USE AND CLINICAL OUTCOMES OF VASOPRESSORS AND INOTROPES AMONG PATIENTS ADMITTED AT MOI TEACHING AND REFERRAL HOSPITAL -ELDORET

BY

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A thesis submitted to Moi University, School of Medicine's Department of Pharmacology and Toxicology, in Partial Fulfillment of the Requirements for the Award of Master of Pharmacy in Clinical Pharmacy.

DECLARATION

I declare that this is my original work and it has not been submitted to any other university or institution for the award of a degree.

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DEDICATION

I dedicate this work to my friends and family. Thank you for your continued support and encouragement.

ABSTRACT

Background: Inotropes and vasopressors are administered to offer hemodynamic support to patients in shock, as a temporary measure to allow for correction of the underlying disease. Inotropes increase cardiac output while vasopressors increase total peripheral resistance leading to a rise in mean arterial pressure (MAP) and perfusion. Despite the high mortality observed among patients started on vasoactive drugs, there is limited data on their use and outcomes in low-income setting and influence of comorbidities. This study aims to document the outcomes of patients started on vasoactive drugs.

Objectives: To describe the clinical outcomes of patients started on inotropes and/or vasopressors at MTRH, Eldoret.

Methods: This was a prospective observational hospital-based census study that recruited patients who were admitted at the Coronary Care Unit (CCU) in MTRH between December 2018 and June 2019 and received inotropes and/or vasopressors. Data on age, gender, length of stay, medication history, laboratory findings and diagnosis were collected. Patients were followed until discharge from CCU and data on outcomes collected. Sociodemographic and clinical characteristics were analyzed using descriptive statistics. Fischer's exact test was used to determine association between outcomes and the various agents and their combinations used. Multinomial regression was used to determine effect of mean arterial pressure on outcomes. $p < 0.05$ was considered significant

Results: 68 patients with a mean age of 51.1 (SD 23.9) years were recruited. Most were female patients (57.3%), who had been admitted in cardiogenic shock (75.7%) due to acute decompensated heart failure (72.5%), with rheumatic heart disease as the main comorbidity (18.2%). Mean baseline MAP was 61.8 mmHg while systolic and diastolic blood pressure was 82 mmHg and 52 mmHg respectively. Most patients (52.9%) received dobutamine as the first agent. A second agent, norepinephrine, dobutamine or milrinone, was administered to 28 (41.2%) patients who had not initially responded adequately. Characteristics of participants who received various agents were similar. The mean arterial pressure in patients treated with one inotrope was significantly higher than in patients who were treated with at least two inotropes ($p < 0.001$). Thirty-seven (54.4 %) patients died, 9(13.2 %) were discharged to the wards and 22(32.4 %) were discharged home. There was no significant association between outcomes and the initial agent administered $(p= 0.807)$ or the various combinations ($p=0.334$). Patients with an elevated mean arterial pressure after inotrope treatment were more likely to be discharged to the wards (OR 1.3 [95% CI 1.1-1.6, $p=0.001$]) or discharged home (OR 1.2 [95% CI 1.1-1. 3, $p=0.002$]) than to die.

Conclusion: Patients with higher MAPs after inotrope/vasopressor administration had better clinical outcomes compared to those with lower MAPs. There was no significant association between the type of inotrope/vasopressor and outcomes. Additionally, there was no significant difference between the use of either one or two inotropes/vasopressors.

Recommendations: Further studies with bigger sample sizes need to be conducted to further explore the findings of this study.

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DEFINITION OF TERMS

Chronotropy	Firing of the sino atrial node which influences the heart rate
Disposition	The location to which the patient is discharge i.e., back to the wards, through the cardiology clinic or home.
Dromotropy	Velocity of conduction through the atrio ventricular node
Hemodynamic instability	Low blood pressures and/or signs of tissue hypo perfusion including reduced urine output or deranged liver function tests, cold extremities and altered mental status.
Inotrope.	A vasoactive agent used to increase cardiac output in a patient with hemodynamic instability.
Length of CCU stay	The time between admission of a patient and when attending physicians decide to discharge the patient.
Vasoactive agent	A bioactive agent that changes vasomotor tone by acting on various receptors in peripheral blood vessels. For the purpose of this document, this term will be used to refer to inotropes and vasopressors
Vasopressor.	A vasoactive agent used to increase total peripheral resistance in patients with hemodynamic instability.

Legally authorized representative/guardian	*An individual or entity who by the authority of the countries laws, can give consent to participate in a research study on behalf of a potential participant who is unable to consent for themselves (https://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/guidelines/informed_consent_i.html.)*

LIST OF ABBREVIATIONS

ACEIs	Angiotensin converting enzyme inhibitors
AHA/ACCA	American Heart Association/ American College of Cardiology
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CCB	Calcium channel blockers
CCU	Cardiac Care Unit
CK MB	Creatinine kinase MB
CT	Computer tomography
Egfr	Estimated glomerular filtration rate
Hb	Hemoglobin
HbAIc	Glycosylated hemoglobin
MRI	Magnetic resonance imaging
MTRH	Moi Teaching and Referral Hospital
PITC	Provider initiated testing and counseling
STEMI	ST elevated myocardial infarction
cICU	Cardiac Intensive Care Unit
COPD	Chronic Obstructive Pulmonary Disease
RHD	Rheumatic Heart Disease
LVD	*Left Ventricular Dysfunction*
DCM	*Dilated Cardiomyopathy*
AFib	*Atrial Fibrillation*

CHAPTER ONE

1.0 Introduction

1.1 Background

In clinical practice, hemodynamic instability is described as a systolic blood pressure less than 90 mm Hg and/or inadequate end organ perfusion (Weil, 2005). Shock is best defined as a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells. It is characterized by cellular dysfunction due to the circulations inability to supply enough oxygen to meet cellular demand. There is therefore a ventilation perfusion mismatch that results in increased lactate levels and clinical manifestations of impaired microcirculation including cold clammy skin (Cecconi et al., 2014). Based on pathophysiology, shock can be classified as cardiogenic, distributive, obstructive, hypovolemic or mixed shock (Djogovic et al., 2015). The most commonly encountered types of shock at the CCU in MTRH include cardiogenic shock, obstructive shock due to pulmonary *embolism and distributive shock due to sepsis. Most patients who were admitted to the unit have cardiac lesions and require closer monitoring which may not be feasible in the general wards. Although not all admitted patients require inotrope or vasopressors, many receive these agents during the course of their admission.*

Inotropes and vasopressors are agents typically administered to offer hemodynamic support patients in shock, as a temporizing measure to allow for the correction of the underlying disease. Catecholamine inotropes and vasopressors are agonists at various receptors in the heart and walls of the blood vessels, including β_1, β_2 and α_2, to varying degrees. Non catecholamine agents act on other receptors including the V1 and AT1 receptors. The choice of inotrope and vasopressors is influenced by the type of shock (Overgaard & Džavík, 2008a).

The common agents used in the MTRH CCU include dobutamine, milrinone, dopamine, nor epinephrine and epinephrine. Dobutamine is an inotrope that increase cardiac output by increasing cardiac contractility and heart rate while reducing afterload by causing peripheral vasodilation. Epinephrine and nor epinephrine cause systemic vasoconstriction and act on $\beta_{1,}$ β_2 and α_1 receptors to varying degrees. Dopamine at, lower doses, is predominantly inotropic but causes vasoconstriction at higher doses (Djogovic et al., 2015).

The choice of the type of inotrope or vasopressor and its dose is influenced by several factors. First, these agents act on several receptors and produce several effects, some of which may be undesirable. They include, dose dependent dysrhythmias, hypoperfusion and myocardial ischaemia. Different receptors are also activated at various doses necessitating careful titration to achieve the desired therapeutic effect. Finally, use of these agents is subject to physiologic regulation for instance, vasoconstriction leading to increased systemic vascular resistance (SVR) may result in reflex bradycardia and reduced cardiac output (Ellender & Skinner, 2008).

Distributive shock is characterized by diffuse peripheral vasodilation and loss of systemic vascular resistance leading to hypotension. The Surviving Sepsis guidelines recommend use of inotropes and vasopressors for septic patients who do not respond adequately to fluid resuscitation, within six hours of presentation. The first line recommended agent is norepinephrine with vasopressin or epinephrine added if MAP above 65 mm Hg is not achieved. Dopamine is recommended as the second line agent in patients who are considered to be at low risk for arrhythmias (Rhodes et al., 2017a). This recommendation is informed by several studies which have demonstrated that nor epinephrine may have a lower risk of arrhythmias when compared to dopamine (Avni et al., 2015; De Backer et al., 2012; De Backer et al., 2010).

Cardiogenic shock results from pump failure, caused by structural (e.g., ventricular failure in acute myocardial infarction) or electrophysiological defects (e.g. arrythmias) in the heart, leading to reduced cardiac output and the inability of perfuse peripheral tissues. In sub Saharan Africa, some of the most common etiologies include rheumatic heart disease, hypertensive heart disease and HIV cardiomyopathy, all of which may lead to pump failure (Bloomfield et al., 2013).

American Heart Association/American College of Cardiology (AHA/ACCA) guidelines recommend the use of vasopressors for management of hypotension that does not resolve after fluid resuscitation, where applicable, in patient with cardiogenic shock caused by ST elevated myocardial infarction (STEMI). For low cardiac output states attributable to pump failure, dobutamine is the recommended agent. These recommendations are, however, based on expert opinion with limited studies available in this field (Antman et al., 2004). The Canadian Association of Emergency Physicians 2017 recommends use of norepinephrine for cardiogenic shock, based on the SOAP II study, with addition of dobutamine if an inotrope is considered necessary (De Backer et al., 2010a; Djogovic et al., 2015).

AHA/ACCA recommendation on the use of vasoactive agents are based on heart failure staging. Stage A heart failure describes patients who are at risk of developing heart failure but do not have overt signs e.g., structural cardiac abnormalities or signs of cardiac stress and symptoms of heart failure. Stage B heart failure describes patients without current symptoms of heart failure but have structural cardiac abnormalities or signs of cardiac stress Stage C heart failure describes patients who have or have had signs and symptoms of heart failure. Stage D heart failure describes patients with overt signs and symptoms of heart failure who experience marked limitation in daily living and have had recurrent hospitalization (Heidenreich. et al.,

2022). Use of positive inotropes including dopamine, dobutamine and milrinone is recommended for in patients with stage D heart failure who do not respond to guideline recommended medication therapy or who are experiencing an acute decompensation. This should be a short-term continuous infusion with long term continuous infusions only recommended as palliative care. However, long term use of intermittent or continuous infusion of parenteral inotropes or their use in patients without symptoms of systolic dysfunction, hypotension or impaired cardiac output is potentially harmful and is not recommended (Yancy et al., 2013).

Obstructive shock is caused by pump failure of extra-cardiac nature leading to reduced right ventricular output as seen in pulmonary embolism whereby the right ventricular failure results from pulmonary artery hypertension. AHA/ACCA Guidelines recommend administration of norepinephrine dopamine or vasopressin in patients with right ventricular (RV) failure while trying to reduce pulmonary artery pressure using inhaled pulmonary vasodilators. The choice of inotrope should be based on its effect on heart rate, SVR and its half-life (van Diepen et al., 2017).

In recent times, COVID 19 has become one of the leading causes of death in cardiac ICU hospitalized patients. There are several reports of the virus causing cardiogenic shock (Chau et al., 2020; Jean-Marie et al., 2022; Sánchez-Recalde et al., 2020). Long term effects of the metabolic and cardiovascular system have also been reported (Roth et al., 2022; Steenblock et al., 2021). The impact of COVID 19 on the choice of inotropes and vasopressors is yet to be determined but experts recommend norepinephrine as the vasopressor of choice (Maximous et al., 2021)

Several studies have demonstrated an increase in mortality, especially in patient with cardiogenic shock, when inotropes and vasopressors are administered. A retrospective

analysis of the ALARM HF registry, comprising of eight countries in Europe and South America, showed a 1.5-fold and 2.5-fold increase in mortality when dopamine/dobutamine and norepinephrine/epinephrine respectively were used (Mebazaa et al., 2011). Another retrospective analysis of the ADHERE registry, made up of countries in North America, found a 1.24 odd ratio of death when dobutamine was used (Abraham et al., 2005). A study conducted among patients who receive a left ventricular assist device (Impella) also revealed an increase in mortality among patients on inotropes and vasopressors, with the highest increase observed among those with 2 or more agents (Rohm et al., 2021). Specific agents, notably dopamine and epinephrine, have also been associated with a higher mortality in this patient population (De Backer et al., 2010a).

Other studies have reported contrasting results, having observed no effect on mortality. In Cardshock study, conducted European ICUs, there was no increase in 90-day mortality when vasoactive agents were administered to cardiogenic shock patients (Tarvasmäki et al., 2016). In addition, a meta-analysis of randomized control clinical trials found no difference in mortality when vasoactive agents were used (Belletti et al., 2015). It should be noted that most of these studies have been conducted in resource rich settings therefore generalizing their results to our setting may be inaccurate.

The observed mortality may also be a related to the severity of underlying disease as was observed using the sequential organ failure assessment (SOFA) score and the acute physiology and chronic health evaluation (APACHE) score (Ferreira et al., 2001; Tian et al., 2022).

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1.2 Statement of the Problem

Several recommendations on the management of different types of shock with inotropes and vasopressors have been published. They are however largely based on data obtained from high income countries. Application of these international guidelines to our setting may be limited by several factors including availability, cost and risk associated with use of these agents (Misango et al., 2017).

Many differences exist between the practice in developed countries and in our setting. In septic shock, for example, guidelines recommend fluids as the first line agents with vasoactive agents introduced after failure of fluid therapy. The use of fluids in management of children, in septic shock, from Sub Saharan Africa was, however, associated with an increase in mortality (Maitland et al., 2011). It may, therefore, be necessary to initiate inotropes and vasopressors before administration of fluids. Such differences in management may have an impact on the outcomes of therapy. Some findings from clinical trials that inform these guidelines may therefore not apply.

Patient demographics and etiologies of shock in Kenya also differ from those in high income countries. Rheumatic heart disease (RHD) is the commonest form of valvular heart disease and a major cause of heart failure in Sub Saharan Africa, accounting for approximately 17% of cases (Bloomfield et al., 2013). Although its prevalence rate in Sub Saharan Africa has not been consistently documented, it is estimated to be much higher than prevalence rates in developed countries e.g. the United State of America and Britain where most studies are conducted (Tibazarwaet al., 2008). It is not clear what agents are of the most benefit in such a situation with guidelines failing to give clear direction.

The use of inotropes and vasopressors is not devoid of adverse effects. Epinephrine nor epinephrine, dobutamine and dopamine have been associated with Cardiac arrhythmias, cardiac ischaemia and excessive vasoconstriction which may manifest as oliguria and tissue necrosis (Saric et al, 2017). Dobutamine may also rarely cause hypersensitive myocarditis an allergic reaction characterized by sudden, unexplained, renal failure and eosinophilic infiltration on myocardial biopsy. In such cases, dobutamine should be discontinued and should only be reintroduced with caution if absolutely necessary to prevent recurrence (Francis et al., 2014; Shah & Cowger, 2014).

This study intended to describe the characteristics and outcomes, including any adverse events, of patients admitted at the CCU in MTRH, who had received inotropes and/or vasopressors, in attempt to identify patterns and generate hypothesis for future research, with a view of the development of treatment protocols and guidelines for low-income settings.

1.3 Justification

Inotropes and vasopressors are used in MTRH for the management of hemodynamic instability. The specific cardiac indications, patient characteristics, doses and clinical outcomes have not been described in this setting. The only other study, conducted by Victoria Simiyu (2014) at Kenyatta National Hospital, sought to document the inotropes and vasopressors used, how they are administered and their modes of monitoring. However, this study did not address patient outcomes (Simiyu, 2014).

Due to lack of high-quality data from randomized clinical trials, guidelines are often based on expert opinion hence are not very clear. Decisions regarding the most appropriate agent depend on the clinicians' judgment, which may also have an impact

on clinical outcomes. For example, for cardiogenic shock of other etiologies other than myocardial infarction, management is based solely on expert opinion with little supporting data. Catecholamines are the most widely recommended agents although little evidence for their use and prognosis is limited. They increase myocardial oxygen consumption and should be used at minimum doses, for the shortest time possible. This study will try to provide data that may inform further research on inotropes and vasopressor.

The importance of ensuring a full-time supply of these agents cannot be overstated. Currently, the impact of these shortages may not be felt acutely since the CCU is usually covered by the pharmacist run revolving fund pharmacy (RFP). Unlike agents acquired from the hospital pharmacy, the cost agents acquired from the RFP are not covered by the National Hospital Insurance Fund (NHIF) and can only be paid for out of pocket, increasing the patients financial burden.

1.4 Research Questions

- What are the characteristics of patients admitted to the CCU in MTRH who receive vasopressors and inotropes?
- What are the clinical outcomes associated with the use of inotropes and vasopressors?

1.5 Objectives of the Study

1.5.1 Broad objective

- To describe clinical outcomes of vasopressors and inotropes among patients admitted at Moi Teaching and Referral Hospital -Eldoret

1.5.2 Specific objectives

- To describe the characteristics of patients receiving inotropes and vasopressors at the CCU in MTRH
- To assess clinical outcomes of patients receiving inotropes and vasopressors at the CCU in MTRH

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Introduction

Vasoactive agents, inotropes and vasopressors, are administered as a temporary measure to patients in shock while correcting the underlying cause of shock. Shock may vary in aetiology and pathophysiology, an important factor in choosing the most appropriate agent for use.

2.2 Definition of Shock

Shock is as a life-threatening condition characterized by cellular dysfunction resulting from circulatory failure and leading to cellular hypoxia, increased lactate levels and other clinical manifestations of impaired microcirculation including cold clammy skin. Increase blood lactic acid levels results from impaired oxygen utilization and has been shown to be a predictor of mortality in patients with shock (Scolari et al., 2020; Thomas-Rueddel et al., 2014). It is therefore a result of reduced tissue oxygen delivery and/ or increased tissue oxygen demand (Suh & Lee, 2018). Hyperlactemia may also be a result in reduced clearance through the kidneys that occurs as part of end organ damage consequent to reduced perfusion. Early reduction in lactic acid levels has been associated with better outcomes in patients with septic shock (Cecconi et al., 2014; Nguyen et al., 2004).

Circulatory shock can also manifest as a drop in systolic blood pressure (SBP) to <90mmHg or MAP to <65 mmHg. Although hypotension is a critical sign of circulatory shock, it may not be present in all patients. This may be because the initial compensatory response to reduction in cardiac output involves vasoconstriction to maintain a SBP >90. This necessitates assessment of other clinical signs of altered tissue perfusion (Cecconi et al., 2014).

Altered tissue perfusion can be observed through three 'windows'. The peripheral window uses the skin as the primary assessment tool. Shock patients may present with cold and clammy skin, mottling skin, an altered skin temperature gradient and a reduced capillary refill time. These parameters have been shown to be accurate predictors of mortality in patients with septic shock (Ferraris et al., 2018; Hariri et al., 2019). Microvascular abnormalities in circulation may also be observed through the renal window where there is reduced urine output to < 0.5 ml/kg/hr and neurologic window there is altered mental status with disorientation and confusion (Vincent & De Backer, 2013).

2.3 Types of Shock

Hemodynamic instability caused by perfusion failure is known as circulatory shock and may be as a result of 4 major pathophysiologies classified as hypovolemic, cardiogenic, obstructive or distributive (Weil, 2005). **Hypovolemic shock** occurs as a result of reduced central blood volume occasioned by a loss in blood or extracellular fluid volume. Hemorrhagic shock is a type of hypovolemic shock caused by loss of blood volume resulting in reduced cardiac output (Cannon, 2018). It is commonly caused by trauma but may also result from surgical, gastrointestinal and vaginal bleeding. Loss of extra cellular volume may also cause hypovolemic shock. This fluid loss can occur through the gastrointestinal system e.g., in diarrhea and vomiting. Volume may also be lost renally as a result of excessive diuresis or through the skin when afflicted by burns or in hot and dry climates (Taghavi et al., 2022).

Obstructive shock is triggered by a physical impedance in blood flow resulting in impaired cardiac filling during diastole as is observed in cardiac tamponade or increased afterload as it occurs in pulmonary embolism (Cecconi et al., 2014;

Zotzmann et al., n.d.). This results in inability of the heart to produce enough cardiac output despite being structurally and electrophysiologically normal and having adequate blood volume (Smith & Hernan, 2011).

Cardiogenic shock results from impaired ability of the heart to pump oxygenated blood to the brain, kidney and other vital organs due to structural and/ or electrocardiographic abnormalities in the heart. This results in impaired myocardial contractility with the resulting 'pump failure' leading to impaired cardiac output. To compensate for the reduction in cardiac output, there is an initial compensatory constriction of peripheral vessels leading to an increase in cardiac afterload. Eventually, the compensatory mechanisms are overwhelmed, resulting in overt cardiogenic shock (Vahdatpour et al., 2019). Cardiogenic shock can therefore present as pre- shock where there is hypoperfusion without hypotension, shock where there is hypotension and refractory shock where there is little response to at least to vasoactive drugs (Chioncel et al., 2020).

In an attempt to standardize cardiogenic shock classification, the Society of Cardiovascular Angiography and Intervention (SCAI) had a multidisciplinary team develop a schema consisting of five classes. It divided cardiogenic shock patients into stage A, stage B, stage C, stage D and stage E based on presenting signs and symptoms as well as requirement of hemodynamic support (D. A. Baran et al., 2019). A single center validation study has shown that SCAI stage is a strong predictor of mortality (D. Baran et al., 2020).

Distributive shock, characterized by excessive vasodilation, is commonly septic, anaphylactic or neurogenic in nature. Less common causes of distributive shock include adrenal insufficiency and capillary leak syndrome. In neurogenic shock,

reduced delivery of catecholamines to adrenergic receptors in the heart and walls blood vessels leads to vasodilation and bradycardia. In adrenal insufficiency, reduced alpha 1 receptor expression due to cortisol deficiency leads to shock (Alyesil et al., 2017). Septic shock is described as a systemic inflammatory response syndrome with hypotension that is non responsive to fluids and requires use of vasopressors (Hotchkiss et al., 2016).

2.4 Principles of Management of Shock

There are three major principles of the management of shock; oxygen administration, infusion of fluids and use of vasoactive agents. Oxygen should be administered to patients with saturations less than 90%. Over oxygenation may, however, be detrimental to the patient as it results in vasoconstriction. (Vincent et al., 2012). Administration of oxygen in patients with normal saturations causes peripheral vasoconstriction hence increasing systemic vascular resistance leading to further reduction in cardiac output. In patients with cor pulmonale secondary to chronic obstructive pulmonary disease, over oxygenation may cause hypercapnia by widening ventilation perfusion mismatch (McDonagh et al., 2021)

Fluid boluses though recommended in hypotensive patients, should be used with caution in patients with heart failure (Vincent & De Backer, 2013). Fluid therapy with crystalloids that contain water soluble metal ions including sodium and potassium, or colloids, increases cardiac output thereby increasing oxygen delivery to tissues. (Epstein & Waseem, 2022). When compared to 0.9% sodium chloride (normal saline), balanced or buffered crystalloids like ringer's lactate, Hartmann's solution and plasma-lyte A have an ionic content closer to that of plasma. In place of chloride ions, they contain other ions like lactate and gluconate ions. For this reason, balanced

crystalloids, unlike normal saline, pose a lower a risk of shifting acid base balance and are unlikely to cause hyperchloremic metabolic acidosis (Epstein & Waseem, 2022).

The SMART trial randomized approximately fifteen thousand critically ill ICU admitted adults to receive either normal saline or balanced crystalloids (plasma-lyte A/ ringers lactate) with the aim of determining if fluid composition had any effect on patient outcomes. The balanced crystalloid group had marginally lower, but statistically significant, incidence of dialysis and persistent kidney dysfunction as well as lower rates of in hospital mortality and lower odds having and adverse renal event (Semler et al., 2018).

In contrast, the PLUS study, randomized, double blind study conducted among five thousand and 37 ICU patients in New Zealand in which patients received Plasmalyte-148 or normal saline found no difference in mortality or adverse kidney events among the two groups. This was consistent with results of the BaSICS trial, in which 10520 patients across 75 Brazilian ICUs were randomized to receive either normal saline or a balanced crystalloid. Based on the results of the three trials, the decision on whether to give balanced crystalloids or normal saline should be added while considering the unique condition of each patient (Finfer et al., 2022; Ostermann & Randolph, 2022; Zampieri et al., 2021)

Colloids are high molecular weight oncotically active molecules dispersed in 0.9% sodium chloride or a buffered crystalloid solution. Albumin and fresh frozen plasma are natural colloids while hydroxyethyl starch is an artificial colloid (Sidebotham & Gillham, 2007). Although colloids are more effective at expanding intravascular volume, they are expensive, may be associated with more adverse events, have no clearly demonstrable advantage over crystalloids and may even be harmful (Caironi et

al., 2014; Lat et al., 2021; Zarychanski et al., 2013). A study that enrolled seven thousand patients and assigned them to hydroxyethyl starch or normal saline found the incidence of renal injury to be higher in the hydroxyethyl starch arm (Myburgh et al., 2012). Other studies have shown that it causes coagulopathy and increases the risk of bleeding (Haase et al., 2013; Sossdorf et al., 2009). Based on these results, the European Medicines Association has temporarily suspended marketing of hydroxyethyl starch

The choice of vasoactive agent is based on mechanism of action and the underlying pathophysiology of shock. There being paucity of high-quality data from randomized clinical trials, selection is left to the prescribing clinician. Inotropes increase cardiac output (CO) while vasopressors increase peripheral vascular resistance (PVR) leading to an increase in SBP and MAP (Hollenberg, 2011).

According to the European Society of Intensive Care Medicine guidelines 2014, it is important to monitor response to shock therapy to determine if it is resolving or progressing. Simple noninvasive methods of monitoring shock include blood pressure and heart rate monitoring which can be used to calculate the shock index. Cardiac output can be measured using pulmonary artery catheter or transpulmonary thermodilution while osygen delivery to tissues is estimated by measuring serial blood lactate levels and central venous oxygen saturations (ScvO2) in patients with a central venous catheter. These monitoring methods are however invasive and carry some risk (Cecconi et al., 2014; Suh & Lee, 2018). However, in developing countries, these procedures may not be feasible due to staffing and cost constrains. Simple bedside tools including the skin mottling test, capillary refill and skin temperature gradients, although not based on a lot of evidence, can be used (Misango et al., 2017).

Management of shock should be a multidisciplinary affair with the aim of utilizing the expertise of various team member in making early diagnoses, hastening clinical assessment and treatment intervention as well as closely monitoring and following-up progress. Several studies have demonstrated an improvement in outcomes when these 'shock teams' were put in place (Hutson et al., 2018; Ko et al., 2016; Lee et al., 2020).

2.5 Pharmacology of Vasoactive Drugs

Inotropes and vasopressors act on various receptors in the heart and walls of vessels to increase MAP, CO and SVR. Inotropes raise cardiac output by increasing myocardial contractility and /or heart rate while vasopressors cause vasoconstriction and therefore increase SVR.

2.6 Receptor Physiology

There are various receptors found in the heart and walls of the blood vessels namely α, β, doperminergic (D) and vasopressin (V) receptors. Alpha 1 (α1) receptors located in the walls of blood vessels are G protein coupled. These receptors are coupled to the G protein (Gq) which is made up of a GDP bound Gqα subunit and a βγ subunit. Ligand binding leads to dissociation of the Gqα subunit which then activates phospholipase C (PL-C) leading to cleavage phosphatidylinositol 4,5 biphosphate to produce inositol triphosphate (IP3) and diacyly glycerol. IP3 then potentiates intracellular calcium mobilization thus increasing actin myosin interaction. This results in vasoconstriction of peripheral and coronary vessels and an increase in total peripheral resistance. Alpha 2 (α_2) receptors in the walls of peripheral blood vessels, on the other hand, act via the nitric oxide pathway leading to vasodilation (Brodde et al., 2001; Ellender & Skinner, 2008).

β receptors are G protein couple and can be β1 or β2 receptors. β_1 receptors are mainly found in the heart. These receptors are coupled to the stimulatory G protein (Gs) which is made up of a GDP bound Gαs subunit and a βγ subunit. Ligand binding leads to dissociation of the Gαs subunit which then activates enzyme adenylyl cyclase. This leads to the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) and the activation of protein kinase A (PK-A). PK-A phosphorylates serine and threonine residues of the L type calcium channels which in turn increases calcium release hence producing positive chronotropic and dromotropic effect by stimulating atrio ventricular (AV) and sino atrial (SA) node conduction. There is also increase cardiac muscle contraction and therefore have an inotropic effect (Lucia et al., 2018). β_2 receptors, on the other hand, are found mainly in vascular smooth muscle where their activation results in vasodilation. When a ligand binds to the β_2 receptor, the increase in cAMP leads to inhibition of myosin light chain kinase which is responsible for phosphorylation of smooth muscle myosin. This results in vasodilation. Additionally, β_2 receptors have mild chronotropic and inotropic effects on the heart (Brodde et al., 2001; Ellender & Skinner, 2008).

All dopaminergic receptors are G protein coupled and either activate adenylyl cyclase via the protein $G\alpha_s$ for D1-like (DI and D5) receptors or inhibiting cAMP via protein $G\alpha_i$ for D2-like (D2, D3 and D4) receptors. They increase or decrease protein kinase A activity respectively. D1 and D4 receptors are found in the heart where they exert a positive inotropic effect while D1 and D2 receptors are found in the renal, splanchnic and mesenteric vasculature. In the kidney, they mediate natriuresis and diuresis (Bangash, et al., 2012; Beaulieu & Gainetdinov, 2011).

Vasopressin or antidiuretic hormone is released from the heart, pituitary and adrenal glands. It acts on V_{1a} receptors in the peripheral vasculature causing vasoconstriction

and V_{1b} receptors in the pituitary gland. V_1 activation cascade is similar to that of α_1 and begins with activation of PL-C and ends with release of intracellular calcium. V_2 receptors in the renal tubules cause reabsorption of water hence production of a small volume of concentrated urine. V_2 receptor cascade is similar (Hus-Citharel et al., 2021; Overgaard & Džavík, 2008a).

2.7 Mechanisms of Action of Inotropes and Vasopressors

2.7.1 Inotropes

Dobutamine

It is a strong β_1 but mild β_2 receptor agonist, binding to them in a 3:1 ratio. At lower doses of < 5 mcg, β_2 activity predominates resulting in vasodilation while at higher dose > 15mcg, α1 agonist activity resulting in vasoconstriction. At intermediate doses, it may have no effect on TPR due to its net vasodilatory and vasoconstrictory effects. Since it has positive inotropic and chronotropic activity, dobutamine increases myocardial oxygen consumption. It may not be appropriate in situations where reduction in myocardial oxygen consumption is desired e.g. in myocardial infarction (Overgaard & Džavík, 2008a).

Owing to its positive chronotropic effect, it induces a dose dependent tachycardia. It has a short half-life of about 2 minutes and a quick onset of action allowing for quick titration to doses that give a desirable MAP. In rare cases, dobutamine causes eosinophilic myocarditis an allergic reaction characterized by sudden, unexplained, renal failure and eosinophilic infiltration of the myocardium. Dobutamine should be discontinued immediately and future use should be avoided or reintroduced with caution in patients who develop this reaction (Jacob C. Jentzer et al., 2014; Shah & Cowger, 2014).

Phosphodiesterase inhibitors

Phosphodiesterase (PDE) III inhibitors e.g., milrinone and enoximone are non-catecholamine inotrope that acts by inhibiting phosphodiesterase mediated metabolism of cAMP. This leads to increased PK-A mediated phosphorylation of serine and threonine residues of the L type calcium channels. In the heart, increased calcium release produces positive chronotropic and dromotropic effect by stimulating atrio ventricular (AV) and sino atrial (SA) node conduction. In the periphery, they cause vasodilation. PDE III inhibitors therefore indirectly activates β_1 and β_2 receptors resulting in increased cardiac output and reduced systemic and pulmonary vascular resistance. Milrinone is particularly useful in patients who may have β receptor downregulation e.g. those with chronic heart failure (J. H. Levy et al., 2002).

Milrinone is mostly excreted in urine unchanged hence its use in patients with renal dysfunction, which is often the case in patients with shock, requires dosage adjustment. Enoximone on the other hand is metabolized in the liver hence may be preferred in case of renal dysfunction. Milrinone causes hypotension especially if the 50mcg/kg loading doses are given and after prolonged infusions. Since it has a long half-life of around 2- 3 hours, titration of doses is slower and since its renally cleared (Jacob C. Jentzer et al., 2014; Zima et al., 2020).

A formulation of oral milrinone was available in the late 1990s. However, the landmark trial by Parker and colleagues revealed a 28% increase in mortality among patients randomized to receive milrinone compared to those who received placebo. Oral milrinone is therefore not recommended for use (Packer et al., 1991). Enoximone is currently not being marketed in the United States, based on the results of a superiority clinical trial that sought to compare it to levosimendan. The trial was

terminated early after 30-day mortality in the levosimendan arm was determined to be 69% compared to 37% in the enoximone group, clearly demonstrating superiority (Fuhrmann et al., 2008).

Levosimendan

Levosimendan is a calcium sensitizing agent that binds to calcium ions on troponin c stabilizing it and prolonging the interaction between actin and myosin (Pierrakos et al., 2014). Since this action is calcium dependent, it acts during systole when calcium ion concentration is high with minimal effect on relaxation of the heart during diastole (Kasikcioglu & Cam, 2006). Unlike other inotropes which mobilize calcium, levosimendan does not increase free myocyte calcium levels. It is therefore not prone to myocyte dysfunction and increased myocardial oxygen demand (Altenberger et al., 2018). It is administered at doses between 0.05-0.2 microg/kg/minute. Bolus of between 6-12 mcg/kg may be administered although its routine use is not recommended (Antilaet al., 2007).

Its pharmacokinetics can best be described using a two-compartment model. It has a short half life of approximately 1 hour and is highly protein bound. Levosimendan is metabolized by intestinal bacteria after secretion into the intestines. It is also N-acetylated or conjugated with glutathione. Metabolites are then excreted in urine or stool. The major metabolite, OR-1896, is active and has a half life of approximately 80 hours. It is responsible for its prolonged duration of action. Studies have shown that pharmacokinetics of levosimendan are similar in patients with heart failure and healthy volunteers (Jonsson et al., 2003).

The SURVIVE trial compared levosimendan and dobutamine infusions in 1327 patients with acute decompensated heart failure with the aim of determining all-cause mortality at day 180. There was no difference in mortality when the two arms were

compared although there was a higher incidence of arrythmias and hypokalemia in the levosimendan group (Mebazaa et al., 2007). The LIDO trial was the first large trial where levosimendan and dobutamine were compared with the aim of determining the proportion of patients in heart failure who experienced hemodynamic improvement and the rate of adverse event in the two groups. The levosimendan arm was found to have better hemodynamic improvement and lower mortality (Follath et al., 2002). Since then, several studies have been conducted. Metanalyses of studies comparing levosimendan to placebo or dobutamine in different patients populations concluded that levosimendan administration may have lower mortality and less adverse effect (Gong et al., 2015; Landoni et al., 2010; Pollesello et al., 2016).

Digoxin

Digoxin is a Na^+/K^+ ATPase pump inhibitor which pumps out sodium ions in exchange for potassium ions. Inhibition of this pump reduces the Na+ gradient and reduces activity of the Na+/Ca2+ exchanger which exchanges intracellular calcium for extracellular sodium. This leads to accumulation of intracellular calcium thus increasing excitation contraction coupling. Digoxin is available as an IV or oral formulation and may be used in the management of arrythmias as well. It especially useful in management of patients with heart failure and atrial fibrillation. Digoxin has a narrow therapeutic index hence levels should be monitored closely and kept between 0.5-0.9 ng/ml to prevent the occurrence of adverse effect (Francis et al., 2014). It is majorly excreted unchanged in urine hence it should be used cautiously in patients with renal dysfunction and is proarrythmic necessitating close monitoring of electrolytes including calcium and magnesium (David & Shetty, 2022)

The DIG trial was a randomized double-blind placebo-controlled trial that sought to examine the effect of digoxin on all-cause mortality and heart failure hospitalization in patients with chronic heart failure, sinus rhythm and low ejection fraction. Its results revealed that digoxin had no effect on mortality but reduced heart failure hospitalizations (Ahmed et al., 2006; Digitalis Investigation Group, 1997). These results led to a change in guidelines in favor of other drugs, e.g. angiotensin converting enzyme inhibitors (ACEIs) and beta blockers, which have been proven to reduced heart failure mortality, with digoxin being used in end stage heart failure (Yancy et al., 2013).

2.7.2 Vasopressors

Dopamine

Dopamine is a precursor of nor epinephrine in the catecholamine synthetic pathway. It indirectly stimulates its release and directly acts on α_1 and β receptors, producing varied dose dependent effects (Ellender & Skinner, 2008). At low doses of 0.5-3mcg/kg, it stimulate D1 receptors in the walls of coronary, kidney, mesentery and brain vessels and D2 receptors in the vessels causing vasodilation and increased blood flow to these organs (Overgaard & Džavík, 2008a).

Unlike dobutamine which promotes renal blood flow by increasing cardiac output, dopamine acts on the D1 receptors to cause renal vasodilation and enhanced blood flow resulting in a direct natriuretic effect at a low ‘renal’ dose of 0.5- 3 mcg/kg. In addition, dopamine exerts some nonhemodynamic effects on the proximal tubule by inhibiting the Na+/ H+ exchanger and the Na+/ K+ adenosine triphosphatase, thus enhancing sodium and water loss in urine. The increase in sodium delivery to the proximal tubule increases tubular cells’ oxygen demand, cancelling out the effects of increased renal blood flow Thus although low dose dopamine has transient effect on

creatinine clearance, with peak increase observed at doses of 4-7 mcg/kg, it may not be beneficial. However, no studies have demonstrated any benefit of using renal dose dopamine making its use controversial. Some studies even suggest that renal dose dopamine could worsen renal oxygen delivery in patients with acute kidney injury (Jacob C. Jentzer et al., 2014; Jones & Bellomo, 2005; Lauschke et al., 2006).

At doses of 3-10 mcg/kg, it has mixed receptor activity. Activation of β_1 receptor increases heart rate and cardiac output with a mild rise in SVR due to α_1 receptor activation. At higher doses of 10- 20 mcg/kg, the α_1 stimulatory effect predominates and its inotropic effect is counteracted by the increase in SVR (Overgaard & Džavík, 2008a).

Norepinephrine

This is a potent α_1 agonist with some β_1 and minimum β_2 activity making it potent vasoconstrictor and mild inotrope. It should be administered at doses of 0.01-0.03 mcg/kg/min and titrated to a maximum of 0.1 mcg/kg/min. When administered over prolonged periods, it induces myocyte apoptosis via protein kinase A (Macit et al., 2015).It has a half life of 2-3 minutes, therefore it can be titrated rapidly to achieve the desired blood pressure. No dose adjustment is required in patients with renal or hepatic dysfunction (Shankar et al., 2022).

Nor epinephrine increases SVR raising MAP and cardiac output and resulting in reflex bradycardia and reduced cardiac output respectively (Jentzer et al., 2014).

Epinephrine

Epinephrine is a potent β_1 and α_1 receptor agonist with higher β_2 affinity than nor epinephrine. Starting doses should range between 0.01-0.03 mcg/kg/min while maximum doses should range between 0,1-0.3mcg/kg/min (Macit et al., 2015).

β_1 and β_2 activity predominate at lower doses, leading to an increased cardiac output and heart rate. Alpha 1 (α_1) mediated vasoconstriction is countered by higher β_2 activity resulting in net vasodilation. α_1 activity predominates at higher doses resulting in increased SVR and MAP. Its use has been associated increase gluconeogenesis and glycolysis resulting in hyperlactemia and hyperglycemia. Epinephrine induced hyperlactemia may not be harmful but it clouds serial lactate measurements, making them difficult to interpret. Epinephrine also causes tachyarrhythmias, splanchnic vasoconstriction, myocardial death through apoptosis and ischemia caused by coronary vessel vasoconstriction (Herget-Rosenthal et al., 2008).

A meta-analysis of 16 studies in which at least 15% of cardiogenic shock patients received epinephrine alone or in combination with other agents with the aim of assessing short term outcomes revealed that patients who received epinephrine had a threefold increase in mortality when compared to those who received other agents (Léopold et al., 2018,). In other study, 39 patients whose shock did not respond adequately to a combination of dopamine and dobutamine were randomized to receive a combination of norepinephrine and dobutamine of epinephrine alone. Although both regimens improved hemodynamic parameters, epinephrine use was associated with a higher incidence of adverse events including tachycardia, arrythmias and gastric mucosal hypoperfusion (B. Levy et al., 2011).

Phenylephrine

Phenylephrine is a synthetic pure α_1 agonist. Due to its minimal β activity, it has no effect on heart rate and myocardial contractility and does not increase myocardial oxygen demand (Overgaard & Džavík, 2008b). It is recommended for use in septic shock, albeit as a last resort, is there is no response use of 2 or more vasopressors and vasopressin or if use of other catecholamine vasoactive agents results in development of arrythmias. Cautious use of phenylephrine is recommended since its powerful vasoconstrictory activity may result in ischemia (Kislitsina et al., 2019; Lat et al., 2021)

Angiotensin II

The renin- angiotensin-aldosterone system (RAAS) is a major pathway for physiological response to hypotension and hypovolemia. The end result is the conversion of the peptide angiotensin I to angiotensin II by enzyme angiotensin converting enzyme (ACE). Angiotensin II then exerts its activity on the cardiovascular system via the AT 1 receptor, a G coupled receptor found in the many organs including the kidney, heart, vascular smooth muscle and pituitary gland. The receptor mediates vasoconstriction, release of vasopressin and sodium and water retention. For patients with chronic heart failure, it may be responsible for myocardial hypertrophy and remodeling (Corrêa et al., 2015).

The ATHOS 3 trial randomized 344 septic shock patients who had shown poor response to high dose norepinephrine to receive an angiotensin II infusion or placebo. At the third hour, when compared to the placebo arm, more patients in the treatment arm had an increase in systolic blood pressure to at least 75mmHG or by 10 mmHg from baseline. Although the mortality rate appeared to be lower in the treatment

group, the trial was not powered to detect a difference in mortality between the two groups. Although safety and tolerability of angiotensin II has not yet been sufficiently investigated, it is a potential treatment option for catecholamine resistant septic shock patients (Khanna et al., 2017; Shi et al., 2020).

Vasopressin

Vasopressin (AVP) or antidiuretic hormone, is a peptide hormone synthesized endogenously in the hypothalamus and stored in the pituitary gland. It is released in response to increase plasma osmolality, reduced blood volume and pressure. It exerts its activity in the cardiovascular system via V1 and V2 receptors. V1 receptors are found on vascular smooth muscles. They are Gq G protein coupled and their activation leads to a cascade that results in activation of phospholipase C, increased intracellular calcium and vasoconstriction. V2 receptors are found in the distal convoluted tubules and collecting ducts of nephrons. They are coupled to Gs G proteins whose activation leads to activation of adenyl cyclase, increased cAMP and activation of protein kinase A. This results in translocation of aquaporin 2 and its insertion into the apical membrane of the collecting duct and distal tubules where they mediate resorption of water. Vasopressin also activates platelet aggregation and increased von Willebrand factor and coagulation factor VIII. These procoagulant properties are mediated by V1a and V2 receptors (Boone & Deen, 2008; Sharman & Low, 2008).

At low doses of 0.01- 0.04 units/min, AVP improves visceral blood flow. However, at doses >0.04unit/min, it severely impairs visceral perfusion. It is recommended for septic shock refractory to nor epinephrine based on the observation that nor epinephrine levels are reduced in patient with septic shock (Herget-Rosenthal et al., 2008).

The VAAST trial was a randomized double-blind study that compared vasopressin and norepinephrine use among 778 septic shock patients in Australia and North America with the aim of comparing mortality from all causes. There was no significant difference in mortality between the two groups (Russell et al., 2008). The VANISH trial was on the other hand compare vasopressin and norepinephrine use in 409 septic shock patients with the aim of comparing the rates of development of acute kidney injury. Although there was no difference in the number of patient swho died or developed acute kidney injury, fewer patients in the vasopressin arm required renal replacement therapy (Gordon et al., 2016). VANCS and VANCS II trials compared vasopressin and norepinephrine in vasoplegic cardiac surgery and septic oncology patients respectively. In VANCS, the patients in the vasopressin arm had more days alive and free from organ dysfunction as well as fewer side effect especially arrythmias. In VANCS II, there was no significant difference in mortality when the two arms were compared (Hajjar et al., 2017, 2019). Results of these high quality randomized trials suggest that vasopressin is a safe adjunct for management of vasopressor refractory shock.

Terlipressin and selepressin are AVP analogues with greater affinity for vascular V1 receptors. Their use in septic shock has been investigated in clinical trials which revealed no difference in mortality when compared to norepinephrine. Use of terlipressin was associated with high rates digital ischemia, an adverse effect that occurred mainly in the first day of treatment (Laterre et al., 2019; Liu et al., 2018).

2.8 Indications for Use of Inotropes and Vasopressors

Septic shock

The Surviving Sepsis guidelines (SCC) 2016, recommend use of inotropes and vasopressors for septic patients who within six hours of presentation do not respond adequately to fluid resuscitation. The first line recommended agent is norepinephrine with addition of vasopressin or epinephrine added if the response is inadequate. Dopamine is recommended as the second line agent in patients at low risk of arrhythmias (Rhodes et al., 2017a).

The SOAP II trial was a blinded multicenter randomized clinical trial that recruited 1679 shock patients, 1044 of whom had septic shock. Participants were assigned to either nor epinephrine to a maximum of 0.19mcg//kg or dopamine to a maximum of 20mcg/kg with addition of open labeled nor epinephrine, dobutamine or vasopressin if there was inadequate response. The use of open labeled nor epinephrine was noted to be higher in the dopamine group. Although there was no difference in outcomes between the two groups, use of dopamine was associated with higher heart rates and arrhythmias which occurred in 309 patients, with atrial fibrillation occurring in 206 patients. Dopamine was associated with more arrhythmias especially atrial fibrillation. Due to severe arrhythmias, 65 patients had their assigned drug stopped, 52 of who were in the dopamine group.(De Backer et al., 2010a)

A meta-analysis of studies that provided information on outcomes of patients treated with dopamine compared to norepinephrine was also done. It included 5 observational studies and 6 randomized controlled trial with a total of 2768 patients. Due to the significant heterogeneity among the observational studies, there was no difference in mortality in patients receiving dopamine as compared to those receiving

norepinephrine. However, after identification and exclusion of the study that caused the heterogeneity, dopamine was associated with a higher risk of death. No heterogeneity was detected among the randomized trials where dopamine was also associated with a higher risk of death. Two studies looked at arrhythmias as one of the outcomes and found an association between dopamine and higher incidence of arrhythmias,(De Backer et al., 2012)

Another systematic review and meta-analysis that included 32 trials and a total of 3544 patients revealed an 11% risk reduction in death with nor epinephrine compared to dopamine. There was no significant reduction in mortality when nor epinephrine was compared to epinephrine, vasopressin and phenylephrine. The risk of arrhythmias was two times higher with dopamine than norepinephrine. (Avni et al., 2015).

The VASST trial was a multicenter clinical trial that randomized about 800 septic shock patients to receive norepinephrine or vasopressin with aim of determining if vasopressin would decrease mortality when compared with norepinephrine. There was no difference in 28 day or 90 day mortality when the two groups were compared. However, there was a small reduction in mortality in the subset of patients who had less severe septic shock. A similar trial, done among cancer patients who had developed septic shock, yielded similar results (Hajjar et al., 2019).

SCC guidelines do not recommend use of vasopressin as a single agent. In patients with shock or those receiving corticosteroids, vasopressin levels have been shown to be low due to impaired synthesis and secretion respectively. VAAST trial demonstrated a significantly lower mortality in patients receiving vasopressin and a corticosteroid when compared to patient receiving nor epinephrine and a

corticosteroid. This combination may therefore be used in patients with refractory septic shock (Pollard et al., 2015).

Septic shock patients often present with tachycardia resulting from use of catecholamine vasopressors or as a reflex response to systemic vasodilation. A recent animal study suggested that use of esmolol in septic rats improved response to vasopressors and may have an anti-inflammatory effect.

Obstructive shock

Principle treatment of obstructive shock is treatment of the underlying condition. If cardiac tamponade and tension pneumothorax are the underlying causes of shock, pericardiocentesis and decompression respectively should be performed.

In case of thromboembolism, the European Society of Cardiology recommends use of thrombolytics in patients with high-risk PE i.e., those with persistent hypotension or those in cardiogenic shock. The recommended fibrinolytics include recombinant tissue plasminogen activator (rtPA), alteplase, tenecteplase, urokinase and streptokinase (Konstantinides et al., 2020). As a result of increased right ventricular afterload, acute pulmonary embolism causes right ventricular failure due to pulmonary artery hypertension. AHA/ACCA Guidelines recommend administration of norepinephrine dopamine or vasopressin in patients with RV failure while trying to reduce pulmonary artery pressure using inhaled pulmonary vasodilators. The choice of inotrope should be based on its effect on heart rate, SVR and its half-life (Van Diepen et al., 2017).

Cardiogenic shock

Based on the SOAP II trial, the Canadian Association of Emergency Physicians 2017, recommend use of norepinephrine for cardiogenic shock with addition of dobutamine if an inotrope is considered to be necessary. The findings of this trial were based on a post hoc analysis since patients were not initially stratified based on type of shock (Djogovic et al., 2015).

For cardiogenic shock secondary to myocardial infarction, in patients with SBP of 70-100 mm Hg and no signs of shock, dobutamine is recommended. Dopamine is recommended if there are symptoms of shock. Combination of dopamine and dobutamine at 7.5mcg/kg/min each has been associated with better outcomes than doses of 15mcg/kg/min of the individual agents (Macit Kalçık et al.,2015).

Based on heart failure stage, certain agents can be recommended for use. Stage A heart failure describes patients who are at risk of developing heart failure but do not have overt signs e.g., structural cardiac abnormalities or signs of cardiac stress and symptoms of heart failure. Stage B heart failure describes patients without current symptoms of heart failure but have structural cardiac abnormalities or signs of cardiac stress Stage C heart failure describes patients who have or have had signs and symptoms of heart failure. Stage D heart failure describes patients with overt signs and symptoms of heart failure who experience marked limitation in daily living and have had recurrent hospitalization (Heidenreich. et al., 2022)

AHA/ACCA recommends the use of positive inotropes including: dopamine, dobutamine and milrinone in patients with stage D heart failure who do not respond to guideline recommended medication therapy or are experiencing an acute decompensation. This should be a short-term continuous infusion because long term infusions are only recommended as palliative care. Long term use of intermittent or

continuous infusion of parenteral inotropes or their use in patients without symptoms of systolic dysfunction, hypotension or impaired cardiac output is potentially harmful and is not recommended (Yancy et al., 2013).

A small trial that randomized 57 AMI patients who developed shock to receive norepinephrine or epinephrine found a higher incidence of refractory shock and adverse events (arrythmias) in the epinephrine group (B. Levy et al., 2018). The DOREMI study compared outcomes of cardiogenic shock patients randomized to receive either dobutamine or milrinone. There was no significant difference in outcomes when the two groups were compared (Mathew et al., 2021).

Several studies, both randomized and observational, have demonstrated an increase in mortality when inotropes and vasopressors including dopamine and milrinone, are used in patients with cardiogenic shock. These results have however been disputed by several meta-analyses which demonstrated no effect on survival. In other setting e.g., sepsis, use of these agents has been associated with an increase in survival. The effect of vasoactive drugs on mortality may therefore vary based on the type of shock (Belletti et al., 2015; De Backer et al., 2012; Pasin et al., 2014; Tarvasmäki et al., 2016a).

AHA/ACCA recommendation on the use of vasoactive agents are based on heart failure staging. Stage A heart failure describes patients who are at risk of developing heart failure but do not have overt signs e.g., structural cardiac abnormalities or signs of cardiac stress and symptoms of heart failure. Stage B heart failure describes patients without current symptoms of heart failure but have structural cardiac abnormalities or signs of cardiac stress Stage C heart failure describes patients who have or have had signs and symptoms of heart failure. Stage D heart failure describes

patients with overt signs and symptoms of heart failure who experience marked limitation in daily living and have had recurrent hospitalization (Heidenreich. et al., 2022). Use of positive inotropes including dopamine, dobutamine and milrinone is recommended for in patients with stage D heart failure who do not respond to guideline recommended medication therapy or who are experiencing an acute decompensation. This should be a short-term continuous infusion with long term continuous infusions only recommended as palliative care. However, long term use of intermittent or continuous infusion of parenteral inotropes or their use in patients without symptoms of systolic dysfunction, hypotension or impaired cardiac output is potentially harmful and is not recommended (Yancy et al., 2013).

Measurement of total inotrope and vasopressor requirements

There are several ways of measuring total vasopressor/ inotrope requirements, a particularly useful measure where more than one agent is used. The vasoactive inotropic index or score (VIS) is a weighted sum of maximum doses of all vasoactive agents administered. A correction factor is used to account for differences in units of measurement of the different agents. It is calculated as follows:

VIS = dopamine dose [μg kg^{-1} min^{-1}] + dobutamine [μg kg^{-1} min^{-1}] + 100 × epinephrine dose [μg kg^{-1} min^{-1}] + 50 × levosimendan dose [μg kg^{-1} min^{-1}] + 10 × milrinone dose [μg kg^{-1} min^{-1}] + 10 000×vasopressin [units kg^{-1} min^{-1}] + 100 × norepinephrine dose [μg kg^{-1} min^{-1}] (Koponen et al., 2019).

The vasopressor dependency index (VDI) is an expression of the dependency between maximum vasopressor or inotrope dose and MAP. It is calculated as follows

VDI= [(dobutamine dose × 1) + (dopamine dose × 1) + (norepinephrine dose × 100) + (vasopressin × 100) + (epinephrine × 100)] / MAP (Antal et al., 2020).

In a review of current literature, Goradia and colleagues suggest a new formular for the calculation of norepinephrine equivalent dose. It incorporates new vasoactive agents including angiotensin II and metaraminol.

NE = norepinephrine + epinephrine + phenylephrine/ 10 + dopamine/ 100 + metaraminol/ 8 + vasopressin * 2.5 + angiotensin II * 10 (Goradia et al., 2021).

2.9 Administration

Vasopressors and inotropes are administered as an intravenous continuous infusion, titrated every 5- 15 minutes to obtain a MAP of 65 mm Hg and above or urine output of >0.5 ml/kg/min. No effective titration algorithm exists in literature hence care should be taken to avoid hypertension and arrhythmias when up titrating and hypotension when down titrating (Allen, 2014).

These agents should be administered via a Central line whose placement is associated with delays, mechanical, infectious and thrombotic complication. To overcome these problems, peripheral lines may be used, but this is associated with the risk of extravasation which may lead to local tissue necrosis, based on case reports (Loubani & Green, 2015).

In case of extravasation, the alpha antagonist, phentolamine, should be promptly administered. In the absence of phentolamine, topical nitroglycerine and subcutaneous terbutaline may be administered although their use based largely on case reports (Plum & Moukhachen, 2017; Stratton et al., 2017).

CHAPTER THREE

3.0 METHODS

3.1 Study Site

This study was carried out at the MTRH CCU between December 2018 and June 2019. MTRH is the second largest referral hospital in Kenya. It is located in Eldoret, Uasin Gish County, about 310 km northwest of Nairobi. *It serves over 25million people from western Kenya, parts of eastern Uganda, Tanzania, Democratic Republic of Congo and South Sudan. The hospital has a 1020 specialized bed inpatient capacity and provides services to approximately 1300 inpatients and 1500 outpatients every day.In-patient services include adult internal medicine, pediatrics, surgery, obstetrics and gynaecology, orthopedic and trauma, intensive care, cardiology among others (https://www.mtrh.go.ke/about-us).*

The CCU was established in conjunction with Moi University and Duke University, as one of the 11 Collaborating Centers of Excellence established by National Heart Lung and Blood Institute (NHLBI) and United Health Group in response to the rise in the burden of cardiovascular diseases in low- and middle-income countries. Most patient admitted to the unit have cardiac lesions and require closer monitoring which may not be feasible in the general wards. Although not all admitted patients require inotrope or vasopressors, many receive these agents during the course of their admission. According to hospital records, there were 347 admissions to the CCU in 2016. It is served by a team comprising of registered cardiologists, pharmacists, nurses, echo and ECG technicians. Apart from taking part in daily ward rounds, pharmacists have been instrumental in ensuring steady supply of inotropes and vasopressors through the revolving fund pharmacy (RFP) and in the establishment of the anticoagulation clinic (Binanay et al., 2015).

The RFP was set up, in conjunction with donors and local stakeholders, to supplements the government's supply of drugs thus ensuring reliable access to essential medicines. It implements a model in which drugs are sold to patients at a small markup price that is slightly higher than government prices but lower than private pharmacies where quality of medicines may not be assured. This way, government pharmacies are the primary source of medicines with RFPs serving as their back up. These establishments operate semi autonomously are regularly audited to ensure accountability. They are guided by the following principles: facilitated drug procurement, distinct operation, accountability, sustainability, shared ownership and access not profit. The first three RFPs served over 33,000 patients during their first year of operation. Though initially meant for essential medicines, it has evolved to also include other important drugs, including inotropes and vasopressors, that may not be included in the WHO essential medicines list (Manji et al., 2016)

3.2 Study Design

This was a prospective, observational, hospital-based census study. This design was chosen because of the small size of the study population.

3.3 Target Population

The study was conducted among patients admitted to the CCU at MTRH –Eldoret, who required hemodynamic support based on the clinicians' judgment and the patients' cardiac status.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

Patients were recuited into the study if they met *both* of the following criteria:

- Patients over the age of 18, who had an indication for inotropes and/or vasopressors based on the attending cardiologists' assessment.
- Any Structural or electrocardiographic abnormalities of the heart based on echo and ECG findings *because some patients may be admitted to the CCU and require inotropes and vasopressors may be admitted with non-cardiac disease*

3.4.2 Exclusion criteria

- Patients/legal representative who did not give consent.

3.5 Sample Size

This was a census study that enrolled 68 participants. *This design was chosen due to the small number of patients admitted to the CCU who receive inotropes and vasopressors.* Those receiving vasoactive agents and whose consent was obtained, from them or their legally responsible guardian, were included.

3.6 Study Procedure

Patients were screened by the principal investigator to determine their eligibility. Consent was then sought from the eligible patients or their legally acceptable representative with those who willingly consent being recruited into the study. For patients who did not speak or understand English or Swahili, a translator explained the details of the study. Any questions posed by the patients were answered to ensure that they fully understand why and how the study was to be conducted. Once recruited, the patients' file were marked *inconspicuously* to ensure that they were

recruited only once. Each patient was then assigned a study identification number. The master code list was stored separately from collected data and is accessible only to the principal investigator. The de-identified patient data including significant past medical and medication history, periodic biochemical test findings, radiological test findings, 12 lead electrocardiogram and echocardiogram findings, performed at baseline was obtained from the chart. Data was extracted from the nursing flow chart and clinical data routinely collected by the CCU team e.g., kidney and liver function tests, were used to monitor blood pressure and other parameters while adjusting the doses of the inotrope and/or vasopressor until the dose required to obtain a MAP above 65 mm Hg. Every day at 12 noon, the principal investigator collected data on the clinical outcomes. The flow chart was also be reviewed at 5 pm to record the doses required to give a MAP of 65mm Hg. The endpoints included length of CCU stay, the number of patients discharged and their disposition and number of patients who die.

3.7 Data Collection and Management

3.7.1 Data collection

Data was collected using a structured proforma (appendix 3) that included the patients' demographic data, medical history, biochemical test findings such as creatinine, glomerular filtration rate, troponin, creatinine kinase, alanine aminotransferase, aspartate aminotransferase, echo and ECG findings. Indication for vasoactive agents, vitals prior to starting vasoactive drugs, other medications administered, clinical outcomes and disposition were also collected.

3.7.2 Data management

Data collected in the forms was counter checked by the principal investigator to ensure quality and minimize errors. Deidentified data was then transferred to the SPSS version 25 computer program for data analysis. Data from the forms were entered into a password protected computer. The principal investigator holds the password.

Forms used to collect data were stored inside a locked cabinet in a secure room, for 3 years after which they will destroyed.

3.7.3 Data Analysis

Sociodemographic and clinical characteristics were analyzed using descriptive statistics, repeated measures ANOVA was used to determine the effect of treatment on mean arterial pressure (MAP), and multinomial logistic regression was used to evaluate the predictors of the clinical outcome. $p < 0.05$ was considered significant in all cases. A larger study will, however, be required to assess some associations are significant since the sample size is small. Data was presented in the form of tables and graphs.

3.8 Ethical Considerations and Approval

Permission to conduct this study was sought from IREC and MTRH. Consent was sought from individual patients or their legally responsible representatives before they were included in the study.

CHAPTER FOUR

4.0 RESULTS

4.1 Patients' demographics

Table 4-1 indicates the baseline patient characteristics of 68 patients that were enrolled into the study. Their mean age was 51 (SD 23.9) years. Majority of the patients in CCU were between the ages of *51-60* (17.6%) followed by 21-30 (16.2%) and 31-40 (13.2%) years. There were more females than males with the female *participant age ranging from 18-118 years and the male participant age ranging from 18-89 years.*

Table 4.1: Distribution of patients according to age group and gender

Age group	Male (n=29)	Female (n= 39)	Total (n=68)	percentage
11-20	5	2	6	8.8
21-30	5	6	11	16.2
31-40	5	4	9	13.2
41-50	3	6	9	13.2
51-60	8	4	12	17.6
61-70	t6	3	8	11.8
71-80	1	2	3	4.4
81-90	5	3	8	11.8
91-100	0	0	0	0
vu101-110	1	0	1	1.5
111-120	1	0	1	1.5
Mean age	52.1	49.5	51.1	
SD	26.6	20.8	24.2	

4.2 Patients' clinical characteristics

4.2.1 Past medical and medication history

As shown on figure 4-1, 22(32.4%) patients *had not previously been diagnosed with any cardiac comorbidities. Of those with a significant past medical history, 14(20.5%) had been diagnosed with rheumatic heart disease, 9(13.2%) with congestive cardiac failure, 9(13.2%) with atrial fibrillation, 8(11.7%) with hypertension among others.*

Many patients had no known medication history. However, of those with a significant past medication history, 37(54.5%) had been on diuretics while 13(19.1%) had been on beta blockers among other medications (figure 2).

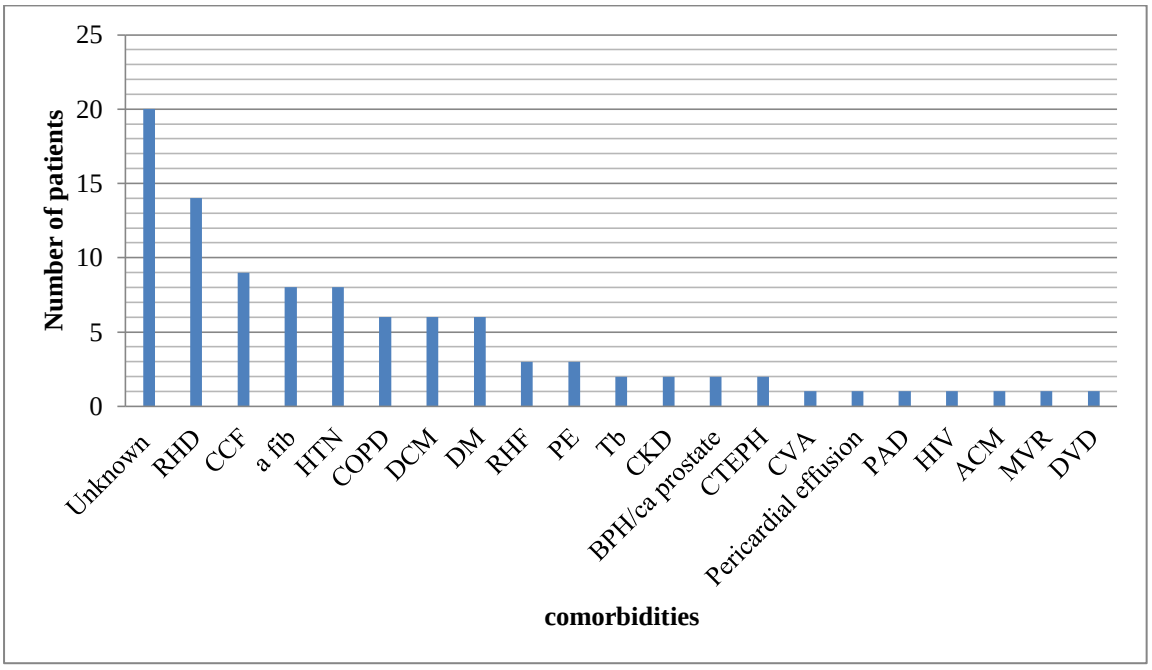

Figure 4.1: Distribution of patients according to comorbidities (abbreviations: a fib- atrial fibrillation, CCF- chronic cardiac failure, HTN- hypertension, COPD- chronic obstructive pulmonary disease, DCM- dilated cardiomyopathy, DM- diabetes mellitus, RHF- right sided heart failure, PE- pulmonary embolism, TB- tuberculosis, CKD- chronic kidney disease, BPH- benign prostate hyperplasia, CTEPH- chronic thromboembolic pulmonary hypertension, CVA - cerebrovascular accident, PAD-

peripheral arterial disease, MVR- mitral valve replacement, DVD- degenerative valve disease, ACM- acute cardiomyopathy)

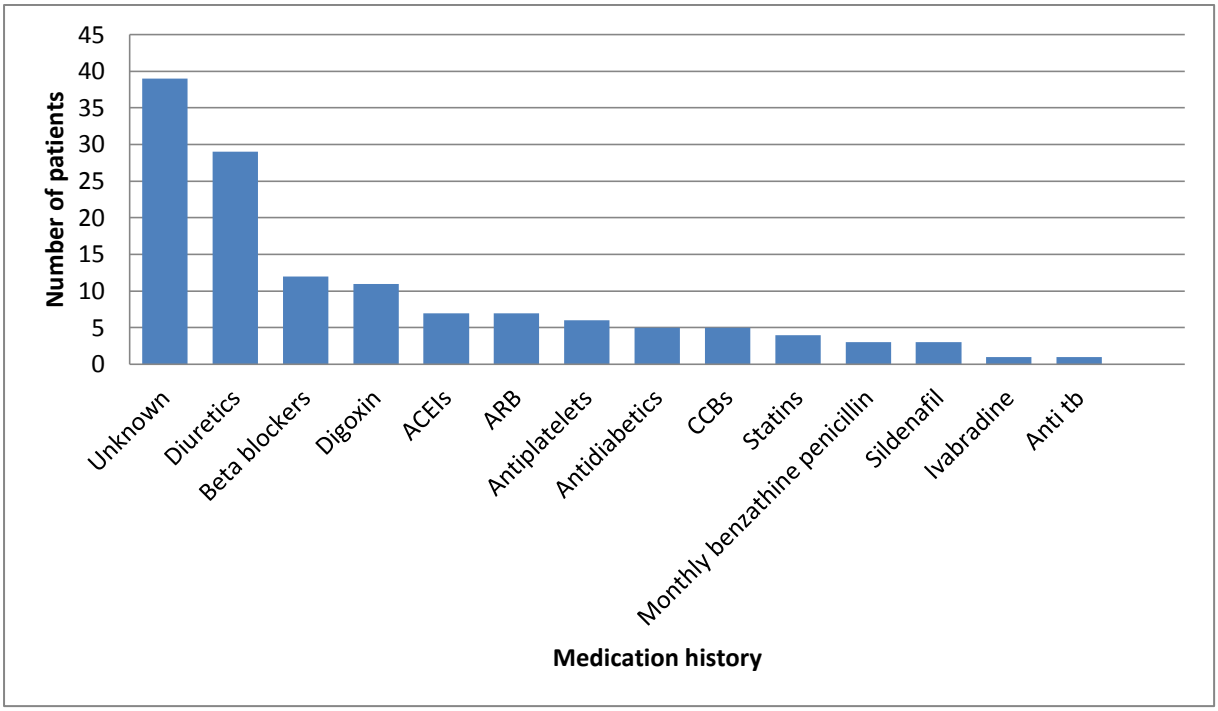

Figure 4.2: Distribution of patients according to past medication history *(abbreviations: ACEIs- angiotensin converting enzyme inhibitors, CCBs- calcium channel blockers, anti-TBs - anti-tuberculosis drugs)*

4.2.2 In-patient hospital investigations

With regard to vital signs at the time of initiation of inotropes and vasopressors, the mean heart rate was normal at 99.7 beats per minute while MAP and SpO_2 ranged from 40-111mmHg and 66%-100% respectively. The patients had poor renal function as evidenced by the low estimated glomerular filtration rate and poor liver function as indicated by higher alanine aminotransferase and aspartate aminotransferase values. The eGFR for males (56.5ml/min/$m^{2)}$ was lower than that of the females (61.5 ml/min/$m^{2)}$. On ECG, 38 (56.7%) patients were in sinus rhythm, 23 (34.3%) had atrial fibrillation among others. There were 49 (73.1%) patients with right ventricular

dysfunction, 37 (55.5%) with valvular heart disease and 20 (41.7%) with an ejection fraction less 40% (table 4-2).

One patient presented with miliary tuberculosis on the chest radiograph while another had interstitial lung disease on chest CT.

Table 4.2: Distribution of patients according to physical, laboratory and radiological findings at admission

.	Females	Males	Total
PHYSICAL FINDINGS			
Mean HR (bpm)	37-172	43-200	37-200
Mean MAP (mmHg)	45-111	0-70	0-111
Mean of SpO_2 (%)	70-100	66-100	66-100
LABORATORY FINDINGS			
Mean HB (g/dl)	7.8-17.4	3.9-17.6	3.9-17.6
Mean WBC (x10^3/uL)	2.0-28.7	2.6-17.1	2.0-28.7
Mean eGFR (ml/kg/min)	3.0-146	6.0-138	3.0-146
Mean AST (mmol/L)	7.6-5489	13-3386	7.6-5489
Mean ALT (mmol/L)	5.2-2254	6.0-3754	5.2-3754
ECG FINDINGS,			
Sinus rhythm, n (%)	23(34.3)	15(22.4)	38(56.7)
Atrial fibrillation, n (%)	13(19.4)	10(14.9)	23(34.3)
Ventricular fibrillation, n (%)	2(3)	0(0)	2(3)
Heart block, n (%)	0(0)	2(3)	2(3)
Paced, n (%)	1(1.5)	0(0)	1(1.5)
ST elevation, n (%)	0(0)	1(1.5)	1(1.5)
ECHO FINDINGS,			
Right ventricular dysfunction, n (%)	21(31.3)	18(26.9)	39(58.2)
Valvular heart disease, n (%)	22(32.8)	15(22.4)	37(55.2)
EF <40%, n (%)	11(16.4)	17(25.4)	28(41.7)
LVH, n (%)	9(13.4)	15(22.4)	24(35.8)
DCM, n (%)	6(9)	12(18)	18(27)
Thrombus, n (%)	1(1.5)	1(1.5)	2(3)
Septal defect, n (%)	1(1.5)	0(0)	1(1.5)
Vegetation, n (%)	0(0)	1(1.5)	1(1.5)

4.2.3 Reasons for admission at the CCU

Seventy five percent of patients were admitted with cardiogenic shock while 25% had mixed shock. Of those with cardiogenic shock, 37(72.5%) had acute decompensated heart failure, 17(33.3%) had atrial fibrillation and 13(25.5%) had rheumatic heart disease (Fig. 4-3).

On admission, 58 (85.3%) patients were prescribed diuretics, 53 (77.9%) anticoagulants, 45 (66.2%) antibiotics among others medications (table 4-3).

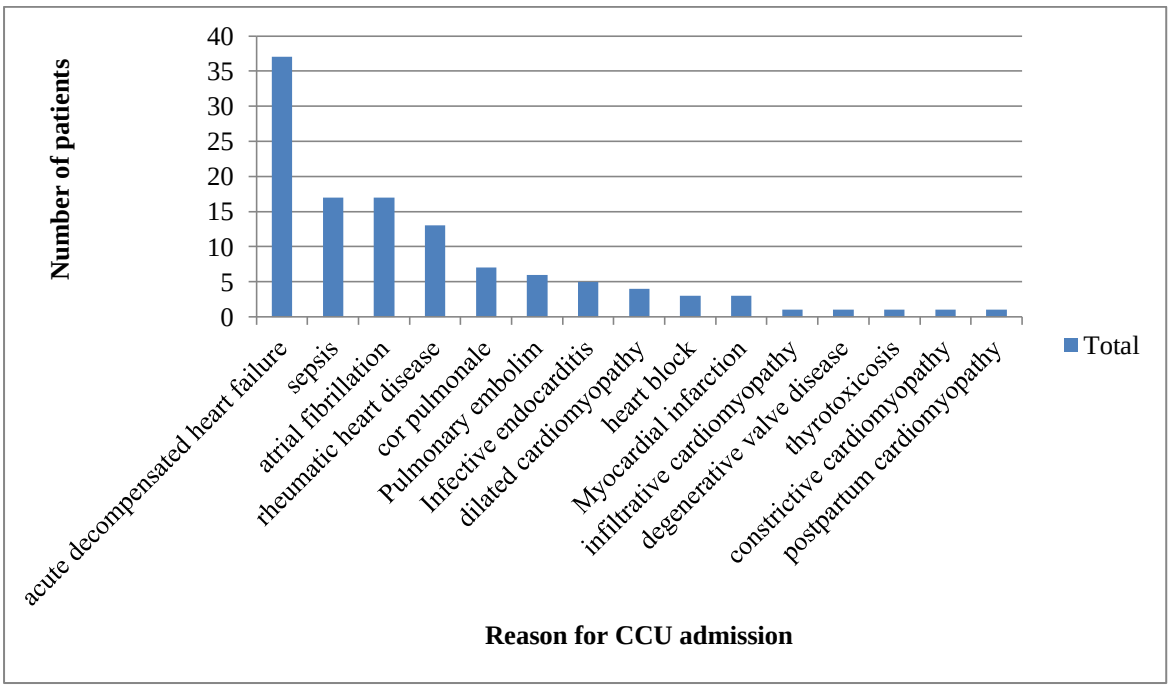

Figure 4.3: Distribution of patients according to reason for admission at the CCU

Table 4.3: Distribution of patients according to medications *initiated* at CCU

Medications	Number of patients
Diuretics	58
Anticoagulants	53
Antibiotics	45
Antiarrhythmics	21
ACEIs	20
Beta blockers	8
Thrombolytics	4
Nitrates	2
Digoxin	1
CCBs	1
Antithrombotics	1

4.3 Inotropes and vasopressors initiated on admission at CCU

Dobutamine was given to 36 patients (52.9%) at doses ranging from 2.5-20 mcg/kg/min while norepinephrine at 15-60mcg/min was administered to 29 (42.6%). Dopamine at doses ranging from 5-15 mcg/kg/min was administered to 2 (3%) and milrinone to 1 (1%) at 0.375mcg/kg/min (Fig. 4-4).

For 28 (41.2%) patients, the desired response was not achieved with one agent. This necessitated giving a second agent. Fourteen (50%) patients received norepinephrine first followed by dobutamine while 8 (28.6%) were given dobutamine followed by norepinephrine.

MAP was higher in patient who received one agent compared to those who received two or more agents ($p<0.001$) with mean MAP increasing from 64.3 (SD 11.9) to 78.7

(SD 10.9) mmHg in patients who received one inotrope and 62.3(SD 15.6) to 70.2(SD 8) mmHg in those patients who received two or more agents respectively (fig. 4-4). Furthermore, Patients with an elevated mean arterial pressure after inotrope treatment were more likely to be discharged to the wards (OR 1.3 [95% CI 1.1-1.6, *p=0.001*]) or discharged home (OR 1.2 [95% CI 1.1-1. 3, *p=0.002*]) than to die.

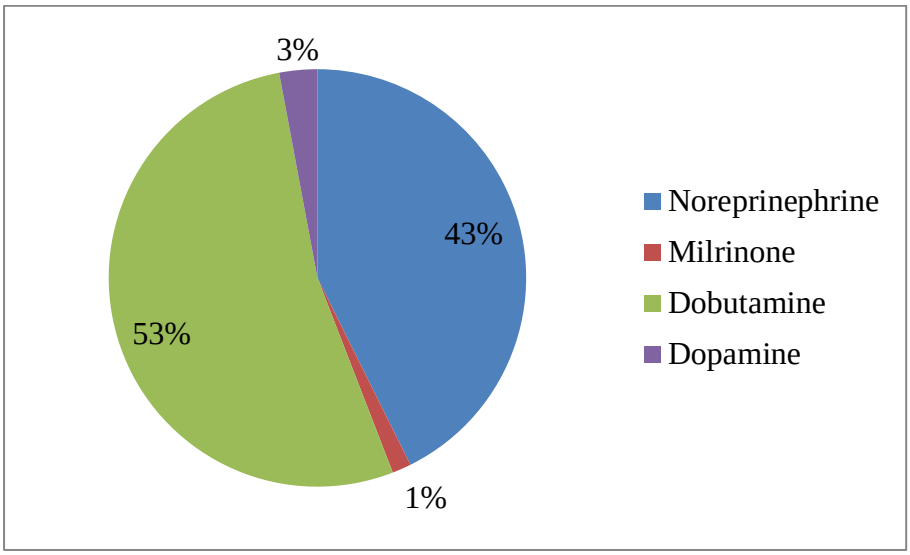

Figure 4.4: Distribution of patients according to the first inotrope/vasopressor

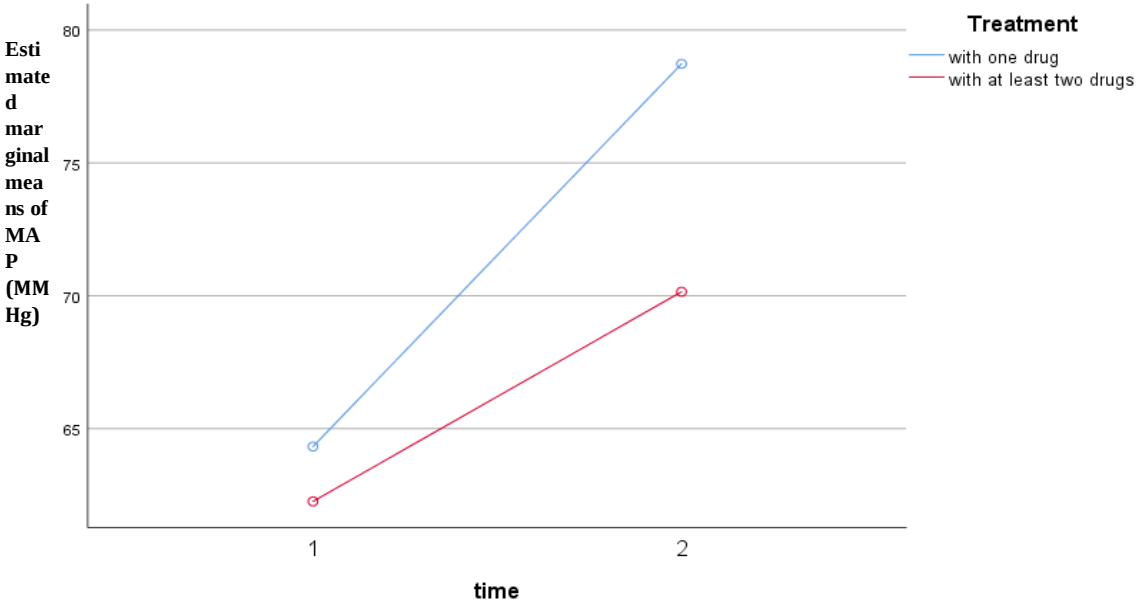

Figure 4.5: Effect of inotrope/vasopressor administration on MAP

As illustrated in table 4-4 below, on bivariate analysis, there was no significant difference in characteristics of patients who receive one agent when compared to those who received more than one agent. This analysis was however limited by the small sample size.

Table 4.4: Bivariate analysis of characteristics of patients who received one agent compared to those who received more than one agent

Required > 1 agent?	Yes (n=28)	No (n=40)	Test stat.	P value
Age			t- test (66 df) = 1.61	0.112
Mean (SD)	45.4 (24.4)	54.9 (23.5)		
Gender			Chisq. (1 df) = 0.94	0.333
Male	10 (35.7)	19 (47.5)		
Female	18 (64.3)	21 (52.5)		
pre-admission medication			Chisq. (1 df) = 0.22	0.639
Yes	17 (60.7)	22 (55)		
No	11 (39.3)	18 (45)		
Spo2			Ranksum test	0.381
median (IQR)	0.9 (0.9,0.9)	0.9 (0.9,1)		
HB			t-test (66 df) = 0.03	0.975
mean (SD)	12.5 (3.2)	12.5 (2.8)		
WBC			Ranksum test	0.859
median (IQR)	8.1 (4.1,13)	7.5 (4,12.3)		
eGFR			t-test (66 df) = 0.46	0.644
mean (SD)	56.9 (35.2)	61.1 (37.7)		
AST			Ranksum test	0.968
median (IQR)	67.7 (29.6,139)	71.9 (32,173)		
ALT			Ranksum test	0.742
median (IQR)	38.6 (20,120)	31 (14.4,191)		

ECHO result			Fisher's exact test	0.174
LVH	2 (7.1)	8 (20.5)		
Pericardial Effusion	26 (92.9)	31 (79.5)		
ECG			Fisher's exact test	0.521
a.fib	9 (32.1)	14 (35)		
Heart block	0 (0)	2 (5)		
paced	0 (0)	1 (2.5)		
sinus rhythm	19 (67.9)	20 (50)		
ST elevation	0 (0)	1 (2.5)		
v. fib	0 (0)	2 (5)		
Length of Stay			Ranksum test	0.759
median (IQR)	5 (4,12.2)	7 (4.8,10.2)		
death			Chisq. (1 df) = 3.47	0.063
Died	19 (67.9)	18 (45)		
Alive	9 (32.1)	22 (55)		

4.4 Clinical outcomes

Our primary outcomes were death, discharge home or discharge to the wards. *Thirty-seven patients died, 22 were discharged home while 9 were discharged to the wards.*

The median length of CCU stay (LOS) was slightly longer (median 8, IQR 6,11.5) for patients who were discharged compared to those who died (media=5, IQR 3,10). Most patients stayed for not more than 10 days (Table. 4-5).

Of those patients who died, *19 (52.4%)* had received dobutamine, *17 (45.9%)* norepinephrine and 1(2.7%) dopamine as the first agent. 28 (75.8%) had cardiogenic shock, 1(1.5%) had septic shock while the rest had mixed shock. 26(70.3%) had a known past medical history while 21 had no known medical history. 25(67.6%) of patients who died were women and 19 (51.4%) of them required a second agent.

Table 4.5: Distribution of patients according to length of hospital stay

Length of stay (days)	Number of patients
1-5	30
6-10	18
11-15	11
16-20	5
21-25	1
31-35	1
41-45	1

As shown on table *4-6*, there was no significant association between the initial inotrope administered and death when Fishers exact test was used. There was no significant difference in odds of death when different combinations of agents were used (table 4-7).

Table 4 6: Association between agent administered and outcomes using Fisher's Exact test

Initial agent administered	Discharged	Died	0.807
Dobutamine	17 (54.8)	19 (51.4)	
Dopamine	1 (3.2)	1 (2.7)	
Milrinone	1 (3.2)	0 (0)	
nor epi	12 (38.7)	17 (45.9)	

Table 4. 7: Odds of death with the administration of different combinations *of inotropes/vasopressors*

Combination	Odds ratio	CI	P value
Norepinephrine plus:			
Dobutamine	1.2	0.2464-5.8444	0.6214
Dopamine	0.1688	0.0071-4.033	0.2719
Milrinone	0.3939	0.0132-11.7585	0.5908
Dobutamine plus:			
Norepinephrine	0.2444	0.0412-1.4487	0.1207
Milrinone+norepinephrine	0.1484	0.0065-0.3.3968	0.2323

4.5 Factors associated with mortality amongst patients on Inotropes and Vasopressors

Table 4-8 below shows the variables included in the bivariate and multivariable logistic regression, to determine the predictors of mortality in the study. On bivariate analysis, no variable was shown to be a predictor of mortality. Covariates that produced p-values less than 0.2 in the multivariate analysis i.e., gender, oxygen saturation, hemoglobin levels, receiving second inotrope and use of dobutamine with an additional agent, were included in the multivariate logistic regression. None of these variables significantly predicted mortality on multivariate analysis.

Table 4.8 : Univariate analysis of factors associated with mortality

	Odds Ratio	**P>z**	**[95% Confidence Interval**	
Male Gender	0.3952941	**0.065**	0.1473257	1.060626
Age	1.001766	**0.862**	0.9819961	1.021934
MAP	1.000048	**0.997**	0.9733039	1.027527
HR	0.9979796	**0.8**	0.9824784	1.013725
Spo2	0.0046284	**0.164**	2.39E-06	8.946939
Septic shock	1			
Cardiogenic shock	1.217391	**0.732**	0.3954128	3.748087
HB	0.8547011	**0.09**	0.7128731	1.024746
eGFR	1.002333	**0.73**	0.9891464	1.015696
WBC	1.021863	**0.521**	0.9565644	1.09162
AST	0.9999825	**0.955**	0.9993677	1.000598
ALT	1.000268	**0.598**	0.9992739	1.001262
Received second inotrope	2.580247	**0.065**	0.9412021	7.073586
Agent administered				
dopamine	0.8947368	**0.939**	0.0518594	15.43701
milrinone	1			
nor epi	1.267544	**0.638**	0.4723879	3.401162
Length of stay	0.9545812	**0.208**	0.887943	1.02622
Medical History				
Non-Cardiac	1.1875	**0.858**	0.1798086	7.842541
Unknown	0.7916667	**0.667**	0.2733832	2.292519

Table 4.9 Multivariate analysis of factors associated with mortality

Covariate	Unadjusted Odds Ratio (95% CI)	p-value for unadjusted OR	Adjusted Odds Ratio (95% CI)	p-value for adjusted OR
Sex				
Male	0.40 (0.15,1.06)	0.065	0.26(0.06,1.16)	0.078
Spo2	0.005 (0.00,8.95)	0.16	0.00(0.00,2.08)	0.066
HB	0.85 (0.71,1.02)	0.09	0.83(0.64,1.08)	0.17
Received Second Inotrope?				
Yes	2.58 (0.94,7.07)	0.65	1.01(0.18,5.70)	0.994
Length of Hospital Stay	0.95 (0.89,1.03)	0.208	0.90(0.80,1.01)	0.064
Dobutamine plus other agent	4.00 (0.78,20.47)	0.096	13.28(0.85,206.56)	0.065

CHAPTER FIVE

5.0 DISCUSSION

The aim of the current study was to evaluate clinical outcomes of inotropes and vasopressors use in patients at the cardiology critical care unit of the Moi Teaching and Referral Hospital in Kenya. The most significant finding of this study was that patients with an elevated mean arterial pressure (MAP) after receiving an inotrope were more likely to be discharged to the wards (OR 1.3 [95% CI 1.1-1.6, *p=0.001*]) or home than to die (OR 1.2 [95% CI 1.1-1. 3, *p=0.002*]). There was no association between the type of vasoactive agent administered and outcomes.

Many patients (38.2%) requiring inotropes and vasopressors in this study were below the age of 40 years and were predominantly women. An Ethiopian study conducted in the ICU setting, in which the most common comorbidities were cardiovascular found similar results (Abate et al., 2021). This is in contrast to a study conducted in North American cardiac intensive care units by Bohula et al., in which most patients were over the age of 60 and had a prior history of cardiac disease (Bohula et al., 2019). Puymirat and colleagues conducted a study in France between 1997 and 2012 among patients admitted with cardiogenic shock and reported that the patient age had reduced over time (Puymirat et al., 2016). Regarding gender, most studies conducted in critical care units failed to clearly demonstrated any relationship between gender and ICU admittance (Larsson et al., 2015; Zettersten et al., 2019). However, these studies were conducted in high income countries among a patient population that is vastly different from ours, limiting the generalizability of the results to our setting. To this end, more studies need to be conducted in the Sub-Saharan Africa population.

In our study, the past medical history for most patients requiring use of vasoactive agents was either unclear or unknown and was not significantly associated with outcomes. These findings are similar to those of the EuroHeart Failure Survey II (EHFS II) in which 40% of patients in the registry had new onset or de novo heart failure (Nieminen et al., 2006). Among those with a clear past medical history, rheumatic heart disease (RHD) was the most frequent comorbidity followed by chronic congestive heart failure, atrial fibrillation, hypertension, chronic obstructive pulmonary disease (COPD), dilated cardiomyopathy (DCM) and diabetes mellitus. A study by Berg at al found smoking, diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, peripheral artery disease and heart failure to be the most common risk factors for cardiovascular disease in North American ICUs (Berg David D. et al., 2019).. The EHFS II however found a high incidence of underlying valvular heart disease, atrial fibrillation and atrial flutter (Nieminen et al., 2006). The valvular disease reported was however unlikely to be rheumatic in nature. These contrasting findings may represent a geographic variation in cardiovascular disease burden.

Patients in our study frequently took diuretics, beta blockers and digoxin at home prior to admission to the CCU. A small trial of 29 patients analyzed the hemodynamic effect of dobutamine when compared to enoximone before carvedilol or metoprolol were initiated and later at 9 and 12 months after beta blockers were started. Carvedilol caused an increase in pulmonary wedge pressure, pulmonary artery pressure and systemic vascular resistance when dobutamine was infused. The magnitude of the effect of metoprolol on these parameters was smaller and these effects were not noticed when enoximone was administered, suggesting that beta blocker administration way negatively impact hemodynamic effects of dobutamine (Metra et

al., 2002). This contrasts with findings of a sub analysis of the DOREMI study which aimed to compare outcomes of dobutamine and milrinone in the treatment of cardiogenic shock. Of the 192 patients enrolled, 48% reported prior receipt of beta blocker therapy. There was **no** difference in hemodynamic response when milrinone and dobutamine were compared. In fact, patients in the beta blocker group had lower risk ratio of early death when compared to those who had no prior beta blocker use (Di Santo et al., 2021)**.**

5.1 Etiology and types of shock

The type of shock varied with the most common subtypes being cardiogenic, mixed and septic shock. This is in agreement with other studies conducted in the cICU (Berg David D. et al., 2019; Jc et al., 2020; Puymirat et al., 2016). The Society of Cardiovascular Angiography and Intervention (SCAI) classifies cardiogenic shock (CS) into five classes based on manifestations of signs and symptoms of cardiogenic shock. SCAI Stage A CS patients are those at risk of developing CS e.g., stable ischemic heart disease patients. Stage B CS patients present with hypotension without any signs or symptoms of hypoperfusion. Stage C CS patients present with classical signs and symptoms of cardiogenic shock and require interventions including administration of vasoactive drugs. Deteriorating patients who fail to respond to initial intervention and require more than one vasoactive drug to achieve the desirable MAP are said to be in stage D CS while those in who are in cardiac arrest or are pulseless are said to be in stage E CS (D. A. Baran et al., 2019). All cardiogenic shock patients in this study can therefore be classified as stage C, D or E because they required at least one inotrope/vasopressor.

In the present study, acute decompensated heart failure was the most common etiology of shock which was similar to the findings of a study by Jc et al (Jc et al., 2020). The European Society of Cardiology defines acute heart failure as onset of heart failure signs and symptoms that is severe enough for a patient to be admitted to a hospital or visit the emergency department (McDonagh et al., 2021). A. fib and RHD cumulatively accounted for nearly half of all patients, while AMI occurred in less than 1% of patients, contrary to the findings of the study by Berg et al where patients with A. fib and valvular heart disease made up 17% of the population while patients with acute myocardial infarction accounted for 30% of all study participants (Berg David D. et al., 2019). These findings are in keeping with those of the EHFS II where atrial arrythmias and valvular heart disease occurred in 33% and 30% of patients respectively. In this European study, non-compliance to prescribed medications was the precipitant in 25% of ADHF cases (Nieminen et al., 2006).

Studies have reported that RHD affects mainly younger patients and women and is often complicated by heart failure, RV dysfunction secondary to pulmonary hypertension, LVH, systolic dysfunction, infective endocarditis and intracardiac thrombi (Lumsden et al., 2016; Zühlke et al., 2016).*A study conducted at MTRH by Koech and colleagues reported that the most common lesions were mitral regurgitation, mitral regurgitation with aortic insufficiency, and mitral stenosis with aortic regurgitation or mitral regurgitation (Koech et al., 2012).* It is important to note that the use of vasoactive agents in management of shock among RHD patients is complicated by challenges in diagnosis, the occurrence of multiple lesions, and paucity of data on their use (Akodad et al., 2019).

Dilated cardiomyopathy (DCM) was another cause of cardiogenic shock among patients admitted to the critical care unit of the study area. It may be of infectious, genetic or autoimmune etiology, but some cases may also be attributed to excessive alcohol consumption or pregnancy (Sliwa et al., 2005). A study conducted by Sylvester et al in Western Kenya revealed that compared to women, a higher proportion of men were affected by DCM (Sylvester, 2016). Peripartum cardiomyopathy is one of the main causes of DCM in women. It is identified a month before childbirth or up to 5 months postpartum. Although its prevalence and risk factors in Kenya are not known, it has been shown to be more prevalent in women of African descent and those with selenium deficiency. Several studies have also demonstrates an higher morbidity and mortality among black women (Brar et al., 2007; Karaye et al., 2019; Sinkey et al., 2022). It is recommended that women with peripartum cardiomyopathy be treated with heart failure medications that have known mortality benefits until there is resolution of left ventricular function. A small randomized trial has shown that use of bromocriptine 2.5 mg twice daily for two weeks followed by 2.5mg once daily for 4 weeks greatly improves left ventricular systolic function (Sliwa et al., 2010). Since it is a procoagulant, women on bromocriptine should be anticoagulated for the duration of treatment (Chopra et al., 2012).

Studies have observed that non-ischemic right sided heart failure is more common among female patients than male patients with many of them exhibiting isolated right ventricular dysfunction on their echocardiogram. It may be plausible that this observation was due to chronic obstructive pulmonary disease caused by indoor pollution, HIV or occupational dust exposure as has been reported by Stewart et al 2011 (Stewart et al., 2011) and Lagat et al 2014 (Lagat et al., 2014). This results

from use of biomass fuels including firewood, charcoal and dung in poorly ventilated rooms (Lambe et al., 2015; Torres-Duque et al., 2008). Other causes of right ventricular failure that have been reported include pulmonary embolism, left heart failure, and valvular insufficiency (Konstam Marvin A. et al., 2018).

5.2 Medications prescribed

Diuretics, including furosemide, metolazone, Aldactone, hydrochlorothiazide and tolvaptan, were the most commonly administered medication. Although they have not been shown to have any mortality benefit, loop diuretics are administered in patients with sign of volume overload including oedema and dyspnoea, to reduce signs and symptoms of congestion (Casu & Merella, 2015). For those who do not respond adequately to loop diuretics alone, dual renin-angiotensin-aldosterone system blockade with a second agent, often a thiazide or potassium sparing diuretic, can be initiated. A systematic review and meta-analysis of clinical trials revealed a reduction in cardiovascular death and heart failure hospitalizations in patients who received dual blockade (Rossi et al., 2019). Additionally, several randomized clinical trials have shown that mineralocorticoid receptor antagonists have mortality benefit (Pitt et al., 2003, 2014; Zannad et al., 2011) Patients in whom diuretics are administered concurrently with vasopressors may have increased urine output without increasing requiring an increase in vasopressors dose (Bandak et al., 2020). When compared to use of diuretic alone, a review of a heart failure registry revealed improved hospital survival when diuretics were combined with vasodilators. However, the study was retrospective in nature, limiting its quality(Mebazaa et al., 2011)

Rhythm control strategy for arrythmias, using digoxin and amiodarone, was preferred initially since they can be administered intravenously and therefore have quicker onset of action. In addition, early rhythm control has been shown to have better issues

when compared to standard of care (Kirchhof et al., 2020). Although rate control with beta blockers has been shown to have fewer side and similar efficacy as rhythm control, they are known antagonists to the action of the catecholamine inotropes and vasopressors and should not be used concomitantly (de Denus et al., 2005; Olshansky et al., 2004).

Critical care patients are considered to be at high risk of developing venous thromboembolism. As such they require primary prophylaxis for prevention and, secondary prophylaxis for treatment of venous thromboembolism (Ejaz et al., 2018). Anticoagulants including enoxaparin and heparin, were the second most commonly prescribed medications in the study area. Heparin is preferred in patients with renal dysfunction since use of enoxaparin has been associated with an increased risk of bleeding (DeBiase et al., 2021). This is in keeping with the American Society of Hematology guidelines which recommends use of fondaparinux, unfractionated heparin or a low molecular weight heparin e.g., enoxaparin in patients who are at low risk of bleeding. For those at high risk of bleeding, mechanical thromboprophylaxis using graduated compression stockings or pneumatic devices is recommended (Schünemann et al., 2018).

In the current study, administration of antibiotics was based on signs and symptoms including fever, elevated c reactive protein and white cell count. In critically ill patients, occurrence of infection is common with the Extended Study on Prevalence of Infection in intensive Care III estimating that approximately 50% of ICU patients had a suspected or confirmed infection. Antibiotics should be administered early while awaiting culture results, especially in patients with septic shock. Antibiotics can then be deescalated to target the cultured microorganisms (Kollef et al., 2021). A study conducted in a tertiary hospital in Malawi revealed that 80% of ICU admitted

patients received antibiotics while a Vietnamese study found that approximately 60% of patients received empiric antibiotic therapy(Dat et al., 2022; Kayambankadzanja et al., 2020)5.2 Inotropes and vasopressors used

Dobutamine, norepinephrine, and dopamine were the most commonly used inotropes used in the study area. They were prescribed to patients exhibiting signs of impaired tissue perfusion and/or those with systolic blood pressure (SBP) <90mmHg or MAP <65 mmHg. In a study conducted at Kenyatta National Hospital, dopamine and norepinephrine were the most frequently used agents while dobutamine was the least frequently used (Simiyu, 2014). However, unlike our study, the study by Simiyu and colleagues was conducted in a general medical ICU where septic shock was the most common type of shock. In a North American study by Jc et al., vasopressors including dopamine and norepinephrine were prescribed more frequently than inotropes including dobutamine and milrinone. However, between 2007 and 2018, temporal trends revealed a decrease in the use of dopamine and an increase in the use of norepinephrine likely as result of the change in practice and guidelines that followed the SOAP II trial results. Although use of dobutamine reduced between 2007 and 2015, its use has been reported to be on the increase since the year 2016 (Jc et al., 2020). Results of an international survey in which physician from 82 countries participated revealed dobutamine to be the first line inotrope among physicians and was given in response to signs and symptoms of shock. Due to lack of clear evidence, it is difficult to recommending use of one agent over another. Even when there is evidence of benefit, clinical significance may still be (Scheeren et al., 2021).

At our CCU, 41.2% of patients who did not respond adequately to the initial agent received > 1 agent, majorly a combination of norepinephrine and dobutamine. Studies conducted in other CCUs in developed countries reported similar proportions with

38.9-55% of patients received >1 vasoactive agent (Jentzer & Hollenberg, 2020; Nandkeolyar et al., 2021; Tarvasmäki et al., 2016b). A meta-analysis was conducted using data derived from observational studies that utilized the EFFICA, ALRM HF and AHEAD databases, with the aim of examining whether use of inotropes alone was better than combining inotropes with a vasopressor. Results suggest that use of inotropes alone may be associated with higher short term mortality when compared to combining an inotrope and a vasopressor (Pirracchio et al., 2013). This is consistent with results of a study that compared the use of a combination of norepinephrine and dobutamine to use of epinephrine alone. It concluded that norepinephrine was associated with more adverse effects than the combination (B. Levy et al., 2011). In septic shock patients, high vasopressor doses are also associated with higher mortality (Auchet et al., 2017). It may therefore be beneficial to use low doses of two agents rather than maximum doses of one (Ammar et al., 2022)

It could be argued that the choice of agent (dobutamine, norepinephrine) in our setting may have been influenced by the pathophysiology of shock, the characteristics of the patient, and probably on expert opinion as has been reported by previous authors (Overgaard & Džavík, 2008a). For example, experts recommend that in RHD patients with mitral regurgitation, there may be a need for afterload reduction to reduce regurgitation and encourage forward blood flow. Moreover, patients with aortic regurgitation, aortic stenosis, and mitral stenosis require vasopressor support (Akodad et al., 2019). Khot et al conducted a study in which they administered nitroprusside to 25 patients with left ventricular dysfunction, aortic stenosis and acute decompensated heart failure. They concluded that nitroprusside improved cardiac function. However the study was limited by its small sample size and included patients who had MAP>60 (Khot et al., 2003).

The Surviving Sepsis Guidelines on the management of sepsis and septic shock recommend nor epinephrine as the first line agent for the management of septic shock in adults, with addition of vasopressin or epinephrine if there is inadequate response to fluid and vasopressor therapy. This may reduce nor epinephrine dose requirements, and with addition of vasopressin, reduce adrenergic overload (Rhodes et al., 2017b). This is based on the SOAP II trial which compared the clinical outcomes following the use of dopamine and norepinephrine in patients with septic shock. The findings of the trial suggested that there was no difference in mortality between the two groups but that those who received dopamine developed more arrhythmias that warranted the cessation of the drug. Moreover, in a subset of patients who had cardiogenic shock, the dopamine group had significantly higher mortality (De Backer et al., 2010b). Septic shock patients may exhibit cardiac lesions that may have been present before or developed as a result of sepsis induced myocardial depression as has been reported by Parillo and colleagues (Parrillo et al., 1990).

Goal directed therapy (GDT) involves use of care bundles so that specific interventions are made with a specific endpoint in mind e.g., administering fluids to achieve a urine output greater than 0.5 ml/kg/min and administering vasoactive drugs to obtain MAP greater than 65 mmHg. GDT has also been shown to improve outcomes in patients with septic shock (Rivers et al., 2001).

The American Heart Association recommends milrinone and dobutamine for management of circulatory shock in patients with cor pulmonale since they are potent pulmonary vasodilators (Konstam Marvin A. et al., 2018). Milrinone is a more potent vasodilator than dobutamine and may better lower right and left ventricular afterload (Monrad et al., 1986). However, it requires adjustment for renal function and may cause hypotension that is less quickly reversible due to it longer duration of action.

Vasoconstrictors may be used cautiously to maintain perfusion at doses that will not cause further pulmonary vasoconstriction (Konstam Marvin A. et al., 2018). For cardiogenic shock due to myocardial infarction, the Canadian Association of Emergency Physician recommends combination of dopamine with dobutamine since this has been associated with better outcomes (Macit Kalçık et al., n.d.-b)

5.3 Outcomes

Our findings indicate that, after vasoactive agent administration, male patients showed a trend towards higher likelihood of being discharged when compared to female patients. This is in contrast to a study conducted by Mahmood and colleagues, which found a higher mortality among men under the age of 50 compare to their female counterparts. Mortality rate among patients over the age of 50 was similar for both men and women (Mahmood et al., 2012).

However, it is not clear why male patients had higher rates of discharge than female patients despite exhibiting higher serum creatinine, aspartate transaminase (AST), and alanine transaminase (ALT). Deteriorating renal and kidney function exemplified by high serum creatinine, AST, and ALT levels have been associated with higher mortality rates (Mandelbaum et al., 2011; Masewu et al., 2016; Reddy et al., 2014; Van den broecke et al., 2018). It may be posited that the higher mortality observed in these patients in may be attributed to the severity of disease rather than the worsening of renal function (Girling et al., 2020).

Cardiogenic shock secondary to ADHF occurred in majority of patients in this study. In addition, many patients had no prior history of cardiac disease. In one study, ADHF patients who developed cardiogenic shock had high mortality close to 40% while those who did not develop cardiogenic shock had mortality rates of less than

10%. In addition, de novo acute heart failure was associated with higher mortality when compared to heart failure in patients who had known cardiac disease (Nieminen et al., 2006).

Many patients in this study setting had sepsis, and heart failure which have previously been reported to be risk factors for the development of acute kidney injury (AKI) (Clermont et al., 2002). Liver failure in critically ill patients may be caused by shock-induced ischaemic liver injury (centrilobular necrosis) or sepsis related cholestasis (Horvatits et al., 2019). Moreover, age could also be a factor behind this observation. *The proportion of women (35.9%)* recruited into this study who were over the age of 60 was higher that of men (28.6 %). Age has been shown to be an independent predictor of mortality among patients admitted to the ICU. Thus this may have contributed to the higher mortality among women (Soares Pinheiro et al., 2020).

Some studies have reported that rheumatic heart disease predominantly affects women while others found no correlation between gender (Rothenbühler et al., 2014; Zühlke et al., 2013). The high mortality observed in RHD patients has however been reported consistently. Data from the REMEDY registry revealed a mortality of 11% while a study conducted by Okello et al in Kampala Uganda among RHD patients aged between 5-60 years found the mortality rate to be 18%. Poor adherence to the monthly doses of Benzathine Penicillin, the occurrence of heart failure, dilated left ventricle, and reduced ejection fraction, all of which are observed in our setting, were associated with higher mortality (Okello et al., 2017; Zühlke et al., 2016). A metanalysis of studies that reported prevalence of RHD among children between the age of five and eighteen, the prevalence of clinically silent rheumatic heart disease was found to be up to eight times higher than the prevalence of clinically manifested disease (Rothenbühler et al., 2014). This silent disease may contribute to the late presentation,

increase complications and high mortality rates observed among RHD patients (Akintunde & Opadijo, 2009; Akinwusi et al., 2013).

Our findings also indicate those who had higher MAPs after administration of inotropes/vasopressors were less likely to die. A study by Burstein et al conducted among North American CCU patients, 72% who required inotropes/ vasopressors, found similar results. There was an inverse increase in odds of death with every 5mmHg decrease in mean MAP (mMAP). Patients with mMAP below 65mmHg had a demonstrable increase in mortality when compared to those whose mMAP was above 65mmHg (Burstein et al., 2020). Another North American Retrospective database analysis demonstrated and increase in mortality with time and decrease in MAP. In this study, the highest mortality was observed among patients whose MAP was below 55 mmHg when compared to those whose MAP was between 80 and 75mmHg. Additionally, compared to patients whose MAP was never below 65 mmHg, mortality of patients whose MAP was below 65mmHg increased with time below this MAP (Vincent et al., 2018). Finally, a retrospective study comparing MAPs of survivors and non survivors of cardiac arrest concluded that higher MAP, was associated with better outcomes regardless of whether or not the patient received inotropes or vasopressors (Beylin et al., 2013)

Our study found no significant association between the agent given, number of agents administered and patient outcomes. Furthermore, there was no significant difference in baseline characteristics among the patients who received one agent and those who received more than one agent. Although administration of inotropes and vasopressors significantly increased MAP regardless of the number of agents used, mean MAP was higher (78mmHg) in patients who receive one agent compared to those who received more than one agent (70 mmHg).

Studies have demonstrated an increase in mortality with increase in dose and number of agents used. Since all patients recruited into this study required hemodynamic support with at least one vasoactive drugs, they all fall under SCAI stage C or higher (D. A. Baran et al., 2019). A retrospective analysis of patients admitted to the CCU at Mayo Clinic revealed a stepwise increase in mortality with progression of the SCAI class (Jentzer et al., 2019). Another North American study demonstrated an increase in mortality with progression of SCAI CS stage, with stage D and E patients exhibiting the highest odds of death (Jentzer & Hollenberg, 2020). In terms of comorbidities, a study conducted among patients with myocardial infarction found also found an increase in mortality with progression of SCAI class (Udesen et al., 2022).

Vasopressor requirements were also low among patients who survived. On average survivors required a total average of 4.5 mcg/kg/min of inotrope/vasopressor while those who succumbed required 6.5 mcg/kg/min. A study conducted among 64 septic shock patients admitted at tertiary hospital who received epinephrine and/or norepinephrine found a 3.3% and 3.6% survival rate among patients receiving over 3 mcg/kg/min of adrenaline and over 100mcg/min of norepinephrine respectively. None of the patients receiving over 200 mcg/min of noradrenaline survived (Jenkins et al., 2009). Another retrospective analysis compared receipt of low dose (less than 40mcg/min) and high dose (over 40 mcg/min) of norepinephrine in ICU patients. The low dose vasopressor group was 4 times more likely to die than the low dose group. Compared to patients who did not receive any vasopressor, the high dose group showed a 28 fold increase in mortality when compared to patients who never received any vasopressor (Sviri et al., 2014). The duration of exposure to norepinephrine and epinephrine may also influence survival. A study by Kastrup and colleagues

concluded that administration of norepinephrine at doses above 0.1mcg/kg/min and epinephrine at doses above 0.4mcg/kg/min for periods of over 5 hours resulted in poor outcomes (Kastrup et al., 2013).The number of agents used may also determine survival of shock patients. In a small study of 66 patients who received 3 or more vasoactive drugs, only 14% survived until ICU discharge while only 9% survived until hospital discharge. No patient receiving four or more agents survived to ICU discharge (Prys-Picard et al., 2013) .

Although these studies were conducted in the medical ICU, representing a different patient population than that in our CCU, these results are consistent with reports that use the vasopressor inotropic index as a measure of circulatory support among CCU patients. The vasoactive inotropic score (VIS) is a quantitative measure of circulatory support required by an individual at a particular point in time. It is derived from the weighted sum of all vasoactive agents administered based on equipotencies of the various inotropes and vasopressors (Belletti et al., 2021). Several studies have demonstrated a higher mortality with higher VIS for various types of shock. A south Korean study conducted among 493 cardiogenic shock patients who had cardiac disease revealed higher rates of cardiac and non-cardiac deaths among patients with higher VIS. Septic shock and sepsis were the most common causes of non-cardiac death (Na et al., 2019). Among 10004 patients admitted to a North America CCU, Jentzer and colleagues demonstrated and increase in dose and number of inotropes with progression of SCAI cardiogenic shock stage. 47.9% of these patients received more than one inotrope and/ or vasopressor (Jentzer et al., 2019). Vasopressor dosing intensity may also be used to quantify inotrope and vasopressor requirements. Is is the total dose of inopressor support in norepinephrine equivalents. A study by Russel and

colleagues demonstrated an increase in mortality, among septic shock patients, with increase in 24 hour vasopressor dependency index (Roberts et al., 2020).

Several studies have demonstrated an increase in mortality, especially in patient with cardiogenic shock, when inotropes and vasopressors are administered. A retrospective analysis of the ALARM HF registry, comprising of eight countries in Europe and South America, and 4953 acute heart failure patients, 75% of whom were admitted to ICUs and CCUs showed a 1.5-fold and 2.5-fold increase in mortality when dopamine or dobutamine and norepinephrine or epinephrine respectively were used. Levosimendan had little to no mortality benefit (Mebazaa et al., 2011). Another retrospective analysis of the ADHERE registry, made up of countries in North America and 65,180 patients., found a 1.24 odd ratio of death when dobutamine was used compared to when vasodilators including nitroglycerin and neseritide were used (Abraham et al., 2005). A study conducted among patients who receive a left ventricular assist device (Impella) also revealed an increase in mortality among patients on inotropes and vasopressors, with the highest increase observed among those with 2 or more agents (Rohm et al., 2021). Specific agents, notably dopamine and epinephrine, have also been associated with a higher mortality in this patient population (De Backer et al., 2010a). Most studies that demonstrate increase mortality are observational and involve retrospective review of data. Furthermore, attending physicians are tasked with choosing the agent they deem most appropriate. These shortcomings therefore limit interpretation of these results.

Other studies have reported contrasting results, having observed no effect on mortality. The Cardshock study, conducted European ICUs, enrolled 216 patients, 75% 0f whom received norepinephrine. 30% of patients received more than one agent. The only agent that was associated with increased 90 day mortality was

adrenaline. However, most patietns who epinephrine had suffered a cardiac arrest. There was no increase in 90-day mortality when other vasoactive agents were administered to cardiogenic shock patients (Tarvasmäki et al., 2016). Belleti et. al conducted a meta-analysis of 177 randomized control clinical trials accounting for a total of 28,280 patients. There was no difference in mortality between patients who received vasoactive agents and those who did not. Patients whoc received levosimendan, as well as those who were septic, vasoplegic or had undergone cardiac surgery exhibited lower mortality (Belletti et al., 2015). It should be noted that most of these studies have been conducted in resource rich settings therefore generalizing their results to our setting may be inaccurate.

The observed mortality among patient receiving inotropes and vasopressors is a complex interlay of several factor including the severity of underlying disease, presence of organ dysfunction among others as observed using the sequential organ failure assessment (SOFA) score and the acute physiology and chronic health evaluation (APACHE) score (Ferreira et al., 2001; Tian et al., 2022). High score have consistently been shown to be associated with increased mortality (Fuchs et al., 2020; Sadaka et al., 2017).

In our study, median length of stay for patients who died was 5 days and 8 days for those who were discharged. There was a non-significant trend towards higher odds of survival with increased length of stay among those who were discharged to the wards. An Australian study found no influence of length of stay on in hospital mortality. There was however a small increase in long term mortality (Williams et al., 2010a). In contrast, a retrospective audit conducted at the ICU of a teaching hospital in Uganda found that patients who stayed for 6 to 15 days had better survival than those who stayed less than 5 days or more than 2 weeks (Kwizera et al., 2012). Another

retrospective observational review of critical care databases in the United States and United Kingdom attempted to determine conditional survival, the likelihood of future patient survival considering that they have already survived a certain number of days in the ICU. It found no increase in mortality among young after the first 5-10 days of ICU admission. For patients over the age of 75, mortality increased with increased length of stay (Marshall et al., 2020). This is in keeping with a North American study in which increasing age, after accounting for comorbidities, was associated with an increase in both 30 day and I year mortality. It should be noted that although age may be a predictor of ICU mortality, the elderly tend to have more comorbidities and higher frailty than younger patients, factors that also contribute to survival and mortality. *Long term (1 year) mortality rather than short term (30- 90 day) mortality has been associated with longer length of hospital stay (Moitra et al., 2016).* has also been noted that deaths in the ICU often occur earlier in the admission (Williams et al., 2010b).

5.4 Limitation of the study

This was an observational study that recruited few patients primarily due to the short study period. The sample size therefore limited the study's power to detect important correlations. Furthermore, the choice of inotrope/vasopressor was subject to availability and the admitting physician judgment. Furthermore, data on laboratory and radiological findings was only collected at entry making it difficult to accurately establish correlation between them and the outcomes.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

1. *Patients recruited into this study were mostly women, younger patients and had no known comorbidies.*
2. *Majority of patients in whom inotropes/vasopressors were initiated were diagnosed with acute decompensated heart failure and were started on dobutamine, dopamine, norepinephrine or milrinone alone or in combination.*
3. *Patients who received on inotrope/vasopressor had higher MAP compared to those who received >1 inotrope/vasopressor. There was no difference in the characteristics of patients who receive one agent compared to those who received more than one.*
4. *Patients who had elevated MAP after inotrope or vasopressor administration were more likely to be discharged home or to the wards.*
5. *There was no difference in outcomes when different agents and combinations were compared.*

6.2 Recommendations

Further studies with bigger sample sizes need to be conducted to further explore the findings of this study. Furthermore, efforts should be directed at prevention and early treatment of cardiac disease since use of inotropes and vasopressor is in itself an indicator of advanced disease which is associated with poor outcomes.

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APPENDICES

Appendix 1: Work plan

	Mar.-jun ‘18	Aug. ‘18	Sept. ‘18	Oct. ‘18	Nov. ‘18	Dec. ‘18	Jan. ‘19	Feb. ‘19	Mar. ‘19	Apr. ‘19	May. ‘19	Jun. ‘19	Jan-Dec. ‘21	Jan-Mar ‘22
Proposal development and approval														
Data collection														
Data analysis														
Thesis write up submission														

Appendix 2: Data Collection Proforma

a. Demographic data.

Name:	Age:	Sex:

b. Medical history.

c. Pre admission medication

d. Vitals on admission

Blood pressure	
Heart rate	
sPO_2	

e. Admission diagnosis

f. Laboratory parameters

Creatinine	
Egfr	
Troponins	
CK MB	
Hb	
Neutrophil count	
AST	
ALT	
HBA1C	
PITC	

g. ECG findings

	yes	no
Sinus rhythm		
Atrial fibrillation/flutter		
Ventricular fibrillation/ tachycardia		
ST elevation		
T wave depression		
Paced		
Heart block		

h.

i. ECHO findings

	yes	No
Valvular heart diseases.		
Ejection fraction < 40		
Left ventricular hypertrophy		
Dilated cardiomyopathy		
Right ventricular dysfunction		
Septal heart defects		

j. Radiological test findings

	yes	No
Miliary or pulmonary TB on chest x ray		
Hemorrhage on head CT/MRI		
Ischaemia on head CT or MRI		

k. Medications during CCU admission

	YES	NO
Antibiotics		
Diuretics		
Antiarrythmics		
B blockers		
ACEIs		
Nitrates		
CCBs		
Thromboltyics		
Antithrombotics		
Anticoagulants		

l. Choice of 1st inotrope or vasopressor.

Inotrope/ vasopressor	Maximum dose	BP obtained

m. Choice of second inotrope/ vasopressor where applicable.

Inotrope/vasopressor	Maximum dose	BP obtained

n. Outcomes

Length of CCU stay	
Total length of hospital stay	
Disposition	
Death	

Appendix 3: Consent Form

Kichwa cha Utafiti: Matumizi na Matokeo ya matumizi ya Vasopressors na Inotropes kati ya Wagonjwa Wanalioko katika Hospitali ya Rufaa na Mafunzo ya Moi –Eldoret

Jina la Mtafiti Mkuu: Sang Natalie Jepkemboi

Wachunguzi wenza:

Jina la Shirika: Chuo Kikuu cha Moi

Jina la Msaidizi: binafsi

Fomu ya Ruhusa ya Kibali kwa:

Wagonjwa walio katika kitengo cha huduma ya moyo katika Hospitali ya Rufaa na Mafunzo ya Moi, ambao wameanzishwa kwa inotropes na vasopressors.

Fomu hii ya Ruhusa ya Ruhusa ina sehemu mbili:

• sehemu ya Taarifa (kukujulisha kuhusu utafiti)

• Hati ya Ruhusa (ikiwa unachagua kushiriki)

Utapewa nakala ya Fomu iliyoidhinishwa ya Ruhusa

Sehemu ya I: Karatasi ya Taarifa

Utangulizi:

Jina langu ni Dr Natalie Sang. Mimi ni mwanafunzi wa mater of Pharmay in Clinical Pharmay katika Chuo Kikuu cha Moi. Ninafanya utafiti juu ya matumizi ya vasopressors na inotropes katika MTRH.

Unastahili kushiriki katika utafiti huu. Taarifa hii hutolewa ili kukuambia kuhusu utafiti. Tafadhali soma fomu hii kwa makini. Utapewa nafasi ya kuuliza maswali. Ikiwa utaamua kuwa katika utafiti huu, utapewa nakala ya fomu hii ya idhini kwa kumbukumbu zako.

Kushiriki katika utafiti huu ni hiari. Unaweza kuchagua kutoshiriki katika. Bado utapata matibabu mengine. Kusema hapana haitaathiri haki zako kwa huduma za afya. Pia ni utakuwahuru kujiondoa kwenye utafiti huu wakati wowote. Ikiwa baada ya ukusanyaji wa data unachagua kuacha, unaweza kuomba kwamba taarifa iliyotolewa na wewe iangamizwe chini ya usimamizi – na hivyo isitumike katika utafiti. Utafahamishwa kama taarifa mpya itapatikana kuhusu hatari au faida za utafiti huu. Kisha unaweza kuamua kama utataka kukaa katika utafiti

Kusudi la utafiti:

Kusudi la utafiti ni kujua kuhusu inotropes na vasopressors zinazotumiwa katika CCU, tabia ya wagonjwa ambao hupewa mawakala haya na matokeo yao

Aina na Mradi wa Utafiti:

Mtafiti atapata taarifa kuhusu historia yako ya matibabu na dawa, uchunguzi wa maabara na radiology kutoka faili yako baadaye atafuata maendeleo yako wakati wa kuingia kwako kwenye CCU hadi kuondoka.

Kwa nini nimejulikana kushiriki katika utafiti huu?

Mtafiti anakaribisha watu wote wazima ambao wameanzishwa kwenye inotropes na vasopressors wakati wa kuingia kwao kushiriki katika utafiti huo.

Utafiti utaendelea muda gani?

Utakuwa katika utafiti huu kwa muda wako wa matibabu katika CCU

Nini kitatokea kwangu wakati wa kujifunza?

Tunakuomba utusaidie kujifunza 99aidi kuhusu matumizi na matokeo ya inotropes na vasopressors. Ikiwa unakubali, utaulizwa kuniruhusu nipate maelezo kutoka kwenye faili yako. Je, ni madhara gani au hatari ambazo ninaweza kutarajia kutoka kwenye utafiti?

Huu ni utafiti mdogo kwa hatari. Mtafiti hawezi kuchagua madawa unayotumiwa wakati wa kuingia kwako.

Je, kuna faida ya kushiriki katika utafiti?

Huwezi kufaidika binafsi kutokana na utafiti huu kwa sasa lakini somo hili linaweza kuunda msingi wa utafiti ujao utakaofanywa ili kuamua ni mawakala gani bora kwa aina 100aidi100 ya mgonjwa.

Malipo:

Hakutakuwa na pesa au zawadi zinazotolewa kwa kushiriki katika utafiti huu.

Nitaita nani ikiwa nina maswali kuhusu utafiti?

Maswali kuhusu utafiti: 0737 5653

Maswali kuhusu haki zako kama somo la utafiti: Unaweza kuwasiliana na Kamati ya Maadili ya Ukaguzi wa Taasisi (IREC) 053 33471 Ext.3008. IREC ni kikundi cha watu ambao huelezea masomo kwa ajili ya usalama na kulinda haki za masomo ya kujifunza.

Je! Habari nitayayatoa itahifadhiwa binafsi?

Jitihada zote za busara zitafanywa ili kuweka maelezo yako ya ulinzi binafsi 100aidi siri. Taarifa Zilizolindwa ni habari ambayo, au imekuwa, imekusanywa au imehifadhiwa na inaweza kuunganishwa kwako. Kutumia (“kutoa taarifa”) taarifa hiyo lazima ifuate miongozo ya faragha ya Taifa. Kwa kusaini waraka wa hati kwa ajili ya utafiti huu, unatoa ruhusa (“idhini”) kwa matumizi na ufunuo wa maelezo yako ya kibinafsi. Uamuzi wa kushiriki katika utafiti huu una maana kwamba unakubali kuruhusu timu ya utafiti kutumia na kushiriki Habari yako ya Ulinzi kama ilivyoelezwa hapo chini. Kama sehemu ya utafiti, Dk Natalie Sang na timu yake ya utafiti wanaweza kupata matokeo ya vipimo vya maabara yako, x-rays, ECG, echocardiogram, CT scans na MRIs. Wanaweza pia kupata sehemu za rekodi yako ya

matibabu, na makundi yaliyotajwa hapo chini: • Bioethics ya Taifa. Kamati, • Kamati ya Ukaguzi na Maadili ya Taasisi, Kanuni za faragha za kitaifa haziwezi kutumika kwa makundi haya; hata hivyo, wana sera zao na miongozo ili kuhakikishia kwamba jitihada zote za busara zitafanywa ili kuweka maelezo yako ya kibinafsi ya kibinafsi 101aidi siri. Matokeo ya utafiti yatahifadhiwa kwenye rekodi yako ya utafiti kwa angalau miaka sita baada ya kujifunza. Taarifa yoyote ya utafiti iliyoingia kwenye rekodi yako ya matibabu itahifadhiwa kwa muda usiojulikana. Isipokuwa imeonyeshwa vinginevyo, ruhusa hii ya kutumia au kushiriki Habari yako ya kibinafsi haina tarehe ya kumalizika muda. Ikiwa unaamua kuondoa ruhusa yako, tunaomba kuwasiliana na Dk. Natalie Sang kwa kuandika na kumruhusu kujua kwamba unatoa ruhusa yako. Anwani ya barua pepe ni Natalie Sang, P.O BOX 59, Eldoret. Wakati huo, tutaacha kukusanya 101aidi habari yoyote kuhusu wewe. Hata hivyo, habari za afya zilizokusanywa kabla ya uondoaji huu inaweza kuendelea kutumika kwa ajili ya taarifa na ubora wa utafiti. Matibabu yako, malipo au usajili katika mipango yoyote ya afya au ustahiki wa faida haitathiriwa ikiwa unachukua kuamua kushiriki. Utapokea nakala ya fomu hii baada ya kusainiwa.

Sehemu ya II: Ruhusa ya Somo:

Nimesoma au nimenisoma maelezo ya utafiti wa utafiti. Mpelelezi au mwakilishi wake ameelezea utafiti kwangu na amejibu maswali yote niliyo nayo wakati huu. Nimeambiwa juu ya uwezekano wa hatari, ugumu na madhara pamoja na faida zinazowezekana (kama ipo) ya utafiti. Mimi kujitolea kwa hiari kushiriki katika utafiti huu.

_____ _____

Jina la Msaidizi Tarehe

(Shahidi kuchapisha kama

somo hawezi kuandika)

_____ _____

Jina la Mwakilishi / Uhusiano wa Shahidi kwa Somo

_____ _____ _____

Jina la mtu Kupata kibali Saini ya mtu Tarehe

Kupata kibali

_____ _____ _____

Jina la kuchapishwa la Mpelelezi Sahihi Tarehe

Appendix 3: IREC Approval

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

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

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2018/190
Approval Number: 0003172

6th December, 2018

Dr. Sang Natalie Jepkemboi,
Moi University,
School of Medicine
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Sang,

RE: FORMAL APPROVAL

The MU/MTRH- Institutional Research and Ethics Committee has reviewed your research proposal titled: -

"Use and Clinical Outcomes of Vasopressors and Inotropes among Patients Admitted at Moi Teaching and Referral Hospital - Eldoret".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 3172*** on 6th December, 2018. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; hence will expire on 5th December, 2019. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date. You will be required to submit progress report(s) on application for continuation, at the end of the study and any other times as may be recommended by the Committee.

Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. You will also be required to seek further clearance from any other regulatory body/authority that may be appropriate and applicable to the conduct of this study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

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

Appendix 4: Hospital Approval (MTRH)

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

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

20th December, 2018

Dr. Natalie Jepkemboi Sang,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Use and Clinical Outcomes of Vasopressors and Inotropes among Patients Admitted at Moi Teaching and Referral Hospital Eldoret".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

20/12/18

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - Senior Director, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM