association between levels of high sensitivity c-reactive protein and poor medication adherence among heart failure patients attending care and treatment at Jakaya Kikwete cardiac institute in Dar es salaam, Tanzania

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ASSOCIATION BETWEEN LEVELS OF HIGH SENSITIVITY C-REACTIVE PROTEIN AND POOR MEDICATION ADHERENCE AMONG HEART FAILURE PATIENTS ATTENDING CARE AND TREATMENT AT JAKAYA KIKWETE CARDIAC INSTITUTE IN DAR-ES-SALAAM, TANZANIA

By

Maganga Mathew Gabriel

A Dissertation Submitted in (Partial) Fulfillment of the Requirement for the Degree of Master of Pharmacy (Hospital and Clinical Pharmacy) of

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CERTIFICATION

The undersigned certify that they have read and hereby recommended for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: **"Association between levels of high sensitivity C-reactive protein and poor medication adherence among heart Failure patients attending care and treatment at Jakaya Kikwete Cardiac Institute (JKCI), in Dar-Es-salaam, Tanzania",** in (partial) fulfillment of the requirements for the degree of Master of Pharmacy (Hospital and Clinical Pharmacy) of Muhimbili University of Health and Allied Sciences.

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DECLARATION AND COPYRIGHT

I, **Maganga Mathew Gabriel,** declare that this **dissertation** is my own original work, and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature…… **Date**……

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DEDICATION

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ABSTRACT

Background: Evidences show that non-adherence to medications in heart failure (HF) patients highly contribute to preventable re-hospitalization, morbidity and mortality. Recently, conjunction of neuro-hormonal and immune system role in heart muscles remodeling and deterioration of HF has been elucidated, in which C-reactive protein (CRP) also plays a role. Plasma changes of very low levels of CRP, measured using high sensitivity CRP (hsCRP) have been found to change with HF progression and hence predict HF prognosis among Western HF cohorts. However, studies on use of hsCRP as a measure of effectiveness and adherence to HF treatment are lacking in our local setting and literature does not show whether hsCRP levels can be used as a marker of medications adherence among HF patients.

Aims: This study aimed at determining the association between HF medications adherence status and hsCRP levels among HF patients attending care and treatment at the Jakaya Kikwete Cardiac Institute (JKCI) in Dar es Salaam, Tanzania.

Methodology: This was a cross-sectional descriptive-analytical study, conducted at JKCI. Consecutive sampling technique was employed to recruit eligible HF patients as they attended their regular clinic visits on Doctors' schedule until the sample size was reached. Case report forms and the 8-item Morisky medications adherence scale tool were used to collect patients' socio-demographic and clinical information, as well as to assess patients' adherence to HF medications. For each patient, venous blood was collected and sent to the Muhimbili Central Pathology Laboratory where it was analyzed for hsCRP, complete blood count and cholesterol panel. Data were analyzed using Statistical Package for Social Sciences (SPSS) software version 21.

Results: In total 210 HF patients who were eligible, and had complete data constitute the current study population. The mean ±SD age of patients was 54 ±15.9 years and 113 (53.8%) were females. One hundred and thirty-eight (65.7%) patients were found to have poor HF medications. In the total study population, the mean ±SD hsCRP was 7.15±4.94mg/L, and 122

(58.1%) patients were found to have elevated (>5mg/L) hsCRP levels. The mean ±SD hsCRP levels were significantly higher among patients with poor adherence (7.75 ±5.00mg/L) when compared to those with good adherence (5.72 ±4.59mg/L), $p< 0.01$. Furthermore, patients with poor medications adherence were more likely to have elevated hsCRP levels (68.1%) when compared to patients with good adherence (38.9%), $p< 0.001$. In multivariate logistic regression analysis, the independent associations of poor medications adherence were elevated hsCRP 4.27(2.14 – 8.51, $p<0.001$) and having ≥stage 2 hypertension on the day of clinic visit 2.72 (1.01 – 7.46, $p = 0.05$).

Conclusion: This study has found that elevated hsCRP is strongly associated with poor HF medications adherence among HF patients attending care and treatment at JKCI, and the possibility to use measurements of hsCRP levels in the routine clinical follow-up investigations of patients with HF in order to know their adherence to medications. Further studies from different clinical settings are recommended to confirm the interesting findings obtained from this study. If confirmed, hsCRP level can, in the future be considered as a surrogate marker of HF medications adherence among HF patients in our local setting.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATION

ACEIs	Angiotensin Converting Enzyme Inhibitors
ARBs	Angiotensin Receptor Blockers
CAD	Coronary Artery Disease
CCBs	Calcium Channel Blockers
CHD	Coronary Heart Diseases
CHF	Congestive HF
CO	Cardiac Output
CRP	C-reactive Protein
ECM	Extracellular Matrix
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fractions
hsCRP	High-sensitivity C-reactive Protein
IL-6	Interleukin-6
JKCI	JakayaKikwete Cardiac Institute
LDL-C	Low Density Lipoprotein Cholesterol
MI	Myocardial Infarction
MIP-1- α	Macrophage Inflammatory Protein -1- α

MUHAS	Muhimbili University of Health and Allied Sciences
NSAIDS	Non-Steroidal Anti-inflammatory Drugs
RAAS	Renin Angiotensin Aldosterone System
RANTES	Regulated on Activation Normal T-Cell Expressed and Secreted
TNF-α	Tumor Necrotic Factor-alpha
TRAIL	TNF-α-related Apoptosis Inducing Ligand
VCAM-1	Vascular Cell Adhesion Molecule -1

DEFINITION OF TERMS

Heart failure: Is a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood, (ejection fraction may be reduced or preserved), hence the heart fails to meet cardiac output required or meets cardiac output at elevated filling pressures.

Drug adherence: Is the extent to which the patient's drug-taking behavior corresponds with an agreed medication regimen from a health care provider**.**

C-reactive protein (CRP): Is an annular (ring shaped), pentameric protein found in blood plasma, whose levels rise in response to inflammation. It was so named because this protein reacted with pneumococcal C-polysaccharide in plasma of patients during an acute phase of pneumococcal pneumonia.

High-sensitivity C-reactive protein (hsCRP): Is the level of C-reactive protein (CRP) concentration useful for prediction of cardiovascular risk, effectiveness of the treatment and prognosis of HF patients. The value ranges from 0.2mg to 3mg/L.

CHAPTER ONE

1.0 INTRODUCTION

Heart failure (HF) is a global health problem affecting an estimated 26 million people worldwide (1,2) and contributes about 40% of annual mortality in the USA alone (3). In Sub-Saharan Africa, HF is emerging as an important non-communicable disease which contributes significantly to morbidity and mortality (4,5), and diagnosis accounts for over 30% of hospital admission in cardiovascular and 3-7% in internal medicine units in Sub-Saharan Africa (6). Mortality due to HF is often under reported in many developing countries but is estimated to be high, ranging from 9% to 12.5% (4,7). In Tanzania, neither the prevalence, nor the mortality of HF is known in the general population.

HF is a final common pathway of many cardiovascular diseases (8,9). The disease reduces the efficiency of cardiocytes by damaging or overloading them. Several pathogenetic mechanisms appear to be operative in HF. These include increased hemodynamic overload, ischemia-related dysfunction, ventricular remodeling, excessive neurohumoral stimulation, abnormal myocyte calcium cycling, excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis, and genetic mutations (2). The important causes of HF include hypertensive heart disease, myocardial infarction, valvular heart disease, cardiomyopathies and diabetes mellitus (5,10,11). Smoking, dyslipidemia, chronic kidney diseases, anemia, and immune mediated peripartum cardiomyopathy (12) are the risk factors. Viral (e.g.Human Immunodeficiency Virus (HIV) cardiomyopathy), parasitic (e.g. Chaga's disease), toxic risk precipitants like chemotherapy e.g. anthracyclines and cyclophosphamide, non-steroidal anti-inflammatory drugs (NSAIDS) and cocaine are other interplay risk factors leading to HF (8).

Genetic (family history, congenital heart disease), morphological (increased left ventricular internal dimensions) and immune activation biomarkers (CRP, interleukin -6, natriuretic peptides) are other well known risk factors for HF (8). Sympathetic nervous and renin angiotensin aldosterone systems (RAAS) were thought to be the only player of cardiocytes remodeling. However, a few decades ago, the role of conjunction of these two systems and immune system in heart muscles deterioration has been seen (13,14). During chronic HF there

is infiltration of macrophages and lymphocytes into cardiomyocytes interstitial as well as elevation of cytokines like, TNF-α, and IL-6 (15).

CRP is a highly conserved protein of the pentraxin family that consists of 5 non- covalently linked subunits (16,17) and is one of several plasma proteins, designated acute-phase reactants, whose levels rapidly increase in response to stress, tissue injury, and a variety of inflammatory stimuli (18-20). It is predominantly synthesized by the liver and is regulated by pro-inflammatory cytokines, primarily tumor necrosis factor alpha and interleukin 6 (16-18, 21). It was first discovered in 1930 through a reaction with the somatic C polysaccharide of Streptococcus pneumonia in patients afflicted with pneumonia (16-18,22). CRP has also been isolated from atherosclerotic plaque where it activates complement (C3) pathway and oxidised LDL-C (19,23,24).

CRP plays a significant role in monocytes adhesion and migration into the interstitial spaces of cardiomyocytes (25). Compared to other inflammatory biomarkers like TNF-α, soluble TNF receptors, Fas, interleukins (I, 6 and 18), osteoprotegerin and adiponectin, CRP's stability in frozen plasma and long half-life of 18-20 hours has been found to assist as an independent biomarker for prediction of cardiovascular events and to diagnose HF patients in apparent healthy men and women (26,27). It is also used to monitor the treatment outcomes with statins as well as to monitor the prognosis of HF and effectiveness of HF treatment (3,18,28,29).

Plasma levels of hsCRP tend to drop with HF treatment (3). Atorvastatin and rosuvastatin are two potent statins which can efficiently lower hsCRP levels (29). β-blockers have the ability to lower hsCRP by 36% to 58% in good adherent HF patients or those with risk for HF (30). Angiotensin converting enzymes inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) tend to lower hsCRP by 14-39%. Study on Calcium antagonists and/or Isosorbide dinitrate on hsCRP in patients with coronary vasospastic angina pectoris with no hemodynamically significant coronary artery disease found that, there was decrease in hsCRP level from 8.17mg/L to 2.95mg/L in three months of treatment (30). Aspirin when given daily by two weeks lowered hsCRP by 29%, while rosiglitazone 4mg or 8mg lowered hsCRP by 58% (30).

Non-adherence includes dosage errors (underuse and overuse), not having a prescription filled, interruption of treatment, failure to take medications at specified times, taking medication at incorrect intervals, or taking medications that are not prescribed. Any deviation from the prescribed medication regimen is considered medication non-adherence. Researchers have estimated that approximately 50% of patients with chronic illnesses do not take their medications as prescribed (31,32). Poor adherence to medication in congestive HF (CHF) is associated with worse outcomes in observational studies, including shorter event-free survival (33). Importantly, absolute mortality differences associated with non-adherence can exceed incremental benefits observed with new therapies (34). Therefore, there is a need to improve adherence to HF medications among patients. For us to solve this problem, first we need to detect if our patients adhere or not. As a result, fast and reliable methods for measurement of adherence are necessary in the management of patients with HF.

Currently, the methods of ascertaining adherence to anti-HF medications are patient self-report, pharmacy refill, pill count medication event monitoring system (MEMS) (35,36), as well as drug plasma concentration determination. Over-estimation of adherence is the main drawback during assessment of adherence status using self-report, pill count and pharmacy refill (35). These methods have been leading to widely reports of medication adherence values. Example, using self-report, medication non-adherence rates of 4-54% in 13 studies, 2-90% using pharmacy refill in eight studies, 2-60% using MEMS in four studies, 15-73% using pill count (35). A variety of different questionnaires were used to measure these adherences (35). In summary, medication non-adherence rates in HF patients ranged from 2-90% depending on how adherence was measure, and most investigators cited rates of about 40-60%. Determination of steady state plasma concentration of medications is more superior to pharmacy refill, pill count and self-reports (37). But polypharmacy nature of the prescription plan in HF patients means steady state methods based on bio-analysis of parent drugs or metabolite molecules is uneconomical, high technologically demanding and tedious. Compared to other assessment methods mentioned above, the 8-Item Morisky medication

adherence scale (8-MMAS) is a widely used, simple, cheap, standard self-report accepted with reliability of 0.83 (32), sensitivity of 93% and specificity of 53 % (38).

A well-established interaction of immune and neuro-hormonal system in HF etiology and disease progress provide a new opportunity for objective method of measuring adherence to anti-HF medications (39). Studies show that hsCRP is an immune biomarker which is stable, with standardized assay and has a strong predictive value in the prognosis of HF and effectiveness of treatment (3,18,28). In short, hsCRP has been observed to change with HF progress, drop with HF medications, doesn't change with food, time of the day, uniform half-life in healthy and diseased, cheap and fast to get the results, could be the better alternative to the present methods of assessing medication adherence. In this study, we determined the hsCRP plasma levels among HF patients; examined their adherence to medications prescribed and finally checked the relationship between these parameters.

1.1 Problem Statement

Despite major improvements in the treatment of virtually all cardiac disorders, HF is an exception, in that its prevalence is rising, and only small prolongations in survival are occurring (2). Regardless of improvement in HF knowledge, it still carries poor prognosis, with high morbidity, readmission and mortality (9,40-42). HF has great social and economic impact in sub-Saharan African countries owing to its high prevalence, mortality and impact on young, economically active individuals (43). HF affects approximately 26 million people in the World and has emerged as a dominant form of cardiovascular disease in Africa (1,7), causing mortality of 8.3% (7).

Poor adherence to medications in HF patients ranges from 40-60% and available data show that non-adherence to medications plays a major role in otherwise preventable re-hospitalizations, morbidity and mortality (31,35). CRP is raised in patients with HF and is a prognostic marker as well as contributory factor in HF progression. HF medications lower CRP levels and in these patients - prognosis, re-admissions and outcomes are improved (15 35,44).

Currently, the methods of ascertaining adherence to anti-HF medications are patient self-report, pharmacy refill, pill count, medication event monitoring system (MEMS) (35), as well as determination of plasma drug concentration. Over-estimation of adherence is the main drawback during assessment of adherence status using self-report, pill count and pharmacy refill (35). Determination of steady state plasma concentration of medications is more superior to pharmacy refill, pill count and self-reports (37). But polypharmacy nature of the prescription plan in HF patients means steady state methods based on bio-analysis of parent drugs or metabolite molecules is uneconomical, high technologically demanding and tedious.

A well-established interaction of immune and neuro-hormonal system in HF etiology and disease progress provide a new opportunity for objective method of measuring adherence to anti-HF medications (39). Studies show that hsCRP is an immune biomarker which is stable, with standardized assay and has a strong predictive value in the prognosis of HF and effectiveness of treatment (3,18,28). Currently, no study has been done in Tanzania to

ascertain association between hsCRP and medication adherence using the 8-Item Morisky Medication Adherence. Therefore, understanding the correlation between adherence status and plasma levels of hsCRP among stable HF patients is important. In this study, we determined the hsCRP plasma levels among HF patients; examined their adherence to medications prescribed and finally checked the relationship between these parameters.

1.2 Rationale of the study

Adherence to medication(s) in HF patients is important to delay deterioration and improve quality of life (31,32,35). Poor adherence has been implicated as one of the major contributors of exacerbation and worsening of HF resulting into otherwise preventable readmission episodes, morbidity and mortality (31,35). Immune system plays a great role in pathogenesis of HF and hsCRP is elevated in HF patients. It has been observed that upon treatment with anti-HF medications levels of hsCRP decreases (3,29,30,45-47), this could be used as a marker of disease progression and effectiveness of the medications.

There has been many approaches to measure medication adherence (36). Determination of steady state plasma concentration of medications is more superior to pharmacy refill, pill count and self-reports (37). But polypharmacy nature of the prescription plan in HF patients means steady state methods based on bio-analysis of parent drugs or metabolite molecules is uneconomical, high technologically demanding and tedious. The 8-Item Morisky medication adherence scale (8-MMAS) is now a widely used, simple, cheap, standard self-report accepted with reliability of 0.83 (32), sensitivity of 93% and specificity of 53 % (38).

The hsCRP has been observed to change with HF progress, drop with HF medications, doesn't change with food, time of the day, uniform half-life in healthy and diseased, cheap and fast to get the results, could be the better alternative to the present methods of assessing medication adherence.

Therefore, information on the relationship between adherence status and levels of hsCRP among HF patients is of paramount importance. The results of this study would provide information on the applicability of hsCRP as a tool to measure medications adherence in our setting. Consequently, the results would help in review of the role of hsCRP as a marker for measuring the effectiveness of medications in HF patients.

1.3 Hypothesis

Ho= There is no relationship between HF medications adherence status and hsCRP levels among HF patients on medications.

H_1= There is a relationship between HF medications adherence status and hsCRP levels among HF patients on medications.

1.4 Research Questions

i. What is the level of hsCRP in HF patients on HF medications?

ii. What is the level of adherence to HF medications among HF patients?

iii. Is there any association between levels of hsCRP and adherence to HF medications among HF patients?

1.5 Study Objectives

1.5.1 Broad objectives

To determine the association between levels of hsCRP and adherence to HF medications among HF patients attending the Jakaya Kikwete Cardiac Institute in Dar es Salaam.

1.5.2 Specific objectives

i. To determine hsCRP levels among HF patients on HF medications

ii. To determine the level of adherence to HF medications among HF patients

iii. To determine the association between hsCRP levels and adherence to HF medications among HF patients

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 The role of immune system, sympathetic and rennin angiotensin aldosterone system (RAAS) in HF

The immune system usually follows after sympathetic and RAAS have started, that means sympathetic and RAAS pave the way to immune system. The failing heart usually results in low cardiac output. To maintain cardiac output, the body activates several complex compensatory mechanisms in an attempt to maintain cardiac output and oxygenation of vital organs. These include increased sympathetic tone, activation of the RAAS, sodium and water retention, and other neuro-hormonal adaptations, which lead to cardiac "remodeling" (ventricular dilatation, cardiac hypertrophy, and changes in left ventricular lumen and shape) (48).

The body's normal physiologic response to a decreased cardiac output is generalized activation of the adrenergic (sympathetic) nervous system as evidenced by increased circulating levels of norepinephrine and other catecholamines. The inotropic (increased contractility) and chronotropic (increased heart rate) effects of norepinephrine initially maintain near-normal cardiac output and preserve perfusion of vital organs such as the central nervous system and myocardium. Other adverse consequences of norepinephrine activation include impaired sodium excretion by the kidneys, restricted ability of the coronary arteries to supply blood to the ventricular wall (myocardial ischemia), increased automaticity of cardiac tissue to provoke arrhythmias, hypokalemia, and oxidative stress to trigger programmed cell death (apoptosis) (2,39). The kidney releases the enzyme renin when renal perfusion pressure is decreased. Renin acts to convert a substrate present in the blood called *angiotensinogen* into the inactive decapeptide, *angiotensin I.* Angiotensin I is further metabolized to the active decapeptide, *angiotensin II,* under the influence of circulating angiotensin-converting enzyme (ACE). Angiotensin II has multiple effects favoring sodium and water retention. Its vasoconstriction effects may further decrease glomerular filtration rate, and it stimulates the

adrenal glands to secrete aldosterone, a hormone that increases sodium reabsorption in the distal tubule. Further, angiotensin II stimulates increased synthesis and release of vasopressin, thereby increasing free water retention and stimulation of thirst centers in the central nervous system. Finally, angiotensin II may directly stimulate norepinephrine release. The net result of the kidney and angiotensin II effects is detrimental. Increased sodium and water retention increase preload, whereas angiotensin II–induced vasoconstriction increases systemic vascular resistance and afterload (48).

The size, shape, and thickness of the extracellular matrix are important determinants of the architecture of the intact ventricles and therefore their pumping function. Remodeling of the extracellular matrix occurs with replacement fibrosis following myocardial infarction, a process that has been referred to as a "morphologic footprint of earlier myocardial necrosis" (2). In the RAAS, aldosterone is the main substance which causes myocardial remodeling. The vicious cycle continues with continuous cardiomyocytes necrosis, apoptosis and fibrocytes proliferation which are the key steps in diseases progression and deterioration of the heart (39).

Dying myocardial cells attract the macrophages to engulf them. This attracts even the cytotoxic T–cells and activates immune reaction hence cause production of large number of inflammatory cytokines (39). Activation of immune system leads to production of inflammatory cytokines participating in development of ventricular dysfunction (19,49). Histopathology evidence shows that immune system is a key player involved in the progression of HF (49). The pro-inflammatory cytokines include tumor necrosis factor-α (TNF-α), soluble tumor necrosis factor receptor 19,(sTNFR19), soluble Fas protein, TNF-α-related apoptosis-inducing ligand (TRAIL), interleukin 6, activin A, myeloperoxidase, pentraxin-3, regulated on activation normal T cell expressed and secreted (RANTES), CRP, monocyte chemotactic protein 1 (MCP1) and macrophage inflammatory protein 1-α (MIP-1-α) (44). The macrophages and cytotoxic T-cells release cytokines like IL-6 and TNF-α, respectively. IL-6,IL-1,TNF-αproduced from vascular endothelial cells and macrophages stimulate hepatocytes to release CRP (15,50).

CRP was discovered in 1930 at Rockefeller Institute of Medical Research-New York, by William Tillet and Thomas Francis. They were studying the blood of patient suffering from acute Streptococcal pneumonia infection, and found that, the sera of these patients formed a precipitin with extract from Streptococcal bacterium. The extract was originally named 'fraction C', and was later confirmed to be a polysaccharide (24). CRP was discovered and named for its binding to pneumococcal somatic C-polysaccharide in which it recognizes the phosphocholine residues which are present in this ribitolteichoic acid (16-18,22,50). Phosphocholine is the natural ligand to which CRP binds with highest affinity and this key ligand is ubiquitous as the polar head group of phosphatidlyl choline in cell membranes and plasma lipoproteins. Phosphocholine is also present in constituents of many bacteria, fungi, parasites and plants. However, CRP does not bind to all materials containing phosphocholine as the residues must be 'available' or in an appropriate stereochemical configuration. Thus CRP binds to dead or damaged cells in which significant amounts of lysophosphatidyl choline are present, but not the surface of living healthy cells. Binding of CRP to apoptotic cells is controversial and the most rigorous evidence suggests that CRP only binds to so-called late apoptotic cells which are effectively necrotic. CRP also binds to oxidized phospholipids, platelet activating factor, modified Low Density Lipoprotein (LDL) cholesterol, concentrated normal Very Low Density Lipoprotein (VLDL) cholesterol and to small nuclear ribonucleoprotein particles (which do not contain phosphocholine) when these are exposed in dead or damaged cells (50).

Persistent inflammation has been implicated in the pathogenesis of coronary heart disease (23,51) and is central to the initiation and progression of atherothrombosis and to triggering cardiovascular disease events (22). The released CRP has wide array of functions to further propagate the inflammatory process which play significant role in atherosclerosis initiation/or propagation and HF deterioration(52). CRP is part of the innate immunity system (3), tends to activate innate immune system and it is a very important acute phase response protein. Opsonization to facilitate phagocytic activities of macrophages is enhanced by CRP (3). CRP has the ability to activate complement via the classical pathway (50,53).

Binding of CRP to its macromolecular ligands has many of the same effects as binding of antibodies to antigens, thus CRP precipitates soluble ligands, aggregates particulate ligands and activates the classical complement pathway. By analogy with antibodies, it is therefore possible that CRP might contribute both to host defense against infection and enhancement of inflammatory tissue damage (50). It can amplify the inflammatory response through complement activation, which may cause myocardial cell apoptosis and thus ventricular damage or dysfunction. Indeed, CRP down-regulates endothelial nitric oxide synthase transcription in endothelial cells (54) and destabilizes endothelial nitric oxide synthase mRNA, resulting in decreased nitric oxide release (55). Therefore, it directly quenches the production of nitric oxide. This inhibition of nitric oxide production facilitates endothelial cell apoptosis and blocks angiogenesis, an important compensatory mechanism in chronic ischemia (3). In so doing, CRP may facilitate the development and worsening of chronic HF (15).

Among other proatherogenic effects, CRP up-regulates adhesion molecules (intercellular adhesion molecule-1 (ICAM-1),vascular-cell adhesion molecule-1 (VCAM-1) and E-selectin through up-regulation of Nuclear factor B (NF-B) involved in the nuclear transcription of several proatherosclerotic genes (3,56) and can facilitate leukocyte transmigration by stimulating the release of monocyte chemotactic protein 1 (MCP-1). It also up-regulates angiotensin type-1 receptor (AT-1) in vascular smooth muscle cells and stimulates migration, proliferation, neointimal formation, and reactive oxygen species production. In addition, CRP inhibits bone marrow-derived endothelial progenitor cell survival and differentiation, impairing maintenance of vascular integrity (3).

CRP has been isolated from atheroma laden plaque and studies have shown that, CRP reacts with oxidized LDL-Cholesterol and accelerate macrophages uptake (57). This shows that CRP plays a significant role in initiation and progression of the atherosclerosis. A modest rise of inflammatory mediators like Tumor necrotic factor-α (TNF-α), Interleukin-6 (IL-6) and hsCRP in patients with chronic HF has also been reported (21). Elevated hsCRP levels can independently predict risk of all-cause, cardiovascular mortality in general population (58). Elevated levels of hsCRP have been suggested as a possible contributing factor to the

initiation or maintenance of atrial fibrillation (51,59). hsCRP elevations have been noted in all risk factors for HF such as rheumatic heart diseases, lymphocytic myocarditis and coronary artery diseases (51,60,61). The serum concentration of hsCRP is also elevated in patients with congestive HF (15).

2.2 hsCRP as a predictor of cardiovascular disease

hsCRP has prognostic value for ischemic cardiopathy and HF and high levels of hsCRP in patients with HF are associated with increased morbidity and mortality in cases of ischemic and non-ischemic etiology (62–64). hsCRP has a prognostic value in HF patients with reduced ejection fraction (HFrEF) as well as HF with preserved ejection fraction (HFpEF) (65,66). In a prospective cohort study of 6,437 Dutch outpatients, hsCRP was found to predict incident HF in men, even after adjustment for traditional cardiovascular risk factors and co-morbid coronary heart disease (67). A meta-analysis of data from 54 long term prospective studies which totaled 160,309 individuals without cardiovascular disease (i.e. 1.31 million person-years at risk) and 27,769 fatal or non-fatal cardiovascular disease outcomes reported association between initial hsCRP levels with subsequent cardiovascular events like heart attack and death (21). Furthermore, the study showed that hsCRP concentration is as consistent within individuals during several years as is total cholesterol concentration and systolic blood pressure (21). In order to assess the predictive value of hsCRP, a follow-up study involving 459 HFpEF patients was conducted (68). During the median follow-up of 9.7 years, 40% mortality was recorded. hsCRP was a significantly stronger predictor of cardiovascular mortality in HFpEF patients than in the control group. Furthermore, hsCRP has been shown to be a predictor of improvement and readmission in HF patients (9,69).

CRP is stable in frozen, stored and fresh plasma (26). Current nephelometry techniques using standardized enzymes linked immunosorbent assay (ELISA) measures CRP at level below 0.3mg/L (70). The concentration measured current is far beyond what was once thought to be the normal range (3-8mg/L) owing to low technology of that time. But now, the technology is able to detect lowest value of 0.2mg/L, and therefore referred to as hsCRP. The HF risk predictive value of hsCRP is within this low concentration (<3mg/L).

The American heart association has categorized hsCRP concentration into three separate risk groups. These groups are <1mg/L, 1-3mg/L and >3mg/L corresponding to low, moderate and high risk respectively (70). Review by Osman reported that, patients with elevated levels of both LDL-cholesterol and hsCRP were shown to have almost 8 times the cardiovascular risk of those with low levels of both markers (3). Moreover, it was suggested that in the primary prevention setting, hsCRP is an even stronger predictor of events than is LDL-cholesterol (71). The reduction of LDL-cholesterol to the lowest quintile would reduce risk by 19% whereas hsCRP reduction to the lowest quintile would theoretically afford a 40% reduction in risk (3) .

2.3 hsCRP tend to decrease with the use of some drugs

A review on critical appraisal of hsCRP throughout the spectrum of cardiovascular diseases indicates that plasma levels of hsCRP tend to drop with HF treatment (3). In the review on biomarkers and surrogate endpoints in cardiovascular therapeutics research, hsCRP has been credited as one of endpoints measures which correlate with the clinical outcomes in HF patients (72).According to the studies done previously, atorvastatin and rosuvastatin are two potent statins which can efficiently lower hsCRP levels (29).

Kapur (2008) made a review on clinical efficacy and safety of statins in managing cardiovascular risk in which hsCRP was used as endpoint outcome measures. The review reported a 5.2% versus 36.4% on reduction of hsCRP for pravastatin and atorvastatin groups respectively (46).The findings from the review concur with the results from a 12-week follow-up trial which involved 69 patients with cardiovascular risk randomized into simvastatin or simvastatin-ezetimibe or placebo group (47). In the latter study, the endpoint levels of plasma hsCRP was lowest, lower and unchanged in the simvastatin-ezetimibe, simvastatin alone and placebo group respectively (47). Review by Ridker al., (2009) concluded that, application of the strategy of hsCRP screening followed by high-dose statin therapy over a 5-year period could prevent more than 250,000 heart attacks, strokes, revascularization procedures, and premature vascular deaths in the US alone (25).

Antiplatelets have also been noted for their ability to lower hsCRP level (73). Bernlochner et al., (2010) recruited 1,223 HF patients on aspirin or clopidogrel antiplatelets therapy and reported that 84.5% of patients on chronic antiplatelets therapy with good adherence had lower hsCRP while the rest had hsCRP >5mg/L. The group with hsCRP >5mg/L had higher rate of readmission and cardiovascular events or death due to MI compared to those with <5mg/L. Aspirin adherence was inversely correlated with hsCRP at 3 months (74). In another study, 121 Chinese patients at high risk of HF were randomized into aspirin 100mg/day or 300mg/day or placebo groups and followed for two weeks. The trial reported a dose dependent decrease of hsCRP whereby patients on 300mg/day aspirin had the lowest level of hsCRP compared to a group received 100mg/day. In placebo group no change was observed between baseline and endpoint hsCRP (75). Another randomized clinical trial (at Sinai Center for Thrombosis research in USA) in which 60 patients undergoing stent and at risk of HF due to heart attack received clopidogrel (300mg/day or 600mg/day) alone while the other similar population group (n=60) were treated with clopidogrel-eptifibatide combination. The combination strategy was accompanied with significant reduction of hsCRP and platelets aggregation compared to the clopidogrel alone group (76).

A review on CRP lowering drugs has reported that β-blockers have the ability to lower hsCRP by 36% to 58% in good adherent HF patients or those with risk for HF (30).The study further showed that many ACEIs and ARBs tend to lower hsCRP by 14-39%. These findings on the effect of ACEIs on hsCRP are in agreement with findings of another study which reported that treatment with ACEIs was associated with lower (2.6-fold; $p<0.0001$) median hsCRP levels in patients following stroke or other related cardiovascular risk (3). A three-month prospective study involving 27 coronary heart disease patients at risk of HF treated by calcium channel blockers and/or isosorbide dinitrate was conducted in Chang Gung Memorial Hospital at Keelung, Taiwan. The results from this study showed a significant decrease in plasma hsCRP (45).

In a study conducted by (45) where they were checking the effects of antispastic agents (calcium antagonist and/or isosorbide dinitrate) on hsCRP in patients with coronary vasospastic angina pectoris and no hemodynamically significant coronary artery disease found that, there was decrease in hsCRP level from 8.17mg/L to 2.95mg/L in three months of treatment. Prasad studied the drugs capable of lowering hsCRP, found the following: Aspirin when given daily by two weeks, lowered hsCRP by 29%, statins, reduced up to 50%, rosiglitazone 4mg or 8mg, beta adrenoceptor antagonists, lowered hsCRP by 58%, ACEIs by 32%, ARBs by 39%, CCBs and isosorbide mononitrate decreased hsCRP by 64% (30).

2.4 Adherence to medications among HF patients

Poor medication adherence is common in HF patients (35). Treatment (complexity of regimen, side effects), patient (gender, age), and healthcare system-related factors (economic factors), all influence adherence (35). Non-adherence is a powerful confounder of evidence-based practice and can affect daily patient management, resulting in inappropriate therapeutic escalation with greater costs and potential for harm. Moreover, it increases risk for adverse cardiac events, including mortality (34). Although the evidence on medication efficacy for certain subgroups of patients with chronic HF is clear, there are also compelling data showing that many of these patients do not take their medications as prescribed by health care providers. This “non-adherence” to medications therefore remains a significant barrier to enhancing the effectiveness of existing treatments (33). Researchers have estimated that approximately 50% of patients with chronic illnesses do not take their medications as prescribed (31,32). Poor adherence to medications in chronic HF is associated with worse outcomes in observational studies, including shorter event-free survival (33,77). Importantly, absolute mortality differences associated with non-adherence can exceed incremental benefits observed with new therapies (34). Therefore, there is a need to improve adherence to HF medications among patients. Effective, fast and reliable methods for measurement of adherence are also necessary in the management of patients with HF.

Adherence to medications in HF patients preserves cardiac function, improve quality of life, and reduce risk for costly exacerbations. Good adherence to medication tends to modify the remodeling process and prolong life (31). Non-adherence to medication in chronic HF patients ranges from 40-60% and available data shows non-adherent do play a major role in preventable re-hospitalization, morbidity and mortality among HF patients (31,35,78). In some reports, only 10% of patients were compliant with HF therapies, with up to 64% of readmissions resulting from poor adherence (34). Inamdar discovered that readmission due to non-compliance ranged 21% to 66% (44). These findings show the importance of concentrating on improving patient's adherence to medication. Therefore, this study aims to understand the correlation of adherence to anti-HF medications and the level of hsCRP a well-known pro-inflammatory mediator involved in immune and neurohormonal system role in HF progress.

Goals emphasized during management of HF include symptoms relief, slow disease progression by attenuating modifiable risk factors hence life prolongation (79). The progressive nature of the disease means different goals for different stage or functional class of chronic HF (class/stage according to American Heart Association, AHA), or American College of Cardiology (ACC) and New York Heart Association (NYHA). Array of drugs which reduce sympathetic and RAAS effects, fluid volume and increase blood vessel dilation are currently the mainstay of HF treatment in NYHA functional class II to IV (80). Principally drugs of HF are focused on reduction of cardiomyocytes workload (the β-blockers), preload (venodilators e.g. nitrates, diuretics, dihydropyridines) and afterload (e.g. hydralazine, nitrates, dihydropyridine etc.) (12). In advanced stage of chronic HF, augmentation of contractility using positive inotropes like dobutamine and digitalis (once predominant) are used to increase myocardial contractility and relief symptoms (79). Body weight reduction through regular exercise, salt and high calorie food restriction, high fiber content food also recommended as additive non-pharmacological therapy in AHA stage A-D and in NYHA functional class I-IV (81).

2.5 Areas of research

A well-established interaction of immune and neuro-hormonal system in HF etiology and disease progress provides a new opportunity for objective method of measuring adherence to drugs used for management of HF (39). hsCRP is one of the immune activation biomarkers which is sensitive (26), stable, dynamic and its plasma levels vary consistently with HF progress status (15). hsCRP tend to rise significantly from sixth hour of acute exacerbation of HF reaching a peak level at 48^{th} hour and start to fall steadily during stabilization phase. It declines to baseline after a period of 7-12 days (82). In the absence of such spikes, however, the year-to-year within person variations in hsCRP concentration are similar to those in total cholesterol concentration (21,82). hsCRP is cleared by hepatocytes with a uniform half-life of 18-20 hours regardless of disease or circulating level. It doesn't have diurnal variation (28). The sole determinant of its plasma level is therefore the synthesis rate (50). Such characteristics could make hsCRP a suitable biomarker for assessing HF progress, treatment effectiveness and adherence to medications. Thus, this study sought to compare and correlate levels of adherence to medications and level of hsCRP among patients using drugs for management of HF.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study area

This study was conducted at Jakaya Kikwete Cardiac Institute (JKCI) in Dar es Salaam. JKCI is a National and University teaching cardiac institute. Due to its level as the National and University teaching institute, JKCI has a number of specialists in different cardiovascular fields and well equipped diagnostic and treatment facilities. Majority of the patients attending JKCI are referral cases from different parts of Tanzania. According to available statistics, about 150-200 outpatients with cardiovascular disease are attended every day (Monday to Friday) at JKCI.

3.2 Study design

Cross-sectional study design was employed to obtain required data with respect to this study.

3.3 Study population

This study involved all HF patients who were attending clinic at JKCI and on HF medications.

3.4 Inclusion criteria

The study involved adults (above 18 years), having diagnosis of HF as per attending physicians and on specific medications for HF (any or all of the following: ACEIs, ARBs, aldosterone inhibitors, vasodilators, hydralazine, digoxin, diuretics and beta blockers).

3.5 Exclusion criteria

Patients on regular use of Aspirin, recent (less than 2 weeks) use of antibiotics and those with current infection were excluded from study**.**

3.6 Sample size calculation

Based on the reported prevalence of medications non-adherence of 40 – 60% from a review article by Wu, et al (35), the population prevalence (p) was taken as 40% in order to obtain a maximum sample size. Setting the confidence level at 95%, (Z=1.96) and a margin of error of 7%, the sample size for this study was 206 patients. The correct formula for calculating sample size using proportion (in percent) is shown below:

$$n = \frac{z^2 p\,(100 - p)}{\varepsilon^2}$$

n = Minimum required sample size

z = percentage point of normal distribution corresponding to the level of confidence=1.96

ε = Maximum likely error/ margin of error = 7%

p= expected proportion with the characteristic of interest = 40%

Substituting gives,

$$n = \frac{(1.96)^2 40(100 - 40)}{7^2} = 188$$

Adding for 10% (=18 patients) participants to cover for participants who would refuse to participate in the study; total sample size is 188+18=206. Therefore, the minimum total sample size for this study was 206 patients.

3.7 Sampling procedure

Consecutive sampling technique (convenient sampling) was employed whereby all patients known to have HF were approached for possible enrollment in the study as they came for their regular clinic follow-up. This was done until the required sample size was obtained. HF patients were identified easily because of JKCI ways of consultations. Normally, all patients who come at the clinic have their appointments to their Doctors. So it was easy for us to know

how many and who would come to a particular doctor. Therefore, diagnosis was from Clinicians. And when the patients come, they register, and then go to Nurses' station to be checked for vitals. So, with good collaboration with Doctors and Nurses at the Nurse station, we were able to identify the HF patients and stated screening them at the Nurses' station before Doctors' consultations. All eligible were asked to participate in the study if one agreed, was given a consent form (Appendix II). Consent forms were then signed.

3.8 Data collection

3.8.1 Data collection procedure

Patients were screened and identified as they entered the Nurse's station. At this station, the initial vital signs were taken e.g. systolic and diastolic blood pressure, pulse rate, whether the patient was new or on regular medication, height and weight, the name of consulted Doctor, and room. This made the task of follow up easy. HF patients were identified basing on Doctors' diagnosis with/and previous echocardiography results. At this step**,** patients' inclusion criteria such as age, and having on HF medication for more than a month, exclusion criteria were checked. All other procedures were done in Doctors' room. Other procedures (lab test request) waited until the patient had seen his/ her Doctor. Patients were given the 8-Item Morisky medications adherence scale form (Appendix IV). Then data collection form (appendix III) was used to collect information on socio-demographic information, medications currently taken by the patient as well as co-morbidities.

Those who were able to read and write filled themselves, those who could not read and write were assisted by either the investigator or the research assistant. Medical history including underlying HF cause, co-morbidities and HF duration was obtained from patients' documents as well as through interviews.

For each patient, 5mls of venous blood was taken and sent to Muhimbili Central Pathology Laboratory for the analysis of hsCRP, Complete Blood Count and Cholesterol panel.

3.8.2 Important variables and patient related factors for the study

Important variables with respect to this study were; hsCRP plasma levels and HF medications adherence status. The other variables included age, sex, type of medications, body weight and height, systolic and diastolic blood pressure, type and underlying cause of HF, co-morbidities, hemoglobin concentration, white blood cell count, and cholesterol levels.

3.8.3 Anthropometric and blood pressure measurements

Height and weight were measured and were used to calculate Body Mass Index (BMI) as weight in kilogram divided by height in metres^2. Obesity was defined as BMI $\geq$30kg/m^2 (83). Waist and hip circumference were measured using a tape measure. Waist circumference was measured at the level of the umbilicus and hip circumference at the level of the widest part of the hip. Waist circumference was considered increased when it was >102cm in men and >88cm in women. Waist to hip ratio was considered increased when the ratio exceeded 0.9 in men and 0.85 in women (84).

Blood pressure and pulse rate were measured using electronic BP machine *(Mindray® Patient Monitor; Shenzhen, China)* and it was measured thrice, and the average of the last 2 measurements was taken as the patient's BP (85,86). Hypertension was categorized as grade 1 (140-159/90-99mmHg), grade 2 (160-179/100-109mmHg) and grade 3 ($\geq$180/$\geq$110mmHg) according to European Society of Cardiology guidelines (87).

3.8.4 Determination of high-sensitivity CRP plasma levels

Blood sample for hsCRP was collected into heparinized tubes and transferred to the Muhimbili Central Pathology Laboratory (CPL) for analysis. At the laboratory the samples were centrifuged to get the plasma. The analysis of hsCRP was done by validated automated ELISA nephelometry, which uses particle-enhanced immunonephelometry technique to quantify hsCRP in serum samples. Samples were automatically diluted at 1:10 by the ARCHITECT c Systems machine prior to analysis. Polystyrene particles coated with monoclonal antibodies against hsCRP became agglutinated when mixed with samples

containing hsCRP. This agglutination (measured by nephelometer) is detected as an absorbency change (572nm), (intensity of light scattering due to the agglutination reaction) with rate of change being proportional to the quantity of hsCRP in a sample. The assay was standardized against the reference material for plasma protein preparation, CRM 470 (18). hsCRP was considered elevated when it was >5mg/L, according to the Muhimbili Central Pathology Laboratory (CPL) reference range as well as from previous literature (73).

3.8.5 Determination of complete blood count and cholesterol

Blood for measuring cholesterol and complete blood count was collected and transferred to MNH Laboratory for analysis. Important parameters analyzed were complete blood count, including hemoglobin concentration, White blood cell count, Monocyte count, Basophil count, Platelet count, Neutrophil count, and Lymphocyte count. Components of blood cholesterol included total blood cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C). These parameters were measured and analyzed.

Anemia was defined as Hemoglobin concentration of<13g/dL in men and <12g/dL in women (88). Total cholesterol was considered elevated when it was above 5.2mmol/L and low density lipoprotein cholesterol was considered elevated when it was above 3.36. White blood cells count was considered raised when it was > 9.8 $*10^9$/L (48).

3.8.6 Determination of adherence to HF medications

Participants were interviewed using Morisky medication adherence questionnaire (Appendix IV). The 8-item Morisky medication adherence scale (MMAS-8) is self-report questionnaire with 8 questions (items) whose wording of the questions/items are formulated to avoid answering “yes” to questions regardless of their content. Items 1 through 7 have response choices “yes” or “no” whereas item 8 has a 5-point Likert response choices. Each ‘‘no” response is rated as ‘‘1” and each ‘‘yes” is rated as ‘‘0” except for item 5, in which each response ‘‘Yes” is rated as ‘‘1”and each ‘‘no” is rated as ‘‘0”. For item 8, if a patient chooses response ‘‘0”, the score is ‘‘1”and if they choose response ‘‘4”, the score is ‘‘0”. Responses ‘‘1, 2, 3” are respectively rated as ‘‘0.25, 0.75, 0.75”. Total MMAS-8 scores can range from 0

to 8 and have been categorized into three levels of adherence: high adherence (score = 8), medium adherence (score of 6 to <8), and low adherence (score <6) (32,38). A person was considered to have good adherence if he/she scores 8, less than that, was considered to have poor adherent (32). The MMS-8 has sensitivity of 93% and specificity of 53% (38).

3.9 Data management

Numbers were used as identity in order to maintain confidentiality of study participants. Collected data were stored in secured fire resistant case accessible only to investigator. Raw data in physical storage were transferred into electronic form for cleaning and data analysis. Accessibility to all storage formats were only under custody of investigators while ensuring all ethical issues had been taken into consideration.

3.10 Data analysis

Data were analyzed by Statistical Package for Social Sciences (SPSS) computer software, version 21. Univariate analysis using mean as a measure of central tendency, and range and standard deviation as measures of dispersion were employed for quantitative variables such as hsCRP plasma concentration, hemoglobin, White blood cell counts, platelet count and cholesterol levels. Proportion(s) were applied for categorical data such as adherence status, sex and type of HF. Bar charts, contingency tables and pie charts were utilized during data summarization accordingly. Comparison of two means was carried out by simple Student's t-test. Analysis of variance (ANOVA) statistical model was used to test for statistical significance of more than two means for a given variable. Chi-square was employed for testing statistical significance for frequency distribution of categorical data. Uni- and multi-variate logistic regression analyses were used to determine the independent associations of poor adherence. Normally, p-value was read from Pearson chi Square except if any cell is found to have less count where fisher exact test or linear by linear association were employed. The results were of statistical significance when *p*-value was <0.05.

3.11 Study limitation and mitigation measures

Known confounding factors such as stress and patient nutrition habits were not recorded due to difficulties of accessing such information. Conducting this study in an advanced Hospital reduces the generalization of the results. Moreover, this was a cross-sectional study and therefore some information that may have been obtained from a follow up study (such as relative risk, life style, diet, ascertaining absence of current infection and effects of estrogen drugs on hsCRP) could not be gathered. However, fair sample size, consistent data collection and stratification for some selected variables like body mass index, age groups and gender were employed to minimize erroneous conclusion. The 8-item Morisky medication Adherence Scale (MMAS) as a means of assessing adherence has it shortcomings. It requires respondent to remember some past events regarding use of her/his medications. This could result into recall bias. But also, if somebody does not tell the truth it is hard to discover. However, prior information to patients about the purpose of the study, standardization of questions and scores may have minimized such bias.

3.12 Ethical clearance

The study commenced after obtaining ethical clearance from Muhimbili University of Health and Allied Sciences Research and Publication committee. Permission to conduct the study was sought from the director of research JKCI. Each study participant freely signed informed consent form (Appendix II) before proceeding with data collection. For confidentiality purposes, each participant was assigned identity number instead of his/her name.

CHAPTER FOUR

4.0 RESULTS

4.1 Socio-demographic characteristics of participants

A total of 500 participants were approached and screened to be included in the study. Of the 500 approached, 176 patients were not eligible, 40 patients declined to participate while 35 withdrew from the study during the data collection process. Of the remaining 249 patients, blood test results of 39 patients could not be retrieved from the laboratory leaving 210 available for the final analysis. Figure 1 summarizes the patients' recruitment process.

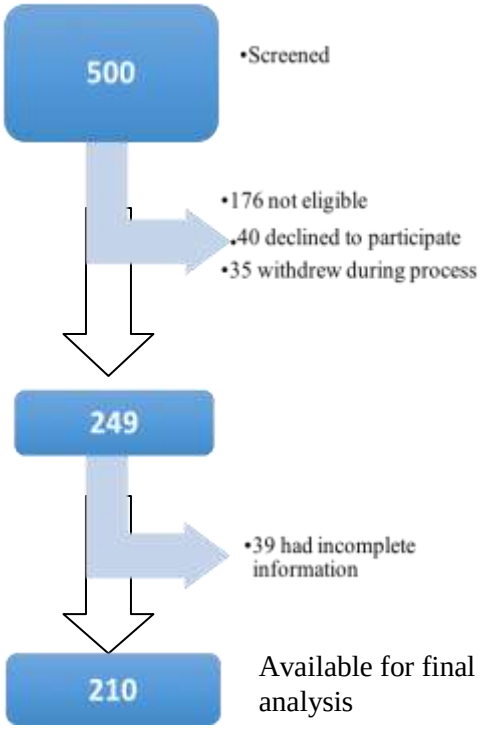


Figure 1: Flow chart showing patients' recruitment

A total of 210 participants had complete data and constitute the current study population. The mean ±SD age of the total population was 54 ±15.9 years and 113 (53.8%) were females. Half (50.0%) of participants were older adults aged above 55years. Also half (50.0%) of the participants had attained primary education, 55 (26.2%) secondary education and 19 (9%) had attended colleges and other forms of higher education. Most (67.6%) participants were married. Participants were equally distributed with regard to their mode of hospital payment (i.e. insured versus not insured). The mean duration from the diagnosis of HF was 3.3 years (range 1 – 36 years), and hypertension was the most common cardiovascular risk factor being present in 147 (70%) of the total population as recorded from patients' files. Table 1 summarizes the socio-demographic characteristics of the study population.

Table 1: Socio-demographic characteristics of the total study population

Characteristics	Frequency (N = 210)	Percent (%)
Age group (years) (range19-95), mean 54(± 15.9)		
≤ 35	32	15.2
36-55	73	34.8
≥56	105	50.0
Sex		
Male	97	46.2
Female	113	53.8
Level of education		
No formal education	31	14.8
Primary education	105	50.0
Secondary education	55	26.2
College/University	19	9.0
Occupation		
Not employed/peasant	103	49.0
Employed/business	80	38.1
Retired	27	12.9
Marital status		
Single	12	5.7
Married	142	67.6
Divorced	5	2.4
Widowed	36	17.1
Separated	15	7.2
Hospital payment mode		
Insured	105	50
Public/Exempted/Private	105	50
Cardiovascular risk factors		
Hypertension	147	70
Diabetes Mellitus	21	10
Alcohol consumption	65	31
Smoking	34	16.2

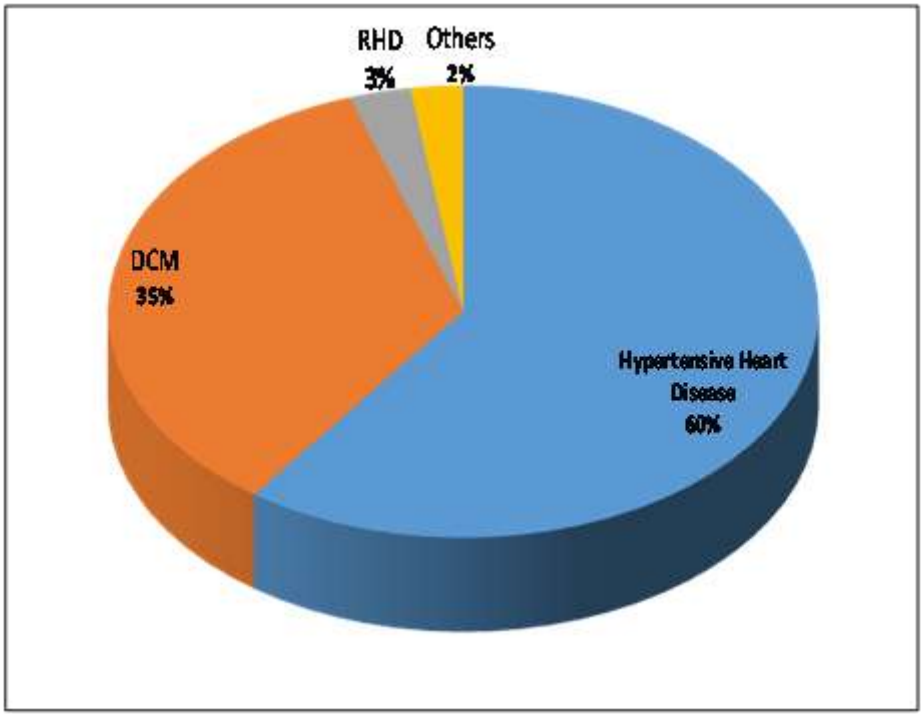
4.2 Anthropometric, blood pressure and clinical findings of participants

The mean ±SD BMI of the total population was 26.7 ±6.2kg/m^2 and obesity defined as BMI >30kg/m^2 was present in 41 (19.5%) participants (Table 2). Majority of participants (81%) had higher than the recommended waist/hip ratio as per WHO criteria (i.e. waist/hip ratio >0.9 for males and >0.85 for females), while elevated waist circumference as a measure of central obesity was present in 73 (34.8%) participants (Table 2). The mean ±SD systolic and diastolic blood pressures were 128 ±32mmHg and 80 ±21mmHg, respectively. In the total population, stage 1-, stage 2- and stage 3-hypertension was present in 24.8%, 11.4% and 7.6% of patients, respectively (Table 2).

Table 2: Anthropometric and blood pressure findings in the total study population

Finding	**Mean ±SD/n (%), n = 210**
Mean ±SD height (cm)	159.7 ± 8.5
Mean ±SD weight (kg)	68.1 ± 16.3
Mean ±SD body mass index (kg/m^2)	26.7 ± 6.2
Obesity status, n (%)	
Normal weight	86 (41.0)
Overweight	83 (39.5)
Obese	41 (19.5)
Mean ±SD waist circumference (cm)	90 ± 14
Mean ±SD hip circumference (cm)	98 ±14
Mean ±SD waist to hip ratio (cm)	0.92 ± 0.04
Proportion with elevated waist/hip ratio, n (%) (central obesity)	170 (81.0)
Proportion with elevated waist circumference, n (%)	73 (34.8)
Mean ±SD pulse rate (beats/min)	84 ± 18
Mean ±SD systolic blood pressure (mmHg)	128 ± 32
Mean ±SD diastolic blood pressure (mmHg)	80 ± 21
Hypertension stage, n (%)	
Normal Blood Pressure	118 (56.2)
Stage 1	52 (24.8)
Stage 2	24 (11.4)
Stage 3	16 (7.6)

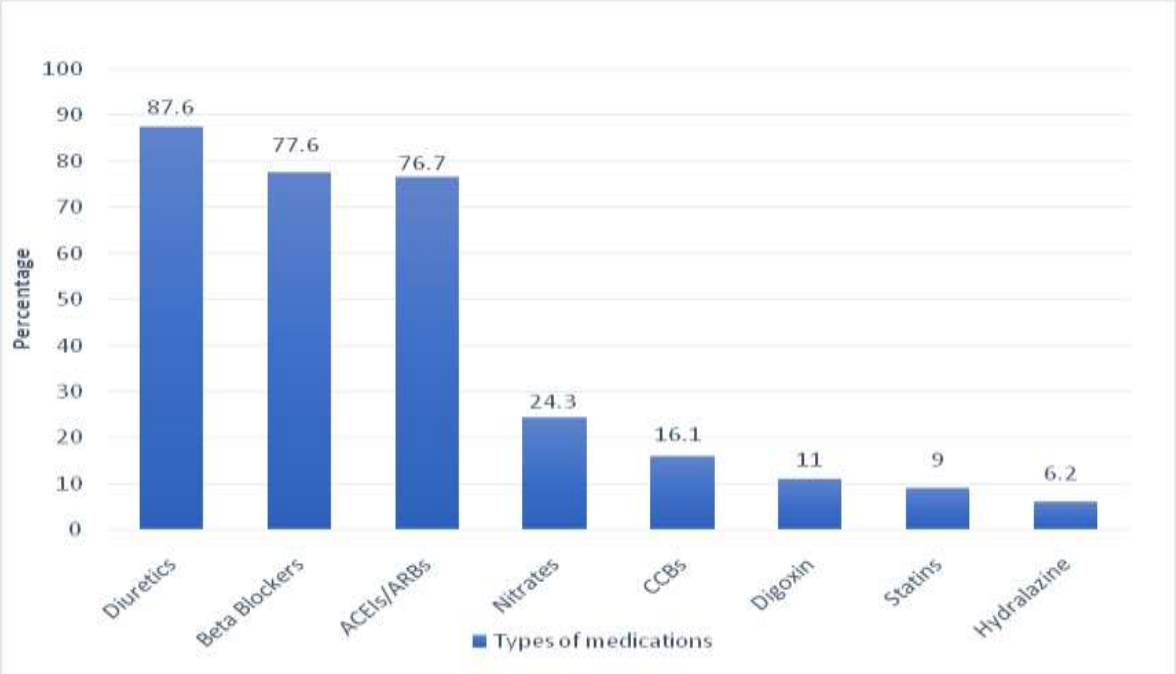
About two thirds (60%) of the study participants had hypertension, followed by dilated cardiomyopathy (34.8%) and rheumatic heart disease (3%) as the underlying causes of HF. Five (2%) patients had "other" causes of HF of which 4 had ischemic heart disease and 1 patient had a congenital heart disease (Tetralogy of Fallot) as the underlying cause of HF.
Figure 2 summarizes the causes of HF in the total study population.



DCM = Dilated Cardiomyopathy, RHD=Rheumatic Heart Disease

Figure 2: Causes of HF in the total study population

Majority of the patients were found to use diuretics, 184 (87.6%). Beta blockers were the second most used class of medications being used by 163 (77.6%) patients while ACEIs or ARBs were being used by 161 (76.7%) patients. Figure 3 summarizes the types and frequency of HF medications used by the study population.



ACEIs = Angiotensin Converting Enzyme Inhibitors; ARBs = Angiotensin Receptor Blockers; CCBs = Calcium Channel Blockers

Figure 3: Types and percentage of medications used in the total study population

4.3 Laboratory findings

The mean hemoglobin of the total study population was 12.2g/dl. Anemia, defined as hemoglobin <12g/dl in women and <13g/dl in men was present in 113 (53.8%) patients (Table 3). The mean total cholesterol was 5.1mmol/l and 107 (51%) patients were found to have elevated levels. The mean LDL-cholesterol and HDL-cholesterol were 3.5mmol/l and 1.12mmol/l, respectively. LDL-cholesterol was found to be elevated in 114 (54.3%) patients while 95 (45.2%) patients had low levels of HDL-cholesterol (Table 3). In the total population, the mean white blood cell count was 6.8 $x10^9$/µL, and 12 (5.7%) patients had elevated total white blood cell counts (defined as white blood cell count >9.8 $x10^9$/µL) (Table 3). The mean ±SD hsCRP in the total population was 7.1 ± 4.9mg/L. Elevated hsCRP defined as the value above 5mg/L was present in 122 (58.1%) patients (Table 3).

Table 3: Laboratory findings in the total study population

Laboratory finding	Mean ± SD/n (%), n = 210
Mean ±SD hemoglobin (g/dl)	12.2 ± 1.5
Proportion with anemia, n (%)	113 (53.8)
Mean ± SD total cholesterol (mmol/L)	5.1 ± 1.2
Proportion with elevated total cholesterol, n (%)	107 (51.0)
Mean ±SD LDL-cholesterol (mmol/L)	3.5 ±1.02
Proportion with elevated LDL-cholesterol, n (%)	114 (54.3)
Mean ±SD HDL-cholesterol (mmol/L)	1.12 ±0.39
Proportion with low HDL-cholesterol, n (%)	95 (45.2)
Mean ±SD WBC count ($x10^9/\mu L$)	6.8 ± 2.13
Proportion with elevated WBC count, n (%)	12 (5.7)
Mean ±SD hsCRP (mg/L)	7.1 ± 4.9 (range 0.2 to 31.0)
Proportion with elevated hsCRP levels, n (%)	122 (58.1)

SD = Standard Deviation; LDL = Low Density Lipoprotein Cholesterol; HDL = High Density Lipoprotein; WBC = White Blood Cell

4.4 Adherence to HF Medications

In the Morisky medications adherence tool, 72 (34.3%) patients scored high (i.e. total scores = 8), 101 (48.1%) patients scored medium (i.e. 6 – 7 scores), while 37 (17.6%) patients scored low (i.e. <6 scores) (Figure 4).

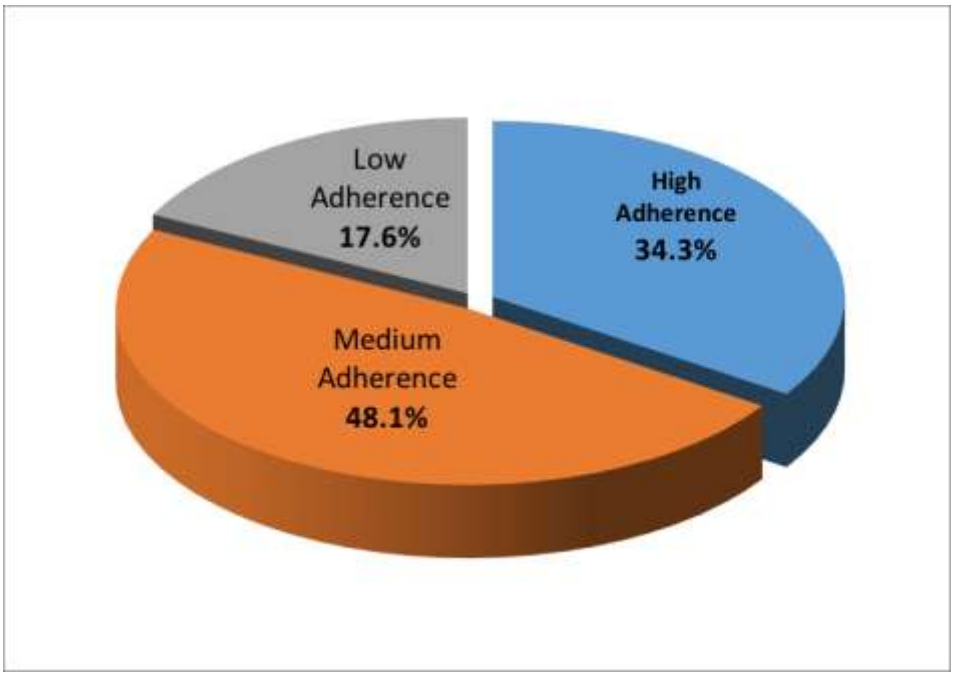


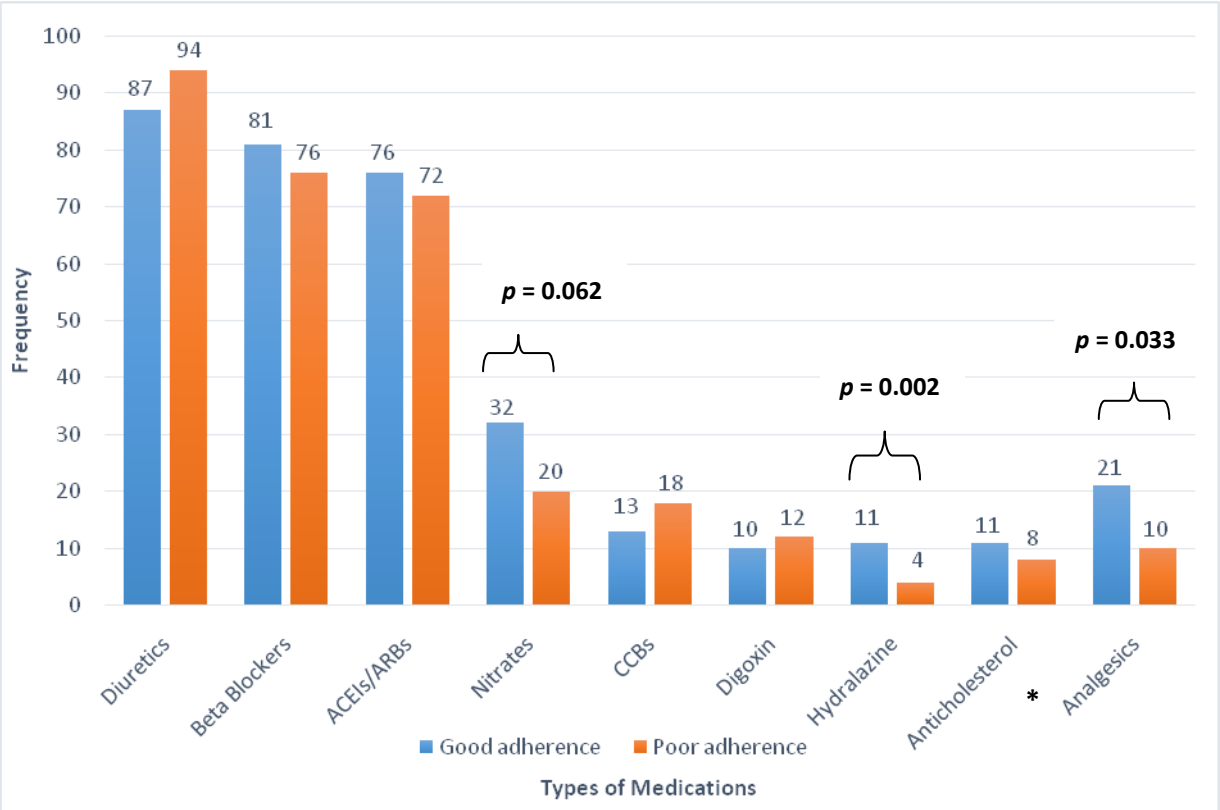
Figure 4: Medications adherence in the total study population

Accordingly, 72 (34.3%) patients who scored high were categorized as having good adherence and 138 (65.7%) who scored medium and low were categorized as having poor adherence (32). Patients with poor HF medications adherence did not differ from those with good adherence in terms of gender distribution, age, marital status, level of education, employment status or whether they were insured or not, all $p > 0.05$, (Table 4). They also did not differ in all clinical and anthropometric parameters including underlying causes of HF, cardiovascular risk profile, levels of systolic dysfunction, obesity as well as blood pressure levels, all $p > 0.05$, (Table 4).

Table 4: Socio-demographic and clinical characteristics of patients in relation to HF medications adherence status

Characteristic	Good Adherence (n = 72)	Poor Adherence (n = 138)	*p*-value
Female gender, n (%)	41 (56.9)	72 (52.2)	0.510
Mean ±SD age (years)	54.2 ± 13.4	54.2 ± 17.1	0.995
Age >55years, n (%)	35 (48.6)	70 (50.7)	0.771
Living without partner, n (%)	24 (33.3)	44 (31.9)	0.831
Below secondary education, n (%)	47 (65.3)	89 (64.5)	0.910
Employment status, n (%)			
Unemployed	37 (51.4)	66 (47.8)	0.884
Employed/business	26 (36.1)	54 (39.1)	
Retired	9 (12.5)	18 (13.0)	
Not insured, n (%)	38 (52.8)	67 (48.6)	0.561
Underlying HF cause, n (%)			
HHD	42 (58.3)	84 (60.9)	0.749
DCM	26 (36.1)	47 (34.1)	
RHD	3 (4.2)	3 (2.2)	
Other causes	1 (1.4)	4 (2.9)	
Hypertensive, n (%)	53 (73.6)	94 (68.1)	0.409
Diabetic, n (%)	11 (15.3)	10 (7.2)	0.066
Taking alcohol, n (%)	24 (33.3)	41 (29.7)	0.590
Smokers, n (%)	11 (15.3)	23 (16.7)	0.795
Mean ±SD Ejection Fraction (%)	39 ± 15	39 ± 13	0.773
Ejection function <35%, n (%)	29 (40.3)	57 (41.3)	0.886
Admitted previous year, n (%)	28 (38.9)	45 (32.6)	0.364
Mean ±SD BMI (kg/m^2)	27.7 ± 7.0	26.2 ± 5.7	0.101
Obese (BMI ≥30kg/m^2), n (%)	17 (23.6)	24 (17.4)	0.280
Mean ±SD Waist circumference (cm)	91.5 ± 13.8	89.3 ± 13.9	0.276
Central obesity, n (%)	25 (34.7)	48 (34.8)	0.993
Mean ±SD Systolic BP (mmHg)	126 ± 30	129 ± 34	0.485
Mean ±SD Diastolic BP (mmHg)	79 ± 18	81 ± 22	0.510
≥Stage 2 hypertension, n (%)	10 (13.9)	30 (21.7)	0.169

HHD = Hypertensive Heart Disease; DCM = Dilated Cardiomyopathy; RHD = Rheumatic Heart Disease; BMI = Body Mass Index; BP = Blood Pressure



ACEIs = Angiotensin Enzyme Inhibitors; ARBs = Angiotensin Receptor Blockers; CCBs = Calcium Channel Blockers

**Analgesics other than aspirin*

Figure 5: HF medications use in relation to adherence status

Figure 5 shows medications used and their frequency in relation to HF medications adherence status of the patients. Patients with poor adherence were less likely to use hydralazine as well as less likely to use analgesics. There was however no difference between the two groups in terms of the use of diuretics, beta blockers, ACEIs/ARBs, nitrates, calcium channel blockers, digoxin or anticholesterol medications, all $p > 0.05$, (Figure 5).

Table 5: Laboratory findings in relation to HF medications adherence status

Laboratory finding	Good Adherence (n = 72)	Poor Adherence (n = 138)	*p*-value
Mean ±SD hsCRP (mg/L)	5.72 ± 4.59	7.75 ± 5.00	0.004
hsCRP tertiles, n (%)			
<1 mg/L	3 (4.2)	5 (3.6)	0.251
1 – 3 mg/L	15 (20.8)	17 (12.3)	
>3 mg/L	54 (75.0)	116 (84.1)	
Elevated hsCRP, n (%)	28 (38.9)	94 (68.1)	<0.001
Mean ±SD hemoglobin (g/dl)	12.1 ± 1.3	12.2 ± 1.7	0.902
Anemia, n (%)	36 (50.0)	77 (55.8)	0.424
Mean ±SD WBC count ($x10^9$/L)	6.7 ± 1.8	6.8 ± 2.2	0.640
Raised WBC count, n (%)	2 (2.8)	10 (7.2)	0.185
Mean ±SD platelets count ($x10^9$/L)	233 ± 70	242 ± 77	0.423
Elevated platelets count, n (%)	1 (1.4)	3 (2.2)	0.693
Low platelet count, n (%)	9 (12.5)	11 (8.0)	0.289
Mean ±SD total cholesterol (mmol/l)	4.8 ± 1.3	5.2 ± 1.2	0.031
Elevated total cholesterol, n (%)	30 (41.7)	77 (55.8)	0.052
Mean ±SD LDL-cholesterol (mmol/l)	3.32 ± 1.02	3.58 ± 1.01	0.072
Elevated LDL-cholesterol, n (%)	32 (44.4)	82 (59.4)	0.039
Mean ±SD HDL-cholesterol (mmol/l)	0.99 ± 0.36	1.18 ± 0.39	0.001
Low HDL-cholesterol, n (%)	42 (58.3)	53 (38.4)	0.006

hsCRP = high sensitivity C-Reactive Protein; WBC = White Blood Cell Count; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein

Patients with poor adherence had significantly higher mean ±SD hsCRP levels (7.75 ±5.00mg/L) when compared to those with good adherence (5.72 ±4.59mg/L), $p = 0.004$, (Table 5). Consequently, the proportion of patients with elevated hsCRP was significantly higher in the group of patients with poor adherence to HF medications, (Table 5). The mean ±SD WBC count did not differ between patients with poor adherence compared to those with good adherence, and neither did the proportion of patients with elevated WBC count; although there was a trend towards higher proportion of patients with elevated WBC to be more in the poor adherence group (Table 5). The mean total cholesterol level as well as mean level of HDL-cholesterol was significantly higher in the group of patients with poor adherence, both $p< 0.05$, (Table 5). Neither the mean hemoglobin nor mean platelet count differed between the good and poor adherence groups of patients (Table 5).

Factors found to have at least weak associations ($p< 0.5$) with poor medications adherence were entered into a multivariate logistic regression analysis in order to determine the independent associations of having poor HF medications adherence among HF patients attending care and treatment at JKCI. Factors entered into the model included being obese (BMI $\geq 30 kg/m^2$), having diabetes mellitus, being admitted in the past 1 year, having ≥stage 2 hypertension on the day of recruitment, having elevated levels of hsCRP, anemia as well as having elevated WBC count and raised total serum cholesterol. In addition, all medications found to have had associations with medications adherence were included in the model. Gender and age were lastly forced into the regression analysis as important confounders (Table 6).

Table 6: Independent predictors of poor HF medications adherence obtained in multivariate logistic regression analysis

	Univariate analysis		Multivariate analysis	
Variable	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Female gender	0.83 (0.47 - 1.46)	0.511	0.95 (0.45 – 2.01)	0.902
Age >55 years	1.09 (0.62 – 1.92)	0.771	1.56 (0.75 – 3.27)	0.239
Obesity	0.68 (0.34 – 1.37)	0.282	0.61 (0.25 - 1.48)	0.273
Diabetes Mellitus	0.43 (0.18 – 1.08)	0.071	0.43 (0.14 - 1.29)	0.128
Admitted last year	0.76 (0.42 – 1.38)	0.365	0.80 (0.40 - 1.60)	0.530
≥Stage 2 hypertension	1.72 (0.79 – 3.76)	0.172	**2.72 (1.01 - 7.46)**	**0.050**
Elevated hsCRP	**3.36 (1.85 – 6.08)**	**<0.001**	**4.27 (2.14 – 8.51)**	**<0.001**
Anemia	1.26 (0.71 – 2.24)	0.424	1.50 (0.76 - 2.94)	0.241
Elevated WBC count	2.73 (0.58 – 12.83)	0.202	2.24 (0.41 - 12.37)	0.354
Elevated Total Cholesterol	1.77 (0.99 – 3.15)	0.053	1.53 (0.79 – 2.97)	0.204
ACEI/ARB use	0.79 (0.41 – 1.52)	0.470	0.88 (0.41 - 1.90)	0.752
Analgesics use	**0.43 (0.19 – 0.95)**	**0.036**	**0.36 (0.14 - 0.92)**	**0.033**
Nitrates use	0.54 (0.28 – 1.04)	0.063	0.51 (0.24 - 1.09)	0.082
Hydralazine use	**0.30 (0.10 – 0.96)**	**0.042**	**0.09 (0.02 - 0.40)**	**0.002**

Having elevated hsCRP was found to be strongly associated with poor medications adherence in univariate analysis (OR = 3.36, 95% CI 1.85–6.08), and remained to be independently and even more strongly associated with poor medications adherence in the multivariate analysis, (OR = 4.27, 95% CI 2.14–8.51), both $p< 0.001$, (Table 6). Furthermore, having ≥stage 2 hypertension on the day of clinic visit became independently associated with the finding of poor medications adherence when all other factors were included in the model OR=2.72 (1.01-7.46), $p= 0.041$, (Table 6). Use of analgesics and hydralazine was negatively associated with poor medications adherence in univariate analysis, and both remained so independently in the multivariate analysis (Table 6). Of note, elevated WBC count (a measure of infection) did not predict poor adherence, and importantly did not alter the association between hsCRP and medications adherence status.

CHAPTER FIVE

5.0 DISCUSSION

This study was done to determine the association between levels of hsCRP and medications adherence status among HF patients attending care and treatment at a tertiary health facility in Dar es Salaam, Tanzania. The main findings of the study are 3-fold: First, the prevalence of poor medications adherence among HF patients in this population is high (65.7%); second, the proportion of HF patients with elevated levels of hsCRP (indicating underlying on-going inflammatory process) is also high (58.1%) and third, elevated hsCRP levels are strongly and independently associated with poor medications adherence in this population.

Poor adherence to medications among HF patients is a known problem worldwide and previous literature indicates the problem to range from 40% to 60% (31,35). The prevalence of poor medications adherence found in this study is therefore almost similar to that reported in the previous studies. However, the prevalence reported in the present study is different from that reported at Chris Hani Baragwanath Hospital in Soweto, South Africa in which researchers examined the pattern of treatment adherence, self-care and treatment knowledge in 200 patients with chronic HF (89). In the later study, the prevalence of poor HF medications adherence was 29%, much lower than the findings in the present study. The difference between ours and the study from South Africa is most likely due to the fact that the South African study was part of an on-going HF registry and it is possible that patients in that study population better adhered to their medications because they knew they were actively been followed up. Furthermore, this South African study used pill count and Questionnaire (no details of this type of questionnaire, probably locally designed) to assess adherence. The 65.7% prevalence found in this study is however much lower than that reported at the cardiology clinic in Abidjan, Ivory Coast which was 88.4% (90). In that study, the investigators used heart failure compliance questionnaire, and pointed out too much use of traditional medicine among HF patients as a factor that influenced poor medications adherence in that population (90).

Both the mean level of hsCRP (7.1±4.95mg/L) and the proportion of HF patients with elevated hsCRP (58.1%) were high in the present study. Our findings confirm previous findings in documented literature and adds to the existing knowledge on the fact that patients with HF have an existing and on-going low level of inflammation, evidenced by increased levels of hsCRP in these patients (15,51). The prevalence of elevated hsCRP found in the present study is remarkably similar to that found in big registries of HF patients following acute myocardial infarction in the United States of America; the TRIUMPH (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status) and the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) registries (91). The registries included 3,410 patients and the prevalence of elevated hsCRP was reported to be 58.6%. The prevalence of elevated hsCRP levels in this study is however slightly higher than the 50% prevalence reported by the Val-HeFT trial (Valsartan in HF Trial), which involved 4,202 HF patients participating in a multinational randomized clinical trial to assess the efficacy of the Angiotensin receptor blocker Valsartan versus placebo in patients with NYHA classes 2-4 (62).

There is paucity of documented literature on hsCRP among HF patients in Sub Saharan Africa, and only few studies have been reported from the region (92). In a study by Sliwa et al (2006) that studied inflammatory markers as predictors of outcome in 100 patients with newly diagnosed peri-partum cardiomyopathy at Chris Hani Baragwanath Hospital in South Africa, the reported median hsCRP was 10mg/L (range 1 – 90mg/L), and 45% of patients had elevated levels of hsCRP. Of note, the cut-off point in the later study for elevated hsCRP level was >10mg/L, as opposed to the present study's cut-off point of >5mg/L, which is most likely the reason of the differences in prevalence among the two studies. There was no information as to why this cut of point of 10mg/L was used as a number of researchers have reported that normal hsCRP is up to 5mg/L for Blacks, and less than 3mg/L for other races (93,94). The 5mg/L is also a normal range value in Muhimbili National Hospital lab (CPL).

This study confirms previous knowledge that elevated hsCRP is associated with poor medications adherence among HF patients, and adds to the existing literature that among HF patients in a tertiary health facility in Sub Saharan Africa, elevated levels of hsCRP is associated with up to 4 times increased likelihood of having poor medications adherence. The mechanisms for higher hsCRP levels among HF patients who are not adherent to their HF medications have been explained (51,60,61). Most of the explanation lies in the fact that, because HF is also partly an inflammatory process (95,96), this means that drugs known to alleviate the on-going HF process by either reducing the remodeling process, reducing ischemia-related ventricular dysfunction, reducing the excessive neurohumoral stimulation as well as reducing cellular apoptosis – all have the potential to lower hsCRP levels (3,62). This effect has been reported in patients with ischemic and non-ischemic heart failure (62). Although the present study did not look at the individual medication's effect on lowering of hsCRP (this was not within the scope of the present study), the study did find that patients were generally prescribed the commonly known HF medications as per HF guidelines (87). ACEIs, ARBSs, Aldosterone Inhibitors, Beta Blockers, Nitrates – have all been shown to reduce hsCRP levels at different capacities, ranging from 14 to 64% (3,30,45). Of note except for hydralazine, most of the HF medications in this study were equally prescribed in both the good and the poor adherent groups, so one can conclude that the difference in the hsCRP levels seen between these two groups is mainly due to patients' adherence status.

The finding that having blood pressure readings equivalent to stage 2 or more hypertension (systolic blood pressure ≥160mmHg, and/or diastolic blood pressure ≥100mmHg) on the day of clinic visit is independently associated with poor medications adherence is an interesting one. Patients not adhering to their prescribed HF medications are also likely not to adhere to other chronically used medications, including those for blood pressure control. This finding is not unique as has been reported by previous researchers (97,98), and is a recognized barrier to optimal care in patients with multiple drug use (99). The finding is however very clinically important as control of hypertension among patients with HF is equally important due to the progressive nature of HF when co-morbid conditions, including hypertension are not controlled. Medications adherence is a potentially modifiable behavior that should be

monitored in patients taking long term medications. It is only through efficient use of medications that the benefits of new therapies and advances in HF management will make an impact on the individual patient's outcome (34).

We found in this study that patients prescribed to use hydralazine and those prescribed analgesics were less likely to be non-adherent to their overall HF medications use. This finding is difficult to explain; it is however hypothesized that patients prescribed on analgesics are more likely to adhere to their medications due to the immediate effect of analgesics in alleviating pain. Further studies on patients' behaviors towards specific drugs in relation to overall medications adherence are warranted.

A number of socio-demographic, economical and behavioral factors are known to influence medications adherence in patients on long term use of prescribed medications (100). In the present study none of the socio-demographic factors studied (age, gender, marital status, level of education, employment status, insurance status, alcohol use and cigarette smoking) was associated with medications adherence, contrary to findings in previous literature (35,101). As the present work was primarily designed to determine the association between serum hsCRP levels and HF medications adherence, it was therefore not adequately powered to study the socio-demographic or behavioral determinants of poor medications adherence in this population. Further studies using appropriate sample size are recommended in order to ascertain these associations; if any, in our local setting.

The limitations of this study include its cross-sectional nature, and therefore we cannot confirm causality. However, in the present study it is almost only clinically plausible to say that hsCRP levels were raised following non adherent to HF medications and not vice-versa. Other factors that affect hsCRP levels were not systematically studied and it is therefore possible that some patients with good medications adherence continued to have elevated hsCRP due to other factors including improper HF prescription by attending physician, disease progression, etc. The Morisky medications adherence tool has its own limitations, which include a recall bias.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The prevalence of poor medications adherence among HF patients attending care and treatment at JKCI is high, being present in almost two third of this population, and more than half of the patients have elevated levels of hsCRP. Furthermore, this study has found that elevated hsCRP is independently associated with poor HF medications adherence among HF patients attending care and treatment at JKCI.

6.2 Recommendations

Further studies from different clinical settings are recommended to confirm the interesting findings obtained from this study. If confirmed, hsCRP level can, in the future be considered as a surrogate marker of HF medications adherence among HF patients in our local setting.

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APPENDICES

Appendix I: Consent Form (English Version)

INFORMED CONSENT FORM

ID NO | | | |

Consent to participate in the study entitled:

COMPARATIVE STUDY ON ADHERENCE STATUS AND C-REACTIVE PROTEIN LEVELS AMONG HF PATIENTS ON MEDICATION

Background: HF is a global public health problem affecting approximately 26 million people worldwide. Few decades ago, conjunction of neurohomornal and immune system role in heart muscles remodeling and deterioration of HF has been elucidated. High-sensitivity C-reactive protein is an immune biomarker which is stable and strong predictive value in HF prognosis and effectiveness of treatment. Therefore, understanding the correlation between adherence status and plasma level of hsCRP among HF patients is important.

Introduction

Hello! This consent form contains information about the research named above. In order to be sure that you are informed about being in this research, we are asking you to read or have read to you this consent form. You will also be asked to sign it or make a mark in front of the witness. You will be given a copy of this form. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you might not understand.

Reason for the research

You are being asked to take part in this research that aims at checking the association between hs-CRP and adherence to medication, and hence come up with recommendations regarding better ways of managing the disease.

General information and your part in the research

If you agree to be in this research you will be required to answer a series of questions in the interview guide or questionnaire. This questionnaire will contain your contact information and will store all the information that is required for the purpose of this study. We will give no additional drug and your file will be viewed. We will need a little blood sample to be able to analyze the amount of hsCRP in your blood.

Risks

We do not expect any harm to happen to you because of joining this study. The amount of blood required is too small to cause any problems to you.

Benefits

By participating in this study you're fostering scientific knowledge which may be useful during periodical revision of health policy and practice.

Right to withdraw and alternatives

Taking part in this study is completely your choice. You can stop participating in this study at any time, even if you have already given your consent. Refusal to participate or withdrawal from the study will not involve penalty.

Confidentiality

Your name will not be documented; only numbers will be used for identification. All the information obtained from this study will be used for the research purpose only, and will not be shared to anyone without participation consent.

Whom to contact

contact: +255 714 662023, Mr. Maganga M. Gabriel, Mpharm Hospital and Clinical pharmacy at Muhimbili University of Health and Allied Sciences, P.O. Box 65013 School of Pharmacy. You can also contact the supervisor of this research Professor Appolinary Kamuhabwa from Muhimbili University of Health and Allied Sciences (Mobile phone: +255 755 576 985) or Dr Pilly Chillo. If you have questions about this study, you should contact the Director of

Research and Publications Muhimbili University of Health and Allied Sciences, Dr. **Joyce Masalu**, P.O. Box 65001, Dar es Salaam. Phone number: 2150302-6

Signature:

Do you agree?

Participant agrees ……. Participant does not agree…….

I, _____have read the contents in this form.

My questions have been answered. I agree to participate in this study.

Signature of the participant _____

Signature of the research assistant _____

Date of signed consent _____

Appendix II: Consent Form (Kiswahili Version)

FOMU YA MAELEZO KUHUSU UTAFITI:

NAMBA YA UTAMBULISHO: ☐☐☐

Fomu ya utafiti wenye kichwa cha habari:

UTAFITI WA KULINGANISHA KIASI CHA MAFUNGAMANO YA UTUMIAJI DAWA NA KIWANGO CHA KEMIKALI JAMII YA C-REACTIVE PROTEIN (si-riakitivu protini (hamirojo) hsCRP) KATIKA DAMU MIONGONI MWA WAGONJWA WA MOYO WANAO TUMIA DAWA WAHUDHURIAO KILINIKI.

Utangulizi: Kushindwa kwa ufanisi wa moyo nitatizo la kiafya katika jamii ulimwenguni kote na limeathiri watu milioni 26. Miongo kadhaa iliyopita tafiti zimegundua uhusiano wa mfumo wa fahamu na mfumo wa kinga ya mwili katika uchocheaji wa mabadiriko yamisuli ya moyo yanayopelekea ufifiaji zaidi wa moyo ulioshindwa. Kemikali aina ya hamirojo/ protini iitwayo C-reactive (si-riakitivu) huzalishwa na kinga ya mwili na inatabia ya uimara, uwezo wa kutabiri maendeleo ya moyo na ufanisi wa matibabu ya moyo ulioshindwa. Hivyo kufahamu mahusiano kati ya mafungamano/namna ya utumiaji dawa na kiasi cha kemikali jamii ya si-riakitivu hamirojo miongon mwa wagonjwa wa kushindwa kwa moyo ni jambo muhimu.

Utangulizi

Haloo, hii fomu ina taarifa kuhusu utafiti tajwa hapo juu. Ili kuwa na uhakika kwamba unataarifa kuhusu kuwapo katika utafiti huu tunakuomba usome au tukusomee fomu hii ya kukubali. Fomu hii ya kukubali yaweza kuwa na maneno ambayo hayajazoeleka kwako. Tafadhali tuulize tukufafanulie chochote ambacho hujaelewa.

Lengo la utafiti

Unaombwa kushirirki katika utafiti huu ambao unataka kuchunguza uhusiano katiya ‘hsCRP’ na utumiaji wa dawa, ilikupata ushauri wa njia bora za kutibu ugonjwa.

Taarifa zaujumla na sehemu yako katika utafiti ukikubali kuwapo katika utafiti.

Kama ukikubali kuwapo katika utafiti huu, utatakiwa kujibu maswali katika fomu ya usaili. Fomu ya usaili itakuwa na taarifa zako na zitatumika kwa ajili ya utafiti huu. Tutahitaji damu kidogo ili tuweze kupima kiwango cha 'hsCRP' katika damu yako.

Madhara

Hatutazamii wewe kupata dhara lolote kwa sababu ya kushiriki katika utafiti huu. Damu inayohitajika ni kidogo sana kiasi kwamba haiwezi sababisha tatizo kwako.

Faida

Kwakushiriki katika utafiti huu, unaongeza uelewa wa kisayansi ambao waweza kuwa muhimu wakati wa kupitia tena sera za afyana utekelezaji.

Haki ya kujitoa

Kushiriki katika utafiti huu ni hiari yako. Unaweza kuacha kushiriki muda wowote hata kama umeshakubali. Kukataa kushiriki au kujitoa hakuna adhabu.

Usiri

Jina lako halitaandikwa, namba tu zitatumika kwa utambulisho. Taarifa zote zilizopatikana zitatumika kwa madhumuni ya utafititu, na hatapewa mtu yeyote bila idhini yako.

Nani wa kuwasiliana nae

Wasiliana kupitia +255 714 662 023, Mr.Maganga M. Gabriel, Mpharm Hospital and Clinical pharmacy, Chuo Kikuu cha Afya na Sayansi shirikishi, Muhimbili, P.O. Box 65013,Shule ya Famasi. Unaweza pia wasiliana na Msimamizi wa utafiti huu Profesa Apolinary Kamuhabwa wa Chuo Kikuu cha Afyana Sayansi shirikishi Muhimbili, namba ya simu +255 755 576 985 au msimamizi wa utafiti mwenza, Dr. Chillo

Kama una maswali Zaidi kuhusu utafiti huu, wasiliana na Mkurugenzi wa tafiti, Chuo Kikuu cha Afya na Sayansi shirikishi, Dr. Joyce Masalu, P.O.Box 65001, Dar es Salaam. Namba ya simu ya mezani 2150302-6.

Saini

Unakubali?

NDIYO……HAPANA……...

Mimi……...nimesoma maelezo yaliyo humu ndani. Maswali yangu yamejibiwa. Nakubali kushiriki katika utafiti huu.

Saini ya mshiriki……

Saini ya Mtafiti /Mtafiti msaidizi……Tarehe ya kusainiwa …….

Appendix III: Data Collection Form

MEDICATION ADHERENCE STATUS AND C-REACTIVE PROTEIN LEVELS AMONG HF PATIENTS ON MEDICATION

A: Socio-demographic characteristics

1. Study Identification number: …….
2. JKCI file number: …….
3. Date of interview: …….
4. Patient's initials: …….
5. Patient's phone number: …….
6. Next of kin phone number: …….
7. Date of birth……age in years……
8. Sex ……... (M/F)
9. Marital status: i) Single ii) Married iii) Divorced iv) Widowed
10. Level of education: i) No formal education ii) Primary iii) Secondary iv) University
11. Occupation: i) Not employed ii) Employed iii) Business iv) Peasant v) Retired
12. Mode of hospital payment i) Private ii) Public iii) Exempted iv) Insured

B: Cardiovascular risk profile

13. Hypertension ……. (yes/no), duration……. (years)
14. Diabetes …… (yes/no), duration: …. (years) type of DM :….(type 1/type 2)
15. Alcohol use ……(yes/no)
16. Ever smoked: ……. (yes/no) age started smoking:….(years)
17. Current smoker... (yes/no),
18. Stopped smoking?..... (yes/no), when stopped:……(date)

C: Disease history

19. When were you diagnosed with HF?.....(indicate duration in months)
20. What is the underlying cause of HF? …… (as per case notes)
21. What was the last Ejection Fraction? …… (as per case notes)
22. When were you last seen at the clinic?.....(indicate duration in months)
23. When was the last time you were admitted due to your current disease?.....
24. For the past 1 year, how many times were you admitted due to HF?……
25. What is the level of shortness of breath do you experience at the moment?
    a. No shortness of breath (NYHA Class 1)
    b. On exertion (like climbing stairs or a hill?) (NYHA Class 2)
    c. On doing daily activities (like sweeping the floor or walking) (NYHA Class 3)
    d. At rest (NYHA Class 4)
    e. On lying flat in bed (NYHA Class 4, Orthopnoeic)
26. Apart from shortness of breath, what other symptoms do you currently experience?
    a. Chest pain: (yes/no)
    b. Palpitation: (yes/no)
    c. Lower limbs swelling (yes/no)
    d. Abdominal swelling (yes/no)
    e. Right upper abdomen pain (yes/no)
    f. Fatigue (yes/no)

D: Drug history: Were you prescribed the following medications in your last visit?

27. Diuretics: (yes/no), which one?.....(when last taken) ……(days)
28. CCB: (yes/no), which one?.....(when last taken) ……(days)
29. ACEI: (yes/no), which one?.....(when last taken) ……(days)
30. ARB: (yes/no), which one?.....(when last taken) ……(days)
31. Beta blocker: (yes/no), which one?.....(when last taken) ……(days)
32. Hydralazine: (yes/no), which one?.....(when last taken) ……(days)
33. Digoxin: (yes/no), which one?.....(when last taken) ……(days)
34. Nitrates: (yes/no), which one?.....(when last taken) ……(days)

35. Anticholesterol: (yes/no), which one?.....(when last taken) ……(days)
36. Other drugs:……
37. Reasons for not taking prescribed medications:
    a. Ran out of stock (got finished)
    b. Could not buy (due to financial reasons)
    c. Was not told to continue
    d. Had side effects
    e. Got well (cured)

E: Anthropometric and Blood Pressure measurements

38. Height ……. (cm)
39. Weight ……(kg)
40. Waist circumference……. (cm)
41. Hip circumference……. (cm)
42. Pulse rate……. (beats/minute)
43. Blood pressure i) …… ii)……. iii)……. (mmHg)

F: Physical Examination

44. Jugular Venous Pressure……(normal/raised/flat)
45. Gallop ……. (yes/no), i) S3 ii) S4
46. Ankle edema……. (yes/no)
47. Basal crepitations……. (yes/no)
48. Tender hepatomegally……. (yes/no)

G: Laboratory Investigations

49. HsCRP ……units
50. Hemoglobin ……g/dl
51. White blood cells count (Total) ……units
52. Monocytes count ……units

53. Basophil count ……units
54. Platelet count ……units
55. Neutrophils count ……units
56. Lymphocytes count ……units
57. Cholesterol total…… mmol/L
58. Low Density Lipoprotein Cholesterol (LDL-C) …….mmol/L
59. High Density Lipoprotein Cholesterol (HDL-C) ……mmol/L

Signature …… Date completed:……..

Appendix IV: The 8-Item Morisky Medication Adherence Scale

S/N	ITEM	YES	NO
1	Do you sometimes forget to take your HF medications?		
2	In the last two weeks, was there any day when you did not take your HF medication?		
3	Have you ever stopped taking your medications or decreased the dose without first warning your doctor because you felt worse when you took them?		
4	When you travel or leave the house, do you sometimes forget to take your medications?		
5	Did you take your HF medication yesterday?		
6	When you feel your HF sign and symptoms controlled, do you sometimes stop taking your medications?		
7	Have you ever felt distressed for strictly following your HF treatment?		
8	How often do you have difficulty to remember taking all your HF Medications? i. Never ii. Almost never iii. Sometimes iv. Frequently v. Always		

Appendix V: Ethical clearance letter

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR OF POSTGRADUATE STUDIES

P.O. Box 65001
DAR ES SALAAM
TANZANIA
Web: www.muhas.ac.tz

Tel G/Line: +255-22-2150302/6 Ext. 1015
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E-mail: dpgs@muhas.ac.tz

Ref. No. MU/ PGS/SAEC/Vol. XI/30

5th July, 2017

Mr. Maganga M Gabriel
M.Pharm. Hospital and Clinical Pharmacy
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED: "CREATIVE PROTEIN LEVELS AS A SURROGATE MARKER FOR DRUG TREATMENT ADHERENCE AMONG HEART FAILURE PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITALO"

Reference is made to the above heading.

I am pleased to inform you that, the Chairman has, on behalf of the Senate, approved ethical clearance for the above-mentioned study. Hence you may proceed with the planned study.

The ethical clearance is valid for one year only, from 5th July, 2017 to 4th July, 2018. In case you do not complete data analysis and dissertation report writing by 4th July, 2018, you will have to apply for renewal of ethical clearance prior to the expiry date.

Prof. Andrea B. Pembe
DIRECTOR OF POSTGRADUATE STUDIES

cc: Director of Research and Publications
cc: Dean, School of Pharmacy

Appendix VI: Introduction letter

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR OF POSTGRADUATE STUDIES

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Ref. No. HD/MUH/T.295/2015

14th July, 2017

Executive Director
Jakaya Kikwete Cardic Institute
DAR ES SALAAM.

Re: INTRODUCTION LETTER

The bearer of this letter Mr. Maganga M. Gabriel is a student at Muhimbili University of Health and Allied Sciences (MUHAS) pursuing M.Pharm. Hospital and Clinical Pharmacy.

As part of his studies he intends to do a study titled:"***Creative protein levels as surrogate marker for drug treatment adherence among heart failure patients attending Muhimbili National Hospital".***

The research has been approved by the Chairman of University Senate.

Kindly provide him the necessary assistance to facilitate the conduct of his research.

We thank you for your cooperation.

Ms. A. Ndyeikiza
For: DIRECTOR, POSTGRADUATE STUDIES

cc: Dean, School of Pharmacy
cc: Mr. Maganga M. Gabriel

Appendix VII: Permission letter

JAKAYA KIKWETE CARDIAC INSTITUTE

Cables: "Muhimbili"
Telephone: +255-22-2151379
FAX: +255-22-2150534
Email: info@jkci.or.tz

JAKAYA KIKWETE
CARDIAC INSTITUTE

Postal Address:
P.O. Box 65141
DAR ES SALAAM

In reply please quote;

Ref: JKCI/RESEARCH/14/17 **Date:** 11/12/2017

To Cardiology Department,

RE: PERMISSION LETTER FOR MAGANGA M. GABRIEL TO CONDUCT HIS DISSERTATION AT JKCI

Reference is made to the above heading. Maganga Gabriel is a Master of Pharmacy student at MUHAS. As a partial fulfillment for completion of his studies he is required to conduct a research. His research is titled **"CREATIVE PROTEIN LEVELS AS A SURROGATE MARKER FOR DRUG TREATMENT ADHERENCE AMONG HEART FAILURE PATIENTS ATTENDING JAKAYA KIKWETE CARDIAC INSTITUTE"**.

He has been granted ethical clearance from MUHAS. With this letter, I am pleased to inform you that the Chairman of the JKCI Ethical committee has granted permission for the research of the above named student. Kindly provide him the necessary assistance to facilitate the conduct of his study.

Thanking you sincerely,

Pédrö Pallangyo M.D., M.P.H., M.Med
Chairman, Ethical Committee
Head, Research, Training & Consultancy

C.C
Head of Cardiology Department – JKCI
Head of OPD - JKCI