FACTORS ASSOCIATED WITH DRUG THERAPY PROBLEMS IN PATIENTS ON ANTICOAGULANTS AT KENYATTA NATIONAL HOSPITAL

MWANGI GAKOME KAMAU (B.PHARM)

U56/37978/2020

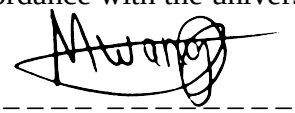
A dissertation submitted in partial fulfilment of the requirements for award of Masters of Pharmacy in Clinical Pharmacy at the University of Nairobi

November 2023

DECLARATION

I, Mwangi Gakome Kamau, declare that:

1. I understand what plagiarism is and I am aware of the university's policy in this regard.
2. I declare that this research dissertation is my original work and has not been submitted elsewhere for examination, award of a degree or publication. Where other people's work or my own work has been used, this has been properly acknowledged and referenced in accordance with the University of Nairobi's requirements.
3. I have not sought or used the services of any professional agencies to produce this work.
4. I have not allowed and shall not allow anyone to copy my work with the intention of passing it off as their own work.
5. I understand that any false claim in respect to this work shall result in disciplinary action, in accordance with the university plagiarism policy.

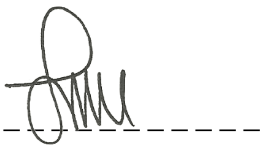
Signed  Date 27/11/2023

Mwangi Gakome Kamau – U56/37978/2020

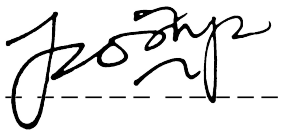
SUPERVISORS

This is to certify that this research proposal has been submitted for review with our approval as supervisors.

1. Dr. George Arthur Mugendi (BPharm, Mpharm, PhD)
   Snr Lecturer, Department of Pharmacology, Clinical Pharmacy and Pharmacy Practice

   Signature  Date 27 NOVEMBER 2023

2. Dr. Rosaline Njoki Kinuthia (Bpharm, MPharm)
   Clinical Pharmacist, Pharmacy Division, Kenyatta National Hospital

   Signature  Date 27/11/2023

DEDICATION

To my loving wife, Esther, thank you for your unwavering support and encouragement in my pursuit of this noble goal.

ACKNOWLEDGMENTS

I'd like to thank The Almighty for giving me strength, focus and patience to undertake this work.

I also extend my gratitude to my supervisors, Dr George Mugendi and Dr Rosaline Kinuthia for their invaluable input and tireless efforts to guide me in making this disseration.

To all my classmates in the clinical pharmacy class of 2023, I thank them for their support and constructive criticism.

Lastly I express my appreciation to all the teaching and non-teaching staff at the School of Pharmacy, University of Nairobi for facilitating my learning.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Anticoagulants are used to manage thrombosis. Achievement of the goals of therapy may be complicated by drug therapy problems. Disruption of anticoagulation can be detrimental to patients and can have severe effects.

Objectives: This study sought to identify the drug therapy problems encountered frequently by patients using anticoagulants, to ascertain the frequency of the problem and investigate the factors associated with drug therapy problems.

Methodology: This was a cross-sectional study. A questionnaire and data collection tool was used to get data by interviewing consenting patients and abstracting data from their medical records. The study was confined to adult patients in the medical wards of Kenyatta National Hospital. Convenience sampling was used to recruit study participants. The data was analysed to give the prevalence of the drug therapy problems in the study population, the associated factors and the anticoagulant drugs in which drug therapy problems are common. Chi-square, Fisher's exact and logistic regression analysis were used to identify associated factors.

Results: There were 125 participants recruited into the study, 52.8% female and 47.2% males. Drug therapy problems occurred in 37.6%. The main drug therapy problem encountered was drug-drug interactions in 18.4% and treatment safety problems in 16%. Most patients were on enoxaparin (81%) but drug therapy problems were more common in warfarin. There were no significant associated factors identified in the study.

Conclusion and Recommendations: Drug therapy problems are common in patients using anticoagulants. Drug-drug interactions in anticoagulants thought to be safe should not be overlooked. All members of the healthcare team should be alert to identify and intervene in case these problems arise.

The healthcare team should be aware of the common drug therapy problems in patients on anticoagulant therapy and be prepared to intervene.

A follow up prospective study with a larger study population should be done to reveal associations that were not captured by this study.

ABBREVIATIONS AND ACRONYMS

DOAC – direct oral anticoagulant

DRP – drug related problem

DTP – drug therapy problem

DVT- deep vein thrombosis

IHD – ischaemic heart disease

INR – international normalized ratio

KNH – Kenyatta National Hospital

LMWH – Low molecular weight heparins

MRP – medication related problem

PCNE – Pharmaceutical Care Network of Europe

PE – pulmonary embolism

VKA – vitamin K antagonist

VTE –venous thromboembolism

CHAPTER ONE: INTRODUCTION

1.1 Background

Drug therapy problems are any unwelcome incidents that occur during the use of medication and interfere with the achievement of the desired goals of therapy (1). These medication related problems should be resolved for the patient to have optimal outcomes of therapy.

The Pharmaceutical Care Network of Europe (PCNE) validated and updated their system for classification of drug therapy problems in February 2019(2). PCNE classification V 9.0 has 3 primary domains for problems, 9 primary domains for causes and 5 primary domains for interventions.

The DTPs under the PCNE classification V 9.0 are treatment safety, treatment effectiveness and others. The causes of DTPs are classified into drug selection, drug form, dose selection, treatment duration, dispensing, drug use process, patient related, patient transfer related and others. Under this classification, planned interventions for DTPs are classified as no intervention, at prescriber level, at patient level, at drug level and others(2)

Anticoagulants are drugs that prevent pathologic thrombosis by exerting their action on different stages of the clotting cascade such as inhibition of vitamin K dependent factors and inhibition of thrombin(3).

Anticoagulant therapy is a common pharmacologic intervention employed in the management of a number of conditions such as myocardial infarction, ischaemic stroke, pulmonary embolism, deep vein thrombosis and atrial fibrillation. The main pharmacologic agents used for anticoagulation are antagonists of vitamin K like warfarin, low molecular weight heparins, unfractionated heparin and direct acting oral anticoagulants like rivaroxaban (2).

Risks, benefits and pharmacologic attributes of a drug are considered when selecting an appropriate anticoagulant for a specific patient(4)

1.2 Problem statement

The Global Burden of Disease report of 2019 estimated the prevalent cases of ischaemic heart disease (IHD) and stroke at 197 million and 101 million respectively(5). In 2010, ischaemic heart disease and stroke were estimated to cause 25% of all deaths globally(6). One of the main underlying pathologies causing IHD, stroke and venous thrombo-embolism is thrombosis(6). The incidence and prevalence of stroke and ischaemic heart disease in Kenya is not known (7). It is projected that the incidence of stroke in Sub Saharan Africa is 316 /100,000 people (7).

Venous thrombosis, a term used to refer to pulmonary embolism and DVT, is approximated to have an incidence of 1-2 per 1000 persons annually (8).

VTE has a significant association with cancer. According to the Global Cancer Observatory the number of incident cancer cases in Kenya for the year 2020 were 42,116 and the deaths due to cancer were 27,092(9). This trend is expected to rise in the coming years and thus cases of VTE due to cancer will also increase.

VTE is also likely to occur in pregnancy, prolonged immobilization and hospitalization of patients (10) (11) (12).

Severe acute respiratory syndrome Coronavirus 2 (SARS-Cov-2) has been associated with coagulopathy where micro and macro thrombosis occurs (13). Anticoagulation therapy is needed in the management of SARS-Cov-2 induced coagulopathy

The high burden of disease caused by thrombosis indicates that anticoagulant therapy is critical in managing morbidity and mortality. The increase in risk factors for non-communicable illnesses such as obesity, sedentary lifestyle, poor diet and increased lifespan means that the use of anticoagulant therapy will remain high, if not increase.

Medication related problems in patients using anticoagulant therapy are common due to narrow therapeutic window of some of the drugs, drug-food interactions, drug-drug interactions, poor monitoring of therapy and patient errors in ambulatory use of these drugs.

Investigating the drug therapy problems, their causes and potential interventions will lead to improved outcomes and a reduction in morbidity and mortality of patients using these drugs to manage their conditions.

1.3 Study justification

Studies on the DTPs encountered by patients on anticoagulant therapy in Kenya are lacking. This study will highlight the scale of the problem, causes and factors associated with the problems and ways in which these issues can be counteracted.

This information gap should be addressed to give healthcare professionals the information they need to avoid and minimize the medication related problems in their patients who are on anticoagulation therapy.

1.4 Objectives

1.4.1 General Objectives

To identify and characterize drug therapy problems among patients using anticoagulants at Kenyatta National Hospital.

1.4.2 Specific Objectives

1. To determine the prevalence of drug therapy problems in patients on anticoagulants
2. To determine the main types of drug therapy problems frequently encountered by patients on anticoagulants
3. To determine the factors associated with medication related problems in the study subjects
4. To establish the frequency of drug related problems experienced with the use of different classes of anticoagulant drugs

1.5 Research Questions

1. What is the prevalence of drug therapy problems in patients receiving anticoagulants?

2. Which are the main types of drug therapy problems frequently encountered by patients on anticoagulants?

3. What are the factors associated with medication related problems?

4. What is the frequency of drug related problems with use of different classes of anticoagulant drugs?

1.6 Significance and Anticipated Output

This information will be useful to medical professionals across the spectrum of the drug use process from clinicians, pharmacists and nurses who interact with the drugs and the patients. Interventions can be implemented to prevent drug therapy problems before they occur.

Insights drawn from this study will also be used to counsel patients on how to use their anticoagulants effectively. This will reduce readmissions caused by poor patient compliance to medication and in turn reduce healthcare costs.

Policy makers and stakeholders such as drug manufacturers can also use the content of the study to make changes that minimise the MRPs such as change of drug strength, changes in product literature and changes in available drug formulations.

1.7 Delimitations

The study was limited to Kenyatta National Hospital due to financial constraints as the study was self-funded.

The study was done as a cross-sectional study with data collection restricted to 3 months. Financial considerations and few investigators attached to the study also meant that the number of variables studied were few.

1.8 Limitations

This was a cross-sectional study and patient follow-up was minimal. Drug therapy problems that occurred after interaction with the investigator as the patient continued with therapy were not captured. Interventions and resolution of drug therapy problems that occurred after data collection from the participants were not captured due to the nature of the study. Many patients were on these drugs for a long period and a lack of patient follow up was a limitation of this study.

Poor record keeping of the participant medical records also limited the amount of relevant data captured for the study. KNH lacks an electronic health records system and the paper records are usually lost or misplaced for some patients in the wards. Some patients failed to give their informed consent for participation in the study.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter will summarize the current knowledge on anticoagulation therapy and drug therapy problems.

2.2 Physiology of Coagulation

Haemostasis is a dynamic process in which there is a balance between mechanisms leading to clotting and mechanisms maintaining fluidity of the blood (14). A breakdown of this process can result in thrombosis or bleeding. The equilibrium between thrombosis and haemorrhage is controlled by interplay among multiple components of the vascular system, namely the coagulation system, fibrinolytic system, platelets and the vessel walls (**Table 2.1**) (14).

Table 2. 1 Thrombogenic and Antithrombogenic Components in the Body: source Palta S, Saroa R, Palta A. Overview of the coagulation system. Indian J Anaesth. 2014;58(5):515–23

Site	Thrombogenic	Antithrombogenic
Vessel wall	Exposed endothelium	Heparin
	Tissue factor	Thrombomodulin
	Collagen	Tissue plasminogen
Circulating elements	Platelets	Antithrombin
	Platelet activating factor	Protein C and S
	Clotting factor	Plasminogen
	Prothrombin	
	Fibrinogen	
	Von Willebrand Factor	

Clotting of blood occurs when fibrinogen is converted into fibrin by thrombin, which results in stabilization of the platelet plug (15). Clotting factors, which are also referred to as coagulation proteins, propagate the coagulation process (14). Most of these proteins are produced in the liver. Many of these proteins are produced as precursors and must undergo post-translational modification for them to function properly in their role in coagulation (14).

The clotting cascade is broken down into the intrinsic pathway and extrinsic pathway which merge to activate factor X (**figure 2.1**) (14). The extrinsic pathway is activated by tissue factor, which is found in sub-endothelial tissue. Trauma of the vascular walls exposes tissue factor to other circulating clotting proteins. Tissue factor, factor VIIa and calcium bind and then mediate factor X to be converted to activated factor X (14). The intrinsic pathway activates thrombin through factor XII (**figure 2.1**). The common pathway is when factor X is activated and then combines with factor V, calcium, tissue phospholipids and platelet phospholipids to form a prothrombinase complex. The prothrombinase complex mediates conversion of prothrombin into thrombin (14). Thrombin converts soluble fibrinogen into insoluble fibrin, which stabilizes the clot. The nomenclature of clotting factors is shown in **table 2.2.**

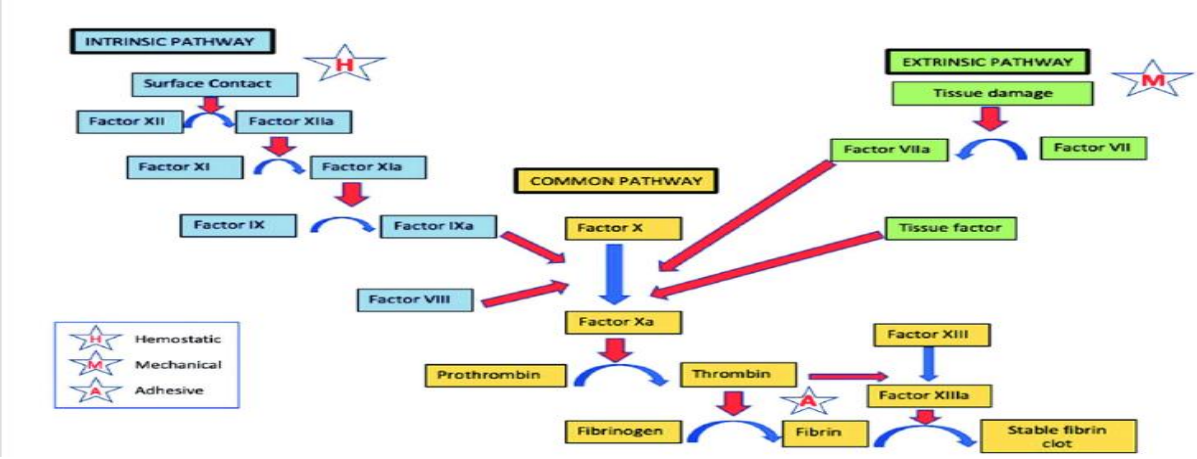


Figure 2. 1: Clotting Factors and Their Role in The Coagulation Cascade: source Dammann, K., Gifford, A., Kelley, K., Stawicki, S. P. . Operative Hemostasis in Trauma and Acute Care Surgery: The Role of Biosurgical Agents. In: Firstenberg, M. S., Stawicki, S. P.,

Table 2. 2: Nomenclature of Clotting Factors: source Palta S, Saroa R, Palta A. Overview of the coagulation system. Indian J Anaesth. 2014;58(5):515–23

Clotting factor Number	Clotting Factor Name	Function	Plasma Half Life (h)
I	Fibrinogen	Clot Formation	90
II	prothrombin	Activation of factor I,V,VII,VIII,XI,XII, protein C & S, platelets	65
III	Tissue factor	Co-factor of VIIa	-
IV	Calcium	Facilitates coagulation factor binding to phospholipids	-
V	Proaccelerin, labile factor	Co-factor of X-prothrombinase complex	15
VI	Unassigned		
VII	Stable factor, proconvertin	Activates factor IX, X	5
VIII	Antihaemophilic factor A	Co-factor IX-tenase complex	10
IX	Antihaemophilic factor B or Christmas factor	Activates X, forms tenase complex with factor VIII	25
X	Stuart Power factor	Prothrombinase complex with factor V: activates factor II	40
XI	Plasma Thromboplastin antecedent	Activates factor IX	45
XII	Hageman factor	Activates factor XI, VII, prekalikrein	-
XIII	Fibrin stabilizing factor	Crosslinks fibrin	200
XIV	Von Willebrand Factor	Binds to factor VIII, mediates platelet adhesion	12

2.3 Anticoagulation Therapy

Anticoagulant drugs are used in the management of thrombosis. The main classes of drugs used as anticoagulants are direct oral anticoagulants, vitamin K antagonists, low molecular weight heparins and unfractionated heparin (16). Vitamin K antagonists include warfarin. Some examples of DOACs are dabigatraban, apixaban, rivaroxaban and edoxaban. Enoxaparin and dalteparin are some of the low molecular weight heparins.

Unfractionated heparin and LMWHs act by binding to antithrombin. The complex of heparin and antithrombin inhibits factor IIa, factors IXa, Xa, XIa and XIIa (4). This reduces formation of clots. Heparins do not have fibrinolytic properties; they only prevent growth of existing clots while they cannot lyse existing clots. Heparins are administered intravenously or subcutaneously due to their limited oral bioavailability(4).

Warfarin is an antagonist of vitamin K that inhibits the manufacture of factors II, VII, IX, X, proteins C, S and Z, which are known as the vitamin K-dependent factors (4). These specific clotting factors need to undergo gamma carboxylation of their glutamate residues for them to be active. (**Figure 2.2**). Warfarin inhibits vitamin K epoxide reductase and also inhibits vitamin K_1 reductase which convert vitamin K into vitamin KH_2 , the reduced form needed for gamma carboxylation(4).

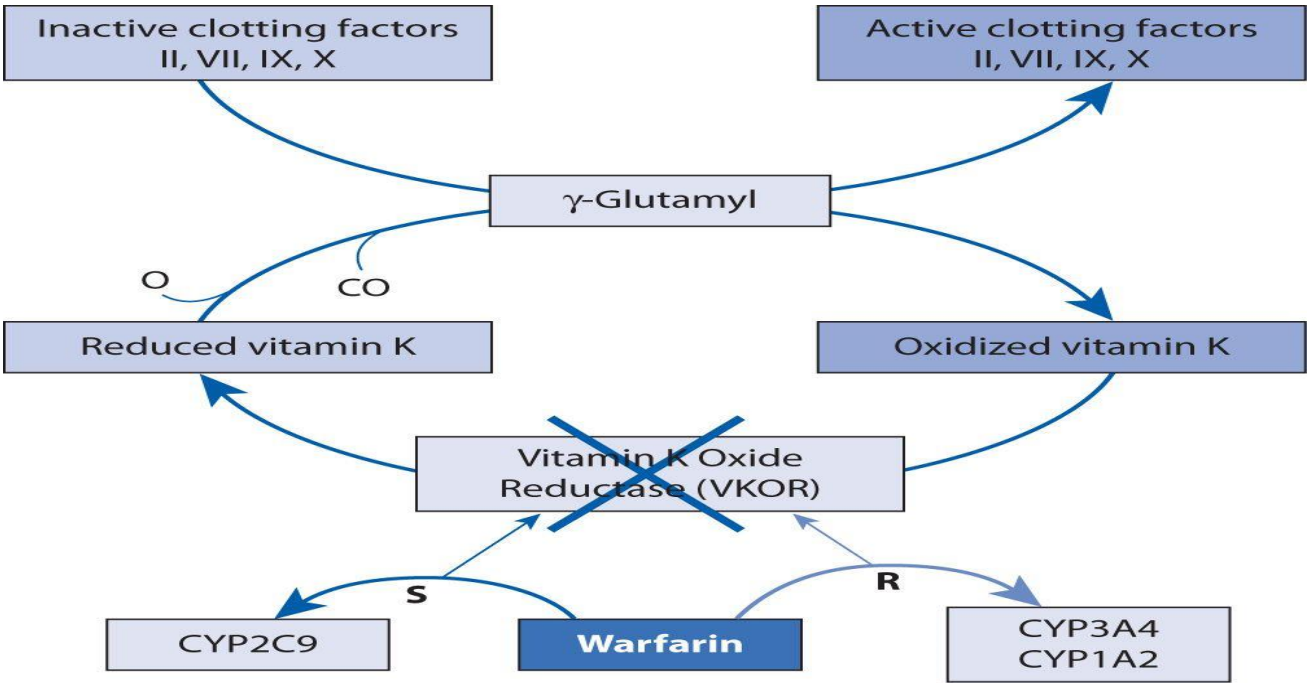


Figure 2. 2: Mechanism of Action of Warfarin: Mechanism of action of warfarin: source Valery l.

Warfarin does not interfere with already circulating clotting factors, which may have long half-lives. The full anticoagulant effect of warfarin may take 3-7 days to be effected (4). Warfarin interacts with other drugs and foods. Cimetidine, azole antifungals, cotrimoxazole, metronidazole, amiodarone, phenylbutazone, clopidegrol, isoniazid and fluoxetine inhibit the breakdown of warfarin by CYP2C9 enzyme and this will cause a heightened risk of bleeding (15). Barbiturates, rifampicin and carbamazepine induce CYP2C9 enzyme, causing reduced levels of warfarin. Antibiotics which interfere with gut normal flora can lead to increased INR when using warfarin due to decreased synthesis of vitamin K (15).

Rivaroxaban is an inhibitor of factor Xa. The inhibition of activated factor X reduces formation of thrombin, reduces platelet aggregation and reduces fibrin formation(4). Rivaroxaban has high oral bioavailability.

2.4 Classification of Drug Therapy Problems

PCNE defines a drug therapy problem as an event or circumstance involving drug therapy that interferes or has the potential to interfere with desired health outcomes(2). A 2014 study identified 20 different DTP classification systems (17). The commonly used systems of classification of DTPs include PCNE System(version 9.0), Hepler-Strand Classification, Granada Consensus, Hanlon Approach and Westerlund System(18).

The table below shows the basic classification of drug therapy problems, causes, interventions and status using the PCNE (V 9.0) classification (**Table 2.3**).

Table 2.3: Basic Classification of Drug Therapy Problems: source PCNE. Classification for Drug Related Problems V9.00. PCNE Classif Drug Relat Probl V900. 2019;1–10

	Code V9.0	Primary domains
Problems (also potential)	**P1**	**Treatment effectiveness** There is a (potential) problem with the (lack of) effect ofthe pharmacotherapy
	P2	**Treatment safety** Patient suffers, or could suffer, from an adverse drug event
	P3	**Other**
Causes (including possible causes for potential problems)	**C1**	**Drug selection** The cause of the DRP can be related to the selection of the drug
	C2	**Drug form** The cause of the DRP is related to the selection of the drug form
	C3	**Dose selection** The cause of the DRP can be related to the selection of the dosage schedule
	C4	**Treatment duration** The cause of the DRP is related to the duration of treatment
	C5	**Dispensing** The cause of the DRP can be related to the logistics of theprescribing and dispensing process
	C6	**Drug use process** The cause of the DRP is related to the way the patient gets the drug administered by a health professional or carer, in spite of proper instructions (on the label)
	C7	**Patient related** The cause of the DRP can be related to the patient and their behavior (intentional or non-intentional)
	C8	**Patient transfer related** The cause of the DRP can be related to the transfer of patients between primary, secondary and tertiary care, ortransfer within one care institution.
	C9	**Other**
Planned Interventions	**I0**	**No intervention**
	I1	**At prescriber level**
	I2	**At patient level**
	I3	**At drug level**
	I4	**Other**
Intervention Acceptance	**A1**	**Intervention accepted**
	A2	**Intervention not accepted**
	A3	**Other**
Status of the DRP	**O0**	**Problem status unknown**
	O1	**Problem solved**
	O2	**Problem partially solved**
	O3	**Problem not solved**

2.4.1 Drug Therapy Problems

2.4.1.1 Treatment Effectiveness

This primary problem domain refers to an issue with the effect of drug therapy such as no effect of drug treatment, effect of drug treatment not optimal and untreated symptoms or indications (2).

2.4.1.2 Treatment Safety

This is used when a patient is likely to suffer or suffers from an adverse drug reaction(2). ADRs are noxious, unintended effects occurring after use of a medicine at the recommended dose (19). Adverse drug reactions often predict negative outcomes with future administration of the drug thus, prevention is critical. Withdrawal and reducing of the dose of the drug are other interventions used to alleviate adverse drug reactions (19).

2.4.1.3 Other

Though treatment safety and treatment effectiveness are the main DTPs considered in the PCNE model, other problems such as drug-drug interactions and poor adherence may also be a hindrance to achieving desired treatment outcomes.

Drug interactions are common in oral anticoagulants. Warfarin has been documented to interact with more than 200 drugs (20). Warfarin is metabolised by cytochrome 2C9 enzyme. Any drugs that induce or inhibit CYP2C9 enzyme can cause increased levels or reduced levels of warfarin. This will result in sub-therapeutic drug levels resulting in failure to achieve anticoagulation or high levels that cause adverse events such as bleeding (20).

Pharmacodynamic interactions of warfarin with antiplatelet drugs and non-steroidal anti-inflammatory drugs may increase the risk of bleeding (20).

Around 30% of patients using warfarin miss 1 in 5 of their doses (21). Medication non-adherence will result in poor treatment outcomes.

2.4.2 Causes of Drug Therapy Problems

2.4.2.1 Drug Selection

Drug selection is one of the possible causes of DTPs. MRPs may be attributed to choosing an inappropriate drug that runs contrary to established guidelines, using a contraindicated drug, selecting a drug with no indication in the patient, using an unsuitable drug combination, therapeutic group or active ingredient duplication, drug treatment incomplete and overprescribing drugs for the same indication (2). These causes may be traced to either the healthcare worker or patient.

2.4.2.2 Drug Form

MRPs may originate from poor choice of a drug form (2). A patient may receive an oral dosage form of a medicine while they are supposed to receive a parenteral dosage form such as an injection. Prescribers may also administer injections to patients with no indications for parenteral administration, due to habit or personal preference. Different drug dosage forms may be contraindicated in different patients due to comorbidities or physiologic state. Errors in selecting the right drug formulation will lead to ineffectiveness of the drug or increase the risk of unwanted drug reactions.

2.4.2.3 Dose Selection

The dose of a drug may be too high or too low. The frequency of dosing may be too frequent or infrequent. Dosing instructions to the patient may be wrong, unclear or missing (2) These issues will cause DTPs. Medicine effectiveness and safety will be compromised by mistakes in the dose selection.

2.4.2.4 Treatment Duration

The duration of treatment may be shorter or longer than recommended (2). Optimal treatment duration is crucial to achieve the desired treatment outcomes. An example is the choice to stop or continue anticoagulant therapy in the treatment of DVT and PE, which is usually problematic(22). Recurrence of VTE may occur if anticoagulant therapy is stopped too soon and

there is a risk of bleeding if anticoagulant therapy is given for too long(22). Treatment duration is a major cause of DTPs.

2.4.2.5 Dispensing

DRPs may be caused by medication errors at the dispensing level(2). Unavailability of prescribed drug and not providing necessary information to patients are some of the causes of DTPs due to dispensing. Others include dispensing the wrong drug, dispensing wrong dose and dispensing the wrong strength (2). Dreijer et al. established that 8.1% of all medication errors involving anticoagulants, in the Netherlands, occurred at the dispensing level (23). This classification system records prescribing errors that cause DTPs under the category of dispensing(2). Prescribing errors are common in anticoagulant therapy. Henriksen et al. concluded that most fatal and serious MRPs, in Denmark, occurred at the prescribing level(24).

2.4.2.6 Drug Use Process

This is where the MRP is caused by wrong administration of the drug to the patient by a healthcare professional or caregiver despite having the right dosage instructions (2). This can occur by inappropriate dosing intervals, over-administered drug, under-administered drug, wrong drug administered and administration of drug via the wrong route(2). 29.8% of DTPs in patients on anticoagulants were found to emanate from mistakes in the drug use process in a recent Dutch study (23).

2.4.2.7 Patient Related

Patients' actions, intentional or non-intentional, can cause DTPs. Some of the ways in which patient actions can cause MRPs is where a patient takes less drug than prescribed, does not take drug at all, takes more drug than prescribed, abuses drug, takes unnecessary drug, eats foods that interact with the drug, stores drugs incorrectly, takes drug at inappropriate intervals, wrongly administers the drug, does not understand instructions and uses the wrong dosage form (2). A study carried out in Belgium showed that patient related factors such as non-compliance to direct

acting oral anticoagulants and vitamin k antagonists lead to MRPs such as adverse drug events (25). The physicians interviewed in this study cited forgetfulness, carelessness and lack of understanding as some of the reasons patients did not comply with their medication (25).

2.4.2.8 Patient Transfer Related

As a patient is being transferred from one level of care to another such as from a tier three facility to a tier four facility or from one health facility to another, DRPs can occur due to negligence or other factors(2). The causes of transfer related drug therapy problems include medication reconciliation not being carried out during patient transfer, discharge information on patient medication incomplete or missing, insufficient clinical information about the patient and patient not receiving necessary medication at discharge(2).

2.4.2.9 Other

Other causes of drug therapy problems that can occur in patients taking anticoagulants may be due to drug-food interactions (26). Presence of insoluble and soluble fibres may cause a decrease in the oral bioavailability of direct oral anticoagulants such as rivaroxaban (26). A reduction in oral bioavailability will have a negative impact on treatment outcomes with these drugs.

Foods high in vitamin K such as spinach and avocado can interfere with the pharmacologic effect of warfarin (27). Constituents in grapefruit juice inhibit CYP3A4 enzyme leading to high levels of warfarin (27). This will predispose patients to adverse effects such as bleeding.

2.4.3 Planned Interventions

Various interventions can be done to tackle DTPs including no interventions, prescriber level interventions, patient level interventions, drug level interventions and other interventions(2). At prescriber level the interventions include prescriber informed only, prescriber asked for information, intervention proposed to prescriber and intervention discussed with prescriber(2).

At patient level, the interventions carried out include patient counselling, written information provided, patient referred back to prescriber and instructions given to caregiver/family member(2).Drug level interventions include drugs changed, dosage changed, formulation changed, instructions for use changed, drug stopped and drug started(2)

2.4.4 Acceptance of Intervention Proposals

Interventions can be accepted or rejected by the patient or the prescriber. An intervention may be accepted and fully implemented, may be accepted and partially implemented, accepted but not implemented and accepted but implementation unknown(2).

Interventions may not be accepted for not being feasible. Interventions may not be accepted because there is no agreement and interventions may also not be accepted for other reasons or unknown reasons(2).

2.4.5 Status of DTP

This section is used to document whether a DTP has been resolved. The status of a DTP may be unknown, solved, partially solved and not solved(2).

2.5 Previous Studies

Studies on this topic are few globally and even fewer regionally and nationally. A study in Lebanon by Bassam et al. found the prevalence of DRPs to be 87.2% in patients taking oral anticoagulants (28) and was highest among patients taking vitamin K antagonists. The most common DRPs found in this study were drug interactions (83.3%), inappropriate monitoring (42.6%) and excessive dosing (26.7%) (28). The factors associated with DTPs in this study were renal disease, use of proton pump inhibitors and use of non-steroidal anti-inflammatory agents (28)

Regionally, an Ethiopian study concluded that in patients using anticoagulation the most prevalent DRPs were doses below therapeutic threshold, doses above therapeutic threshold and

potential drug-drug interactions (29). The same study in Ethiopia estimated the prevalence of DTPs in patients on anticoagulants to be at 51% (29).

A 2016 multicentre cross-sectional study done in France, showed the prevalence of DRPs in patients taking direct oral anticoagulants was 8.4% (30). 100 DTPs were identified out of 1188 hospital stays. The highest occurrence of MRPs was among patients taking rivaroxaban. The most common DTPs in this study were drug dose too low, drug dose too high and contraindications (30). The authors suggested that the complex dosing regimen of DOACs make their proper prescribing difficult (30). Older age(>75 years), low creatinine clearance(<30ml/min) and use of DOACs for treatment of atrial fibrillation were found to be factors associated with DTPs (30).

Stafford *et al.* found 157 DRPs out of 109 medication reviews for patients taking warfarin (31). The main DRP in this study was drug selection. The interventions offered to rectify the DTPs were patient education, surveillance and change of therapy (31).

Bassam *et al.*found that the factors related with occurrence of DTPs in patients on anticoagulant therapy include renal disease, smoking, concurrent intake of proton pump inhibitors and concurrent intake of nonsteroidal anti-inflammatory drugs (28). A 2017 study carried out in Spain concluded that concurrent use of antiplatelet drugs, concurrent use of angiotensin receptor blockers, older age and higher BMI are factors related with DTPs in patients taking anticoagulation therapy (32).

Comorbidities, depression, use of hypoglycaemic drugs and diet were associated with poor INR control in patients using anticoagulation therapy in a Spanish study published in 2022 (33). A regional study done in Ethiopia come to the conclusion that use of more than 2 concurrent drugs, presence of heart failure, presence of diabetes mellitus and use of aspirin were associated with negative outcomes in atrial fibrillation patients using anticoagulants (34).

2.6 Summary Review

DTPs are a common occurrence in patients taking anticoagulants. Characterization of these medication issues is important to facilitate proper interventions and optimize outcomes of therapy. There is a gap in research in Kenya and this study will help to reduce the knowledge gap in this field.

2.7 Conceptual Framework

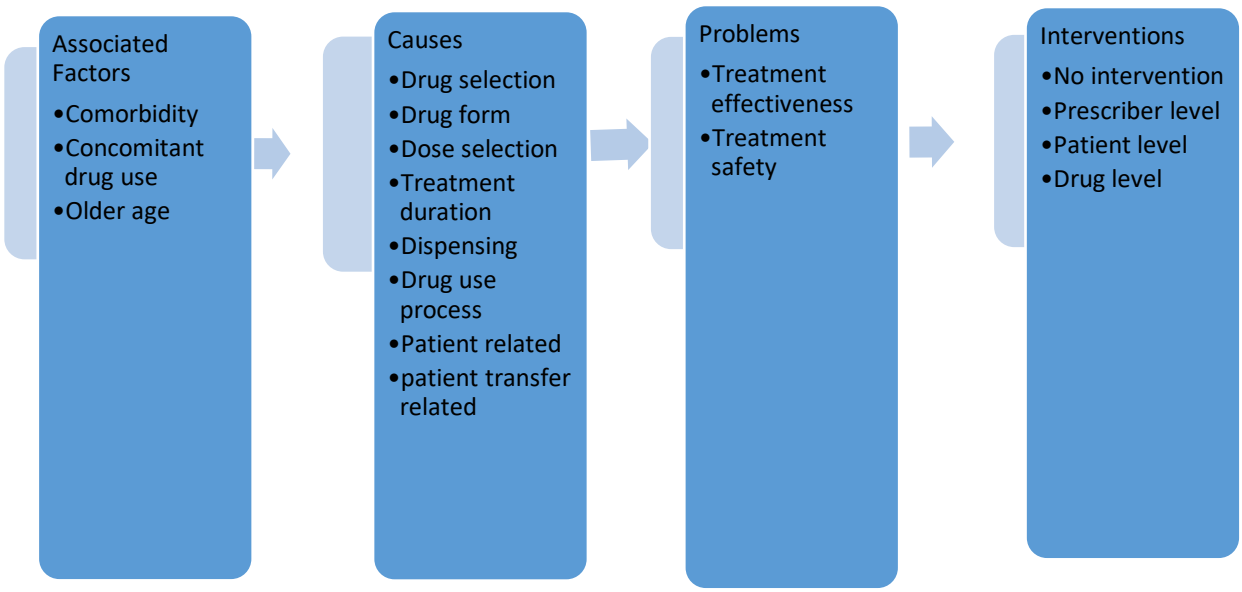


Figure 2. 3: conceptual framework

CHAPTER THREE: METHODOLOGY

3.1 Introduction

This chapter contains the study design, study site, study population, eligibility criteria, sampling, data collection techniques, data analysis and ethical considerations of the study. It is a systematic outline of how the data was collected and handled.

3.2 Research Design

The study was a cross sectional study of adult patients who were on anticoagulant therapy in the medical wards of KNH. A follow up of the patients who were yet to be discharged or who were admitted for an extended period, was carried out where possible to collect data on interventions and outcomes. However, the overall study design remained cross-sectional. A questionnaire was used to collect data on drug therapy problems from the patients who were interviewed by the researcher (appendix 2) Additional information such as INR, dose administered and clinical signs of adverse drug reactions was extracted from the patient files. The questions asked to the patient and the tool for collecting data from patient files were combined into one standard data collection tool. (appendix 2) Informed consent was sought from the patients before every interview.(appendix 1A) Data was collected between May 2023 and August 2023.

3.3 Location of Study

The study was done on inpatients in the medical wards at Kenyatta National Hospital. KNH is situated in Nairobi and is the biggest tertiary hospital in the country with a bed capacity of over 1800 in 50 wards.

3.4 Target Population and Study Population

The target population was adult patients on anticoagulant therapy in Kenya. The Study population was adult inpatients on anticoagulant therapy in Kenyatta National Hospital.

3.5 Eligibility Criteria

3.5.1 Inclusion Criteria

1. Adult patients (over 18 years of age) who were on anticoagulant therapy and gave their informed consent to participate in the study

3.5.2 Exclusion Criteria

1. Adult patients on anticoagulant therapy who could not communicate verbally.

2. Pregnant patients were excluded from the study

3. Patients whose records were missing or incomplete

3.6 Sample Size

Local studies on the prevalence of DTPs in patients on anticoagulant therapy are lacking. Regionally, a study carried out in Ethiopia showed the prevalence of DTPs in VTE patients was at 51% (29). The total number of eligible adult patients in the medical wards are 288. The Cochrane formula for sample size calculation was used:

$$N = \frac{Z^2 * P * q}{e^2}$$

Where N = desired sample size

Z = Z score of 95% confidence interval which is 1.96

P = prevalence of DRPs in patients using anticoagulants

q = 1-P

e = acceptable margin of error which is 5 %

$N = \frac{1.96^2 \text{ X } 0.51 \text{ X } (1-0.51)}{(0.05)^2} = 384$

Due to the large sample size derived from the Cochrane formula and the limitations of the study a correction formula was used to reduce the sample size. The formula for correction of small sample size was applied:

$$n = \frac{n_o}{1 + \frac{n_o - 1}{N}}$$

Where n = adjusted sample size

n_o = calculated sample size

N = population size

$\frac{384}{1+\frac{384-1}{288}}$ =165

n= 165 participants

3.7 Sampling Technique

Convenience sampling was used to recruit participants from medical wards in KNH. A list of patients admitted in each ward was always available at the nurse's desk. This list also included the patients' diagnoses. From this list, patients with diagnoses that led to prescription of anticoagulants were identified. The use of anticoagulant drugs was then confirmed using the treatment sheets in the respective patient files. Patients were approached to become study participants as long as they met the inclusion criteria.

Once the potential study participants on anticoagulant therapy were identified, their informed consent was sought to include them in the study (appendix 1A). Only patients who agreed to participate in the study were included. When patients refused to participate in the study or were

unable to give the required information, the researcher moved on to the next potential study subject.

3.8 Research Instruments

Informed consent form to seek consent from the patients before their inclusion into the study. They were made available in both English and Kiswahili (appendix 1A).

Standard data collection form, which combined questionnaires and a tool to extract data from the patient files (appendix 2).

3.9 Pretesting

The standard data collection tool was pretested on 10 participants who give their consent before the start of actual data collection. Any discrepancies or parts that needed to be corrected were modified before the beginning of the study.

3.10 Validity

Pretesting of the data collection forms helped in evaluating their validity. External validity was established by assessing the characteristics of study subjects to see whether the results obtained can be generalized to the target population.

Internal validity was established during the pretesting phase of research.

3.11 Reliability

Reliability was checked by pretesting the data collection form. A lack of internal consistency was corrected by changing the data collection tool until a reliable tool is developed.

3.12 Definition of Outcomes

Treatment effectiveness was derived by looking at different parameters for different drugs. For warfarin, a patient with an INR of 2-3 and with no signs or symptoms of thrombosis was considered as having effective treatment.

For patients taking unfractionated heparin, treatment was considered effective if they had no signs or symptoms of thrombosis and their activated partial thromboplastin time was 1.5 – 2 times the baseline. Treatment, for patients using LMWHs, was considered effective when they had no signs and symptoms of thrombosis and an activated partial thromboplastin time (aPTT) of 1.5 – 2 times the baseline. Effective treatment for patients taking direct oral anticoagulants was when they had no signs and symptoms of thrombosis.

Treatment safety for anticoagulation therapy was judged by investigating for bleeding, unexplained bruises and thrombocytopenia.

3.13 Data Collection Techniques

Data was collected from study participants using a standard data collection tool. The first part of the tool had structured questions which were filled through interviews. This captured the participant biodata and potential drug therapy problems. The second part of the tool was filled by the researcher picking data from the patient records such as treatment sheets and doctor's notes.

Participants were assigned unique identifier codes to protect their privacy and maintain confidentiality. The data collection forms were only available to the investigator. The data collection forms were kept under lock and key once they were filled with patient data.

3.14 Data Analysis

Data collected was entered into Microsoft Excel©. Data collected was backed up in an external hard drive and in the Google Cloud Platform. All data collected was coded, cleaned, processed and stored every day by the researcher. Data was password-protected to maintain patient confidentiality. After the end of the data collection period, analysis was carried out using Stata©.

Descriptive statistics such as mean, standard deviation and frequencies were used to summarize and describe patient demographics and clinical characteristics, types of drug therapy problems and the prevalence of DTPS. This was visualized using charts and graphs.

Inferential statistics such as chi-square, Fischer's test and logistic regression analysis were used to determine the relationships between drug therapy problems and associated factors.

3.15 Ethical Considerations

Informed consent was sought before recruiting patients into the study. The forms for informed consent were made available in both English and Kiswahili. Anyone who failed to give their consent was not included in the study.

Patient privacy and confidentiality were maintained at all times. Patient names were not used in the data collection forms. Unique identifier codes were assigned to all study participants. The inpatient numbers of the participants were picked and assigned to the respective unique code for the participants. This was done to avoid picking data from the same patient twice. However, the inpatient numbers were kept separate from the main data collection forms to avoid leaking of information that could be used to identify a particular patient.

Approval for carrying out the research at Kenyatta National Hospital was granted by the KNH-UON ethics and review board, **ref KNH-ERC/A/128** (appendix 3). The medicine department of Kenyatta National Hospital granted the researcher, approval to collect data at interview patients in the medical wards, **ref: KNH/HOD-MED/47/VOL.II** (appendix 4).

CHAPTER 4: RESULTS

4.1 Introduction

This chapter contains the results of the study. This includes the socio-demographic data, clinical profile of the participants, drug therapy problems reported by the patients and drug therapy problems determined by the investigator.

From a sample size of 165 participants, only 125 participants were enrolled in the study. Data collection was done between May 2023 and August 2023. The reduced sample size led to lower statistical power where the study is less likely to yield true associations. There was also an increased risk of committing type II errors due to the smaller sample size.

4.2 Descriptive Analysis

4.2.1 Sociodemographic and Behavioural Characteristics of the Study Participants

The social demographic data and baseline characteristics of the study participants are summarized in **table 4.1**. 47 (37.6%) of the study participants were between 20-40 years of age. More than half, 66 (52.8%) were females while 59 (47.2%) were male.

Table 4.2 shows that a majority of the study subjects were non-smokers, 102 (81.6%). A majority of the participants, 96 (76.8%) responded that they do not consume alcohol. Lastly, 90 (72%) of the patients carry out regular physical activity (at least 30 minutes for at least 4 days a week).

Out of the 125 patients interviewed, more than half, 78 (62.4%) did not have drug therapy problems while 47 (37.6%) had DTPs as illustrated in **figure 4.1**.

Table 4. 1: Socio-Demographic Characteristics of Patients on Anticoagulants at KNH

Variable	n=125		Freq	Percent
Age	Below 20 years		7	5.6%
	20-40 yrs		47	37.6%
	40-60 yrs		43	34.4%
	Above 60 yrs		28	22.4%
Gender	Male		59	47.2%
	Female		66	52.8%
Marital status	Single		34	27.2%
	Separated		8	6.4%
	Married		73	58.4%
	Divorced		2	1.6%
	Widowed		8	6.4%
Employment	Employed		22	17.6%
	Self-Employed		55	44.4%
	Unemployed		25	20.0%
	Student		6	4.8%
	Retired		17	13.6%
Level of Education	Primary		44	35.2%
	Secondary		64	51.2%
	Diploma		7	5.6%
	Degree		7	5.6%
	Masters		2	1.6%
	PHD		1	0.8%
BMI (min=14.19, max= 41.67)	Mean= 23.99	Std= 4.7		

Table 4. 2: Behavioural Characteristics of Patients on Anticoagulants at KNH

Behaviour		Freq	Percent
Smoke cigarette	Yes	23	18.4%
	No	102	81.6%
Years of cigarette smoking	Less than 10 yrs	5	21.7%
	10-19 yrs	7	30.4%
	>20 yrs	11	47.8%
Drink Alcohol	Yes	29	23.2%
	No	96	76.8%
Units of alcohol taken	<= 7 Units	5	17.2%
	8-14 Units	6	20.7%
	>14 Units	18	62.07%
Physical activity	Yes	90	72%
	No	35	28%

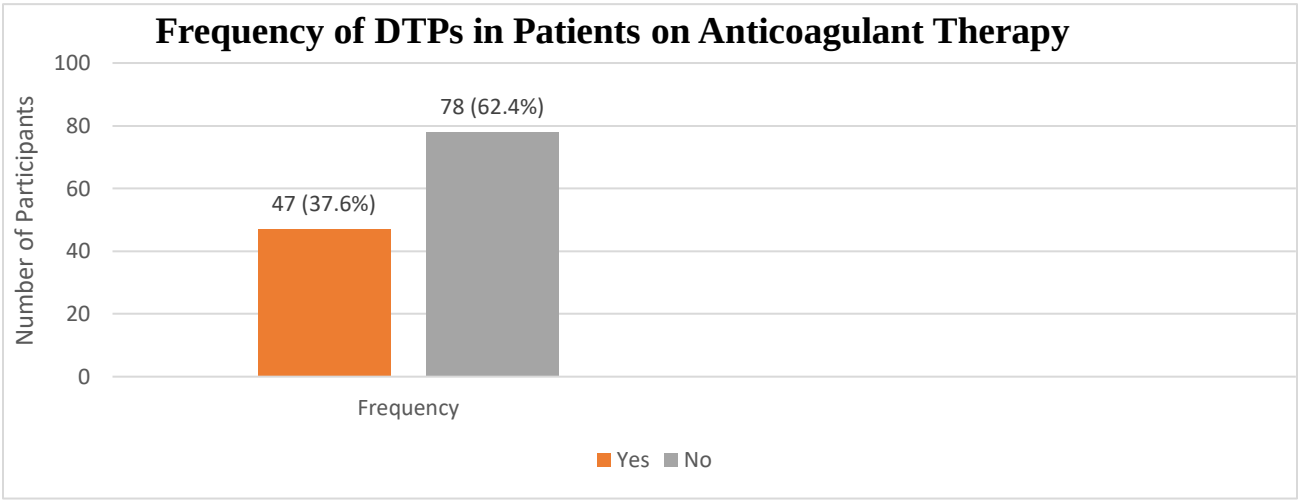


figure 4. 1: Prevalence of Drug Therapy Problems in Patients on Anticoagulant Therapy

4.2.2 Potential DTPs From Study Participant Responses

A small minority of patients, 19 (15.2%) reported that they had no changes in their symptoms after startinh medication as shown in **figure 4.2**. About 63 (50.4%) participants reported an exacerbation of VTE symptoms. Only 14 (12.6%) participants reported episodes of bleeding while on anticoagulant therapy. There were 3 (2.4%) study participants who described having experienced unexplained bruising and 13 (10.4%) participants reported having black stools. 11 (8.8%) of the patients in the study reported that there were instances of missed doses of anticoagulant therapy. 105 (84%) of the participants declared they were satisfied with their drug therapy.

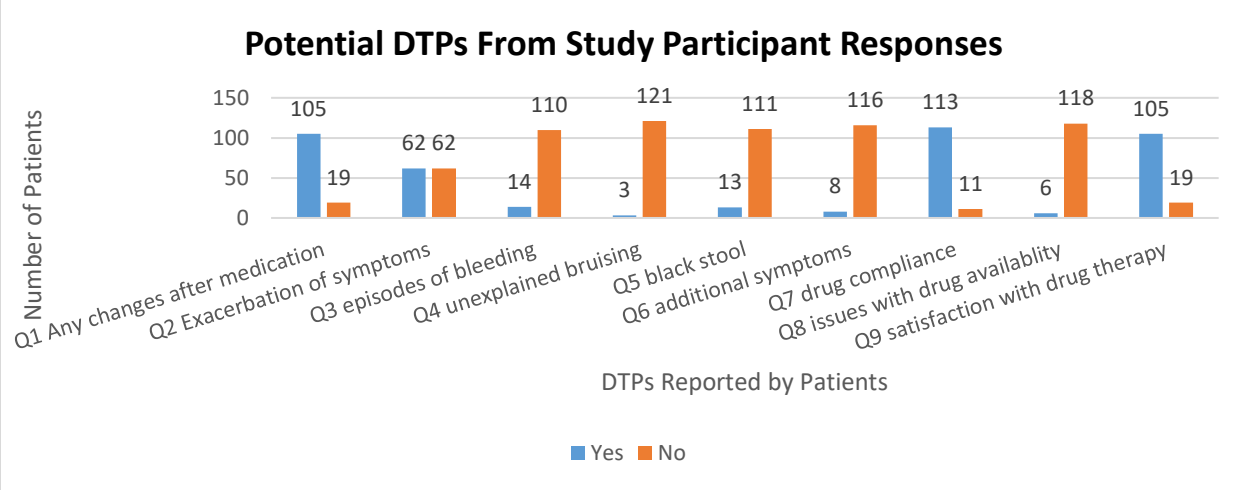


figure 4. 2: Potential Drug Therapy Problems from Study Participant Responses

4.2.3 DTPs Frequently Encountered by Patients on Anticoagulants

Table 4.3 shows that the main drug therapy problem experienced was ‘others’, which was mostly drug-drug interactions between anticoagulants and other classes of drugs such as antibiotics. The main antibiotics found to be interacting with anticoagulants were ceftriaxone, clarithromycin and sulphamethoxazole. This category of DTPs accounts for any other drug therapy problem except treatment effectiveness and treatment safety. In the case of this study, drug-drug interactions were the main DTP that fell under this category.

The main cause of DTPs was drug selection (24%). For most patients with DTPS, no interventions were done. Most interventions (6.4%) were done at prescriber level. Only a small number of DTPs, 19.2%, were solved.

Table 4. 3: Classification and Frequency of DTPs Encountered by Study Participants

	Primary Domains	Yes n (%)	No n (%)
Problems	Treatment effectiveness	4 (3.2%)	121 (96.8%)
	Treatment safety	20 (16%)	105 (84%)
	Others	23 (18.4%)	102 (81.6%)
Causes	Drug selection	30 (24%)	95 (76%)
	Drug form	0 (0%)	125 (100%)
	Dose selection	5 (4%)	120 (96%)
	Treatment Duration	0 (0%)	125 (100%)
	Dispensing	2 (1.6%)	123 (98.4%)
	Drug Use process	0 (0%)	125 (100%)
	Patient related	3 (2.4%)	122 (97.6%)
	Patient transfer related	1 (0.8%)	124 (99.2%)
	Other	6 (4.8%)	119 (95.2%)
Planned interventions	No intervention	34 (27.2%)	91 (72.8%)
	At prescriber level	8 (6.4%)	117 (93.6%)
	At patient level	1 (0.8%)	124 (192%)
	At drug level	2 (1.6%)	123 (98.4%)
	Other	2 (1.6%)	123 (98.4%)
Intervention Acceptance	Intervention accepted	11 (8.8%)	114 (91.2%)
	Intervention not accepted	0 (0%)	125 (100%)
	Other	36 (28.8%)	89 (71.2%)
Status of DTP	Problem Status Unknown	11 (8.8%)	114 (91.2%)
	Problem solved	24 (19.2%)	101 (80.8%)
	Problem partially solved	4 (3.2%)	121 (96.8%)
	Problem not solved	8 (6.4%)	117 (93.6%)

4.2.4 Frequency of Usage of Different Anticoagulant Drugs Among Study Subjects

Most of the study participants were being treated with enoxaparin (81%) as shown in **figure 4.3**.

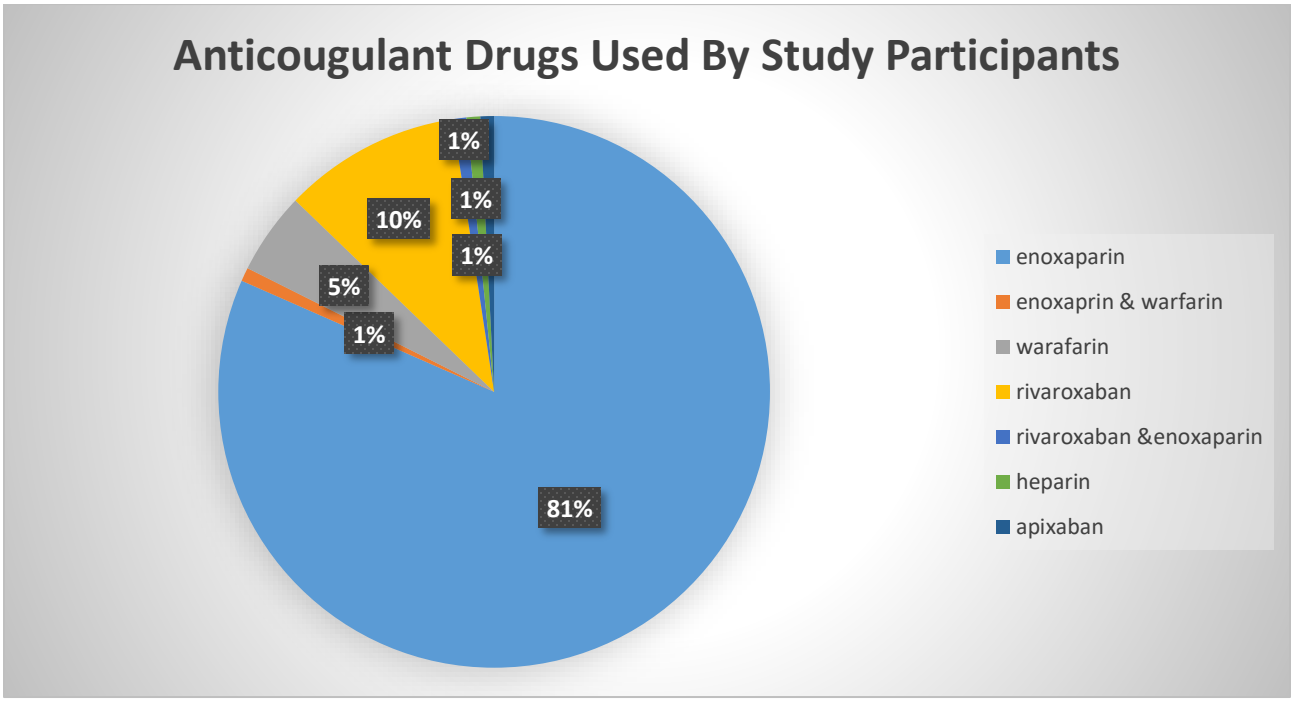


figure 4. 3: Frequency of Usage of Various Anticoagulant Drugs by the Study Participants

4.2.5 Frequency of Occurrence of DTPs with Different Anticoagulant Drugs

Table 4.4 shows the frequency of occurrence of DTPs in patients who were using different anticoagulants. DTPs were more likely to occur in patients using warfarin (50%).

Table 4. 4: Table of Frequency of DTPs in Different Anticoagulant Drugs

	DTPs	
Medication	**Yes**	**No**
Enoxaparin	39 (38.2%)	63(61.7%)
enoxaparin & warfarin	0 (0%)	1 (100%)
warfarin	3(50%)	3(50%)
Rivaroxaban	2 (15.4%)	11 (84.6%)
rivaroxaban & enoxaparin	1 (100%)	0 (0%)
heparin	1 (100%)	0 (0%)
Apixaban	1 (100%)	0 (0%)
Total	47	78

4.3 Factors Associated With Drug Therapy Problems

4.3.1 Baseline Characteristics of Study Participants and Their Association with DTPs

After carrying out Chi square test for independence to determine presence of significant association between baseline characteristics and DTPs, no significant associations were found as shown in **table 4.5**.

Table 4. 5: Prevalence of DTPs by Baseline Characteristics and Their Association

Variable	Category	DTPs		p value
		Yes n (%)	No n (%)	
Gender	Male	22 (47.83)	37 (46.84)	0.915
	Female	24 (52.17)	41 (53.16)	
Age	Below 20 yrs	3 (6.52)	4 (5.06)	0.273*
	20-40 yrs	17 (36.96)	30 (37.97)	
	40-60 yrs	13 (28.26)	30 (37.97)	
	Above 60	13 (28.26)	15 (18.99)	
Marital status	Single	17 (36.96)	17 (21.52)	0.076*
	Separated	1 (2.17)	7 (8.86)	
	Married	22 (47.83)	51 (64.56)	
	Divorced	1 (2.17)	1 (1.27)	
	Widowed	5 (10.87)	3 (3.80)	
Level of Education	Primary	22 (47.83)	22 (27.85)	0.305*
	Secondary	20 (43.48)	44 (55.70)	
	Diploma	2 (4.35)	5 (6.33)	
	Degree	2 (4.35)	5 (6.33)	
	Masters	0 (0.00)	1 (1.27)	
	PhD	0 (0.00)	1 (1.27)	
Employment	Employed	6 (13.04)	16 (20.25)	0.725*
	Unemployed	10 (21.74)	15 (18.99)	
	Self-employed	20 (43.48)	35 (44.3)	
	Student	3 (6.52)	3 (3.80)	
	Retired	7 (15.22)	10 (12.66)	
Drinking Alcohol	Yes	12 (26.09)	17 (21.52)	0.560
	No	34 (73.91)	62 (78.48)	
Units of alcohol	< 7 Units	2 (16.67)	3 (17.65)	0.915*
	8 to 10 Units	3 (25.00)	3 (17.65)	
	> 14Units	7 (58.33)	11 (64.71)	
Smoking cigarettes	Yes	9 (19.57)	14 (17.72)	0.798
	No	37 (80.43)	65 (82.28)	
Years of smoking cigarettes	Less than 10 yrs	2 (22.2)	3 (21.43)	0.694*
	10-19 yrs	4 (44.44)	3 (21.43)	
	>20 yrs	3 (33.33)	8 (57.14)	
Physical activity	Yes	35 (78.09)	55 (69.52)	0.437
	No	11 (23.91)	24 (30.38)	

Key * - Fisher's Exact used.

4.3.2 Clinical Profile of Study Participants and their Association with DTPs

Comorbidities and drug allergies of the participant did not have a statistically significant association with DTPs as shown in **table 4.6**.

Table 4. 6: Association between Clinical Profiles of Study Participants and DTPs

Variable	Category	DTPs		p-value
		Yes n (%)	No n (%)	
Comorbidity	Yes	18 (39.13)	41 (51.90)	0.168
	No	28 (60.87)	38(48.10)	
Which Comorbidity	Hypertension, HIV	0 (0.00)	1 (0.81)	0.526*
	Hypertension, hyperthyroidism	0 (0.00)	1 (0.81)	
	Hypertension, asthma	0 (0.00)	1 (0.81)	
	Hypertension, diabetes mellitus	4 (3.22)	7 (5.65)	
	HIV	6 (4.84)	3 (2.42)	
	Acromegaly	0 (0.00)	1 (0.81)	
	Asthma	0 (0.00)	1 (0.81)	
	Diabetes mellitus	2 (1.61)	8 (6.45)	
	Dyspepsia	0 (0.00)	1 (0.81)	
	Gout	0 (0.00)	1 (0.81)	
	Heart failure	0 (0.00)	2 (1.61)	
	Hypertension	5 (4.03)	11 (8.87)	
Drug allergies	Yes	6 (13.04)	6 (7.59)	0.652
	No	40 (86.96)	73 (92.41)	

Key: * - Fisher's exact used

4.3.3 Various Laboratory Investigations and Their Association with DTPs

In **table 4.7**, only haemoglobin (p=0.011), estimated glomerular filtration rate (p=0.008) and creatinine (p=0.015) were significantly associated with DTPs.

Table 4. 7: Laboratory Investigations and Their Association with DTPs

Lab data	Levels	Yes n (%)	No n (%)	p value
Prothrombin time	Normal	32 (69.57)	62 (78.48)	
	Above Normal	14 (30.43)	17 (21.52)	0.266
Activated partial thromboplastin time	Normal	39 (84.78)	70 (88.6)	
	Above Normal	7 (15.22)	9 (11.4)	0.537
D-dimer	Normal	43 (93.48)	76 (96.20)	
	Above Normal	3 (6.52)	3 (3.80)	0.668*
INR	Normal	33 (71.74)	67 (84.81)	
	Above Normal	13 (20.26)	12 (15.19)	0.078
Platelets	Below Normal	7 (15.22)	5 (6.33)	
	Normal	36 (78.26)	71 (89.87)	
	Above Normal	3 (6.52)	3 (3.80)	0.181*
Red blood Cells	Below Normal	12 (26.67)	10 (12.66)	
	Normal	31 (68.89)	67 (84.81)	
	Above Normal	2 (4.44)	2 (2.53)	0.073*
Haemoglobin	Below Normal	18 (39.13)	14 (17.72)	
	Normal	27 (58.70)	64 (81.01)	
	Above Normal	1 (2.17)	1(1.27)	**0.011***
Albumin	Below Normal	14 (30.43)	27 (34.18)	
	Normal	32 (69.57)	52 (65.82)	0.667
AST	Normal	43 (93.48)	77 (97.47)	
	Above Normal	3 (6.52)	2 (2.53)	0.356*
ALT	Normal	45 (97.83)	75 (94.94)	
	Above Normal	1 (2.17)	4 (5.06)	0.651*
ALP	Normal	39(84.78)	71 (89.74)	
	Above Normal	7(15.22)	8 (10.26)	0.398
γGT	Normal	43 (93.48)	74 (93.67)	
	Above Normal	3 (6.52)	5 (6.33)	1.00*
Estimated glomerular filtration rate	Below Normal	14 (30.43)	9 (11.39)	
	Normal	32 (69.57)	70 (88.61)	**0.008**
Creatinine	Normal	32 (69.57)	69 (87.34)	
	Above Normal	14 (30.43)	10 (12.66)	**0.015**
Troponins	Normal	43 (93.38)	77 (97.47)	0.356*
	Above normal	3 (6.52)	2 (2.53)	
HbA1C	Below Normal	1 (2.17)	0 (0.00)	0.307
	Normal	38 (82.61)	71 (89.87)	
	Above Normal	7 (15.22)	8 (10.13)	
Calcium	Below Normal	1 (2.17)	1 (1.27)	
	Normal	45 (97.83)	78 (98.73)	1.000*
Sodium	Below Normal	7 (15.22)	12 (15.18)	
	Normal	39 (84.78)	67 (84.81)	0.997
Potassium	Below Normal	1 (2.17)	2 (2.53)	
	Normal	44(95.65)	74(93.67)	1.000
	Above Normal	1(2.7)	3(3.79)	

Key: * - Fisher's exact

4.3.4 Logistic Regression to Determine Associated Factors for DTPs

Table 4.8 shows logistic regression analysis for the DTPs and the variables that showed a significant association after chi square and fisher's exact method were used. For the outcome of treatment effectiveness, haemoglobin (p= 0.018) and red blood cell count (p=0.040) showed significant association when bivariate testing was done. Multivariate testing for these two variables showed no significance. Thus, no true association was found for these two variables.

For treatment safety DTP, comorbidity (p=0.099), red blood cell count (p=0.035) and haemoglobin (p=0.055) had a p value of below 0.2 and were thus subjected to multivariate regression analysis. The associations did not prove to be true associations after multivariate analysis. None of the three variables had a significant p value.

For other DTPs, there were no significant associations obtained after multivariate analysis of RBC (p=0.091) which was significant at bivariate level.

Some variables like creatinine and egfr, which had significant association after testing for chi, were dropped when odds ratios of 1.000 were obtained after bivariate analysis.

Table 4. 8: Table of Logistic Regression of Various Variables and Drug Therapy Problems

DTPs	Variables	Bivariate analysis		Multivariate analysis	
		cOR (95% CI)	p-value	aOR (95% CI)	p-value
Treatment Effectiveness	Marital status	1.03 (0.416 – 2.554)	0.947	-	-
	Comorbidities	1.123 (0.153 – 8.232)	0.909	-	-
	RBCs	0.085 (0.008 – 0.895)	**0.040**	1.181 (0.001 – 1471.382)	0.963
	Haemoglobin	0.031 (0.002 – 0.547)	**0.018**	0.027 (0.001 – 50.009)	0.346
Treatment Safety	Marital status	0.851 (0.550 – 1.316)	0.468	-	-
	Comorbidity	0.420 (0.150 – 1.178)	**0.099**	0.506 (0.175 – 1.460)	0.207
	INR	0.516 (0.175 – 1.515)	0.228	-	-
	RBCs	0.218 (0.053 – 0.896)	**0.035**	0.382 (0.676 – 2.154)	0.275
	Haemoglobin	0.274 (0.073 – 1.030)	**0.055**	0.520 (0.114 – 2.379)	0.400
Others	Marital status	1.269 (0.834 – 1.930)	0.265	-	-
	Comorbidity	1.031 (0.417 – 2.551)	0.947	-	-
	INR	0.878 (0.291- 2.651)	0.818	-	-
	RBC	0.341 (0.098 – 1.187)	**0.091**	0.341 (0.098 – 1.186)	0.091
	haemoglobin	0.504 (0.171 – 1.487)	0.215	-	-

Key: bolded – statistically significant

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

The prevalence of DTPs in patients on anticoagulant therapy was 37.6%. One study carried out in Lebanon in 2022, had a prevalence of 87.2% (28) while a 2016 study done in Ethiopia had a prevalence of 51% (29). Viprey *et al.* established a prevalence of 8.4% (30). The higher prevalence rates from other studies differ with the figure obtained in this study. Prevalence rates for DTPs in patients taking anticoagulants vary from setting to setting. The differences in prevalence rates could be due to different study designs and differences in study populations.

Bleeding was one of the adverse effects that occurred in study participants. A study done in 2008, estimated that the incidence of bleeding as a complication of anticoagulants ranged from 1.5 – 4.5 % (35). One of the main interventions was stopping anticoagulant therapy in study participants who had signs of bleeding. The prevalence of events of bleeding with anticoagulant use was higher in this study. A number of study subjects had black stools, which is a sign of gastrointestinal bleeding. The risk of gastrointestinal bleeding with warfarin was 3.9% per patient-year while direct oral anticoagulants had a 25% higher risk of gastrointestinal bleeding than warfarin in a study done, in Romania, on patients using anticoagulants for atrial fibrillation (36). The rate of gastrointestinal bleeding was 1.19% in patients on anticoagulants in a study by Gu *et al.* (37). Gastrointestinal bleeding is a major contributor to drug therapy problems in a significant number of patients on anti-coagulant therapy.

Missed doses of anticoagulant therapy were another DTP reported by 8.8 % of study participants. Missed doses occurred in 11.5% of hospitalized patients who were on anticoagulant therapy in a study done in Brigham Hospital, United Kingdom (38). The two studies showed almost similar rates of missed doses. Missed doses lead to sub therapeutic levels of drugs and this will interfere with treatment outcomes.

The main type of drug therapy problem experienced by study participants was drug-drug interactions which was classified under the category, 'other' in the PCNE drug therapy problems classification tool. Some participants experienced drug-drug interactions involving anticoagulants during their hospitalization. The main classes of drugs involved in these drug interactions were low molecular weight heparins and antibiotics. Antibiotics such as ceftriaxone, clarithromycin, sulphamethoxazole and piperacillin reduce the metabolism of enoxaparin leading to increased plasma levels of the anticoagulant. This may lead to unwanted effects such as bleeding. An Indian research paper revealed similar findings on drug-drug interactions being the main DTP encountered in hospitalized patients (39). Bassam *et al*. came up with similar conclusions while investigating DTPs in patients on anticoagulant therapy where a majority (86.2%) of their participants suffered from drug-drug interactions (28).

Treatment safety was the second most common DTP in the study population. Patients who had adverse effects such as bleeding, melena stools and unexplained bruises were put in this category. Wung *et al*. found that treatment safety was the main drug therapy problem in patients on anticoagulant therapy where 68.4% of the recruited participants experienced treatment safety DTPs (40). The Wung *et al*. study, carried out in Taiwan, is in contradiction with this study that found treatment safety to be the second most common DTP in patients on anticoagulant therapy. The differences in results of the two studies may be due to the Wung *et al* study being retrospective in nature, with a bigger sample size and data collection was done from an electronic medical records system.

Treatment effectiveness was the least common DTP affecting the study subjects. This DTP was caused by suboptimal therapeutic levels of anticoagulant therapy, which may be due to under-dosing or missed doses. Some patients complained of missed doses either due to inability to purchase medicine from outside the hospital or medication errors by the healthcare providers. An

Ethiopian study found that treatment effectiveness due to sub-therapeutic doses was the most prevalent DTP (26). Bassam *et al.* found that problems with treatment effectiveness were caused by too low drug dose in 26.7% and too high drug dose in 15.5% of their participants (28). This study reported lower rates of treatment effectiveness DTP. The difference in results from this study and the other two studies could be due to the cross-sectional nature of the study where interaction with the participants was done once while the other studies were prospective. This could have provided ample time for occurrence of new signs and symptoms and more episodes of inappropriate dosing which led to more DTPs of treatment effectiveness to be reported.

The main cause of DTPs was drug selection. This was due to choosing unsuitable drug combinations, or choosing a contraindicated drug. These errors are attributable to the prescriber. In a Taiwanese study published in 2022, drug selection was not one of the causes of DTPs (40). Another study in Northern Cyprus concluded that drug selection and drug dose were the main causes of DTPs (41). Stafford *et al., 2011* also concluded that drug selection was the main cause of DTPs (31) The different results for the main cause of DTPs may be due to differences in study population.

Dose selection was the second most common cause of DTPs. Giving too high dose or too low dose leads to suboptimal therapeutic levels of the anticoagulant drug. Daba *et al*. concluded that a majority of the DTPs in patients taking anticoagulants for VTE management were caused by sub-therapeutic and over-therapeutic doses (29). Stafford *et al*. had dose selection as a minor cause of DTPs, contributing to 2.6% of DTPs. This variation between the studies may be due to this study looking at anticoagulation medication as a broad class while the other two studies concentrated on specific anticoagulants such as warfarin and direct oral anticoagulants.

Warfarin had the highest proportion of occurrence of DTPs, followed by enoxaparin and then rivaroxaban. A study done in USA, revealed similar findings where DOACs are the least likely to cause DTPs in patients while warfarin was the most likely to cause DTPs in patients (42).

In this study the socio-demographic and clinical characteristics of patients did not yield statistically significant associated factors related with occurrence of DTPS in the study participants. This may be due to limitations in the study, especially the sample size which was small causing low statistical power. Bassam *et al*. established that renal disease, smoking, concurrent intake of PPIs and NSAIDs were significant factors contributing to DTPs in patients taking anticoagulants (28). Ruiz Ortiz *et al*, in 2018 found the factors related with DTPs in patients taking anticoagulants are concurrent use of antiplatelet drugs, concurrent use of angiotensin receptor blockers, concurrent use of aldosterone antagonists, older age and higher BMI(32).

A limitation of the study was that it was done in an in-patient setting and the findings of the study may not apply to patients in an outpatient setting. However, this study brought to light that drug-drug interactions are the main drug therapy problem affecting this population.

5.2 Conclusion

Drug therapy problems are common in patients taking anticoagulant therapy. These patients will get adverse drug events, increased morbidity, increased hospital stays, suboptimal therapy and increased costs due to these DTPs. Drug-drug interactions are a major DTP in patients taking anticoagulant therapy. This study revealed that low molecular weight heparins also have a number of common and potentially serious drug interactions that everyone should be on the look out for. Enoxaparin interacts with a number of antibiotics like ceftriaxone, clarithromycin and piperacillin which increase its' plasma levels by inhibiting metabolism. Patients taking warfarin had the highest proportion of drug therapy problems as compared to the other anticoagulants.

5.3 Recommendations

The healthcare team should be aware of the common DTPs in patients on anticoagulant therapy and be prepared to intervene.

A follow up study using a different study design like a prospective study with a larger study population may reveal the associations for DTPs in patients on anticoagulant therapy that were not captured by this study. This is a direction for future research on this topic.

REFERENCES

1. Niriayo YL, Kumela K, Kassa TD, Angamo MT. Drug therapy problems and contributing factors in the management of heart failure patients in Jimma University Specialized Hospital, Southwest Ethiopia. PLoS ONE. 2018;13(10):1–14.

2. PCNE. Classification for Drug Related Problems V9.00. PCNE Classif Drug Relat Probl V900. 2019;1–10.

3. Anticoagulation - StatPearls - NCBI Bookshelf [Internet]. [cited 2022 Aug 17]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560651/?report=classic

4. Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Pharmacology of anticoagulants used in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):15–31.

5. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982–3021.

6. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, et al. Thrombosis: A major contributor to global disease burden: ISTH steering committee for world thrombosis day the members of the ISTH steering committee for World Thrombosis Day. Thromb Res. 2014;134(5):931–8.

7. Waweru P, Gatimu SM. Stroke Epidemiology, Care, and Outcomes in Kenya: A Scoping Review. Front Neurol. 2021;12(December).

8. Scheres LJJ, Lijfering WM, Cannegieter SC. Current and future burden of venous thrombosis: Not simply predictable. Res Pract Thromb Haemost. 2018;2(2):199–208.

9. Globocan. Kenya Source. 2020;799:2020–1.

10. Ewins K, Ní Ainle F. VTE risk assessment in pregnancy. Res Pract Thromb Haemost. 2020 Feb;4(2):183–92.

11. Engbers MJ, Blom JW, Cushman M, Rosendaal FR, Van Hylckama Vlieg A. The contribution of immobility risk factors to the incidence of venous thrombosis in an older population. J Thromb Haemost. 2014 Mar;12(3):290–6.

12. Bjøri E, Johnsen HS, Hansen JB, Brækkan SK. Hospitalization as a trigger for venous thromboembolism - Results from a population-based case-crossover study. Thromb Res. 2019 Apr;176:115–9.

13. Hadid T, Kafri Z, Al-Katib A. Coagulation and anticoagulation in COVID-19. Blood Rev. 2021;47:100761.

14. Palta S, Saroa R, Palta A. Overview of the coagulation system. Indian J Anaesth. 2014;58(5):515–23.

15. Casavant MJ. Goodman and Gilman's The Pharmacological Basis of Therapeutics. Vol. 288, JAMA: The Journal of the American Medical Association. 2002. 2052–2052 p.

16. Franchini M, Liumbruno GM, Bonfanti C, Lippi G. The evolution of anticoagulant therapy. Blood Transfus. 2016;14(2):175–84.

17. Basger BJ, Moles RJ, Chen TF. Application of drug-related problem (DRP) classification systems: A review of the literature. Eur J Clin Pharmacol. 2014;70(7):799–815.

18. Van Mil JWF, Westerlund LOT, Hersberger KE, Schaefer MA. Drug-Related Problem Classification Systems. Ann Pharmacother. 2004;38(5):859–67.

19. Kant A, Bilmen J, Hopkins PM. Adverse drug reactions. Pharmacol Physiol Anesth Found Clin Appl. 2018;16(5):130–43.

20. Vazquez SR. Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions. Hematology. 2018 Nov 30;2018(1):339–47.

21. Sevilla-Cazes J, Finkleman BS, Chen J, Brensinger CM, Epstein AE, Streiff MB, et al. Association Between Patient-Reported Medication Adherence and Anticoagulation Control. Am J Med. 2017 Sep 1;130(9):1092-1098.e2.

22. Kearon C, Akl EA. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood. 2014;123(12):1794–801.

23. Dreijer AR, Diepstraten J, Bukkems VE, Mol PGM, Leebeek FWG, Kruip MJHA, et al. Anticoagulant medication errors in hospitals and primary care: A cross-sectional study. Int J Qual Health Care. 2019;31(5):346–52.

24. Henriksen JN, Nielsen LP, Hellebek A, Poulsen BK. Medication errors involving anticoagulants: Data from the Danish patient safety database. Pharmacol Res Perspect. 2017;5(3):1–8.

25. Sennesael AL, Larock AS, Devalet B, Mathieux V, Verschuren F, Muschart X, et al. Preventability of serious thromboembolic and bleeding events related to the use of oral anticoagulants: a prospective study. Br J Clin Pharmacol. 2018;84(7):1544–56.

26. Grześk G, Rogowicz D, Wołowiec Ł, Ratajczak A, Gilewski W, Chudzińska M, et al. The Clinical Significance of Drug-Food Interactions of Direct Oral Anticoagulants. Int J Mol Sci. 2021 Aug 8;22(16):8531.

27. Vranckx P, Valgimigli M, Heidbuchel H. The Significance of Drug-Drug and Drug-Food Interactions of Oral Anticoagulation. Arrhythmia Electrophysiol Rev. 2018 Mar;7(1):55–61.

28. Bassam S, Mansour S, Ajrouche R, Kisserwan H, EL-Hajj M, Zein S, et al. Drug-Related Problems and Factors Involved in the Imbalance of Oral Anticoagulants in Lebanese Patients: A Cross-Sectional Study. Dr Sulaiman Al Habib Med J. 2022;4(2):77–85.

29. Daba FB, Tadesse F, Engidawork E. Drug-related problems and potential contributing factors in the management of deep vein thrombosis. BMC Hematol. 2016;16(1):1–8.

30. Viprey M, Jeannin R, Piriou V, Chevalier P, Michel C, Aulagner G, et al. Prevalence of drug-related problems associated with direct oral anticoagulants in hospitalized patients: a multicenter, cross-sectional study. J Clin Pharm Ther. 2017;42(1):58–63.

31. Stafford L, Stafford A, Hughes J, Angley M, Bereznicki L, Peterson G. Drug-related problems identified in post-discharge medication reviews for patients taking warfarin. Int J Clin Pharm. 2011;33(4):621–6.

32. Ruiz Ortiz M, Muñiz J, Raña Míguez P, Roldán I, Marín F, Asunción Esteve-Pastor M, et al. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: prevalence and associated factors. A subanalysis of the FANTASIIA Registry. EP Eur. 2018 Oct 1;20(10):1577–83.

33. Reig-Garcia G, Camara-Liebana D, Jiménez-Quiñones R, Vilanó-Vives J, Figa-Vaello J, Garre-Olmo J, et al. Control of Therapeutic Levels of Anticoagulation and Associated Factors: A Prospective Cohort Study. J Prim Care Community Health. 2022 Jan;13:215013192211299.

34. Yimer NS, Abiye AA, Hussen SU, Tadesse TA. Anticoagulation Control, Outcomes, and Associated Factors in Patients with Atrial Fibrillation Receiving Warfarin at Tertiary Care Hospital in Ethiopia. Clin Appl Thromb. 2021 Jan 1;27:10760296211049786.

35. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood. 2008 May 15;111(10):4871–9.

36. Scridon A, Balan AI. Challenges of Anticoagulant Therapy in Atrial Fibrillation—Focus on Gastrointestinal Bleeding. Int J Mol Sci. 2023 Apr 7;24(8):6879.

37. Gu ZC, Wei AH, Zhang C, Wang XH, Zhang L, Shen L, et al. Risk of Major Gastrointestinal Bleeding With New vs Conventional Oral Anticoagulants: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2020 Apr;18(4):792-799.e61.

38. Fanikos J, Stapinski C, Koo S, Kucher N, Tsilimingras K, Goldhaber SZ. Medication errors associated with anticoagulant therapy in the hospital. Am J Cardiol. 2004 Aug;94(4):532–5.

39. Biradar S, Indu P, G M, V K, Ambali A, Naikwadi A, et al. Impact of drug-related problems and clinical pharmacist interventions on therapeutic outcomes of the patients admitted to a tertiary care hospital. Int J Med Sci Public Health. 2017;6(4):1.

40. Wung JC, Lin HC, Hsu CC, Lin CC, Wang SY, Chang SL, et al. Drug-related problem characterization and the solved status associated factor analysis in a pharmacist-managed anticoagulation clinic. van Rein N, editor. PLOS ONE. 2022 Aug 15;17(8):e0270263.

41. Al-Baghdadi H, Koca Al-Baghdadi Ç, Abdi A, Gültekin O, Meštrović A, Demirdamar R, et al. Introducing clinical pharmacy services to cardiovascular clinics at a university hospital in Northern Cyprus. Int J Clin Pharm. 2017 Dec;39(6):1185–93.

42. Cohen A, Keshishian A, Lee T, Wygant G, Rosenblatt L, Hlavacek P, et al. Effectiveness and Safety of Apixaban, Low-Molecular-Weight Heparin, and Warfarin among Venous Thromboembolism Patients with Active Cancer: A U.S. Claims Data Analysis. Thromb Haemost. 2021 Mar;121(03):383–95.

APPENDICES

APPENDIX 1A: INFORMED CONSENT FORM

Part 1. Participant Information Form

Title of the Study: Factors Associated With Drug Therapy Problems in Patients on Anticoagulants at Kenyatta National Hospital**.**

Principal Investigator. Mwangi Gakome Kamau, Masters of Pharmacy in Clinical Pharmacy, University of Nairobi. P.O Box 36838-00200 Nairobi.

Supervisors: Dr. George Arthur Mugendi, PhD, UoN

Dr. Rosaline Kinuthia, MPharm, KNH.

Introduction

I'm Mwangi Gakome Kamau, a 3rd year postgraduate student at the school of pharmacy, University of Nairobi. As part of the curriculum, I'm conducting a study to determine the drug therapy problems in patients on anticoagulant therapy at Kenyatta National hospital.
The KNH-UoN ethics and review committee has approved this study. The KNH-UoN ERC ensures that your rights as a study subject are respected and observed during the course of the study.

Purpose of the study

Anticoagulants are a commonly prescribed class of drugs. The purpose of this study is to determine whether there are problems encountered by patients when using the drugs that may interfere with the achievement of treatment outcomes.

Procedures involved

If you agree to participate in this study, a structured questionnaire will be availed to you to enable a short interview at your convenience. The questions will include your socio-demographic data, medication history and your experience with the medication.

The interview will last approximately 15 minutes. The investigator will also extract more information from your medical records. Your privacy during data collection will be ensured.

The rights of a participant

1. Voluntary participation
2. Right to withdraw from the study at will
3. Right to ask any questions before consenting to participate in the study
4. No information provided will be traced back to your
5. Participant information will be utilized sorely for the purposes of this study.

Risks, harms and cost of participation

There will be no direct risks to the patients since there will be no drug or intervention administered to the patients. Study will involve extraction of information from medical records and patient interviews. No costs of this research will fall on the participant.

Benefits of participation

The results of this study will help inform on potential problems and actual problems faced by patients when taking this class of medication and interventions and preventive measures to overcome this obstacles to ensure treatment safety and efficacy.

Reimbursements for participation

There will be no fiscal payments, incentives or tokens for participating in this study.

Confidentiality

All information collected will be regarded as confidential. The questionnaires and any other data will be stored under lock and key and password protected for the electronic data. Only the investigator will have access to the information.

Contacts

In case you have any questions regarding the study before, during or after participation, you can contact the following anytime.

1. Dr. Mwangi Gakome Kamau,

   Department of Pharmacology, Clinical Pharmacy and Pharmacy practice,

   School of Pharmacy,

   University of Nairobi.

   Mobile; 0726522039.

   Email: gakomekamau@gmail.com

2. Dr. George Arthur Mugendi, PhD -Supervisor

   Department of Pharmacology, Clinical Pharmacy and Pharmacy practice,

   School of Pharmacy,

   University of Nairobi.

   Phone number: 2726771/2726300 Ext.43791

   Email: george.mugendi@uonbi.ac.ke

3. Dr. Rosaline Njoki Kinuthia, MPharm – Supervisor

   Pharmacy Division,

   Kenyatta National Hospital.

   Phone number: 0202726300

   Email: rkinuthia@knh.or.ke

4. KNH-UON Ethics and Review Committee,

   P.O. Box 20723-00202,

   Nairobi.

   Phone number: 0202726300

   Email: uonknh-erc@uonbi.ac.ke

Part 2: Certificate of consent.

I have read the above information or had the information read to me. I have had the study sufficiently explained to me by Dr. Mwangi Gakome Kamau. Any questions I asked were answered in a clear language and to my satisfaction. I voluntarily give my written and informed consent to participate in the study through answering a questionnaire and allow review of my medical records. I understand that my rights will be respected throughout the study period

Print Name of Participant_____

Signature of Participant _____

Date _____/_____/_____

Day/month/year

Statement by the investigator

I have adequately and accurately explained the contents of this study and information sheet to the participant named above. I addressed any questions and concerns raised by the participant to the best of my knowledge and they were satisfied. I confirm that the participant has voluntarily given his/her consent without any coercion.

A copy of this informed consent form has been provided to the participant.

Name of the Investigator_____

Signature of Participant _____

Date _____/_____/_____

Day/month/year

APPENDIX 1B: INFORMED CONSENT FORM IN SWAHILI

MAELEZO KUHUSU KUSHIRIKI KATIKA UTAFITI

Mada ya Utafiti: Kutathmini shida za matibabu na sababu za hatari zinazoweza kutokea kwa wagonjwa ambao wanatumia dawa za kuzuia mgando wa damu katika hospitali kuu ya Kenyatta.

Mchunguzi mkuu: Mwangi Gakome Kamau, Shahada ya uzamili ya Famasia , Chuo Kikuu cha Nairobi, Sanduku la Posta 36838-00200 Nairobi.

Wasimamizi Dkt George Arthur Mugendi, PhD, Chuo Kikuu Cha Nairobi

Dkt Rosaline Kinuthia, MPharm, Hospitali Kuu ya Kenyatta

Utangulizi

Mimi ni Mwangi Gakome Kamau, mwanafunzi wa mwaka wa tatu wa shahada ya uzamifu katika kitengo cha famasia, Chuo Kikuu Cha Nairobi. Nina nia ya kufanya utafiti katika eneo la kuthamini shida za matibabu zinazoweza kutokea kwa wagonjwa ambao wanatumia dawa za kuzuia mgando wa damu katika Hospitali Kuu ya Kenyatta.

Chama cha kuhakikisha maadili cha hospitali kuu ya Kenyatta na Chuo Kikuu Cha Nairobi kimepitisha utafiti huu. Chama cha kuhakikisha maadili cha hospitali kuu ya Kenyatta na Chuo Kikuu cha Nairobi kinahakikisha haki za mshiriki zinazingatiwa.

Kusudi La Utafiti

Dawa za kuzuia mgando wa damu hutumika na wagonjwa wengi. Lengo la utafiti huu ni kuchunguza kama wagonjwa wanaotumia haya madawa hupambana na shida zozote zinazozuia wafikie hali bora ya afya.

Taratibu Za Utafiti

Ukikubali kushiriki katika utafiti huu, utapewa dodoso. Kutakuwa na mahojiano, yatayochukua dakika 15 kujibu. Mtafiti atachukua data ingine kutoka faili yako ya matibabu. Faragha yako itatimizwa na taarifa yako ya kibinafsi haitafikia mwingine yoyote isipokuwa mtafiti.

Haki Za Mshiriki

1. Haki ya kushiriki kwa hiari yako

2. Haki ya kujiondoa kwa utafiti wakati wowote

3. Haki ya kuuliza maswali yoyote kabla ya kukubali kushiriki katika utafiti

4.Habari zako za kibinafsi hazitatumika kukutambukisha

5.Habari zako za kibinafsi zinatumika kwa lengo la utafiti pekee.

Hatari, Madhara na Gharama za Kushiriki

Hakuna hatari kwa mshiriki wa utafiti. Mshiriki atajibu maswali pekee bila kupatiwa matibabu yoyote. Mtafiti atachukua habari kutoka rekodi za hospitali na kuhoji mgonjwa. Mshiriki hatagharamia chochote kuhusiana utafiti huu.

Faida ya Kushiriki

Matokeo ya utafiti huu yatasaidia kuboresha matibabu

Marejesheo ya Pesa Ukishiriki Kwa Utafiti Huu

Hakutakuwa na fidia itakayotokana na kuwa mshiriki wa utafiti huu.

Mawasiliano

Kama uko na maswali kuhusu utafiti huu unaweza wasiliana na:

1. Dkt. Mwangi Gakome Kamau,

   Idara ya Pharmacology, Clinical Pharmacy na Pharmacy practice,

   Shule ya Famasia,

   Chuo Kikuu cha Nairobi.

   Nambari ya simu: 0726522039.

   Barua pepe: gakomekamau@gmail.com

2. Dkt. George Arthur Mugendi, PhD -Msimamizi

   Idara ya Pharmacology, Clinical Pharmacy na Pharmacy practice,

   Shule ya Famasia,

   Chuo Kikuu Cha Nairobi.

   Nambari ya simu: 2726771/2726300 Ext.43791

   Barua pepe: george.mugendi@uonbi.ac.ke

3. Dkt. Rosaline Njoki Kinuthia, MPharm – Msimamizi

   Idara ya Famasia,

   Hospitali Kuu ya Kenyatta.

   Nambari ya simu: 0202726300

   Barua pepe: rkinuthia@knh.or.ke

4. Chama cha kuhakikisha maadili cha Hospitali Kuu ya Kenyatta-Chuo Kikuu Cha Nairobi,

   Sanduku la posta 20723-00202,

   Nairobi.

   Nambari ya simu: 0202726300

   Barua pepe: uonknh_erc@uonbi.ac.ke

Taarifa ya Mshiriki

Hii ni kudhibitisha kuwa nimesoma habari hii ya idhini au nimesomewa. Nimejadiliana na mshauri wa utafiti kwa undani kuhusu utafiti huu, na maswali yangu yameshughulikiwa kwa lugha ambayo ninaelewa.

Ninajua faida au/na hatari za kuwa mmoja wa washiriki. Ni wazi kwangu kwamba ushiriki wangu ni wa hiari, na wakati wowote katika somo hili, niko huru kujiondoa. Kwa hivyo, nimekubali kushiriki katika utafiti huu kwa hiara yangu.

Ninaelewa kuwa mtafiti atafanya juhudi zote iwezekanavyo kudumisha usiri wa rekodi zangu za kibinafsi na kitambulisho. Ninaelewa kuwa kwa kukubali utafiti huu, sijatangulia haki zangu za kisheria, ambazo ninastahiki kama mshiriki wa utafiti.

Jina ya Mshiriki: …….

Sahihi: ……...

Tarehe: ……..

Taarifa ya Mtafiti

Baada ya kuelezea mshiriki kila kitu kuhusu utafiti huu, hii ni kudhibitisha kuwa mshiriki anajua haki zake, anaelewa utafiti ni kuhusu nini na nimejibu maswali yote aliyouliza na amesema ameelewa kila kitu na ametoa ruhusa ya hiari kuwa mhusika katika huu

Jina la Mtafiti: ……. ……

Sahihi: ……..

Tarehe: ……

APPENDIX 2: QUESTIONNAIRE AND DATA COLLECTION TOOL
QUESTIONNAIRE AND DATA COLLECTION TOOL

SECTION A: PATIENT SURVEY

Participant's Code Number: . . . . . .

I. SOCIAL DEMOGRAPHIC DATA

Please fill in these details in the spaces provided

1. Age _____
2. Gender Male ☐ Female ☐
3. Weight _____
4. Height _____
5. BMI _____
6. Do you smoke cigarettes?
   Yes☐ No ☐
   If yes, how many years have you smoked cigarettes?
   Less than 10 years ☐
   10 – 19 years ☐
   20 years or more ☐
7. Do you drink alcohol?
   Yes ☐ No ☐
   If yes, how many units of alcohol do you take in a week?
   7 units or less per week ☐
   8 - 14 units per week ☐
   More than 14 units per week ☐
8. Do you carry out regular physical activity (at least 30 minutes for at least 4 days a week)
   Yes ☐ No ☐
9. Marital Status
   Single ☐ Separated ☐ Married ☐ Divorced ☐ Widowed ☐
10. Education level
    Primary ☐ Secondary ☐ Diploma ☐ Degree ☐ Masters ☐ PhD ☐
11. Employment
    Employed ☐ Self-employed ☐ Unemployed ☐ Student ☐ Retired ☐
12. Residence _____
13. Date of current hospital admission _____

II. CLINICAL PROFILE

1. Do you suffer from any comorbidities?
   Yes ☐ No ☐
   If yes, please state any comorbidities that you are diagnosed with.

2. Do you have any drug allergies?
   Yes ☐ No ☐
   If yes, state which drugs the patient is allergic to.

3. What is the patient's medication history?

Medicine	Indication	Duration	Comments(outcome, adverse effects)
Current medication history			
Past medication history			
Home remedies/herbal preparations/dietary supplements			

III. DRUG THERAPY PROBLEMS REPORTED BY THE PATIENT

Treatment Effectiveness

1. Has there been an improvement in your symptoms since you started taking medication?
   Yes ☐ No ☐

2. Have you experienced warmness in your legs, pain and tenderness in your legs, cramping in your legs, discolouration of your legs, swelling of the legs, coughing, difficulty breathing?
   Yes ☐ No ☐

Treatment Safety

3. Have you experienced any episodes of bleeding since starting treatment with the medication?
   Yes ☐ No ☐

4. Have you experienced any unexplained bruising?
   Yes ☐ No ☐

5. Is your stool black in colour?
   Yes ☐ No ☐

6. Do you have any symptoms that you have not told your doctor about?
   Yes ☐ No ☐

Other

7. Do you receive your medication at the same time daily?
   Yes ☐ No ☐

8. Are there any (anticoagulant) medicines that were to be bought outside the hospital but are too expensive for you to buy?
   Yes ☐ No ☐

9. Are you satisfied with your current therapy?
   Yes ☐ No ☐

SECTION B: MEDICAL RECORDS AND MEDICATION REVIEW CHART

I. RELEVANT INVESTIGATIONS

DATE	PARAMETER	VALUE	NORMAL RANGE	INTERPRETATION

II. DIAGNOSIS

What is the current working diagnosis or confirmed diagnosis?

III. MEDICATION CHART

MEDICATION	START AND STOP DATE	DOSE	FREQUENCY	ROUTE	INDICATION	COMMENTS
STAT MEDICATION						
INTRAVENOUS FLUIDS						
OTHER MEDICATION						
HOME REMEDIES/HERBAL PREPARATIONS/DIETARY SUPPLEMENTS						

SECTION C: EVALUATION OF DTPs

1. Did the patient have any DTPs?
   Yes ☐ No ☐
2. If yes, please list the drug/drugs that have drug therapy problems and elaborate further by filling the table below.

	Primary Domains	**Code**	**Tick**
Problems	Treatment effectiveness	**P1**	
	Treatment safety	**P2**	
	Others	**P3**	
Causes	Drug selection	**C1**	
	Drug form	**C2**	
	Dose selection	**C3**	
	Treatment duration	**C4**	
	Dispensing	**C5**	
	Drug use process	**C6**	
	Patient related	**C7**	
	Patient transfer related	**C8**	
	Other	**C9**	
Planned Interventions	No intervention	**I0**	
	At prescriber level	**I1**	
	At patient level	**I2**	
	At drug level	**I3**	
	Other	**I4**	
Intervention acceptance	Intervention accepted	**A1**	
	Intervention not accepted	**A2**	
	Other	**A3**	
Status of the DTP	Problem status unknown	**O0**	
	Problem solved	**O1**	
	Problem partially solved	**O2**	
	Problem not solved	**O3**	

3. Any additional notes on DTPs in the patient?

APPENDIX 3: ETHICS REVIEW BOARD APPROVAL

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

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

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

Ref: KNH-ERC/A/128

27th March, 2023

KENYATTA NATIONAL HOSPITAL 27 MAR 2023 KNH/UoN-ERC P.O. Box 20723 - 00202 NAIROBI

Mwangi Gakome Kamau
Reg.No.U56/37978/2020
Dept. of pharmacy
Faculty of Health Science
University of Nairobi

Dear Mwangi,

RESEARCH PROPOSAL: DRUG THERAPY PROBLEMS AND ASSOCIATED RISK FACTORS IN PATIENTS ON ANTICOAGULANT THERAPY AT KENYATTA NATIONAL HOSPITAL (P865/11/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P865/11/2022.** The approval period is 27th March 2023 – 26th March 2024.

This approval is subject to compliance with the following requirements;

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

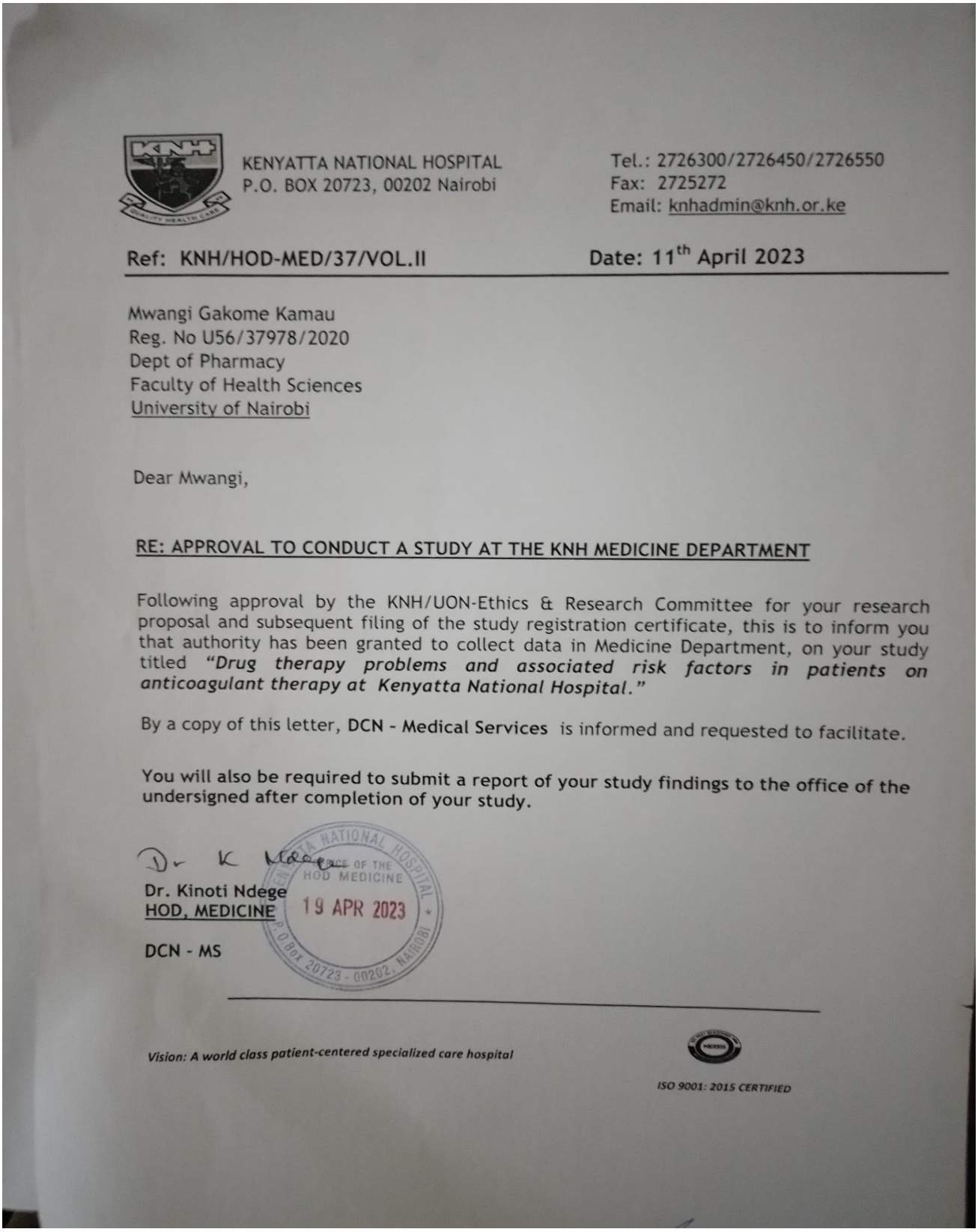
Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Assistant Director, Health Information Dept., KNH
The Chairperson, KNH- UoN ERC
The chair, Dept. of Pharmacy, UoN
Supervisors: Dr. George Arthur Mugendi Dept. of Pharmacy, UoN
Dr. Rosaline Njoki Kinuthia, Clinical Pharmacist, KNH

APPENDIX 4: APPROVAL TO CONDUCT STUDY



KENYATTA NATIONAL HOSPITAL
P.O. BOX 20723, 00202 Nairobi

Tel.: 2726300/2726450/2726550
Fax: 2725272
Email: knhadmin@knh.or.ke

Ref: KNH/HOD-MED/37/VOL.II

Date: 11th April 2023

Mwangi Gakome Kamau
Reg. No U56/37978/2020
Dept of Pharmacy
Faculty of Health Sciences
University of Nairobi

Dear Mwangi,

RE: APPROVAL TO CONDUCT A STUDY AT THE KNH MEDICINE DEPARTMENT

Following approval by the KNH/UON-Ethics & Research Committee for your research proposal and subsequent filing of the study registration certificate, this is to inform you that authority has been granted to collect data in Medicine Department, on your study titled *"Drug therapy problems and associated risk factors in patients on anticoagulant therapy at Kenyatta National Hospital."*

By a copy of this letter, **DCN - Medical Services** is informed and requested to facilitate.

You will also be required to submit a report of your study findings to the office of the undersigned after completion of your study.

Dr. K Ndege

Dr. Kinoti Ndege
HOD, MEDICINE

KENYATTA NATIONAL HOSPITAL
OFFICE OF THE HOD MEDICINE
19 APR 2023
P.O Box 20723 - 00202, NAIROBI

DCN - MS

Vision: A world class patient-centered specialized care hospital

ISO 9001: 2015 CERTIFIED

APPENDIX 5: PLAGIARISM REPORT

27 NOVEMBER 2023

FACTORS ASSOCIATED WITH DRUG THERAPY PROBLEMS IN PATIENTS ON ANTICOAGULANTS AT KENYATTA NATIONAL HOSPITAL

ORIGINALITY REPORT

14%	12%	7%	4%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	erepository.uonbi.ac.ke:8080 Internet Source	2%
2	erepository.uonbi.ac.ke Internet Source	1%
3	www.um.edu.mt Internet Source	1%
4	www.pcne.org Internet Source	1%
5	link.springer.com Internet Source	<1%
6	Wilson W. S. Chu, Gary Chung Hong Chong. "Chapter 30 The Role of Clinical Pharmacists in the Multidisciplinary Care of Geriatric Patients: Now and the Future", Springer Science and Business Media LLC, 2022 Publication	<1%
7	Submitted to University of Nairobi Student Paper	<1%

27/11/23