

**MEDICINE UTILIZATION REVIEW OF HEPARIN AT KENYATTA
NATIONAL HOSPITAL**

BY

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DEDICATION

I dedicate this thesis to my family who sacrificed their all to ensure I pursue my education.

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My sincere gratitude to my supervisors for their invaluable guidance and support.

My colleagues for their support in this journey we travel together.

My family, for their never ending love and support.

Above all, Almighty God for keeping me safe and sound.

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ABBREVIATIONS AND ACRONYMS

ACCP	-	American College of Chest Physicians
ACS	-	Acute Coronary Syndromes
AF	-	Atrial Fibrillation
APTT	-	Activated Partial Thromboplastin Time
AT	-	Antithrombin
CBC	-	Complete Blood Count
CI	-	Confidence Interval
CrCL	-	Creatinine Clearance
DBP	-	Diastolic blood pressure
DVT	-	Deep Venous Thrombosis
E GFR	-	Estimated Glomerular Filtration Rate
FFP	-	Fresh Frozen Plasma
GFR	-	Glomerular Filtration Rate
HIT	-	Heparin Induced Thrombocytopenia
IQR	-	Interquartile Range
INR	-	International Normalized Ratio
IU	-	International Units
IV	-	Intravenously
Kg	-	Kilogram
KNH	-	Kenyatta National Hospital

LMWHs	-	Low Molecular Weight Heparins
MI	-	Myocardial Infarction
mg	-	Milligram
m L	-	Millilitres
MTC	-	Medicines and Therapeutics Committee
MUR	-	Medicine utilization review
NICE	-	National Institutes for Health and Care Excellence
NSAIDs	-	Non-Steroidal Anti-inflammatory Drugs
NSTEMI	-	Non-ST Elevation Myocardial Infarction
OD	-	Once daily dosing
PE	-	Pulmonary Embolism
SBP	-	Systolic Blood Pressure
SC	-	Subcutaneously
SIGN	-	Scottish Intercollegiate Guidelines Network
STEMI	-	ST-Elevation Myocardial Infarction
UFH	-	Unfractionated Heparin
USA	-	United States of America
VKA	-	Vitamin K Antagonists
VTE	-	Venous Thromboembolism

OPERATIONAL DEFINITIONS

Adverse Effects:	This refers to undesirable and untoward occurrence to an individual during or after treatment with a given drug.
All-cause mortality:	This is the number of deaths in a defined population over a specified period of time.
Anticoagulation:	Refers to the use of pharmacological agents to prevent clot formation.
Criteria:	This refers to predetermined parameters of medicine prescribing and use established in a medicine utilization review program for comparison to the actual practice.
Concurrent medicine utilization review:	This involves evaluation of medicine use in the course of medicine therapy
Medicine Utilization Review Criteria:	Refers to the ongoing systematic criteria based evaluation of drug use that is aimed at appraising aspects related to prescribing, dispensing, administering and monitoring of drug therapy.
Prevalence:	The number of cases of a disease/adverse effects existing in a given population at a specific period of time (period prevalence) or at a particular moment in time (point prevalence)
Performance Threshold:	A percentage established in a medicine utilization review study that identifies the point at which a medicine use problem exists.

Venous Thromboembolism prophylaxis: Refers to the administration of pharmacological agents to prevent deep venous thrombosis and/or pulmonary embolism.

ABSTRACT

Background

Unfractionated heparin and low molecular weight heparins are effective anticoagulant options for prevention and treatment of thrombosis in diverse clinical settings. However heparin anticoagulation has potential for serious adverse effects which include heparin induced hemorrhage, heparin induced thrombocytopenia, osteopenia and electrolyte disturbances. Evaluation of individual patient benefit-risk profile is critical in optimizing heparin anticoagulation and prevention of adverse effects associated with heparin. Individualization of therapy is achieved through careful risk stratification of patients before initiation of treatment and routine clinical and laboratory monitoring in the course of therapy.

Objective

The study aimed to assess the prescribing, clinical and laboratory monitoring of unfractionated heparin and enoxaparin, as well as establish the prevalence of heparin induced adverse effects at Kenyatta National Hospital (KNH).

Methodology

The study involved medicine utilization review (MUR) of unfractionated heparin (UFH) and enoxaparin based on predetermined criteria. The study was conducted at the medical, general surgical, orthopedic and cardiothoracic surgical wards and renal unit of Kenyatta National Hospital. The population studied included patients who were aged 18 years and above, hospitalized and who received UFH or enoxaparin. Descriptive data analysis was carried out to describe the study population. Categorical data was described as proportions and percentages while continuous data was summarized using means or medians. Data analysis also described the proportion of patients who met each one of the criteria set out in the MUR for both UFH and enoxaparin.

Results:

Unfractionated heparin was indicated for prevention of thrombosis in hemodialysis at KNH. Compliance with MUR performance threshold ranged from 0% for bridge therapy and

anticoagulant reversal criteria to 100% for justification of use, dosage, frequency and route of administration. Reported UFH induced adverse effects include bleeding episodes which occurred in 17.8% of patients. Reported clinical outcomes for patients who received UFH were recovery and discharge in 90.3% of the patients and all-cause mortality in 9.7% of the patients. Similarly 1.6% of the patients experienced hemorrhagic stroke.

Majority of the patients (61, 84.7%) received enoxaparin for venous thromboembolism (VTE) prophylaxis. Four patients (5.6%) were offered enoxaparin for treatment of pulmonary embolism while the same was indicated for treatment of deep venous thrombosis in seven patients (9.7%). Enoxaparin was also indicated for atrial fibrillation in one patient (1.4%). Justification of use of enoxaparin was appropriate in all patients and met the performance compliance threshold of 100%. Bleeding was reported in 2.8% of patients who received enoxaparin. Clinical outcomes reported in these patients were recovery and discharge (69, 95.8%), all-cause mortality (3, 4.2%) and new thrombotic events (2, 2.8%). Compliance with MUR performance threshold in patients treated with enoxaparin varied between 0% for laboratory monitoring during therapy and bridge therapy criteria, and 100% for justification of enoxaparin use.

Conclusions

Medicine Utilization Review criteria were developed to assess the prescription practices and use of UFH/enoxaparin as well as to determine the range and extent of use of laboratory tests in monitoring of heparin use at KNH. The average compliance with the MUR criteria was minimal in patients who received UFH. Partial compliance with MUR criteria was observed in patients who received enoxaparin. This is in comparison with the set performance threshold of 100% for each criterion set out in the MUR. Significant bleeding episodes were reported among patients who received UFH at KNH. There is need to put interventions in place to ensure safe use of UFH and enoxaparin at KNH.

CHAPTER ONE: INTRODUCTION

1.1 Background

Heparin anticoagulation is one of the mainstays of treatment and prevention of thrombosis in different clinical settings. Heparin is effective in reducing mortality and morbidity associated with acute coronary syndromes, venous thromboembolism, non-Q wave unstable angina and acute ischemic stroke. Heparin is a stable univalent or bivalent salt of heparinic acid whose anti-clotting properties have been known for many years [1].

Heparins are indirect anticoagulants. The presence of antithrombin (AT) is necessary for inhibition of clotting factors such as factors Xa and IIa. The two factors contain an active pentasaccharide sequence that binds and activates antithrombin, after which it dissociates readily. The pentasaccharide subsequently binds to additional AT, this process results in continuous anticoagulant effect.

Unfractionated heparins refer to mucopolysaccharides of heterogeneous nature containing glycosaminoglycans of molecular weights varying from 3000 to 30000 Daltons. Unfractionated heparin (UFH) is short acting with best reversal capability and hence it provides the best option for patients who require high heparin doses, patients with underlying bleeding risks and those who are critically ill with organ dysfunction [2].

Low Molecular Weight Heparins (LMWHs) comprises of heparin molecules that have lower molecular weights as compared to unfractionated heparin. They are obtained by the process of chemical or enzymatic depolymerization of UFH. Upon depolymerization of UFH into low molecular weight fragments, the relative inhibition of factors Xa and IIa varies in accordance to the relative abundance of the saccharide fragments. The inhibitory effect of factor Xa on antithrombin is enhanced by very short fragments, while larger polysaccharides with molecules of 16 units and above are needed for inhibitory effects on factor II and thrombin.

There are a number of LMWHs; they include tinzaparin, dalteparin and enoxaparin. Others include reviparin, nadroparin, fraxiparin, certoparin and bremiparin. Low molecular weight heparins (LMWHs) are indicated for thromboprophylaxis among critically ill and acutely ill medical patients and post-operative patients who require parenteral VTE prophylaxis.

Low molecular weight heparins (LMWHs) have to a great extent replaced UFH in management of patients who require heparin anticoagulation in ambulatory settings without laboratory monitoring. Low molecular weight heparins have are also applied in management of acute ischemic stroke and non-Q wave Myocardial Infarction (MI). A study [3] established that patients diagnosed with ST-segment elevation Myocardial Infarction (STEMI), who were treated with fibrinolysis and LMWHs had a lower incidence of death. A different study found that LMWHs lowered the incidence of death, myocardial infarction and urgent revascularization among patients diagnosed with unstable angina/ non-ST segment elevation MI, as compared to UFH [4].

Heparin use is associated with a number of significant risks. The most common risk associated with heparin therapy is heparin induced bleeding. The risk of bleeding is determined by various factors. Intensity of heparin anticoagulation is an important predictor of bleeding [3], and studies have shown that low-dose prophylactic heparin increases the risk of major hemorrhage by two-fold, while the absolute incidence remains low [5]. Patient characteristics may constitute risk factors for hemorrhage among patients receiving heparin [5]. Elderly patients are at a higher risk as compared to younger patients. Co-morbidities such as renal and hepatic insufficiency increase the risk of bleeding among patients receiving heparin therapy. Concomitant administration of medicines that affect both the coagulation system and platelet function such as anti-platelet agents and fibrinolytics also puts the patient treated with heparin at the risk of bleeding [6]. Low molecular weight heparins are associated with a lower risk of bleeding in treatment of VTE as compared to unfractionated heparin [5]. High doses of unfractionated heparin and LMWHs are associated with important risk of bleeding in ischemic stroke [5].

Patients treated with heparin may develop heparin induced thrombocytopenia (HIT). The clinical presentation of HIT is characterized by the presence of heparin reactive antibodies in a patient who is receiving heparin or who was recently treated with heparin [7]. The clinical symptoms include a fall in platelet count, >50% as compared to the baseline, anaphylactic reactions and/or new thrombotic event [7]. Platelet count monitoring at baseline and during course of therapy is useful in the diagnosis of HIT.

The major types of heparin used at Kenyatta National Hospital (KNH) include UFH and enoxaparin [8,9]. Clinical indications for UFH at the hospital include prophylactic treatment of

VTE and therapeutic treatment of established VTE [8] in medical and surgical patients and in pregnancy. Unfractionated heparin is also indicated for ischemic stroke and acute coronary syndromes. Enoxaparin is indicated for prophylactic treatment of VTE and therapeutic treatment of established deep venous thrombosis (DVT). It is also indicated for management of unstable angina, ischemic stroke and acute coronary syndromes.

1.2 Problem Statement

Unfractionated heparin and Enoxaparin are frequently prescribed at Kenyatta National Hospital for prophylactic and therapeutic treatment of VTE [8] and for management of acute coronary syndromes. A study conducted by Nyamu *et al* (2017) on anticoagulation practices at KNH, found that anticoagulation practices were not standardized at the facility [10]. KNH does not have a standardized clinical guideline on how to carry out risk stratification for patients who need anticoagulation in different settings within the hospital. Risk stratification is important in assessing patients to be treated with heparin for VTE prophylaxis. There also exists a variation in the laboratory monitoring of heparin anticoagulation for different patients at KNH. Non-standardized approaches to heparin anticoagulation can lead to under-use or over-use of heparin thromboprophylaxis among patients who are eligible for treatment [8]. Inadequate laboratory monitoring, sub-therapeutic or supra-therapeutic dosing of heparin coupled with fatal adverse effects are other potential consequences of non-standardized heparin anticoagulation practices [11].

1.3 Study justification

Unfractionated heparin and enoxaparin are life-saving prophylactic and therapeutic agents for patients who suffer from disorders such as coronary artery disease, ischemic coronary events, atrial fibrillation, heart valve disease, pulmonary embolism and deep venous thrombosis (DVT) [8,9]. However they have potential for serious adverse effects which include bleeding, heparin-induced thrombocytopenia, osteopenia and electrolyte disturbances. Heparins are associated with high incidence of drug-related problems due to their inherent pharmacological activities as well as human errors.

Studies on the extent of laboratory monitoring of heparin use and clinical outcomes for patients treated with heparin have not been done in Kenya. Understanding of prescribing practices and

patterns of use of UFH and enoxaparin at KNH will inform comparison with evidence-based practices (international guidelines) and assessment of appropriateness of heparin anticoagulation at the facility.

The study findings on significant deviations from the MUR criteria as well as the prevalence of heparin induced adverse effects will be shared with the medicines and therapeutics committee (MTC) of KNH. These will form the basis for recommendations of interventions to improve heparin anticoagulation practices at KNH.

1.4 Objectives

1.4.1 Broad objective

To assess the prescribing and laboratory monitoring of UFH and enoxaparin therapy well as establish the heparin induced adverse effects among medical and surgical in-patients at KNH and compare compliance with international acceptable best practices.

1.4.2 Specific objectives

1. To examine the prescription and use (dosing, route of administration, duration of treatment, termination of therapy and reversal of anticoagulation) of unfractionated heparin and enoxaparin.
2. To determine the range and extent of use of laboratory tests in the monitoring of heparin use.
3. To establish the prevalence of new thrombotic events, heparin-induced adverse effects and all-cause mortality as outcome indicators of unfractionated heparin and Enoxaparin use.

1.5 Research questions

1. What are the prescription practices and patterns of use UFH and enoxaparin at Kenyatta National Hospital?
2. To which extent and range does KNH employ laboratory monitoring of heparin use?

3. What is the prevalence of new thrombotic events, heparin-induced adverse effects and all- cause mortality among patients treated with heparin at Kenyatta National Hospital?

CHAPTER TWO: LITERATURE REVIEW

2.1 Definition and classification of heparin

Unfractionated heparin comprises of naturally occurring glycosaminoglycans which are derived from porcine intestines or mucosal tissues of bovine lung [12]. Unfractionated heparin that is produced for commercial use, comprises of heterogeneous mixture of highly sulfated polysaccharides of variable molecular weights, (3000-30,000) daltons or approximately 45 saccharide units. The process of chemical or enzymatic depolymerization is applied to produce LMWHs. This process yields fragments approximately one-third the size of heparin [12]. They include tinzaparin, dalteparin, enoxaparin, fraxiparin, reviparin, nadroparin, bremiparin and certoparin.

2.2 Mechanism of action and pharmacokinetics of heparin

The main anticoagulation effects of heparins is produced by inactivation of thrombin and subsequent activation of factor X (Xa), via interaction with antithrombin III [13]. Heparin molecule binds and potentiates the activity of antithrombin (AT) to inactivate factor Xa and prevent conversion of prothrombin to thrombin as well as prevent conversion of fibrinogen to fibrin [13]. Inactivation of thrombin prevents fibrin formation and inhibits thrombin induced activation of platelets and factors V and VII. Heparin also binds non-specifically to various plasma proteins and endothelial cells, resulting in unpredictable dose-response relationship [14].

Low molecular weight heparins have reduced inhibitory activity on thrombin because smaller fragments cannot bind simultaneously to AT and thrombin [14]. They bind and accelerate the activity of AT, with preferential longer lasting effect on factor Xa. Low molecular weight heparins have lower binding affinity to plasma proteins due to their decreased chain length. The anticoagulant effect of LMWHs is more predictable and they exhibit less inter-patient variability and longer duration of action as compared to UFH [14].

Unfractionated heparin is administered parenterally, either by bolus injection or by continuous intravenous infusion. It can also be administered by subcutaneous (SC) injection [13]. When given subcutaneously, higher doses are administered to overcome low bioavailability, which is about 30 %. Anticoagulant response after SC injection is highly variable among individuals. This is because UFH exhibits high non-specific binding to plasma proteins [14].

The ability of unfractionated heparin to bind to endothelial cells and macrophages complicates the pharmacokinetics further. The pharmacokinetic properties of UFH are unpredictable. The elimination of UFH is dose-dependent and is via two mechanisms that are independent. They include saturable and non-saturable pathways. The initial phase is enzymatic degradation which is mediated through rapid zero-order kinetics. The second phase is through non-saturable renal mediated first order mechanism, which is slower. Low doses of UFH are metabolized mainly by enzymatic processes while high doses are eliminated mainly via the renal route [12].

The bioavailability of LMWHs after SC injection nears 100%. The peak activity of anti-factor Xa occurs 3-4 hours following subcutaneous dose. Enoxaparin and dalteparin are broken down in the liver by desulfation and depolymerization. Metabolites are low molecular weight fragments that have reduced biological activity. 10% of enoxaparin is cleared via the renal route as active fragment. They have predictable anticoagulant response as compared to UFH [14]. The shorter heparin chains in LMWHs have reduced affinity for heparin binding proteins in plasma. They also have longer half-life as compared to UFHs. The half-life is dose-dependent. Low molecular weight heparins with longer chains exhibit shorter half-lives as compared to those with longer chains. Enoxaparin and dalteparin exhibit increased half-lives among patients with chronic kidney disease due to reduced clearance. Dose-adjustment is necessary to prevent accumulation and toxicity among these patients [13]

2.3 Clinical uses of heparin

Both UFH and LMWHs are used for prophylactic treatment of VTE among medical and surgical patients. Unfractionated heparin is indicated for treatment of patients diagnosed with deep venous thrombosis (DVT) and pulmonary embolism (PE) [16,17]. It is also indicated for treatment of acute coronary syndromes such as unstable angina and non-ST elevation MI. Unfractionated heparin is also used in prevention of thrombosis during hemodialysis [15], intra-cardiac thrombosis, systemic arterial embolism, selected stroke syndromes and in atrial fibrillation anterior wall myocardial infarction [18].

Low molecular weight heparins are indicated for thromboprophylaxis among acutely ill medical patients and surgical patients who are at risk of VTE [17,19,20], therapeutic treatment of deep venous thrombosis (DVT) for in-patients and ambulatory patients [21], secondary prophylaxis

and extended treatment among cancer patients [21]. A study found that 40mg of enoxaparin administered subcutaneously, daily for prophylactic treatment, was safe and effective in reducing the risk of VTE among patients with acute medical illness [22]. In a meta-analysis of randomized controlled trials, that compared safety and efficacy of LMWHs and UFH, it was found that LMWHs were associated with reduced mortality rates after acute DVT [23]. Low molecular weight heparins are as safe and effective as UFH in preventing recurrence of thromboembolism among patients who are at risk. They are also indicated in treatment of unstable angina and non-ST segment elevation MI and acute ST-segment elevation MI (STEMI). Low molecular weight heparins have also been found to be useful in preventing thrombosis during hemodialysis [23].

2.4 Venous thromboembolism

2.4.1 Epidemiology of venous thromboembolism

Literature search and review conducted in a study found that the incidence of VTE is 3.3 per 100 hospitalizations in developed countries, while the incidence in low income countries is 3.0 per 100 hospitalizations [24]. Reports from the United States of America (USA), indicate that the annual incidence of VTE among white people is 108 per 100000 person years with about 250000 incident cases occurring annually [24]. The incidence is about 78 per 100000 person years among African-Americans. A study reported high age-adjusted incidence rate for men (130 per 100000) as compared to women (110 per 100,000) in USA [25].

2.4.2 Pathophysiology and risk factors for venous thromboembolism

Formation of thrombi can occur both in veins and arteries. The rupture of atherosclerotic plaques that occurs in diseases such as acute coronary syndromes and ischemic stroke would result typically in arterial thrombosis. Venous thrombosis is a result of factors in the Virchow's triad [26,27]. It occurs in deep venous thrombosis and pulmonary embolism (PE). The Virchow's triad comprises of endothelial damage, hypercoagulability and stasis [27]. Exposure of sub-endothelial tissue factor and collagen results in endothelial damage, which offers substrate for platelet binding, with subsequent activation and aggregation that leads to clot formation [26]. Endothelial damage may be caused by chronic in-dwelling of central venous catheter, surgery or trauma. It also occurs as a consequence of smoking and hypertension [28].

Hypercoagulability occurs when there is change in blood coagulation pathway, where the balance shifts towards coagulation. Individuals carrying factor V Leiden and those with protein S deficiency are at risk of hypercoagulation [29]. Acquired factors that predispose to hypercoagulation include cancer, chemotherapy, hormonal replacement therapy, pregnancy, oral contraceptive therapy [27,30] and heparin induced thrombocytopenia. Stasis is another factor of the Virchow's triad that predisposes to clot formation. Stasis is the slowing or stopping of blood flow. It occurs as a result of immobility, polycythemia and congestive heart failure.

Patients with risk factors in the Virchow's triad develop deep venous thrombosis which can ascend up the inferior vena-cava to the right heart and finally lodge in the pulmonary vasculature. Subsequently vasoconstriction and vascular compromise occurs leading to arterial hypoxemia which is compensated by increased minute ventilation. If vascular occlusion is significant, forward blood flow to the left heart is decreased causing heart failure and shock [31,32].

Patient assessment for risk of VTE at admission is important in order to determine whether the patient will benefit from thromboprophylaxis [33]. Active cancer, age > 60 years, critical care admission, obesity with BMI >30kg/m² and known thrombophilias [34] are known risk factors for VTE. Other risk factors include co-morbidities; heart diseases, endocrine, metabolic and respiratory disorders, acute infectious diseases and inflammatory conditions [33]. Varicose vein phlebitis, hormonal replacement therapy and use of estrogen containing contraception predisposes patients to the risk of VTE [33]. Patient's and/ or family history of VTE are important predictors of risk of VTE. Other patient characteristics that increase risk of VTE include pregnancy, post-partum states, recent trauma or surgery.

2.4.3 Clinical features of venous thromboembolism

Deep venous thrombosis manifests clinically as asymmetric leg/calf swelling and pitting edema on the affected side. The patient also presents with erythema, pain and localized tenderness along the deep venous system. This is a manifestation of vascular inflammation [32]. The patient may also present with dilated superficial veins (non-varicose) due to obstruction of the deep venous system.

Patients with PE present with dyspnea, tachypnea, and wheezing due to hyperventilation. The other signs include palpitations and tachycardia which are triggered by sympathetic activity in response to decreased cardiac output. Pleural friction rub, pleuritic chest pain and signs of pleural effusion are common features in PE. Other common clinical features include hemoptysis, cough, syncope, hypotension, and cyanosis.

2.4.4 Venous thromboembolism in the elderly, renal impairment and obesity

VTE is not uncommon in elderly patients [35,36], morbidly obese and renal impaired patients. In addition, treatment in these groups of patients remains sub-optimal. A study conducted by Naess *et al* (2007) found that the incidence of VTE increased exponentially with increasing age [37]. A meta-analysis of twenty-one case control and cohort studies found that the risk of VTE among obese patients was 2.33 with 95% CI , of 1.68 to 3.24 [38]. Management of VTE in elderly patients is similar to that of the general population; however care must be taken as they may have renal impairment and are at risk of bleeding [39]. Dose adjustments and monitoring is necessary. Patients with renal impairment (GFR<30ml/min) should be treated with unfractionated heparin [39,40]. The risk of toxicity with LMWHs is high among patients with severe renal impairment. LMWHs are mainly cleared through the renal route, therefore patients who suffer from chronic kidney disease are at risk of drug toxicity due to accumulation [39,40].

In obese patients, LMWH should be dosed by actual body weight [41] and capping the dose is not recommended as it may lead to management with sub-therapeutic doses and hence increase the risk of recurrent VTE [41].

2.4.5 Management and prevention guidelines for venous thromboembolism

Evidence based guidelines have been developed over the years to enhance best practices of anticoagulation therapy in management of VTE. They are aimed at optimizing efficacy and safety of anticoagulants applied in therapeutic treatment and prevention of VTE. Reference is made to American college of Chest Physicians (ACCP), CHEST guidelines [42], National Institutes for Health and Care Excellence (NICE) guidelines [34] and Scottish Intercollegiate Guidelines network (SIGN) [43].

The NICE guideline recommends that patients with confirmed DVT should be offered LMWH or fondaparinux. However the choice of treatment should take into consideration, co-morbidities,

contraindications and cost of medicines. Patients diagnosed with severe renal disorders or established renal dysfunction ($GFR < 30 \text{ ml/min/1.73m}^2$) should be offered UFH with dose adjustments based on activated partial thromboplastin time (APTT), or a LMWH where doses are adjusted based on anti-Xa assay [33].

Patients at high risk of bleeding should be offered UFH while patients with Pulmonary Embolism (PE) and hemodynamic instability, it is recommended they should be treated with UFH and thrombolytic therapy. Patients diagnosed with DVT or PE and have active cancer should be offered LMWH to be continued for six months. Risks and benefits of continuing with anticoagulation should be evaluated at 6 months.

Patients who present with unprovoked proximal PE, it is recommended that they should be treated beyond three months with Vitamin K Antagonists (VKA). It is important to evaluate the risk of VTE recurrence and risk of bleeding among these patients. Patients who present with unprovoked proximal DVT should be assessed for the risk of VTE recurrence and risk of bleeding. Patients with a high risk of VTE recurrence and do not have additional risk of major bleeding, should be treated beyond three months [34].

The NICE guidelines also recommend that patients should be given information in regard to the duration of anticoagulation treatment, how to use anticoagulants, possible side effects, interactions with other medications, foods and alcohol, monitoring aspects of treatment and how therapy affects their pregnancy plans, sports and travel, dental treatment and also when and how to seek help [34].

The ACCP, CHEST guidelines recommends and suggests the following; three months anticoagulation therapy is recommended for patients with established proximal DVT and PE [39] three months therapy with dabigatran, rivaroxaban, apixaban or edoxaban is suggested over vitamin K antagonists (VKA) for patients with DVT of the leg or PE and have no cancer. Patients with DVT of leg and PE, with no cancer and not treated with dabigatran, rivaroxaban, apixaban or edoxaban, vitamin K antagonists (VKA) is suggested over LMWH [42].

Patients without cancer and are diagnosed with DVT of the leg or PE should be offered LMWH, it is suggested over VKA therapy [42]. Patients who present with first time VTE that is unprovoked (proximal DVT or PE) and have lower or moderate bleeding risk, should be treated

on extended therapy (greater than three months), while those at high risk of bleeding it is recommended three months of therapy over extended therapy. Patients with second unprovoked VTE, who have low risk of bleeding, extended therapy is recommended (beyond three months with no plans of stopping), while those at high risk it is suggested they should be treated for three months [42].

Patients diagnosed with unprovoked proximal DVT or PE, and have to discontinue anticoagulant therapy; aspirin is suggested over no aspirin to prevent recurrent VTE for those who have no contraindication to aspirin. Patients who have recurrent VTE while being treated on long term LMWH (and are believed to be compliant), dose adjustments of LMWH should be effected by about one-quarter to one-third [42].

The Scottish intercollegiate guidelines network (SIGN) recommends thromboprophylaxis for patients undergoing abdominal surgery who are at risk of VTE due to the nature of the procedure or personal risk factors. They should be offered LMWHs, UFH or fondaparinux [43]. Procedures that include hip replacement or total knee replacement pose a risk of VTE. Patients undergoing these procedures should be offered LMWHs or fondaparinux and extended prophylaxis should be considered. Pharmacological prophylaxis is recommended for medical patients to prevent asymptomatic or symptomatic VTE [43]. The pharmacological agents recommended for use include UFH, LMWHs and fondaparinux. Patients diagnosed with cancer should be offered prophylactic treatment with LMWHs, UFH or fondaparinux.

Patients who are suspected to have pulmonary embolism (PE), should be offered therapeutic doses of UFH or fondaparinux until diagnosis is deemed unlikely or is confirmed [43]. Once confirmed UFH or fondaparinux should be administered until a patient's INR is therapeutic. Patients with suspected deep venous thrombosis (DVT) should be offered therapeutic doses of LMWHs or fondaparinux until diagnosis is deemed unlikely or is confirmed [43]. Once confirmed, LMWHs or fondaparinux should be continued until patients INR is therapeutic. UFH may be an appropriate alternative if thrombolysis is considered or in cases where there is a particular risk of bleeding post-operatively. Cancer patients with DVT should be offered LMWHs for three to six months and reviewed thereafter [43].

The Ministry of Health, Kenya has developed clinical guidelines (2002) on pharmacological management of DVT. The guideline recommends that 5000-10000 IU of UFH should be administered SC/IV 8-hourly for 2-5 days. Warfarin should be started with a dose of 10mg OD for the first two days and subsequent doses should be adjusted until the prothrombin time index stabilizes in therapeutic range (1.3-1.5 times the control). The guideline recommends that calf vein thrombosis should be treated for six weeks with warfarin while in proximal vein thrombosis; warfarin should be administered for 3-6 months. PE should be managed with UFH, 10000 IU IV/SC 8-hourly. The guideline also recommends that prophylactic treatment should be offered in conditions where DVT is likely to occur such as hip surgery and prolonged immobilization. Prophylactic treatment with heparin 5000 IU/SC twice daily is recommended until the condition is treated [44].

Kenyatta National Hospital formulary of 2013 provides for the following in regard to uses of UFH and enoxaparin; UFH is indicated for use in treatment of DVT and PE. In adults, a loading dose of 5000 IU IV is recommended for DVT and 10000 IU IV for pulmonary embolism. This is followed by continuous IV infusion of 15-25 IU/kg/hour or by SC injection of 15000 IU, 12 hourly for both conditions. In addition UFH is indicated for prophylactic treatment in general surgery where 5000 IU should be given 2 hours before surgery, and then 8 to 12 hourly for a period of 7 days or until the patient is no longer immobilized [45].

The hospital formulary provides that enoxaparin is indicated for prophylactic treatment of DVT in surgical patients and medical patients. Enoxaparin is also used in treatment of DVT and PE as well as treatment of unstable angina and non-ST segment-elevation myocardial infarction. In moderate risk surgical patients, it is recommended that 20mg SC injection should be given 2 hours before surgery followed by 20mg SC injection, once daily for 7-10 days after surgery. High risk surgical patients should be offered 40mg before surgery, then 40mg once daily for 7-10 days. Prophylactic treatment of medical patients is provided as 40mg SC once daily for at least 6 days until the patient is ambulant (maximum 14 days). Therapeutic treatment of DVT and PE is provided as enoxaparin 1.5mg/kg SC injection once daily for at least 5 days or until the patient is therapeutic on oral anticoagulation. Patients diagnosed with unstable angina and non-ST segment elevation myocardial infarction should be offered enoxaparin 1mg/kg SC injection, 12 hourly for a period of 2-8 days [45].

2.5 Use of heparin in acute coronary syndromes

Acute Coronary syndromes (ACS) are a group of clinical symptoms that describe unstable coronary artery diseases which include unstable angina and transmural myocardial infarction.

The etiology of acute coronary syndromes is common and it involves the formation of thrombus in an inflamed and complicated atheromatous plaque. One study reported that enoxaparin has better profile as compared to UFH in treatment of ST-elevation myocardial infarction [3]. Enoxaparin was however associated with increased incidence of major bleeding. LMWHs were associated with reduced number of heart attacks with fewer complications in patients with acute coronary syndromes, as compared with UFH [46].

2.6 Heparin use in acute ischemic stroke

Studies have found that high doses of UFH given within three hours of occurrence of an ischemic stroke, significantly reduces death or dependence [47]. Both UFH and LMWHs are very effective in prevention of both symptomatic and asymptomatic VTE in patients with stroke [47]. The LMWHs were found to significantly reduce DVTs in stroke patients as compared to UFH, without additional hazard. Intravenous UFH or subcutaneous LMWHs followed by warfarin therapy are effective in treatment of cerebral venous thrombosis which is a rare cause of stroke [48].

2.7 UFH use in hemodialysis

Hemodialysis is a life-saving procedure that is used by millions of patients around the world. The procedure experienced setbacks of clotting of dialyzer circuit in 1920s, before introduction of heparin. Since the introduction of UFH, it has become the most commonly used anticoagulant due to its short half-life, ease of use, safety and low cost [15].

Patients undergoing hemodialysis have an increased risk of bleeding due to accumulation of uremic toxins that lead to platelet dysfunction. Paradoxically, these patients also have an increased risk of thromboembolism. A cohort study of patients with atrial fibrillation and had an estimated glomerular filtration rate of $< 30\text{mL}/\text{min}/1.73\text{m}^2$ showed that the risk of thromboembolism among the patients was 39% higher as compared to those with estimated glomerular filtration rate $\geq 60\text{mL}/\text{min}/1.73\text{m}^2$ [51]. Another study found that the incidence rate

of major bleeding among hemodialysis patients was 3.1-6.3 events/100 person-years. The incidence rate was dependent on concomitant use of warfarin and aspirin [52].

Information on safety of using UFH in hemodialysis does not exist despite the potential risks that are well documented [53]. Furthermore, there are no standard heparin dosage guidelines on long term use of UFH in hemodialysis. Dosage adjustments are tailored to meet patient's individual needs. A bolus dose of 25-30 IU/kg initially, followed by an infusion dose of 500-2000 IU/hourly is recommended [53].

Heparin-free dialysis

Heparin-free dialysis is indicated for patients with increased risk of bleeding and those who have heparin contraindication. Individual patient clinical and laboratory data assessment is critical in determining whether a patient should undergo heparin-free dialysis. The decision is based on the careful balance between bleeding risk of the patient and the risk of clotting of the dialyzer [53].

2.8 Relative contraindications and precautions of heparin use

Heparin is contraindicated for patients with heparin hypersensitivity, those with previous history of heparin induced thrombocytopenia, patients who are actively bleeding and those who have had a recent hemorrhagic stroke [52]. Heparin is contraindicated among patients with severe uncontrolled hypertension of systolic blood pressure greater than 180mmHg and/or diastolic blood pressure greater than 110mmHg. Heparin is also contraindicated in patients with abnormalities of hemostasis such as hemophilia and also patients with active peptic ulceration except when benefits far outweigh the risks [52]. Caution should be applied when using heparin among patients with increased risk of hemorrhagic complications and also during the period of less than 72 hours post-operatively. Low molecular weight heparins should be used with caution among patients who have severe renal dysfunction (Glomerular filtration rate of less than 30 mL/min), [50] except when used as an anticoagulant during hemodialysis [50].

2.9 Dosing protocols of unfractionated heparin

The recommended dosing of UFH for prophylactic treatment of VTE is 5000 IU subcutaneously given 8 or 12 hourly [54,55]. The recommended loading dose of intravenous heparin for therapeutic treatment of VTE is 80 IU/kg bolus, followed by 18 IU/kg/hour infusion [55], or

administered as a bolus of 5000 IU, followed by infusion of at least 32,000 IU / day [55]. Unfractionated heparin can also be administered as 5000 IU initial bolus, followed by 250 IU/kg subcutaneously twice daily, for therapeutic management of VTE. Alternatively, initial S/C dose of 333 IU/kg, followed by 250 IU/kg twice daily is recommended. Appropriate dose adjustments should be made based on anticoagulation laboratory monitoring and in reference to heparin dose-adjustment normograms. In management of acute coronary syndromes, UFH dosing is 60 IU/kg IV bolus (maximum 4000 IU) followed by 12 IU/kg/hour (maximum 1000 IU) plus fibrinolysis, adjusted to maintain APTT at 1.5 -2.5 times the control [43]. When UFH is applied for bridge therapy in Atrial Fibrillation cardioversion, it should be offered as 60-80 IU/kg bolus with target APTT range of 50-70 seconds [43].

2.10 Dosing protocols for enoxaparin

Patients at risk of thrombosis are offered enoxaparin for VTE prophylaxis. They include patients undergoing abdominal, pelvic, thoracic, orthopedic surgery, major joint surgery and curative cancer surgery. Acutely ill and critically ill patients who are immobilized and are at risk of VTE are also treated with prophylactic enoxaparin. The recommended dose for VTE prophylaxis is 40mg subcutaneously once daily for 7-10 days or until the patient is mobilized [57]. For patients undergoing total hip replacement, dosing should be continued up to four weeks after surgery. Appropriate dose adjustments should be made in renal impairment [58].

Enoxaparin dosing in therapeutic treatment of VTE is 1mg/kg subcutaneously 12 hourly or 1.5 mg/kg 24 hourly [57]. Dose adjustments should be made based on creatinine clearance. The 24-hourly regimen is not recommended for in-patients, cancer patients or patients at high risk of bleeding. When enoxaparin is applied in treatment of Non-ST Elevation Myocardial Infarction (NSTEMI), the patient should be offered 1mg/kg of enoxaparin subcutaneously every 12 hours. Appropriate dose adjustments should be made based on creatinine clearance [56]. Patients with ST-Elevation Myocardial Infarction (STEMI) should be offered anticoagulants in addition to dual antiplatelet therapy. Enoxaparin 30mg IV bolus should be offered immediately prior to thrombolysis followed within 15 minutes by 1mg/kg subcutaneously every 12 hours [56].

Weight based dosing is recommended for enoxaparin therapy and prophylaxis [41] with no dose capping for obese patients. Complete blood count (CBC) should be done at baseline and at day 7

to assess for heparin-induced thrombocytopenia. Complete blood counts should be ordered on the third day for patients who had been exposed to heparin six months earlier [11].

2.11 Adverse effects of heparin

The main adverse effects associated with heparin treatment are bleeding and heparin induced thrombocytopenia (HIT). Heparin can also cause osteopenia (osteoporosis) and electrolyte disturbance.

2.11.1 Heparin induced bleeding

The risk of bleeding among patients treated with UFH varies with intensity of anticoagulation [59]. The risk increases with increased dose, recent surgery and recent invasive procedures [59]. The risk of bleeding is also affected by route of administration of heparin and co-administration of anti-platelet agents and fibrinolytic therapy [6]. Patient risk factors are important and they include age, gender, low body weight. Other risk factors are co-morbid diseases such as active malignancy, bleeding disorders such as hemophilia, active or recent peptic ulcer disease and severe uncontrolled arterial hypertension [6]. Patients who have undergone spinal tap or epidural catheterization and those with kidney, liver and heart disease are at higher risk of bleeding. Nose bleeding, hematuria or melena may be the first signs of bleeding.

Bleeding is classified as major or non-major. Major bleeding may contribute to death, is clinically overt, the patients' hemoglobin falls by $\geq 2\text{g/dl}$ and requires that the patient is transfused with at least 2 units of packed red blood cells. Non-major bleeding is considered clinically relevant. It is characterized by overt gastrointestinal bleeding, gross hematuria, substantial epistaxis that requires intervention and extensive hematoma or bruising [6].

A prospective cohort study by Cossette et al (2010) found that creatinine clearance and APTT values as well as the type of heparin administered, form significant predictors of bleeding in patients receiving UFH or LMWHs [60]. Appropriate dose adjustments are required to prevent this adverse effect.

2.11.2 Management of over-anticoagulation and heparin induced bleeding

Therapy with heparin should be reviewed daily for any signs and symptoms of heparin induced adverse effects. Patients in ambulatory care settings who are treated with heparin should be

instructed to report and seek medical care when they experience any abnormal signs and symptoms. Patient education is critical in this aspect [33]. When heparin is suspected to have caused bleeding in a patient, it should be withheld or discontinued immediately. Management of heparin induced bleeding requires adequate volume support and maintenance of good urine output. For bleeding induced by UFH, 1mg of protamine sulfate should be offered for every 100 units administered in previous 2-3 hours [61,62]. Administration of 1 mg of protamine sulfate per 1mg of enoxaparin administered in the last 8 hours, up to a maximum of 50mg over 10 minutes should be considered [63]. Investigation of the cause of bleeding, which may include change in pharmacokinetics, incorrect dose or drug interactions should be undertaken [57].

A systematic evaluation was conducted by Crowther et al (2008), on the literature available to guide management of patients with anticoagulant associated bleeding [63], and made recommendations on how to manage bleeding.

2.11.3 Heparin Induced Thrombocytopenia (HIT)

Heparin Induced Thrombocytopenia (HIT) is an adverse drug reaction of heparin and is mediated via antibodies [64,65]. It is associated with venous and arterial thrombosis. Diagnosis of this condition can be clinical and/ or serological. Minimum platelet count fall of 30%, after initiation of heparin therapy is associated with HIT. Other clinical signs and symptoms include venous or arterial thrombosis (DVT, PE or others), acute anaphylactic reaction that is characterized by tachycardia, fever/chills, dyspnea and cardiopulmonary arrest after bolus injection. Patients also present with skin lesions at the site of injection [65]. A fall of platelet count >50% and or/thrombotic event that occurs between day 4 and 14 [65], following initiation of therapy is indicative of HIT among patients receiving heparin or who had received heparin within previous two weeks. Monitoring of platelet count should be done at least every two or three days from initiation of therapy up to day 14, or until heparin is stopped, whichever occurs first, among patients receiving therapeutic dose of UFH [65].

In a meta-analysis by Martel et al (2005), the absolute risk for HIT associated with LMWHs was 0.2% and with UFH was 2.6 % [64].

2.11.4 Heparin induced hyperkalemia

Heparin induced hyperkalemia is an adverse effect of heparin that manifests within a few days following initiation of therapy [66,67]. The potassium levels are raised above the normal range. The mechanism involves reversible effect of heparin on aldosterone through blockage of enzymatic step in synthesis of Angiotensin II receptors in the adrenal gland. The number and affinity of Angiotensin II receptors in the zona glomerulosa is reduced leading to hypoaldosteronism [66]. The processes lead to hyperkalemia and natriuresis. Heparin induced hyperkalemia is common in the elderly patients, patients with renal insufficiency and diabetic patients. Potassium should be monitored periodically in patients treated with UFH and LMWHs especially in high risk patients [67]. In a prospective study by Michowitz et al (2003), it was found that levels of potassium increased from baseline on the third day following treatment with enoxaparin [67]. In another prospective cohort study by Bengalorkar et al (2011), patients receiving UFH and enoxaparin had increased potassium levels and decreased sodium levels compared to baseline [66].

2.11.5 Heparin Induced osteopenia

It is a rare but serious adverse effect of heparin that occurs after long-term therapy with heparin, usually more than one month and has been reported in pregnancy and post-partum period [68]. It is characterized by decreased bone mass, back pain and spontaneous fractures. The pathogenesis is not well known. Osteopenia is explained by the direct effect of heparin on bone cells causing decreased osteoblastic activity [68,69]. Osteopenia is also thought to be caused by increased bone resorption due to abnormal collagen activation and disturbances in vitamin D metabolism. Heparin may inhibit calcification due to its high affinity for calcium ions. A systematic review on long term effects of LMWHs on bone density in non-pregnant adults, found that extended exposure to LMWHs for up to 24 months may adversely affect bone mineral density [68].

Low molecular weight heparins present less risk of osteoporosis as compared to UFH [70]. A prospective longitudinal study on bone mineral density changes among women with antiphospholipid syndrome treated with UFH and LMWHs, found that pregnant women who received extended treatment of heparin depicted small but significant decrease in bone mineral density at lumbar spine and neck of the femur [70].

2.12 Clinical and laboratory monitoring of heparin therapy

The inconvenience and limited precision of monitoring UFH therapy has favored the use of LMWH which does not require extensive laboratory monitoring [71]. Studies have demonstrated that LMWHs are safe and efficacious when administered in fixed dosage and without laboratory monitoring [72]. However there is need to monitor LMWH therapy in certain subgroups of patients especially those at increased risk of bleeding, children, pregnant women, very obese patients and patients with renal failure [71]. Antithrombotic and pro-hemorrhagic responses cannot be predicted for this group of patients because of altered pharmacokinetic profile of LMWHs [71].

There is a relationship between efficacy, safety of UFH and the dosing regimen. Activated Partial Thromboplastin time (APTT) values, which is sensitive to the inhibitory effects of heparin on thrombin and factors Xa and IXa, remains the most frequently used method for monitoring anticoagulation response to heparin [73]. Bleeding risk increases with the increasing dose of heparin. Similarly the risk of bleeding increases with concomitant administration of fibrinolytics. Prolongation of APTT by 1.5 to 2.5 times the normal reference interval is recommended. The mean normal value of APTT is recalculated with each change in reagent lot number. The current mean normal value is reported with each test result [73].

Following initiation of a patient on heparin therapy, APTT should be ordered every 6 hours until the results falls within the therapeutic range, and whenever the dosage of heparin is changed the same frequency of monitoring should be applied [74]. Daily collection of specimen should be at standard time (preferably prior to 10AM) to avoid diurnal variation in APTT [74].

Monitoring of complete blood count (CBC) and electrolytes is critical during heparin therapy. Hemoglobin decrease of $\geq 2\text{gl/dl}$ from baseline should be evaluated for possible heparin induced bleeding. Decrease of platelet count of greater than a third of baseline value should also be evaluated for possible HIT. Patients' neurologic status should be regularly reviewed for any deterioration.

Anti-Xa assay can quantitatively determine the plasma level of UFH as well as LMWH. Anti-Xa assay is useful in laboratory monitoring of LMWHs therapy [75].

Patients on heparin treatment should be routinely inspected for line/surgical/wound bleeding and symptoms that indicate bleeding such as hematomas should be regularly checked. Other signs that could point to bleeding include bruising and respiratory symptoms.

2.13 Medicine Utilization Reviews

A Medicine Utilization Review (MUR) is defined as the ongoing systematic criteria based evaluation of drug use [76]. The studies are aimed at ensuring appropriate use of medicines at individual patient level [77]. Medicine utilization review is drug specific and is structured in order to address processes of prescribing, administering and monitoring drug therapy with a focus on individual patient clinical outcomes [76]. Concurrent MUR entails review of drug orders during course of therapy. Patient medical records which comprise of demographic data, medicine administration records, nursing observations, laboratory data and clinical monitoring findings are screened to determine whether drug therapy meets predetermined criteria [76].

Medicine utilization review studies are essential in pharmacoepidemiology as they describe the extent, nature and determinants of drug exposure [76]. It also provides information on morbidity data, therapeutic compliance and effectiveness of drug consumption, incidence of adverse reactions and choice of comparators.

Medicine utilization review criteria are statements that define appropriateness of drug use with regard to various components. They are developed using hospitals' standard treatment guidelines, locally available drug use protocols and international evidence-based clinical practice guidelines [76]. Components of drug use established in the MUR criteria are selected from areas where drug use problem has been identified [77]. These include parameters such as indication for use, dosages, drug interactions, clinical and laboratory monitoring.

Appropriateness of drug use is compared against the predetermined criteria [77]. Following establishment of criteria, performance thresholds are decided for each criterion in order to define goals for compliance with each criterion. Compliance below the set threshold would instigate corrective action [76].

2.14 Medicine Utilization Reviews of Anticoagulants

A utilization evaluation study by Khalili *et al* (2010) found that despite existence of comprehensive guidelines on the use of anticoagulants for prevention and treatment of DVT and PE, the compliance to these guidelines is not adequate [78].

Another anticoagulant utilization evaluation study by Singh *et al* (2015) found that heparin was mainly used for VTE prophylaxis. Enoxaparin and warfarin were other commonly used drugs for VTE prophylaxis [79]. The study also found that laboratory tests such as prothrombin time (PT), INR, and aPTT were routinely performed to monitor therapy. Drug-drug interactions were observed commonly with warfarin. Adverse drug reactions were observed during the study as well [79].

A study by Anakwue *et al* (2014) on utilization of oral anticoagulants in a tertiary hospital in Nigeria revealed that absence of diagnostic tools and anticoagulation monitoring clinics, in addition to apprehension of adverse effects contributed to making anticoagulation treatment inaccessible to many patients in Nigeria [80].

A medication utilization evaluation of dabigatran and revaroxaban within a large multi-centre health system, a study by Isaacs *et al* (2016), reported appropriate indications in 94% of patients who received dabigatran and 82% of patients who received rivaroxaban [81]. The study reported one DVT that occurred during hospitalization with rivaroxaban therapy. The study also documented bleeds in 5% of dabigatran and 3% of rivaroxaban patients [81].

2.15 Conceptual Framework

The conceptual model (Figure 1) shows the interdependence of indication and laboratory monitoring of Heparin with patient clinical outcomes and heparin induced adverse effects.

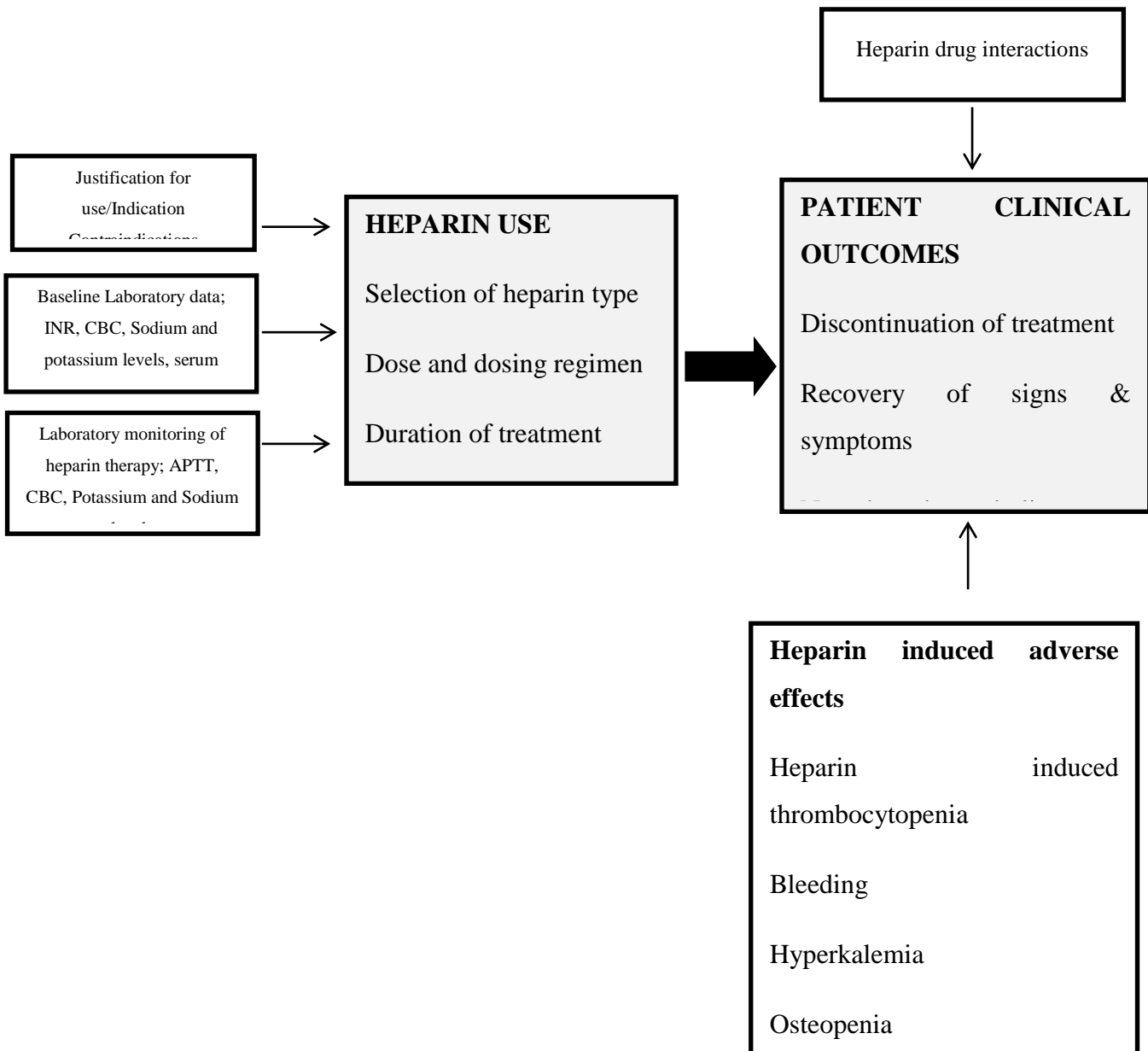


Figure 1: Conceptual Framework

The independent variables include indication for use, baseline laboratory data, laboratory monitoring of heparin, bridge therapy, heparin drug interactions, contraindications and dosage regimens. Dependent variables include patient clinical outcomes and heparin-induced adverse effects.

CHAPTER THREE: METHODOLOGY

3.1 Introduction

This chapter describes the study design that was employed in the research, the sample size determination and procedures that were followed in recruiting study participants. The chapter also describes how data was collected and analyzed.

3.2 Study design

The study employed Medicine Utilization Review design. This design involves criteria-based systematic evaluation of drug use, with focus on aspects of prescribing, administering, monitoring and individual patient clinical outcomes [78].

For this Medicine Utilization Review of heparin, a concurrent cross-sectional review of data abstracted from the medical records of adult inpatients admitted at the medical and surgical wards or renal unit of KNH and who received UFH or enoxaparin was undertaken. Information that was not documented in patient files was obtained from the patient through interviewer administered questionnaires. Criteria along with thresholds derived from evidence-based guidelines were applied in assessing appropriateness of UFH and enoxaparin use.

Medicine utilization reviews (MUR) contribute to optimal quality of medicines therapy by identifying, documenting and analyzing drug use problems and monitoring the impact of interventions. The studies are a powerful tool for ensuring appropriate and cost-effective use of medicines in society.

Concurrent MUR offers opportunity to review patients' medicine therapy and to make appropriate interventions if necessary.

3.3 Study area

The study was conducted at Kenyatta National Hospital. Kenyatta National Hospital (KNH) is a tertiary referral and teaching hospital. KNH has a total bed capacity of 2,000 beds of which 196 are found in the medical wards with equal number in the surgical wards. KNH has several specialized units including the renal unit. Participants that were included in the study were recruited from medical wards, general surgical, orthopedic and cardiothoracic surgical wards and

the renal unit. Studies conducted at KNH medical and surgical wards [8,9], indicated that UFH and enoxaparin are frequently prescribed for patients admitted in these wards.

3.4 Study population

3.4.1 Inclusion Criteria

The study population included hospitalized patients aged 18 years and above, admitted at the medical, general surgical, orthopedic and cardiothoracic surgical wards or the renal unit, who received UFH or enoxaparin for prophylactic or therapeutic treatment of thromboembolic disorders at KNH, from March 2017 through July 2017. Only patients who consented were allowed to participate in the study.

3.4.2 Exclusion Criteria

Patients with hemophilia, hereditary bleeding disorders and history of bleeding disorders not associated with heparin and those who did not consent to participate in the study were excluded. Patients with renal disease were not excluded.

3.5 Sample size determination

The sample size was determined based on a study conducted by Marijani (2009) at KNH to determine prevalence of HIT among medical and surgical patients. The study found that the overall prevalence of HIT was 2.70% among patients receiving heparin [9]. In two other studies by Lisa et al (2000) [79] and Gould et al (1999) [80] meta-analyses were carried out to determine efficacy and safety of UFH and LMWHs. The studies found that UFH indicated for treatment of VTE was associated with major bleeding of rates between 0-7%. LMWHs were associated with major bleeding of rates ranging from 0-3%.

Based on these findings, this study adopted an estimated prevalence of 5% for heparin induced adverse effects.

Using Fisher's formula:

$$n = \frac{Z^2 PQ}{d^2}$$

Where;

n- Minimal sample required

Z- The standard normal deviate at 95% confidence interval, corresponding to (1.96)

P- Estimated prevalence of heparin induced adverse effects in patients receiving UFH and enoxaparin at KNH.

Q- (1-P)

d- Level of desired precision at 5%

$$n = \frac{1.96*1.96(0.05)(1-0.05)}{(0.05)^2} = 73$$

The calculated target sample size was 73 for each of the drugs, namely UFH and enoxaparin. The total minimum sample for the study was 146.

A total of 62 patients who received UFH and 72 patients who received enoxaparin were recruited in this study. Some patients from the renal unit, where participants on UFH were drawn from, were discharged before completion of the requisite follow up period. These patients were excluded from the study. This explains the sample size that was achieved among patients who were offered UFH.

3.6 Sampling technique

The study employed consecutive sampling technique. Patients who met the eligibility criteria and voluntarily gave consent to participate in the study and met the criteria for inclusion was recruited consecutively until the required sample size was achieved. Patients were sampled proportionally from the surgical and medical wards, i.e. wards 4B, 4C, 5A, 5D, 6C, 7A, 7B, 7D, 8A, 8B, 8C, 8D and the renal unit.

3.7 Research Instruments

A Screening Eligibility Form (Appendix I): The form was used to determine patients who met the inclusion criteria.

Consent explanation form and Consent declaration form (Appendices II and III): These forms were used to obtain informed consent from patients who met the other eligibility criteria. Those who did not understand English language were given Kiswahili version of the same.

Data collection form: (Appendix VI): Standardized and structured data collection forms were used to abstract data from the patient's medical records. The first section of the form captured demographic data of the patient. The second section comprised of MUR criteria against which patients' data was abstracted. The third and fourth sections included information on adverse effects experienced by the patient and patient clinical outcomes, respectively.

Interviewer administered Questionnaire (Appendix VII): A well-structured questionnaire was used to collect information from the patient after he/she had given consent to participate in the study. It was divided into two sections; the first section captured patients clinical and laboratory information that was not captured in their medical records. The second section captured data on medication history that was not documented in the patient's records. The Kiswahili version was also availed (Appendix VII).

3.8 Recruitment and consenting procedure

Information in the study protocol was explained in detail to the patient by the principal investigator. The principal investigator applied the screening and eligibility form (Appendix I) to ascertain eligible patients. The patient was taken through explanation on the risks, benefits and confidentiality of personal data as outlined in the Consent Explanation Form (Appendix II). Those who voluntarily gave consent were required to sign a Consent Declaration Form (Appendix III).

3.9 Data collection procedure

A Structured questionnaire (Appendix VII) was used to interview patients who consented to participate in the study. Patients were assessed every three days up to a period of 13 days. The questionnaire was applied on every follow up interview.

A Structured and standardized data collection form that captured MUR criteria was used to abstract data from patients medical records (Appendix VI). Data was abstracted from patient medical records every three days, up to a period of 13 days. The duration of follow was adequate to observe the adverse effects associated with both enoxaparin and UFH.

3.10 Study Variables

The Independent variables in the study included; patient demographic data (age, gender, and weight), principal diagnosis/justification for heparin use, baseline laboratory profile (CBC, sodium and potassium levels, INR and serum creatinine levels), dosage regimens (dose, frequency, duration, and route of administration), contraindications (epidural catheter, severe thrombocytopenia, active bleeding, severe uncontrolled hypertension, recent hemorrhagic stroke), reversal of heparin anticoagulation, bridge therapy, and laboratory monitoring of UFH heparin therapy (INR, APTT, potassium and sodium levels and CBC).

The dependent variables (clinical outcome indicators) include discontinuation of treatment with UFH and enoxaparin, recovery and all-cause mortality. Other dependent variables included heparin induced adverse effects such as major bleeding/hemorrhage, heparin induced thrombocytopenia and hyperkalemia.

3.11 Quality Assurance

The patients were recruited from medical wards, surgical wards and renal unit at KNH, and only those who met the inclusion criteria were allowed to participate.

Investigator administered questionnaire and a structured data collection form were pre-tested by applying them to collect information from an initial five randomly selected patients and their files. To maintain consistency in questions asked, all questions were administered by the principal investigator in the same manner. Necessary modifications were made after the pretesting to improve the data collection instruments and the quality of data that was collected.

3.12 Validity and Reliability of instruments

External validity is assured by the choice of an appropriate sample and sample size. The internal validity is confirmed by accuracy of data collection tools through modifications that was informed by the pretesting of these tools.

Data collection tools were pretested for reproducibility of data. If any ambiguities were detected, they were promptly corrected before conduct of the main study.

3.13 Data management

Filled data collection forms were collected and kept in a secure location by the Principal investigator. The collected data was entered into a password protected Epi Info Version 7 database, and the entered data was verified for accuracy and completeness. Data entry was done on the day it was collected and backing up was done every two days on an external disc.

3.14 Data Analysis

Data was analyzed using Stata version 13.0 statistical software (STATA corp. USA). Descriptive data analysis was carried out to describe the study population. Categorical data such as gender, patient clinical outcomes and heparin induced adverse effects was described as percentages and proportions. Continuous data such as age and laboratory data was summarized using means (standard deviations), or medians (inter-quartile range).

Data analysis also involved a Medicine Utilization Review of heparin. To assess the prescribing and laboratory monitoring practices as well as clinical monitoring practices of both UFH and enoxaparin at KNH, evidence-based MUR criteria were developed (Appendices IV and V). The criteria were developed through appraisal of evidence based clinical practice guidelines on use of heparin in management and prevention of venous thromboembolism. The guidelines include the American college of chest physicians (ACCP) CHEST guidelines [42], National Institutes for Health and Care Excellence (NICE) guidelines [34], the Scottish Intercollegiate Guidelines network (SIGN) [43] and Standard treatment guidelines of Kenyatta National Hospital [45].

Performance threshold was set at 100% for all the MUR criteria in both UFH and enoxaparin therapy. When the performance threshold is set at 100% it indicates that absolute compliance to the criterion is required. If the criterion scores less than 100%, it indicates drug use problem.

Criterion 1: Justification for heparin use/indication

This criterion assessed the appropriateness of the justification/ indication of use for UFH/enoxaparin.

Criterion 2: Dosage, frequency and route of administration of UFH

This criterion assessed the compliance of dosage, frequency and route of administration with the dosing protocols of UFH/enoxaparin established under this criterion.

Criterion 3: Baseline Laboratory Monitoring

The criterion assessed the extent of baseline laboratory of patients who received UFH/enoxaparin. The tests included complete blood count (CBC), INR values, sodium and potassium and estimated glomerular filtration rate for those who received enoxaparin.

Criterion 4: Laboratory monitoring in the course of UFH therapy

The criterion assessed extent as well as frequency of laboratory monitoring in the course of treatment for patients who received UFH/enoxaparin. The tests included APTT count, platelet count, and potassium levels for UFH. The tests for those who received enoxaparin included platelet count and potassium levels.

Criterion 5: Contraindications

This criterion assessed whether patients had at least one co-morbidity or condition that was contraindicated in use of UFH/enoxaparin at baseline. The conditions assessed include hypersensitivity to heparin, severe thrombocytopenia, abnormalities of hemostasis, hyperkalemia, epidural catheter, severe uncontrolled hypertension and a recent hemorrhagic stroke.

Criterion 6: Bridge Therapy

This criterion assessed the number of patients who received bridge therapy during the course of UFH /enoxaparin therapy. It also assessed the proportion of patients who had minimum five day overlap of UFH and warfarin among those who received bridge therapy. In addition patients who achieved therapeutic INR, two to three days prior to stopping UFH therapy were evaluated.

Criterion 7: Anticoagulant reversal

The criterion assessed how undesirable anticoagulation effects of UFH were reversed. This included the pharmacological agents used in reversal, whether UFH was discontinued and blood transfusions in cases of bleeding.

Criterion 8: Drug-drug interactions

The criterion assessed the extent of use of concomitant medicines that had potential harmful drug-drug interactions with UFH/enoxaparin. The medicines assessed include aspirin, Non-steroidal anti-inflammatory drugs (NSAIDs), clopidogrel and dipyridamole.

3.15 Ethical considerations

Approval by KNH-UoN Ethics and Research Committee (KNH/UoN-ERC)

Study approval was sought from KNH-UoN Ethics and Research Committee and approval was granted (Ref. KNH-ERC/A/425, dated October 31st 2016, Appendix VIII).

Informed consent

Informed consent was obtained in writing from all participants. A thorough explanation on what the study entails was offered to the patient in a language that he/she understood. The patient was informed that participation in the study was absolutely voluntary and that they had the liberty to withdraw at any particular time without any penalty or consequence. The risks, benefits and confidentiality of personal information were conveyed to each participant in detail before they consented to the study (Appendices II and III).

Confidentiality of patient records/data

Principal investigator maintained confidentiality of patient files/records and data obtained from therein. Information collected was only used for the purpose of this study. Personal identifying information was excluded from all data collection forms and computer files and any codes linking patient files to the data was secured.

CHAPTER FOUR: RESULTS

Data that was abstracted from patient records and data that was obtained by interviewing study participants together with physical examination of patients is summarized under this chapter. The findings from the MUR assessment of the prescribing and laboratory monitoring practices as well as clinical monitoring practices of both UFH and enoxaparin at KNH are also reported herein.

4.1 Unfractionated Heparin

4.1.1 Demographic characteristics of study participants on Unfractionated Heparin

A total of sixty two patients receiving UFH who met the eligibility criteria were recruited. The representation of male and female gender was equal at 50% each. The majority of patients who were recruited were aged between 35-49 years (21, 33.9%). Table 4.1 illustrates baseline demographic characteristics for participants on UFH.

Table 4. 1: Baseline demographic characteristics

Demographics	f	%
Age		
18-24	14	22.6
25-34	14	22.6
35-49	21	33.9
50 and above	13	21
Gender		
Male	31	50
Female	31	50

4.1.2 Clinical characteristics of study participants on Unfractionated Heparin

4.1.2.1 Diagnoses of patients who received UFH

Hypertension was the most prevalent diagnosis among patients who received UFH (26, 41.9%). Further, twenty-two patients (35.6%) suffered from end stage renal disease, followed by thirteen patients (21%) who suffered from HIV/AIDs disease while the rest had different diagnoses as shown in Table 4.2. Some patients had more than diagnoses.

Table 4. 2: Diagnoses of patients who received UFH

Diagnoses	f	%
Hypertension	26	41.9
End stage renal disease	22	35.5
HIV/AIDS	13	21
Chronic kidney disease	13	21
Acute on chronic kidney disease	13	21
Acute kidney injury	9	14.5
Chronic glomerulonephritis	3	4.8
Gastritis	3	4.8
others	13	20.8

Others- Diagnoses that had frequency of two and less: Congestive cardiac failure, multiple myeloma, Deep venous thrombosis, obstructive uropathy, Pulmonary tuberculosis, Dilated cardiomyopathy, Chronic obstructive pulmonary disease, Intestinal obstruction, Anaemia, Diabetic foot, Urosepsis, Nephrotic syndrome, Acute kidney injury secondary to primary glomerulonephritis, Cancer of cervix, Acute decompensated heart failure in Rheumatic heart disease, Cancer of bladder, Post-transplant organ rejection with sepsis, HELLP syndrome, Acute kidney injury in pre-eclampsia toxemia, Gastropathy, Meningitis, Urethral injury, Hemorrhagic stroke, Pneumonia, Nephropathy and Uraemic encephalopathy.

4.1.2.2 Prior exposure to unfractionated heparin

Twenty one patients (33.9%) reported to have been exposed to UFH treatment before the current treatment. Seventeen patients among those who reported prior exposure had been exposed a month prior while four patients had been exposed two weeks prior. None of the patients had been exposed to UFH a week prior to the current treatment.

4.1.2.3 Physical examination of patients

Physical examination revealed that eight patients (12.9%) had unilateral leg swelling, while two patients (3.2%) had catheter site bleeding. Six patients (9.7%) had calf muscle tenderness and calf muscle pain during the study period

4.1.2.4 Blood transfusions

Nineteen patients (30.7%) received blood transfusion during the study period, all of whom were transfused because of anemia; ten of these patients were transfused intradialysis during hemodialysis, while one patient was transfused because of a surgical procedure.

4.1.2.5 Heparin free dialysis

Five patients (8.3%) underwent heparin free dialysis. These patients had their UFH therapy discontinued (interrupted) for one or two dialysis sessions because of bleeding.

4.1.3 Medicine Utilization Review Criteria for UFH

Criterion 1: Justification for UFH use/ Indication

Unfractionated heparin was indicated for the prevention of thrombosis in hemodialysis for all patients who were recruited. The use of UFH was therefore justified in 100% of the patients who received it.

Criterion 2: Dosage, frequency and route of administration of UFH

Standard protocols as captured in the MUR criteria recommend an initial bolus dose of 2000-4000 IU followed by an infusion of 500-2000 IU/hr for the duration of hemodialysis. The alternative regimen consists of a bolus dose of 2000IU without an infusion dose. Adjustments are to be made for patients of extreme weights, or in patients who experience bleeding or clotting.

In this study, patients received an initial bolus dose of UFH followed by an infusion dose for the duration of hemodialysis event. Both the bolus and infusion dosages were administered intravenously. Majority of the patients received an initial bolus dose (49, 79%). The bolus dose was 2500 IU for all patients. Similarly a majority of the patients (60, 96.8%) were offered infusion dose for the duration of the hemodialysis event. The median maintenance dose at was 1000 IU/hour, IQR [250], with maximum dose of 1000 IU/hour and minimum dose of 250 IU/hour.

The mean duration of infusion of maintenance dose of UFH was 3.4 hours (0.9), with the maximum duration of 4 hours and minimum duration of 2 hours. For patients who did not receive UFH dosage in accordance to the criterion, adjustments had been done as a result of bleeding episodes or low platelet count. The dosages, frequency and route of administration of UFH for all patients met the 100% threshold for compliance with criteria under the indicators of MUR for UFH therapy.

Criterion 3: Baseline Laboratory Monitoring

The tests that were carried out at baseline, for patients who received UFH include the complete blood count, INR values, serum sodium and serum potassium levels. CBC was not monitored for thirteen patients (21%) at baseline. Majority of the patient (52, 92%) were not monitored for INR at baseline. Four patients of those monitored had INR value of less than 2.0 (the target INR is 2.0 to 3.0). Baseline serum potassium and sodium was not monitored for fourteen patients (22.6%) who received UFH at baseline. In this study, the required baseline monitoring of laboratory parameters was observed in only 8% of patients who received UFH.

The MUR criteria provides that baseline monitoring of INR, CBC, sodium and potassium levels should be carried out for all patients who are offered UFH i.e. the set threshold is 100%. Therefore, baseline monitoring of laboratory parameters did not meet the threshold for performance compliance.

Criterion 4: Laboratory monitoring in the course of UFH therapy

The laboratory tests that were monitored in the course of UFH therapy include aPTT, platelet count, and potassium levels. Ideally aPTT, platelet count and serum potassium levels should be

monitored in the course of UFH therapy. This is in accordance with recommendations of the MUR criteria for UFH therapy.

Serum Potassium monitoring

Criteria in MUR for UFH therapy provides for potassium monitoring every three days in the course of treatment duration.

The proportion of patients monitored for potassium varied on different treatment days, from 8.1% on the 3rd day to 11.8% on the 11th day of UFH therapy (Figure 4.1). Overall, the required potassium monitoring was observed in 8.1% of patients receiving UFH at KNH. Potassium monitoring practices did not meet the performance threshold in the MUR criteria for UFH therapy which is set at 100%.

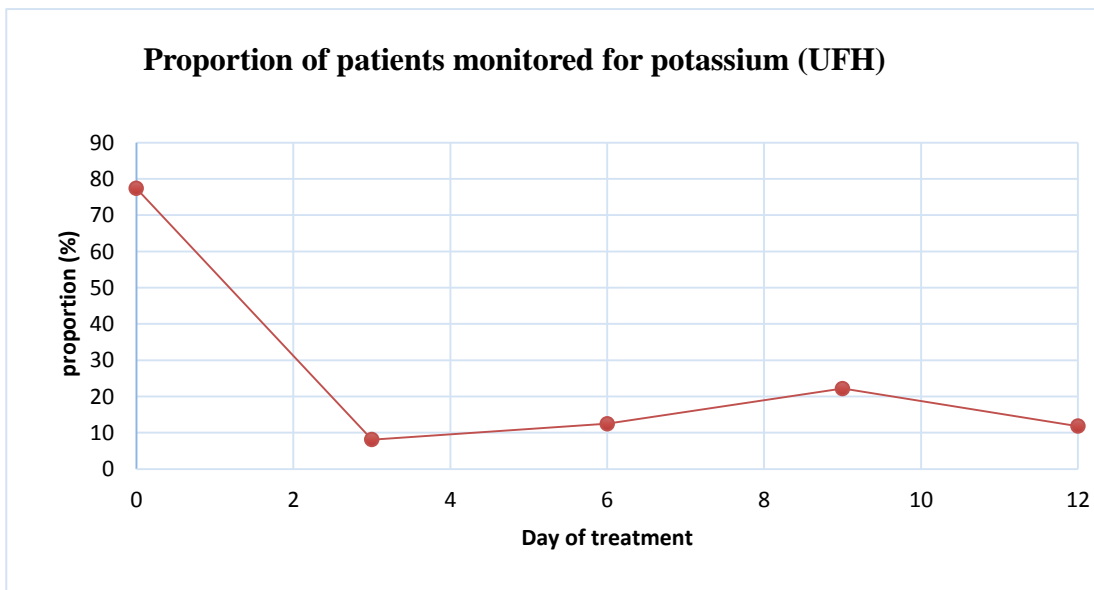


Figure 4.1: Proportion of patients monitored for serum potassium

Monitoring of Platelet count

The MUR criteria for UFH therapy recommends that platelet count should be monitored every 2-3 days from day four of treatment up to day fourteen of treatment. Performance compliance threshold is set at 100%, i.e. all patients should be monitored. Seven patients (12.5%) were monitored for platelet count on day four and day seven of treatment while three patients had their

platelet count monitored on day ten of treatment. Twelve patients were monitored for platelet count on day thirteen of treatment as well. Monitoring of platelet count in accordance with MUR criterion was done in 12.5% of the patients. Overall platelet count monitoring for patients receiving UFH at KNH did not meet the set performance threshold

APTT Monitoring

The MUR criteria recommend that aPTT data should be obtained 6 hours after initiation on UFH treatment. This should be followed by 24 hourly monitoring of aPTT or 6 hourly in case of change of heparin dosage.

Five study participants (8.1%) were monitored for aPTT on day one of treatment while none of the patients had their aPTT monitored 24 hourly as required. All patients who were monitored on day one of treatment recorded aPTT values outside the target range of 1.5 to 2.5 times the normal range. Overall, none of the patients received adequate laboratory monitoring of aPTT. Therefore aPTT monitoring for patients receiving UFH at KNH did not meet the performance threshold.

Criterion 5: Contraindications

The MUR criteria for contraindications recommend a compliance threshold of 100% i.e. all patients should be free from contraindications to UFH use.

Hypersensitivity to Heparin

None of the patients who received UFH reported any known allergy to heparin. However one patient (1.6%) reported to have experienced a feeling of coldness and shivering shortly after bolus administration of UFH.

Severe Thrombocytopenia

The MUR criteria define severe thrombocytopenia as platelet count of less than 50000/mm³. Among those who were monitored for platelet count, none of the patients experienced severe thrombocytopenia at baseline.

Hyperkalemia

Hyperkalemia, which is defined by potassium levels greater than 5.50mmol/L in the MUR criteria, is contraindicated for UFH therapy. Among those who were monitored for serum potassium, fifteen patients (31.3%) had hyperkalemia at baseline.

Abnormalities of hemostasis (Hemophilia)

None of the study participants reported to have a history of bleeding disorder, neither was any study participant diagnosed of an abnormality of hemostasis during the study period.

Epidural catheter

None of the patients who received UFH had an epidural catheter inserted.

Recent hemorrhagic stroke

One patient (1.6%) had a recent hemorrhagic stroke at baseline.

Severe uncontrolled hypertension

The MUR criteria define systolic blood pressure of greater than 180mmHg and diastolic blood pressure of greater than 110mmHg as severe hypertension. Among those monitored for blood pressure, five patients had systolic blood pressure >180mmHg at baseline. In addition, seven patients among those monitored for blood pressure had diastolic blood pressure >110mmHg at baseline. The practices at KNH did not comply with performance threshold set at 100%.

Overall, at least one contraindication to UFH was observed in 15 patients (31.3%) receiving UFH at KNH. This did not comply with performance threshold set at 100% i.e. that no patient receiving UFH should have a contraindication.

Criterion 6: Bridge therapy

The MUR criterion on bridge therapy recommends that patients receiving bridge therapy (those with active clot or at high risk of clotting) should be offered a minimum five day overlap of UFH and warfarin treatment and that therapeutic INR should be achieved two days prior to stopping

UFH. This should apply to all patients receiving bridge therapy; i.e. 100% compliance threshold is required.

Bridge therapy was administered to two patients (3.2%). Among those who received bridge therapy, the minimum five day overlap of warfarin and UFH was achieved in both of them. However it was not possible to determine whether therapeutic INR was achieved in these patients two days before UFH was stopped since INR monitoring was not done prior to cessation of UFH. Therefore bridge therapy for patients receiving UFH at KNH did not meet the performance threshold set.

Criterion 7: Anticoagulant Reversal

The MUR criterion on anticoagulant reversal for UFH recommends holding of further doses of UFH for patients who require anticoagulant reversal. This should be followed by administering protamine sulfate 1% solution intravenously (1mg per 100 IU of UFH given in previous 2-3 hours, maximum 50mg should be offered). Other approaches include volume resuscitation, supportive management and blood transfusion. The criteria require that all patients who need anticoagulant reversal should be offered anticoagulant reversal.

In this study, Vitamin K injection was administered to two study participants (3.2%) who bled during or after administration of UFH. None of the patients received protamine sulfate for anticoagulant reversal. Therefore none of the patients received the recommended anticoagulant reversal. Anticoagulant reversal for patients receiving UFH at KNH did not meet the performance threshold.

Criterion 8: Drug-drug interactions

The MUR criteria on drug interactions identifies the following medicines that have potential to interact with UFH; aspirin, NSAIDs, clopidogrel and dipyridamole.

One patient (1.6%) received clopidogrel while another patient received aspirin. These concomitant medicines increase the risk of bleeding in patients receiving UFH. Therefore, they were used inappropriately. Overall, at least one potential drug-drug interaction with UFH was observed in 3.2% of patients receiving UFH at KNH. This practice did not comply with

performance threshold set at 100%, i.e. that no patient should receive drugs that have potential harmful interactions with UFH.

Summary of MUR of UFH

The compliance of UFH therapy at KNH with each of the MUR criteria is summarized in Table 4.3.

Table 4.3: MUR Criterion Assessment per set performance threshold

	MUR CRITERIA	PERFORMANCE THRESHOLD (%)	OBSERVED COMPLIANCE (%)	COMMENT
1	Justification for UFH use/Indication	100	100	Full compliance with performance threshold
2	Dosage, frequency and route of administration	100	100	Full compliance with performance threshold
3	Baseline laboratory monitoring (before initiation of treatment)	100	8	Minimal compliance with performance threshold
4	Laboratory monitoring during therapy	100	0 ^a	Non-compliance with performance threshold
5	Contraindications	100	52.5	Partial compliance with the performance threshold
6	Bridge therapy	100	0 ^b	Non-compliance with performance threshold
7	Anticoagulant reversal	100	0 ^c	Non-compliance with performance threshold
8	Drug-drug interactions	100	96.8	Partial compliance with the performance threshold

^a. Infers non-compliance to the complete process of laboratory monitoring during the course of UFH therapy, as outlined in the UFH MUR criteria, among all study participants. Does not mean total lack of laboratory monitoring.

^b. Infers non-compliance to the complete process of bridge therapy, as outlined in the UFH MUR criteria, among all study participants who were offered bridge therapy. Does not mean total lack of bridge therapy.

^c. Infers non-compliance to the complete process of anticoagulant reversal, as outlined in the UFH MUR criteria, among all study participants who were eligible for anticoagulant reversal. Does not mean total lack of intervention in cases of UFH toxicity.

4.1.4 Clinical outcomes

All-cause Mortality

Six patients (9.7%) died while majority (90.3%) of study participants recovered and were discharged during the study period.

Heparin-induced adverse effects

One patient (1.6%) experienced blood in stool while six patients (9.7%) experienced bleeding at dialysis catheter site. One patient experienced nose-bleeding, similarly two patients (3.3%) experienced hemoptysis. Three patients (4.8%) experienced per vaginal bleeding. One patient (1.6%) experienced hemorrhagic stroke during the study period.

Table 4.4 shows the incidence of clinical outcomes experienced by patients who received UFH.

Table 4. 4: Incidence of clinical outcomes

Clinical outcome	f	%
Recovery and discharge	56	90.3
All-cause mortality	6	9.7
Catheter site bleeding	6	9.7
Hemoptysis	2	3.3
Blood in stool	1	1.6
Nose bleeding	1	1.6
Hemorrhagic stroke	1	1.6

4.2 Enoxaparin

4.2.1 Demographic characteristics of study participants on enoxaparin

A total of 72 patients receiving enoxaparin and who met the eligibility criteria were recruited. The median age of the patients who were offered enoxaparin was 38 years, IQR [20-72]. Majority of the patients were aged between 35-49 years (23, 31.9%), followed by those who were aged 50 years and above (22, 30.6%). Equally, majority of the patients were of female gender (40, 55.6%) and male gender were 32 (44.4%).

Table 4. 5: Baseline demographic characteristics

Demographics	f	%
Age		
18-24	5	6.9
25-34	22	30.6
35-49	23	31.9
50 and above	22	30.6
Gender		
Male	32	44.4
Female	40	55.6

4.2.2 Clinical characteristics

4.2.2.1 Diagnoses of patients who received enoxaparin

HIV/AIDS was the most prevalent diagnosis (17, 23.6%) among patients who received enoxaparin. This was followed by hypertension (13, 18.1%) and DVT (9, 12.5%). Table 4.4 illustrates the distribution of diagnoses among patients who received enoxaparin.

Table 4. 6: Diagnoses of patients who received enoxaparin

Diagnoses	f	%
HIV/AIDS	17	23.6
Hypertension	13	18.1
Deep venous thrombosis	9	12.5
Chronic kidney disease	9	12.5
Severe head injury	9	12.5
Diabetes Mellitus	7	9.7
Cardiovascular accident	4	5.6
Congestive cardiac failure	3	4.2
Pulmonary embolism	3	4.2
Others	16	22.2

Others-Diagnoses that had frequency of two and less: Multiple myeloma, breast cancer, diabetic neuropathy, obstructive uropathy, chronic myeloid leukemia, guillenbarre syndrome, ascites, dilated cardiomyopathy, meningioma, systemic lupus erythromatosus, chronic obstructive pulmonary disease, infective endocarditis, cerebral edema, subdural hematoma and cryptococcal meningitis.

4.2.2.2 Prior exposure to enoxaparin

One patient (1.4%) reported to have been exposed to enoxaparin treatment before the current treatment.

4.2.2.3 Physical examination of patients who received enoxaparin

A physical examination was carried out on patients after they had consented to participate in the study. The physical examination established that thirteen patients (18.1%) had unilateral leg swelling while eleven patients (15.3%) experienced calf muscle pain and calf muscle tenderness.

4.2.2.4 Blood transfusions

Blood transfusion was offered to eight patients (11.1%) during the study period. Among those who received blood transfusion all of whom were transfused because of anemia, while three patients were transfused intradialysis.

4.2.3 Medicine Utilization Review criteria for enoxaparin

Criterion 1: Justification for enoxaparin use/ Indication

Majority of the patients (61, 84.7%) received enoxaparin for VTE prophylaxis. Four patients (5.6%) were offered enoxaparin for treatment of pulmonary embolism while enoxaparin was indicated for DVT treatment in seven patients (9.7%). Enoxaparin was indicated for atrial fibrillation in one patient (1.4%). Justification of use of enoxaparin was appropriate in all patients and met the performance compliance threshold of 100%.

Criterion 2: Dosage, frequency and route of administration of enoxaparin

Standard protocols as captured in MUR criteria recommend that all patients diagnosed with VTE should be offered enoxaparin 1mg/kg 12 hourly or 1.5mg/kg 24 hourly subcutaneously. Further, patients treated for VTE prophylaxis should be offered enoxaparin 40mg subcutaneously, 24 hourly for 7-10 days or until mobilized. Fixed dosing was offered to all patients (13, 15.3%) with DVT and pulmonary embolism as opposed to weight based dosing at KNH.

Enoxaparin was administered subcutaneously for all patients during the study period. Median dose of 40 [40] mg was offered to patients with maximum dose of 80mg and minimum dose of 20mg depending on the indication. Majority of the patients received 24 hourly dosing (63, 87.5%) while the remaining patients were offered 12 hourly dosing (9, 12.5%).

Overall, 84.7% of patients received enoxaparin at the stipulated dosage, frequency and route of administration. The practices at KNH did not meet the 100% performance compliance threshold as set out in this criterion.

Criterion 3: Baseline Laboratory Monitoring for patients who received enoxaparin

The baseline tests that are recommended in the MUR criterion for all patients receiving enoxaparin include INR, CBC, sodium, potassium, and estimated glomerular filtration rate. In this study, the tests that were carried out at baseline include CBC, INR, serum sodium, serum potassium and estimated glomerular filtration rate.

Complete blood count was not monitored for twenty-five patients (34.7%) at baseline. Majority of the patients (70, 97.2%) were not monitored for baseline INR. Estimated glomerular filtration rate (eGFR) was not monitored for twenty-nine patients (40.3%) of study participants at baseline. Baseline serum potassium and sodium was not monitored for majority of the patients (37, 51.4%).

In this study, the required baseline monitoring of laboratory parameters was observed in 2.8% of patients receiving enoxaparin at KNH. Therefore, baseline monitoring of laboratory parameters for patients receiving enoxaparin did not the threshold for compliance.

Criterion 4: Laboratory monitoring in the course of enoxaparin therapy

Serum Potassium monitoring

The MUR criteria recommend that serum potassium should be monitored every 3 days until treatment is stopped in patients receiving enoxaparin. The performance threshold was set at 100% which required that potassium levels should be monitored for all patients in the course of treatment with enoxaparin.

The proportion of patients monitored for potassium levels varied on different treatment days, from 1.4% on the 3rd day of treatment to 8.3% on the 12th day of treatment (Figure 4.2). Overall, none of the patients receiving enoxaparin at KNH was offered the required potassium monitoring. Potassium monitoring practices at KNH did not meet performance threshold which is set at 100%.

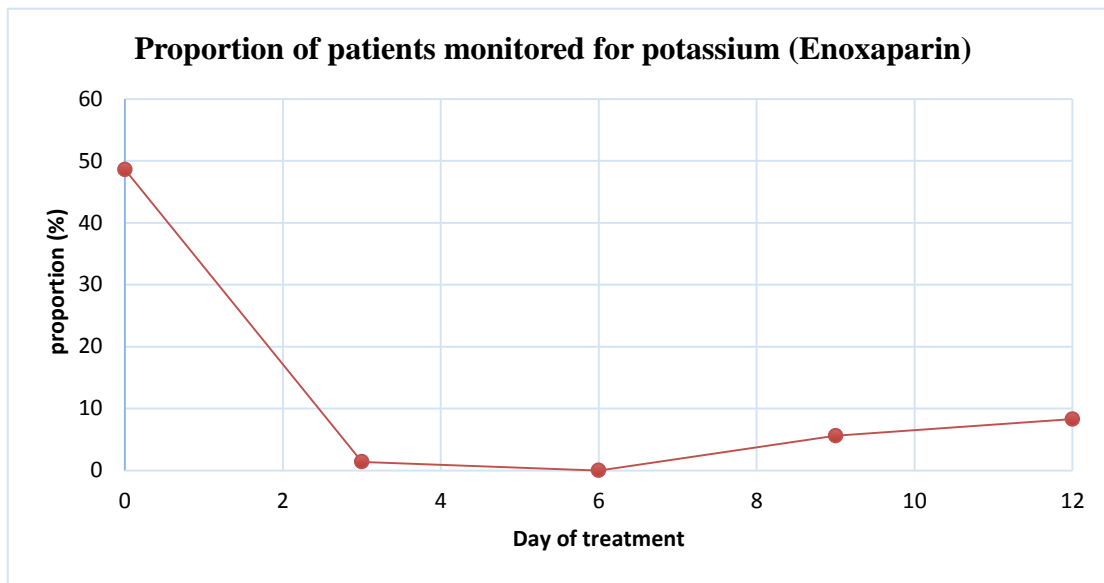


Figure 4.2: Proportion of patients who were monitored for Serum potassium

Monitoring of Platelet count

The MUR criteria for enoxaparin therapy recommend that platelet count should be monitored every 2-3 days from day four of treatment to day fourteen of treatment. Performance threshold is set at 100%, i.e. all patients should be monitored.

Only one patient (1.4%) was monitored in accordance with the criterion for platelet monitoring. Platelet monitoring at KNH did not meet the set performance threshold.

Criterion 5: Contraindications

The MUR criteria for contraindications recommend a compliance threshold of 100%, i.e. all patients should be free from contraindications to enoxaparin use.

Hypersensitivity to Heparin: .None of the patients who received enoxaparin reported any known history of heparin allergy. However, one patient (1.4%) reported to have experienced symptoms of coldness, difficulty in breathing and shivering shortly after enoxaparin administration.

Severe Thrombocytopenia: The MUR criteria define severe thrombocytopenia as platelet count of less than 50000/mm³. Among those who were monitored for platelet count, one patient had severe thrombocytopenia at baseline.

Hyperkalemia: Elevated potassium levels of greater than 5.50mmol/L are contraindicated for enoxaparin therapy. Among those who were monitored for serum potassium, three patients experienced hyperkalemia at baseline.

Abnormalities of hemostasis (Hemophilia)

None of the study participants reported to have a history of bleeding disorder at baseline.

Severe uncontrolled hypertension: The MUR criteria define Systolic blood pressure of greater than 180mmHg and diastolic blood pressure of greater than 110mmHg severe hypertension. Among those monitored for blood pressure, one patient (2.6%) had systolic blood pressure >180mmHg, at baseline. In addition, two patients (5.1%) had diastolic blood pressure >110mmHg at baseline.

Estimated glomerular filtration rate <30mL/min/1.73m²: Enoxaparin is contraindicated in severe renal dysfunction. Among those monitored for eGFR at baseline, five patients (11.6%) had eGFR less than 30mL/min/1.73m².

Overall, at least one contraindication to enoxaparin use was observed in 28.8% of the patients receiving enoxaparin at KNH. This practice did not comply with performance threshold set at 100%, i.e. that no patient should have a contraindication.

Criterion 6: Bridge therapy

The MUR criterion recommends that patients receiving bridge therapy (i.e. those with active clot or at high risk for clotting) should be offered a minimum five day overlap of enoxaparin and warfarin treatment and that therapeutic INR should be achieved two days prior to stopping enoxaparin. This should apply for all patients receiving bridge therapy, i.e. 100% performance threshold.

Twelve patients (16.7%) were offered bridge therapy. Among those who received bridge therapy, eleven patients achieved the minimum five day overlap of enoxaparin and warfarin. The proportion of patients who achieved therapeutic INR following bridge therapy could not be determined since INR monitoring was not done prior to cessation of enoxaparin therapy. Therefore bridge therapy for patients receiving enoxaparin at KNH did not meet the performance threshold.

Criterion 7: Anticoagulant Reversal

The MUR criterion on anticoagulant reversal for enoxaparin recommends holding of further doses of enoxaparin for patients who require anticoagulant reversal. This should be followed by administering protamine sulfate 1% solution intravenously (1mg per 1mg of enoxaparin given in previous 8 hours, maximum 50mg) over 10 minutes. Other approaches include volume resuscitation, supportive management and blood transfusion.

None of the patients was offered protamine sulfate for anticoagulant reversal. Enoxaparin dosing was withheld for two patients out of the three patients who experienced bleeding episodes. None of the patients received blood transfusion. The practice at KNH did not comply with the performance threshold set for anticoagulant reversal.

Criterion 8: Drug-drug interactions

Other medicines that patients received and have potential for harmful drug-drug interaction with enoxaparin include aspirin and Non-steroidal anti-inflammatory drugs (NSAIDs). Three patients (4.2%) were offered aspirin concomitantly with enoxaparin while five patients (6.9%) received other NSAIDs.

These concomitant medicines increase the risk of bleeding in patients receiving enoxaparin. Therefore, they were used inappropriately. Overall, at least one potential drug-drug interaction with enoxaparin was observed in 11.1 % of the patients receiving enoxaparin at KNH. This did not comply with the performance threshold set at 100%, i.e. that no patient should receive drugs that have potential harmful interactions with enoxaparin.

Summary of MUR of enoxaparin

The compliance of enoxaparin use at KNH with each of the MUR criteria is summarized in Table 4.7.

Table 4. 7: MUR Criteria Assessment per set Performance Threshold

	MUR CRITERION	PERFORMANCE THRESHOLD (%)	OBSERVED COMPLIANCE (%)	COMMENT
1	Justification for enoxaparin use/Indication	100	100	Full compliance with performance threshold
2	Dosage, frequency and route of administration	100	84.7	Partial compliance with performance threshold
3	Baseline laboratory monitoring (before initiation of treatment)	100	2.8 ^a	Minimal compliance with performance threshold
4	Laboratory monitoring during therapy	100	0 ^b	Non-compliance with performance threshold
5	Contraindications	100	71.2	Partial compliance with performance threshold
6	Bridge therapy	100	0 ^c	Non-compliance with performance threshold
7	Anticoagulant reversal	100	66.6	Partial compliance with performance threshold
8	Drug interactions	100	88.9	Partial compliance with performance threshold

a. Infers that only 2.8% of study participants received laboratory monitoring that complied 100% with the complete process of monitoring as outlined in the UFH MUR criteria, at baseline.

b. Infers non-compliance to the complete process of laboratory monitoring during the course of therapy, as outlined in the enoxaparin MUR criteria, among all study participants. Does not mean total lack of laboratory monitoring.

c. Infers non-compliance to the complete process of anticoagulant reversal, as outlined in the enoxaparin MUR criteria, among all study participants who were eligible for anticoagulant reversal. Does not mean total lack of intervention in cases of enoxaparin toxicity.

4.2.4 Clinical outcomes

4.2.4.1 Mortality

Three patients (4.2%) died during the study period while sixty-nine patients (95.8%) recovered and were discharged.

4.2.4.2 Enoxaparin-induced adverse effects.

One patient (1.4%) reported per vaginal bleeding while 1.4% of study participants experienced nose bleeding, similarly, one patient (1.4%) experienced injection site bleeding during the study period. Three patients (4.2%) experienced hemorrhagic stroke during the study period.

4.2.4.3 Discontinuation of enoxaparin therapy

Enoxaparin therapy was discontinued among eight patients (10.1%). Among them, one patient had enoxaparin treatment discontinued because of bleeding episode. Enoxaparin was discontinued for six patients (7.3%) as a result of ambulant status of the patients while treatment was discontinued for one patient (1.4%) as they had recovered from VTE symptoms.

4.2.4.4 New thrombotic events

Two patients (2.8%) who received enoxaparin developed deep venous thrombosis during the study period.

Table 4.8 illustrates the incidence of clinical outcomes experienced by patients who received enoxaparin.

Table 4. 8: Incidence of clinical outcomes

Clinical outcome	f	%
Recovery and discharge	69	95.8
All-cause mortality	3	4.2
Hemorrhagic stroke	3	4.2
New thrombotic events (DVT)	2	2.8
Injection site bleeding	1	1.4
Per vaginal bleeding	1	1.4

CHAPTER FIVE: DISCUSSION, CONCLUSION, LIMITATIONS AND RECOMMENDATIONS

5.1 Discussion

This study defined optimal heparin anticoagulation practice as the 100% compliance with MUR criteria for UFH and enoxaparin use (Appendices IV and V). A performance threshold of 100% was set for both clinical and laboratory monitoring of UFH and enoxaparin. The study did not aim to compare the two sets of patients i.e. UFH and enoxaparin patients, since they had totally different baseline characteristics.

The study found that some of the heparin anticoagulation practices within KNH achieved 100% compliance to the set performance thresholds/standards. Justification of use/ indication of UFH and enoxaparin at KNH met the set threshold of 100% compliance, meaning that all patients who received enoxaparin had the appropriate indication as per the MUR criteria. Unfractionated heparin was indicated for use in hemodialysis to prevent thrombosis among all study participants who received UFH. Enoxaparin was indicated for VTE prophylaxis, treatment of pulmonary embolism and DVT, in addition to treatment of atrial fibrillation. Such practices should be maintained at KNH.

The study found that a majority of patients (61, 84.7%) who received enoxaparin were managed for VTE prophylaxis. This is in line with indication of enoxaparin use for VTE prophylaxis among acutely ill hospitalized surgical and medical patients [85]. The study established that all patients recruited in the study and who were treated for VTE prophylaxis received enoxaparin as opposed to UFH. This finding is a major shift from the finding by Wambui *et al* (2015) that showed majority of patients (71.9%) in KNH treated for VTE prophylaxis received UFH [8]. This can be attributed to the safety, efficacy and the convenience of once daily administration of LMWHs as compared to UFH.

Enoxaparin was prescribed for treatment of all patients diagnosed with symptomatic PE and DVT as well. A Meta-analysis by Mismetti *et al* (2000) established that UFH significantly reduces the risk of symptomatic VTE [86]. However no evidence is available that proves the anti-thrombotic advantage of LMWHs over UFH. The advantages that LMWHs have are low risk of bleeding and low risk of heparin induced thrombocytopenia (HIT). To this extent practices at KNH met the performance standards and the practices should be maintained.

Dosing protocols for enoxaparin and UFH were found to comply with MUR criterion on dosing except for patients with symptomatic VTE who were offered fixed dosage of enoxaparin instead of weight based dosing. Enoxaparin was administered as fixed dosages, given 24 hourly or 12 hourly subcutaneously depending on the indication and the risk profile of individual patients. The dosages were ranging from maximum dose of 80mg and minimum dose of 20mg.

Majority of the patients received 40mg 24 hourly subcutaneously, indicated for VTE prophylaxis. This complied with MUR criterion on enoxaparin dosing for VTE prophylaxis. A study by Panucci *et al* (2011) found that compliance rates of implementation of VTE prophylaxis protocol was at 90% [87]. The study was carried out at a teaching medical center.

Weight-based dosing was not offered to obese patients. A meta-analysis by Lensing *et al* (1995) found that LMWHs are safe and efficacious when administered in fixed dosages without laboratory monitoring for VTE treatment [88]. However clinical trials exclude patients with increased risk of bleeding, obese patients and patients with severe renal impairment [89].

In addition, this study found a number of patients (5, 11.6%) who received enoxaparin with estimated glomerular filtration rate of less than 30 mL/min/1.73². This violates recommendations from MUR criteria on contraindications. Enoxaparin is eliminated from the body mainly through the renal system [90]. Accumulation of the drug occurs in patients with severe renal impairment can lead to toxic effects of enoxaparin. Increased risk of bleeding is one of the toxic effects.

Unfractionated heparin dosing in hemodialysis met the set performance threshold. Majority of the patients (49, 79%) received a bolus dose of 2500 IU followed by infusion dose of between 500-1000 IU/hour for the whole duration of the procedure. Evidence based guidelines on the preferred UFH regimens in hemodialysis do not exist. Individual patient bleeding and clotting risk stratification together with careful benefit-risk balance should guide the physician on the choice of the optimal regimen [90].

The study also found inadequate monitoring practices of UFH and enoxaparin therapy. Baseline monitoring of INR, platelet count, serum creatinine and serum potassium is essential for optimal UFH and enoxaparin therapy. These criteria on monitoring was set at 100% which required that all patients offered UFH be monitored for INR, CBC, potassium and

sodium at baseline while all patients offered enoxaparin should be monitored INR, CBC, sodium, potassium and estimated glomerular filtration rate at baseline.

Similarly the MUR criteria require that aPTT should be checked 6 hours after initiation of treatment with UFH and 24 hourly afterwards. The goal is to achieve a value that is 1.5-2.5 times the control. In addition, all patients offered UFH or enoxaparin should be monitored for platelet count every 2-3 days from day 4 to 14 of treatment. Serum potassium should be monitored every three days in the course of treatment.

However the study found that the practices at KNH achieved only minimal compliance. The study found that only 5 patients (8.1%) offered UFH were monitored for baseline INR. Complete blood count was monitored for majority of patients (49, 79%) at baseline. Sodium and potassium was monitored in 48 patients (77.4%) at baseline. Platelet count was checked in 7 patients (12.5%) during treatment with UFH, in accordance with MUR criteria. In addition 5 patients (8.1%) were monitored for potassium in accordance with MUR criteria. None of the patients who received UFH was monitored for aPTT in accordance to MUR criteria.

Two patients (2.8%) who received enoxaparin were monitored for INR at baseline. Majority of the patients who were offered enoxaparin were monitored for CBC (47, 65.3%) and eGFR (43, 59.7%) at baseline. Thirty five patients (48.6%) were monitored for sodium and potassium at baseline. In the course of enoxaparin treatment, one patient (1.4%) was monitored for platelet count in accordance to MUR criterion while none of the patients (0%) was monitored for potassium in accordance to the MUR criterion.

At the time of the study, the INR machine at KNH had broken down; therefore most patients were referred outside the facility for the test. The logistics and costs involved in carrying out the test outside KNH are prohibitive and hence the test was not done for most patients when it was ordered. Infrequent monitoring of the other laboratory tests can be explained by low ordering rates of the tests by physicians in addition to long turnaround times of the tests when they are ordered.

Infrequent monitoring of platelet count has been reported in a study by Berg *et al* (2009) which found that the frequency of compliance with platelet count monitoring recommendations was 35.6% for patients exposed to LMWHs and 41.5% for patients exposed to UFH within 100 days [91]. The findings of this study suggest compliance with

MUR criteria on laboratory monitoring of UFH/enoxaparin therapy is low at KNH. Policies and tools to improve compliance with recommendations should be developed to secure the use of enoxaparin and UFH at KNH.

Bridge therapy for patients who received enoxaparin was partly compliant with the MUR criteria. Five day minimum overlap for enoxaparin and warfarin was achieved for majority of the patients (11, 78.6%). However INR monitoring was not offered to patients who received bridge therapy and thus not complying with MUR criteria. Lack of INR monitoring in bridge therapy makes it impossible to establish if the patients achieved therapeutic INR before switch to warfarin only.

The delayed anticoagulant effect of warfarin requires that another drug with rapid anticoagulant effect should be administered concurrently until a therapeutic warfarin level is achieved. The five day minimum is to prevent potential hypercoagulable state upon initiation of warfarin treatment. A clinical trial by Brandjes *et al* (1992), established that patients with DVT require an initial treatment with heparin which can then be safely combined with warfarin until therapeutic warfarin INR is achieved [92].

This area requires improvement in order to achieve optimal bridge therapy for patients who are at a high risk of clotting. Infrequent INR monitoring for patients at KNH can be explained by the breakdown of INR machine in the hospital at the time of the study. There are no previous studies on compliance of INR monitoring for UFH/enoxaparin therapy.

Heparin induced thrombocytopenia (HIT) is a life-threatening complication of heparin therapy whose clinical diagnosis is dependent on monitoring of platelet count. Laboratory diagnosis of HIT entails immunological assays which are not readily available at KNH. The timing of platelet count fall is useful in clinical diagnosis of HIT [93]. The platelet count in HIT typically starts from day 4-14 of treatment. Therefore serial measurement of platelet count is important in diagnosis of HIT.

Thrombocytopenia of HIT can be moderate to severe with platelet count ranging from 50000-80000/mm³. Thrombocytopenia in HIT can also be relative characterized by a drop of 50% or more of platelet count as compared to the baseline [94].The study found that platelet monitoring compliance for both patients who received UFH and enoxaparin was less than 50% at KNH.

Hyperkalemia and severe uncontrolled hypertension are contraindicated in both UFH and enoxaparin therapy. Potassium monitoring at baseline is important to ensure patients who already have hyperkalemia are not offered UFH/enoxaparin. Similarly blood pressure monitoring at baseline to ensure patients who suffer from severe hypertension are not offered UFH/enoxaparin. Hyperkalemia can exacerbate the risk of heparin induced hyperkalemia in patients treated with UFH/enoxaparin [95]. Severe hypertension increases the risk of bleeding among patients treated with UFH/enoxaparin.

The findings of this study show that 15 patients (31.3%) who received UFH and 3 patients who received enoxaparin had hyperkalemia at baseline. In addition 7 patients (13%) who received UFH and 2 patients (5.1%) who received enoxaparin suffered from severe hypertension at baseline. This practice at KNH violates MUR criteria on contraindications for UFH/enoxaparin therapy. Therefore, the practice at KNH did not achieve 100% performance compliance.

This study also established that one patient (1.6%) who received enoxaparin had a recent hemorrhagic stroke at baseline while one patient (2.1%) who was offered enoxaparin had severe thrombocytopenia at baseline. Both conditions are contraindicated for enoxaparin therapy. Enoxaparin therapy in thrombocytopenia increases the risk of bleeding [97].

Five patients with eGFR of less than $30\text{mL}/\text{min}/1.73^2$ at baseline received enoxaparin. Enoxaparin is contraindicated in renal impairment. Increased risk of bleeding has been observed in patients treated with enoxaparin and have moderate to severe renal impairment [96]. Low molecular weight heparins are primarily eliminated through the renal route, therefore a decrease in renal function leads to accumulation of enoxaparin and hence increased risk of bleeding [97].

The use of UFH/enoxaparin in conditions which are contraindicated could be explained by individual patient risk-benefit profiling by the physicians when deciding to offer such patients UFH or enoxaparin. The benefit of treatment or prevention of thromboembolism far outweighed the risk of bleeding.

The practice at KNH did not comply with 100% threshold set in the MUR criteria. No previous studies have been done to establish the extent of compliance with recommendations on contraindications for UFH/enoxaparin therapy.

The MUR criteria require further doses of UFH/enoxaparin to be withheld in all patients who need anticoagulant reversal. In addition, these patients should be offered protamine sulfate 1% solution, given intravenously. Similarly these patients should be offered supportive management, volume resuscitation and blood transfusion if need be.

However, 2 patients (3.2%) who experienced UFH induced bleeding were offered Vitamin K injection at KNH. Three patients (4.2%) who received enoxaparin and experienced bleeding episodes were not offered any form of anticoagulant reversal. The anticoagulation reversal practices at KNH did not meet the performance compliance threshold that was set at 100%. The poor compliance can be explained by lack of knowledge by physicians on the availability of protamine sulfate at KNH. In addition lack of heparin anticoagulation reversal algorithm at KNH could have contributed.

All patients receiving UFH/enoxaparin should not be offered aspirin, NSAIDs, clopidogrel and dipyridamole concomitantly. This is in accordance to MUR criteria. The study found that one patient (1.6%) received clopidogrel concomitantly with UFH and one patient (1.6%) was offered aspirin at the time they received UFH. Similarly 3 patients (4.2%) received aspirin concomitantly with enoxaparin and 5 patients (6.9%) received NSAIDs concomitantly with enoxaparin. Drug-drug interaction between UFH/enoxaparin and the concomitant medicines increase the risk of bleeding [99].

The clinical outcomes for patients who received UFH/enoxaparin were recovery and discharge, all-cause mortality, bleeding episodes and hemorrhagic stroke. In addition 2 patients (2.8%) who received enoxaparin experienced new thrombotic events (DVT). All-cause mortality was higher (6, 9.7%) in patients who received UFH as compared to those who received enoxaparin (3, 4.2%). Similarly the frequency of bleeding episodes was higher (13, 21%) among those treated with UFH as compared to those who received enoxaparin (3, 4.2%).

A systematic review by Giorgio et al revealed that the incidence of major bleeding ranged from 0 to 12.5% (mean 4.4%) in patients who received LMWH, while for patients who received UFH, it ranged from 0 to 11.5% (mean 4.4%) [98]. In this study, the incidence of bleeds in patients who received UFH is higher than what was observed by the systematic review.

The high incidence of bleeds could be a possible consequence of non-compliance or minimal compliance to the parameters in the UFH MUR criteria.

A study by Cossette *et al* (2010) that evaluated the bleeding risk in patients exposed to therapeutic UFH or LMWH found that patients exposed to UFH had a higher risk of bleeding as compared to those exposed to LMWH [99]. The study also established that patients with decreased creatinine clearance had a higher risk of bleeding. The high incidence of bleeding in patients, who received UFH, can be partly explained by the fact that they were undergoing hemodialysis and were more likely to have reduced creatinine clearance.

Three patients (4.2%) who received enoxaparin experienced hemorrhagic stroke as compared to one patient (1.6%) who was offered UFH.

Two patients who received enoxaparin for VTE prophylaxis developed DVT in the course of treatment. A study by Samama *et al* (1999) that compared enoxaparin with placebo for prevention of VTE in acutely ill patients found that the incidence of VTE was 5.5% in the group that received enoxaparin and 14.9% in the group that received placebo [100]. The incidence of VTE in that study was slightly higher than the incidence at KNH (2.8%). Generally, the use of enoxaparin was quite effective in prevention of VTE prophylaxis at KNH and the practice should continue.

A study by Nekoonam *et al* [101] investigated appropriateness of administration of DVT prophylaxis in ICU, at a teaching hospital, found that 67.3% of the study participants did not receive correct prophylaxis. The findings concur with the results in this study which show minimal or non-compliance with majority of the parameters in both UFH and enoxaparin MUR criteria.

Fahim *et al* [102] study on enoxaparin utilization evaluation, rated 28.7% of variables on prescribing, dosing, administration and laboratory monitoring of enoxaparin as inappropriate, among all study participants.

5.2 Conclusion

Unfractionated heparin was indicated for prevention of thrombosis in hemodialysis at KNH. The dosing, frequency and route of administration of UFH met the performance threshold as stated in the MUR criteria. Baseline laboratory monitoring and laboratory monitoring in the course of UFH treatment did not comply with the performance threshold which was set at 100%. The clinical outcomes experienced by patients who received UFH were all-cause mortality (6, 9.3%), bleeding episodes (10, 16.2%) and recovery and discharge (56, 90.3%).

Enoxaparin was indicated for VTE prophylaxis and treatment of symptomatic PE and DVT. These indications for enoxaparin use complied with 100% performance threshold stated in the MUR criteria. The dosage and frequency of enoxaparin therapy did not meet the MUR criterion while route of administration was appropriate. Baseline laboratory and laboratory monitoring in the course of enoxaparin treatment was sub-optimal. The clinical outcomes for patients who received enoxaparin included: all-cause mortality (3, 4.2%), bleeding episodes (2, 2.8%), new DVT (2, 2.8%), and recovery and discharge (69, 95.8%). Enoxaparin treatment was discontinued for patients who experienced bleeding and in those who became ambulant. Similarly enoxaparin was discontinued in patients who recovered from VTE symptoms.

5.3 Study Limitations

Missing data from patient records was a limitation in this study. In addition, information obtained from study participants by way of interview may be inaccurate because of recall bias and this can compromise the validity of the study results. This limitation was minimized by cross-checking the information obtained from patients with data that was documented in the patients' records.

5.4 Recommendations

5.4.1 Policy recommendations

The study recommends the development of standard heparin dosing and monitoring protocols in addition to training of health care practitioners at KNH. This study also recommends the training of all health care professionals on utilization of protamine sulfate for anticoagulant reversal. In addition, the study recommends that all health care practitioners should be sensitized on adverse effects of heparin and how to document them.

5.4.2 Recommendations for practice

This study recommends implementation of standardized heparin dosing and monitoring protocols, which will be derived from evidence-based clinical guidelines. The protocols should be incorporated in patient care plans and clinical audit activities. Implementation of point of care testing for INR and aPTT will help in reducing the turnaround time for these monitoring parameters. Finally pharmacists should take a stewardship role in the anticoagulation program, especially implementation of dosing protocol, clinical and point of care monitoring of laboratory parameters.

5.4.3 Recommendations for further studies

This study recommends a Delphi study to develop institution-based heparin use protocols at KNH. This study further recommends a follow-up study, which should be designed as a pre-post study in order to assess the impact of suggested interventions. In addition, a qualitative study to identify and offer possible explanations and/ or root cause of the minimal compliance or non-compliance to the internationally acceptable best clinical practice guidelines.

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APPENDICES

Appendix I: Screening and Eligibility Form

Screening NO..... Date of screening.....

SECTION A: Inclusion criteria; Items 1-3 need to be answered YES for the participant to be eligible.

1. Is the patient receiving UFH/Enoxaparin? YES NO
2. Is the patient aged 18 years and above? YES NO
3. Has the patient consented to participate? YES NO

Section B: Exclusion criteria; item 4 need to be answered NO for participant to be eligible

4. Does the patient have any known bleeding disorders/bleeding complications
 YES NO
5. Based on the criteria above, is the participant eligible YES NO
6. If not eligible what is/are reason(s) for exclusion

.....
.....
.....

7. Comments (enrolled/not enrolled).....
.....
.....
.....

Appendix II: Consent Explanation Form

STUDY TITLE: MEDICINE UTILIZATION EVALUATION OF HEPARIN AT KENYATTA NATIONAL HOSPITAL.

To be read in the language the patient understands best.

Introduction

My name is Dr. KarimWanga. I am a graduate student in the Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi. I am pursuing a degree of master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance. I am currently conducting a study on Medicine utilization review of Heparin at Kenyatta National Hospital. Results of this study will form background for improved prescribing, use and laboratory monitoring of heparin therapy to optimize patient clinical outcomes and prevent heparin-induced adverse effects at KNH.

I would like to seek your consent to participate in the study. Kindly read the consent form below.

Purpose of the study

This study aims to assess the prescribing and laboratory monitoring practices of unfractionated heparin and enoxaparin at Kenyatta National Hospital, as well as establish heparin induced adverse effects among medical and surgical patients at Kenyatta National Hospital. The study will last approximately three months and will involve review of patients' records to abstract relevant clinical and laboratory data. The study will also involve one on one interview with a patient using a structured questionnaire to obtain additional clinical information and relevant medical and medication history.

Procedure:

If you agree to participate in the study, you will be required to spare 20 minutes of your time every other three days, up to 14 days where you will have a one on one interview with principal investigator. The interview will be guided by a structured questionnaire.

Benefits:

You may not benefit from this study immediately, but on completion of the study, the findings will form background for improving prescribing, use and laboratory monitoring of heparin at KNH. This will optimize clinical outcomes for patients treated with heparin.

Risks:

There will be no risks involved in conduct of this study.

Confidentiality:

Information collected from you will be stored safely under lock and key by the principal investigator, who will be the only one to access it. Your name will not be linked with the information obtained from your records or from one-on-one interview. No single response will be reported on its own, but as summation of all responses. Your personal information will not be disclosed to the public or other researchers.

Compensation:

There will be no form of direct compensation in this study.

Conclusion:

Your participation in this study is purely voluntary. You are free to decline participation in the study at any given time in the course of the study. Decline of participation will not attract any penalty or consequences. Similarly there will be no loss of benefit incurred, if any.

Contacts: In case you have questions related to this study, you can contact the following:

Principal Investigator:

Dr. KarimWanga, Master of Pharmacy (Pharmacoepidemiology and Pharmacovigilance)

Department of Pharmacology and Pharmacognosy, P.O. Box 30197-00400, School of Pharmacy, University of Nairobi.

Telephone: 0727 981650

Supervisors

Dr. Eric M. Guantai

Department of Pharmacology and Pharmacognosy

University of Nairobi.

Dr.Kipruto A. Sinei

Department of Pharmacology and Pharmacognosy,

University of Nairobi.

Dr. Stanley N. Ndwigah

Department of Pharmaceutical Chemistry, University of Nairobi

The Secretary, KNH/UoN-ERC

Kenyatta National Hospital, P.O Box 20723-00202, Nairobi Tel No. 2726300-9/2716450 Ext 44102, Fax 725272

Ethical Approval

Ethical approval will be granted by Kenyatta National Hospital/ University of Nairobi/ Ethics and Research Committee (KNH/UoN-ERC) to conduct this study at the medical and surgical wards of Kenyatta National Hospital.

KIAMBATISHO CHA PILI: MAELEZO YA IDHINI

KICHWA: MEDICINE UTILIZATION EVALUATION OF HEPARIN AT KENYATTA NATIONAL HOSPITAL

Utangulizi

Jina langu ni Dkt. KarimWanga. Mimi ni mwanafunzi washahada ya uzamilifu katika kitengo cha Utabibu dawa, katika chuo kikuu cha Nairobi. Ninafanya utafiti juu ya matumizi ya Heparin kwa matibabu ya magonjwa tofauti katika hospitali kuu ya Kenyatta.

Nia ya Utafiti

Utafiti huu si wa kupeana tiba yoyote ila ni kuangalia jinsi Heparin inavyotumika kutibu magonjwa mbalimbali. Pia utafiti utaangazia uchunguzi wa mahabara wa matumizi ya Heparin pamoja na madhara yeyote yanayotokana na matumizi ya Heparin.

Utaratibu Utakaofuatwa

Ukikubali kushiriki katika utafiti huu basi utahitajika kuweka sahihi yako kwenye fomu ya hati ya makubaliano. Utaulizwa maswali kadhaa kuhusu afya yako na dawa zozote unazotumia kando na zile zinazopeanwa hospitalini. Maswala mengine kuhusu matibabu yako yatatolewa kwenye daftari lako la matibabu.

Hatari

Hamna hatari yeyote inayohusishwa na utafiti huu.

Usiri

Nakala na habari zote zitakazotokana na uchunguzi huu zitahifadhiwa kwa siri na kamwe hazitatolewa kwa wahusika wengine. Pia zitatumika tu kwa ajili ya utafiti huu.

Faida ya Kushiriki

Hakuna faida ya moja kwa moja kutokana na kushiriki kwako kwenye utafiti huu. Ila matokeo ya utafiti yatafaidi zaidi katika kuboresha matumizi ya Heparin kwa matibabu ya magonjwa tofauti kwenye hospitali kuu ya Kenyatta. Utafiti pia utakuwa mwongozo wa utafiti mwengine wa kuchunguza namna ya kuzuia madhara yoyote yanayoweza kusababishwa namatibabu hayo.

Hitimisho

Kushiriki kwako kwenye utafiti huu ni kwa hiari. Unao uhuru wa kukubali au kukataa, na pia waweza kubatilisha nia ya kushiriki wakati wowote. Kujiondoa kwako hakuwezi kukuhatarisha kwa vyovyote na vilevile, huduma unazopata katika hospitali kuu ya Kenyatta zitaendelea kama kawaida.

Kwa maswali yeyote kuhusu utafiti huu, uko huru kuuliza wafuatao;

Mtafiti Mkuu:

Dkt. KarimWanga, Mwanafunzi uzamili (Utabibu dawa)

Idara ya Pharmacology and Pharmacognosy S.L.P 30197-00400, Shule ya Pharmasia, Chuo kikuu cha Nairobi.

Nambari ya simu: 0727 981650

Wasimamizi:

Dkt. Eric M. Guantai

Mhadhiri, Idaraya Pharmacologia na Pharmacognosia

Chuo kikuu cha Nairobi.

Dkt. Kipruto A. Sinei

Mhadhiri, Idara ya Pharmacologia na Pharmacognosia

Chuo kikuu cha Nairobi.

Dkt. Stanley N. Ndwigah

Mhadhiri, Idaraya Pharmaceutical Chemistry

Chuo kikuu cha Nairobi.

Katibu Mkuu,

Kamati ya utafiti ya hospitali kuu ya Kenyatta na chuo kikuu cha Nairobi

KNH/UoN-ERC

Hospitali kuu ya Kenyatta

S.L.P 20723-00202, Nairobi

Nambari ya simu: 2726300-9/2716450 Ext 44102, Fax 725272

Uthibitisho wa kimaadili

Utafiti huu utathibitishwa kimaadili na kamati ya utafiti ya hospitali ya Kenyatta/Chuo kikuu cha Nairobi (KNH/UoN-ERC) ilikupata ithibati ya kufanya utafiti katika hospitali ya Kenyatta.

Appendix III: Consent Declaration Form

I confirm that I have read and understood the information above. Based on this information, I voluntarily agree to participate in this research conducted by Dr.Karim Wanga. I understand that I am free to ask any questions or to withdraw my consent of participation at any time without penalty.

Name of patient.....

Signature.....

Date

Contacts: In case you have questions related to this study, you can contact the following:

Principal Investigator:

Dr. KarimWanga, Master of pharmacy (Pharmacoepidemiology and Pharmacovigilance)

Department of Pharmacology and Pharmacognosy, P.O. Box 30197-00400, School of Pharmacy, University of Nairobi.

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P o Box 19676-00202, School of Pharmacy, University of Nairobi.

Telephone: 0722 955883

The Secretary, KNH/UoN-ERC

Kenyatta National Hospital, P.O Box 20723-00202, Nairobi Tel No. 2726300-9/2716450 Ext 44102, Fax 725272

Kiambatisho 3: Hati Ya Makubaliano

Baada ya kusoma na kuelewa maelezo yaliotolewa kuhusu utafiti huu na Dkt. KarimWanga, na pia kwa kufahamu kuwa kushiriki katika utafiti huu ni kwa hiari na niko huru kujiiondoa wakati wowote bila kuadhirika, natoa idhini yangu kwa hiari, nakutia sahihi fomu hii.

Jina _____ la _____ mgonjwa.....

Sahihi.....

Tarehe.....

Kwa maswali yeyote kuhusu utafiti huu, uko huru kuuliza wafuatao;

Mtafiti Mkuu:

Dkt. KarimWanga, Mwanafunzi uzamili (Utabibu dawa)

Idara ya Pharmacologia na Pharmacognosia, S.L.P 30197-00400, Shule ya Pharmasia, Chuo kikuu cha Nairobi.

Nambari ya simu: 0727 981650

Msimamizi mkuu:

Dkt. Eric M. Guantai

Mhadhiri, Idaraya Pharmacologia na Pharmacognosia

Chuo kikuu cha Nairobi.

S.L.P 19676-00202, Shule ya Phamasia, Chuo kikuu cha Nairobi.

Nambari ya simu: 0722 955883

Katibu Mkuu, Kamati ya utafiti ya hospitali kuu ya Kenyatta na chuo kikuu cha Nairobi

KNH/UoN-ERC, Hospitali kuu ya Kenyatta. S.L.P 20723-00202, Nairobi.

Nambari ya simu: 2726300-9/2716450 Ext 44102, Fax 725272

Appendix IV: Medicine Utilization Review Criteria for UFH

INDICATORS AND CRITERIA FOR UNFRACTIONATED HEPARIN

INDICATORS AND CRITERIA	THRESHOLD
<p>JUSTIFICATION FOR HEPARIN USE/ INDICATION</p> <p>Prevention of thrombosis in hemodialysis</p> <p>Therapeutic treatment of DVT</p> <p>Therapeutic treatment of Pulmonary Embolism</p> <p>Prophylactic treatment of VTE</p> <p>Arterial embolism</p> <p>Acute coronary syndromes (Unstable angina and acute Myocardial infarction)</p> <p>Atrial Fibrillation (AF) and Atrial Flutter with embolization.</p>	<p>100%</p>
<p>DOSAGE, FREQUENCY AND ROUTE OF ADMINISTRATION</p> <p>Prevention of thrombosis in hemodialysis: initial bolus dose of 2000-4000 IU followed by an infusion of 500-2000 IU/hr for the duration of hemodialysis, OR a bolus infusion of 2000IU without an infusion dose.</p> <p>Prophylactic treatment of VTE- 5000 IU SC 8 or 12 hourly</p> <p>Therapeutic treatment of DVT, PE, arterial embolism- 5000 IU IV bolus stat, followed by 32000 IU 24 hourly by IV infusion or 35000-40000 IU 24 hourly SC, also 80 IU /kg bolus, followed by 18 IU/kg/hour infusion adjusted to maintain APTT therapeutic range or</p> <p>333 IU/kg stat, SC followed by 250 IU/kg SC 12 hourly</p> <p>Unstable angina, acute MI- 5000 IU IV bolus followed by 32000 IU 24 hourly IV infusion adjusted to maintain APTT therapeutic range</p>	<p>100%</p>
<p>BASELINE LAB MONITORING(Before initiation of treatment)</p>	<p>100%</p>

<p>INR CBC Sodium and Potassium levels</p>	
<p>LAB MONITORING IN THE COURSE OF THERAPY APTT data 6 hours after initiation of treatment Afterward should be checked 24 hourly, or 6 hourly in case of change of heparin dosage Goal is 1.5-2.5 times the control (reagent specific) Platelet count every 2-3 days from day 4 to 14 Potassium levels every three days</p>	<p>100%</p>
<p>CONTRAINDICATIONS Hypersensitivity to heparin Severe thrombocytopenia(platelet count <50000) Abnormalities of hemostasis (hemophilia) Hyperkalemia Epidural catheter Severe uncontrolled hypertension(SBP >180mmHg, DBP>110mmHg) Recent hemorrhagic stroke</p>	<p>100%</p>
<p>BRIDGE THERAPY For patients receiving bridge therapy (i.e. those with active clot or high risk for clotting), a five day overlap of heparin and warfarin is recommended Therapeutic INR should be achieved 2 days prior to stopping heparin</p>	<p>100%</p>
<p>ANTICOAGULANT REVERSAL Hold further doses of UFH Protamine sulfate 1% solution IV 1mg per 100 units of heparin given in previous 2-3 hours, maximum of 50 mg of protamine sulfate should be offered Supportive management, volume resuscitation</p>	<p>100%</p>

<p>Transfusion (red cells, platelets, Fresh Frozen Plasma) as indicated</p> <p>Consideration of the cause(changed pharmacokinetics, drug interactions or incorrect dose)</p>	
<p>DRUG INTERACTIONS</p> <p>Aspirin</p> <p>Non-Steroidal Anti-inflammatory drugs (NSAIDs)</p> <p>Clopidogrel</p> <p>Dipyridamole</p>	<p>100%</p>

Appendix V: Medicine Utilization Review Criteria for Enoxaparin

INDICATORS AND CRITERIA FOR ENOXAPARIN

INDICATORS AND CRITERIA	THRESHOLD
<p>JUSTIFICATION FOR USE/ INDICATION</p> <p>Therapeutic treatment of DVT</p> <p>Therapeutic treatment of Pulmonary Embolism</p> <p>Prophylactic treatment of VTE</p> <p>Acute coronary syndromes(Unstable angina and acute Myocardial infarction)</p> <p>Atrial Fibrillation (AF) and Atrial Flutter with embolization</p>	<p>100%</p>
<p>DOSAGE, FREQUENCY AND ROUTE OF ADMINISTRATION</p> <p>Therapeutic treatment of VTE- 1mg/kg SC 12 hourly or 1.5 mg/kg SC 24 hourly</p> <p>ACS, ST-segment elevation MI- 30mg bolus IV, followed by 1mg/kg SC 12 hourly</p> <p>Unstable angina/non-Q wave MI- 1mg/kg SC 12 hourly</p> <p>Prophylactic treatment for AF/Cardioversion- 1mg/kg SC 12 hourly or 1.5mg/kg SC 24 hourly</p> <p>Prophylactic treatment of VTE- 40mg SC 24 hourly for 7-10 days or until mobilized</p> <p>Dose adjustment in renal failure</p>	<p>100%</p>
<p>BASELINE LAB MONITORING(Before initiation of treatment)</p> <p>INR</p> <p>CBC</p> <p>Potassium, sodium</p> <p>Estimated GFR</p>	<p>100%</p>
<p>LAB MONITORING IN THE COURSE OF THERAPY</p> <p>Routine monitoring of PT or APTT not necessary</p> <p>Platelet monitoring every 2-3 days from day 4 to 14 or until treatment is</p>	<p>100%</p>

<p>stopped</p> <p>Potassium monitoring every three days until treatment is stopped</p>	
<p>CONTRAINDICATIONS</p> <p>Creatinine clearance <30mL/min except when used during hemodialysis</p> <p>Known hypersensitivity to enoxaparin</p> <p>Active bleeding</p> <p>Severe thrombocytopenia(platelet count <50000)</p> <p>Hyperkalemia</p> <p>Severe uncontrolled hypertension (SBP >180mmHg, DBP>110mmHg)</p>	100%
<p>BRIDGE THERAPY</p> <p>For patients receiving bridge therapy (i.e. those with active clot or high risk for clotting), a five day overlap of heparin and warfarin is recommended</p> <p>Therapeutic INR should be achieved 2 days prior to stopping enoxaparin</p>	100%
<p>ANTICOAGULANT REVERSAL</p> <p>Hold further doses of enoxaparin</p> <p>Protamine sulfate IV 1mg per 1mg of enoxaparin given in previous 8 hours(maximum 50mg) over 10 minutes</p> <p>Supportive management, volume resuscitation</p> <p>Transfusion (red cells, platelets, Fresh Frozen Plasma) as indicated</p> <p>Consideration of the cause(changed pharmacokinetics, drug interactions or incorrect dose)</p>	100%
<p>DRUG INTERACTIONS</p> <p>Aspirin</p> <p>Non-Steroidal Anti-inflammatory drugs (NSAIDs)</p> <p>Clopidogrel</p> <p>Dipyridamole</p>	100%

Appendix VI: Data Collection Form

PATIENT CODE.....

DATE.....

INVESTIGATOR INITIALS.....

SECTION I: PATIENT DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

AGE.....

SEX: MALE FEMALE

WEIGHT (kg).....

PRINCIPAL DIAGNOSIS.....

DATE INITIATED ON TREATMENT.....

SECTION II: DATA ON HEPARIN USE

TYPE OF HEPARIN:.....

INDICATOR	OBSERVED IN PATIENT RECORDS	MEETS CRITERIA?	
		YES	NO
Justification for use/ indication			
Dosage, frequency and route of administration			
Baseline lab monitoring (Before initiation of treatment)			
Lab monitoring in the course of therapy			
Contraindications			
Bridge therapy			
Anticoagulant reversal			

Potential drug interactions			
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SECTION III: DATA ON HEPARIN INDUCED ADVERSE EFFECTS

ADVERSE EFFECTS	PATIENT EXPERIENCED ?		DESCRIPTION OF ADVERSE EFFECT AND RELEVANT LAB DATA
	YES	NO	
Heparin Induced Thrombocytopenia (HIT) -)- Decrease of $\geq 30\%$ platelet count from baseline occurring 4-14 days after initiation of treatment, or formation of new thrombus Bleeding Injection site hematoma Hyperkalemia Other documented adverse events			

SECTION IV: CLINICAL OUTCOMES OF THE PATIENT

CLINICAL OUTCOME	PATIENT EXPERIENCED?		COMMENTS
	YES	NO	
UFH discontinued Recovery All-cause mortality			

Appendix VII: Questionnaire

PATIENT CODE.....

DATE.....

INVESTIGATOR INITIALS.....

SECTION A: PATIENT CLINICAL INFORMATION

1. What is the main reason for being admitted at the hospital?

.....

2. Have you ever been treated with Heparin before?

YES NO

3. If answer is YES in the above question, when was the treatment given last?

One month before current date Two weeks before current date One week before current date 2-5 days before current date

4. Any known allergy to heparin

YES NO

5. Have you experienced a feeling of coldness, shivering and shortness of breath shortly (about 10 minutes) after heparin is administered?

YES NO

6. Have you experienced pain at the site of heparin injection? YES NO

7. Have you had any incident/signs of bleeding after initiation of treatment with heparin(current)

Blood in stool Nose-bleeding Bleeding at site of heparin injection Blood in urine Coughing up blood others (describe)

8. Have you had any blood transfusions after initiation of heparin treatment? (current)

YES NO

9. Has the treatment of UFH/enoxaparin been discontinued (current)?

YES NO

Reasons _____ for discontinuation.....

10. Are you taking any medicines other than what is being offered at KNH, currently?

Name of the drug..... Indication..... Dose
and frequency.....

11. Do you suffer from any of the following conditions?

Disease

Kidney disease YES NO

Liver disease YES NO

Hypertension YES NO

SECTION B: PHYSICAL EXAMINATION

The investigator observed the following on physical examination of the patient:

Skin lesion at site of Heparin injection YES NO

Skin rash YES NO

Bleeding at site of Heparin injection YES NO

Unilateral leg swelling, pain and tenderness of calf muscles YES NO

Other observations associated with heparin therapy.....

KIAMBATISHO 7: KISWAHILI VERSION OF QUESTIONNAIRE

NAMBARI YA UTAFITI YA MSHIRIKI.....

SEHEMU YA KWANZA: AFYA YA MSHIRIKI

1. Je, sababu kuu ya kulazwa hospitali ni nini?
.....
2. Ushawahi kutibiwa na Heparin hapo awali?
 NDIO LA
3. Kama jibuni NDIO, kwenye swali liliyotangulia, ni lini mwisho ulipokea matibabu ya Heparin?
 Mwezi mmoja umepita Wiki mbili imepita Wiki moja imepita Siku mbili hadi tano zimepita
4. Unayo allergy yoyote ya Heparin?
 NDIO LA
5. Umewahi kusikia mabadiliko ya mwili kama vile kutetemeka, baridi, ukosefu wa pumzi, muda mfupi (kama dakika kumi hivi) baada ya kudungwa Heparin?
 NDIO LA
6. Unasikia uchungu pahali umedungwa Heparin?
 NDIO LA
7. Umewahi kuziona dalili za kuvuja damu, tangu matibabu ya Heparin yalipoanza? Kama vile;
 Kwenye choo kwenye mkojo kwenye pua mahali pa kudungwa heparin Damu inatoka kwa kohozi nyenginezo (eleza)
8. Je, umeongezewa damu tangu matibabu haya ya Heparin yalipoanza?
 NDIO LA
9. Matibabu haya ya Heparin yamewahi kusitishwa?
 NDIO LA
Sababu ya kusitisha matibabu.....
10. Kuna dawa zozote unazotumia ambazo hazijaandikwa na daktari wa hapa hospitalini Kenyatta?
Jina la dawa..... Ugonjwa inayotibu.....
Kiwango cha dawa
11. Je, unaugua ugonjwa wowote, kati ya magonjwa yaliyotajwa?

Ugonjwa wa ini NDIO LA

Ugonjwa wa figo NDIO LA

Ugonjwa wa msukumo wa damu NDIO LA

SEHEMU YA PILI: UKAGUZI WA MWILI WA MGONJWA

Mtafiti aliona yafuatayo baada ya kukagua mwili wa mgonjwa:

Kidonda pahali pa kudungwa Heparin NDIO LA

Kuvuja damu pahali pa kudungwa Heparin NDIO LA

Rash kwenye mwili wa mgonjwa NDIO LA

Mguu mmoja umefura, unaleta joto na maumivu NDIO LA

Mengine aliyo yaona mtafiti ambayo yanahusiana na matibabu ya Heparin.....

APPENDIX VIII: KNH-UoN ERC APPROVAL LETTER



UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
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Tel:(254-020) 2726300 Ext 44355



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Website: <http://www.erc.uonbi.ac.ke>
Facebook: <https://www.facebook.com/uonknh.erc>
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC



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

Ref: KNH-ERC/A/425

31st October 2016

Karim Wang
Reg. No.U51/81232/2015
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Karim

REVISED RESEARCH PROPOSAL: MEDICINE UTILIZATION EVALUATION OF HEPARIN AT KENYATTA NATIONAL HOSPITAL (P658/09/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above revised proposal. The approval period is from 31st October 2016 – 30th October 2017.

This approval is subject to compliance with the following requirements:

- a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
- b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
- c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
- d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
- e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
- f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
- g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

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

Yours sincerely,



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

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chairperson, Dept. of Pharmacology and Pharmacognosy, UoN
Supervisors: Dr. Eric M. Guantai, Dr. Kipruto A. Sinei, Dr. Stanley N. Ndwigah

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