II: CONSENT FORM

ADULT PARTICIPANT INFORMATION AND CONSENT FORM FOR ENROLLMENT IN THE STUDY

Title of the Study: PRESCRIBING PATTERNS AND POTENTIAL DRUG INTERACTIONS AMONG PATIENTS WITH HEART FAILURE AT KENYATTA NATIONAL HOSPITAL

Principal Investigator:

Ruth Marita, Master of Pharmacy in Clinical Pharmacy, University of Nairobi

Faculty Advisor:

1. Dr. Peter Ndirangu Karimi, PhD, Senior Lecturer, Department of Pharmaceutics, and Pharmacy Practice, School of Pharmacy, University of Nairobi
2. Dr. David Gitonga Nyamu. PhD, Senior Lecturer, Department of Pharmaceutics, and Pharmacy Practice, School of Pharmacy, University of Nairobi

Introduction:

The pharmacy faculty considers participation in research by participants to be an important educational experience for the students as well as a most important service to the research of the University. Participation is voluntary, if you choose not to participate as a research participant you may participate in another research related activity at no expense to your academic record or standing. Things you should know:

- The purpose of the interview is to characterize the prescribing patterns and potential drug-drug interactions among patients diagnosed with heart failure at Kenyatta National Hospital
- If you choose to participate, you will be asked to participate fully in the study by responding to the instruments of the study. As a study meant to improve the therapy administered in heart disease, we require our participants to be honest at all times with their views during interviews so as to improve the accuracy of the treatment programs to be designed.
- This study has the potential risk of making the respondents re-experience negative emotions. However, when you experience this, we will provide other forms of supportive counselling.

- The study has potential benefits to patients of heart failure in the country and beyond as it seeks to improve the management of the disease through safe and available drugs by providing information that can significantly reduce the incidences of adverse drug interactions in patients.
- Taking part in this research project is voluntary. You don't have to participate, and you can stop at any time.
- No cash or inducements of any kind will be provided, and neither will you be required to pay anything for participating in the study.

May I continue? **YES / NO**

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No. _____

WHAT IS THIS STUDY ABOUT?

The researchers listed above are interviewing individuals who have heart failure. The purpose of the interview is to characterize the prescribing patterns and potential drug-drug interactions among patients diagnosed with heart failure at Kenyatta National Hospital. Participants in this research study will be asked questions about their sociodemographic history, clinically relevant information, adherence to medications, and the symptoms of their condition.

There will be approximately 124 participants in this study. We are asking for your consent to consider participating in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH STUDY?

If you agree to participate in this study, the following things will happen:

You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 30 minutes and will cover topics such as your sociodemographic and clinical data such as your age,

gender, residence, compliance with drugs, and heart failure symptoms among others. After the interview has finished, the interviewer will access information from your medical file related to your social, medical, and medication history

We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others. The reasons why we may need to contact you include: to clarify your usage of the prescribed drugs or heart failure symptoms.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify you in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be absolutely secure, so it is still possible that someone could find out you were in this study and could find out information about you.

Also, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview.

It may be embarrassing for you to have to disclose your personal information, but we will do everything we can to ensure that this is done in private. Furthermore, all study staff and interviewers are professionals with special training in these examinations/interviews. Also, it may be stressful to recall negative emotions, but we will provide other forms of supportive counselling.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

The study has potential benefits to patients of heart failure in the country and beyond as it seeks to improve the management of the disease through safe and available drugs by providing information that can significantly reduce the incidences of adverse drug interactions in patients.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

This study will require you to spare about 30 minutes to answer questions relevant to this study. However, participating in this study will not cost you any money.

WILL YOU GET REFUND FOR ANY MONEY SPENT AS PART OF THIS STUDY?

Since there is no likely expenditure for participating in the study, there will be no compensation arising from being a participant

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff Ruth Marita, +254794093571 or you may also contact my supervisor, Dr. P.N. Karimi +254722436019.

For more information about your rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.

The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time without injustice or loss of any benefits.

RESEARCHER'S STATEMENT

Having explained all the relevant details of this study to the above participant, I trust that he/she has understood and voluntarily given his/her consent to participate.

Researcher's Name: _____

Date: _____

Signature: _____

Role in the study: _____

CONSENT FORM (STATEMENT OF CONSENT)

PARTICIPANT'S STATEMENT

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counsellor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study.

I understand that all efforts will be made to keep information regarding my personal identity confidential.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study:	Yes	No
I agree to provide contact information for follow-up:	Yes	No

Participant's Initials: _____

Participant signature / Thumb stamp: _____

Date: _____

RESEARCHER'S STATEMENT

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher's Name: _____

Researcher's signature: _____

Date: _____

Role in the study:_____

[i.e. study staff who explained informed consent form.]

For more information contact **Ruth Marita at +2540794093571** from 8am to 5pm

APPENDIX III: QUESTIONNAIRE

Part 1:

Name of Investigator	**Date**

PART 1A: PATIENT'S SOCIODEMOGRAPHIC DATA

Unique code	**Gender (M/F)**	**Age (Years)**	**Height (cm)**	**Weight (kgs)**

Date of diagnosis with HF (mm/yyyy)	**Level of Education** . Informal . Secondary . Post-secondary	**Marital Status** . Not married . Married	**Number of Dependents**

Average monthly income (KES) 0-20,000 21,000 – 50,000 51,000 – 100,000 Above 100,000	**Residence** Rural Urban	**Religion** . Christian . Muslim/other	**Employment Status** . Unemployed . Employed

Smoking Status 0. Never 1. Past smoker 2. Current smoker (specify no of sticks/day)	**Alcohol Use** 0. Never 1. Occasionally 2. Frequent (≥7 drinks/week)	**Exercise** . Never . Occasionally . Actively (> 3 times a week)

PART 1B: CLINICAL DATA

Diet Modification (No = 0; Yes = 1)

Salt restrictions	Red meat restrictions	DASH diet	Saturated fats restrictions	No modifications

How are you progressing now, how easily can you do the activities in the table below?

NYHA	Patient's symptoms	No = 0;
Class		Yes = 1
I	I have no limitation of physical activity. Ordinary physical activity does not cause me undue fatigue, palpitation, dyspnea (shortness of breath)	
II	I experience slight limitation of physical activity. Comfortable at rest. Ordinary physical activity does not cause me undue fatigue, palpitation, dyspnea (shortness of breath)	
III	I experience marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity does not cause me undue fatigue, palpitation, dyspnea (shortness of breath)	
IV	I am unable to carry on with physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases	
Have you previously been admitted as an in-patient (in the wards) for this condition?		
Apart from heart failure, have you been diagnosed with other chronic illnesses?		

PART 1C: COMORBIDITIES

Diagnosis	Drugs (Generic name, dose (mg), route of administration, frequency) e.g. Metformin 500mg PO BD

PART 1D: ASSESSING ADHERENCE TO DRUGS	
Assessing Adherence to Medication	**Response**
Do you take the drugs regularly as prescribed by your doctor? **No= 0, Yes = 1**	
How many days do you miss taking your heart failure drugs in a week?	
Are you able to access the same prescribed drugs without change over a long time? **No= 0, Yes = 1**	
Are you able to access/purchase the prescribed drugs easily from your location? **No= 0, Yes = 1**	
Are you able to conveniently afford the drugs without putting a strain on your budget? **No= 0, Yes = 1**	
How much money do you use on average on the heart failure drugs per month in KES?	
Do the drugs give you any side effects? **No= 0, Yes = 1** Explanation: …… …… …… ……	
PART 1E. PRESCRIPTION PATTERNS	
Did the doctor change the drugs for you in the past visit? **No= 0, Yes = 1**	
If yes, how many times has that occurred?	
What were the reasons for the change in drugs prescription? Explain: ……. ……. ……. …….	
Were you the one that requested a change of drugs or the doctor? **No= 0, Yes = 1**	
Have the changes in prescription if any affected you in any way medically? **No= 0, Yes = 1** If yes explain: ……. …….	

…….	
Have the changes in prescription increased your monthly spending on drugs?	

APPENDIX IV: DATA COLLECTION FORM FOR THE RECORDS

Part 2

PART 2A: CLINICAL DATA FROM PATIENT'S FILE		
NYHA Functional Classification . Class I . Class II . Class III . Class IV	Type of Heart Failure . HFREF . HFPEF	Ejection Fraction (%)
Etiology of HF (e.g. Rheumatic heart disease, Hypertension, Cardiomyopathy, Pericardial disease, Cor Pulmonale, Ischemic heart disease, Congenital heart disease etc):		

Drugs Prescribed for HF:				
Class	**Specific Drug**	**Present: No = 0 Yes = 1**	**Target Dose (mg/day)**	**50% Target Dose (mg/day)**
ACEIs	Captopril			
	Enalapril			
	Ramipril			
	Lisinopril			
	Fosinopril			
ARBs	Losartan			
	Irbesartan			
	Valsartan			
	Telmisartan			
b-Blockers	Carvedilol			
	Metoprolol			
	Nebivolol			
	Bisoprolol			
Diuretics	Furosemide			
	Metolazone			
	Chlorothiazide			
	Chlorthalidone			
MRAs	Spironolactone			
	Eplerenone			
	Triamterene			

Vasodilators	Hydralazine			
Nitrates	Isosorbide Dinitrate			
Cardiac glycosides/ Cardiotonic	Digoxin			
I_f channel inhibitor	Ivabradine			
others				

PART 2B: POTENTIAL DRUG-DRUG INTERACTIONS:	
Interacting Drugs	**Possible Outcome(s)**

KEY: HF – Heart Failure, ACEIs – Angiotensin converting enzyme inhibitors, ARBs – Angiotensin receptor blockers, MRAs - Mineralocorticoid Receptor Antagonists, NYHA - The
New York Heart Association, HFrEF - Heart Failure with Reduced Ejection Fraction, HFpEF - Heart failure with Preserved Ejection Fraction, DASH - Dietary Approaches to Stop Hypertension, KES – Kenya shillings.

APPENDIX V: THE QUICK DEMENTIA RATING SYSTEM (QDRS)

QUICK DEMENTIA RATING SYSTEM (QDRS)

The following descriptions characterize changes in the patient's cognitive and functional abilities. You are asked to compare the patient now to how they used to be – the key feature is ***change***. Choose ***one answer*** for each category that best fits the patient – ***NOTE***, not all descriptions need to be present to choose an answer

1. MEMORY AND RECALL	
0	No obvious memory loss or inconsistent forgetfulness that does not interfere with function in everyday activities
0.5	Consistent mild forgetfulness or partial recollection of events that may interfere with performing everyday activities; repeats questions/statements, misplaces items, forgets appointments
1	Mild to moderate memory loss; more noticeable for recent events; interferes with performing everyday activities
2	Moderate to severe memory loss; only highly learned information remembered; new information rapidly forgotten
3	Severe memory loss, almost impossible to recall new information; long-term memory may be affected
2. ORIENTATION	
0	Fully oriented to person, place, and time nearly all the time
0.5	Slight difficulty keeping track of time; may forget day or date more frequently than in the past
1	Mild to moderate difficulty keeping track of time and sequence of events; forgets month or year; oriented to familiar places but gets confused outside of familiar areas; gets lost or wanders
2	Moderate to severe difficulty, usually disoriented to time and place (familiar and unfamiliar); frequently dwells in past
3	Only oriented to their name, although may recognize family members
3. DECISION MAKING AND PROBLEM SOLVING ABILITIES	
0	Solves everyday problems without difficulty; handles personal business and financial matters well; decision-making abilities consistent with past performance
0.5	Slight impairment or takes longer to solve problems; trouble with abstract concepts; decisions still sound
1	Moderate difficulty with handling problems and making decisions; defers many decisions to others; social judgment and behavior may be slightly impaired; loss of insight
2	Severely impaired in handling problems, making only simple personal decisions; social judgment and behavior often impaired; lacks insight
3	Unable to make decisions or solve problems; others make nearly all decisions for patient
4. ACTIVITIES OUTSIDE THE HOME	
0	Independent in function at usual level of performance in profession, shopping, community and religious activities, volunteering, or social groups
0.5	Slight impairment in these activities compared to previous performance; slight change in driving skills; still able to handle emergency situations
1	Unable to function independently but still may attend and be engaged; appears "normal" to others; notable changes in driving skills; concern about ability to handle emergency situations
2	No pretense of independent function outside the home; appears well enough to be taken to activities outside the family home but generally needs to be accompanied
3	No independent function or activities; appear too ill to be taken to activities outside the home
5. FUNCTION AT HOME AND HOBBY ACTIVITIES	
0	Chores at home, hobbies and personal interests are well maintained compared to past performance
0.5	Slight impairment or less interest in these activities; trouble operating appliances (particularly new purchases)
1	Mild but definite impairment in home and hobby function; more difficult chores or tasks abandoned; more complicated hobbies and interests given up
2	Only simple chores preserved, very restricted interest in hobbies which are poorly maintained
3	No meaningful function in household chores or with prior hobbies

6. TOILETING AND PERSONAL HYGEINE	
0	Fully capable of self-care (dressing, grooming, washing, bathing, toileting)
0.5	Slight changes in abilities and attention to these activities
1	Needs prompting to complete these activities but may still complete independently
2	Requires some assistance in dressing, hygiene, keeping of personal items; occasionally incontinent
3	Requires significant help with personal care and hygiene; frequent incontinence
7. BEHAVIOR AND PERSONALITY CHANGES	
0	Socially appropriate behavior in public and private; no changes in personality
0.5	Questionable or very mild changes in behavior, personality, emotional control, appropriateness of choices
1	Mild changes in behavior or personality
2	Moderate behavior or personality changes, affects interactions with others; may be avoided by friends, neighbors, or distant relatives
3	Severe behavior or personality changes; making interactions with others often unpleasant or avoided
8. LANGUAGE AND COMMUNICATION ABILITIES	
0	No language difficulty or occasional word searching; reads and writes as well as in past
0.5	Consistent mild word finding difficulties, using descriptive terms or takes longer to get point across, mild problems with comprehension, decreased conversation; may affect reading and writing
1	Moderate word finding difficulty in speech, cannot name objects, marked reduction in word production; reduced comprehension, conversation, writing and/or reading
2	Moderate to severe impairments in speech production or comprehension; has difficulty communicating thoughts to others; limited ability to read or write
3	Severe deficits in language and communication; little to no understandable speech is produced
9. MOOD	
0	No changes in mood, interest or motivation level
0.5	Occasional sadness, depression, anxiety, nervousness or loss of interest/motivation
1	Daily mild issues with sadness, depression, anxiety, nervousness or loss of interest/motivation
2	Moderate issues with sadness, depression, anxiety, nervousness or loss of interest/motivation
3	Severe issues with sadness, depression, anxiety, nervousness or loss of interest/motivation
10. ATTENTION AND CONCENTRATION	
0	Normal attention, concentration and interaction with his/her environment and surroundings
0.5	Mild problems with attention, concentration, and interaction with environment and surroundings, may appear drowsy during day
1	Moderate problems with attention and concentration, may have staring spells or spend time with eyes closed, increased daytime sleepiness
2	Significant portion of the day is spent sleeping, not paying attention to environment, when having a conversation may say things that are illogical or not consistent with topic
3	Limited to no ability to pay attention to external environment or surroundings
	COGNITIVE SUBTOTAL (QUESTIONS 1, 2, 3, 8)
	BEHAVIORAL SUBTOTAL (QUESTIONS 4, 5, 6, 7, 9, 10)
	TOTAL QDRS SCORE

APPENDIX VI: APPROVAL LETTER FROM KNH-UON ERC

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/227

28th June, 2021

KENYATTA NATIONAL HOSPITAL APPROVED 28 JUN 2021 KNH/UoN-ERC P. O. BOX 20723 - 00202 NAIROBI

Dr. Ruth Mwango Marita
Reg. No.U56/34058/2019
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Dr. Marita

RESEARCH PROPOSAL: PRESCRIBING PATTERNS AND POTENTIAL DRUG INTERACTIONS AMONG PATIENTS WITH HEART FAILURE AT KENYATTA NATIONAL HOSPITAL (P84/02/2021)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 28th June, 2021 – 27th June, 2022.

This approval is subject to compliance with the following requirements:

i. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
ii. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
iii. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from KNH- UoN ERC 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.

Protect to discover

This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

C.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chair, KNH- UoN ERC
The Dean, School of Pharmacy, UoN
The Chair, Dept of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. Peter Karimi,Deptof Pharmaceutics and Pharmacy Practice, UoN
Dr David Nyamu, Dept.of Pharmaceutics and Pharmacy Practice, UoN

APPENDIX VII: STUDY REGISTRATION CERTIFICATE

Code – 1107481 – 3001

KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   RUTH MWANGO MARITA
2. Email address: rurikath@gmail.com Tel No. 0723623571
3. Contact person (if different from PI).....
4. Email address: ..... Tel No. .....
5. Study Title
   Prescribing patterns and potential drug interactions among patients with heart failure at Kenyatta national hospital
6. Department where the study will be conducted Cardiology department
   (Please attach copy of Abstract)
7. Endorsed by KNH Head of Department where study will be conducted.
   Name: DR MARY [illegible] Signature ..... Date 7/7/2021
8. KNH UoN Ethics Research Committee approved study number P94/02/2021
   (Please attach copy of ERC approval)
9. I Dr. RUTH MWANGO MARITA commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Medical Research.
   Signature NRuth Date 6th JULY 2021
10. Study Registration number (Dept/Number/Year) Cardio/377/49/2021
    (To be completed by Medical Research Department)
11. Research and Program Stamp

KENYATTA NATIONAL HOSPITAL * RESEARCH & PROGRAMS * P.O. Box 20723-00202 NAIROBI
03 JUL 2021

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Medical Research and investigators **must commit** to share results with the hospital.

APPENDIX VIII: ANTIPLAGIARISM REPORT

18/11/2021

PRESCRIBING PATTERNS AND POTENTIAL DRUG INTERACTIONS AMONG PATIENTS WITH HEART FAILURE AT KENYATTA NATIONAL HOSPITAL

ORIGINALITY REPORT

11%	7%	5%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	en.wikipedia.org Internet Source	1%
2	Bernhard Straubhaar. "The Prevalence of Potential Drug-Drug Interactions in Patients with Heart Failure at Hospital Discharge", Drug Safety, 2006 Publication	1%
3	Joseph Gallagher, Kenneth McDonald, Mark Ledwidge, Chris J Watson. "Heart Failure in Sub-Saharan Africa", Cardiac Failure Review, 2018 Publication	1%
4	"Poster Session Clinical", European Journal of Heart Failure, 2013. Publication	<1%
5	erepository.uonbi.ac.ke Internet Source	<1%
6	www.ijbcp.com Internet Source	<1%