DRUG THERAPY PROBLEMS AMONG ADULT PATIENTS WITH THROMBOEMBOLIC DISORDERS AT KENYATTA NATIONAL HOSPITAL

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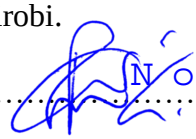
2. Signature:  Date: November 28th, 2023

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DEDICATION

I dedicate this dissertation to my family for their support, prayers and sacrifices that have seen me through my studies.

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ABBREVIATIONS AND ACRONYMS

ACS- Acute Coronary Syndrome

ADR - Adverse Drug Reaction

aPTT- activated Partial Thromboplastin Time

AOR- Adjusted odds ratio

ATC – Anatomical Therapeutic Classification

BMI – Body Mass Index

BTK – Burtons Tyrosine Kinase

CAD- coronary artery disease

CVA- Cerebral Vascular Disease

CVT – Central Vein Thrombosis

DOACs – Direct Oral Anticoagulants

DTPs – Drug Therapy Problems

DVT - Deep Venous Thrombosis

GERD- Gastroesophageal reflux disease

IDA- Iron deficiency anemia

INR – International Normalized Ratio

IQR- Interquartile range

KNH – Kenyatta National Hospital

KNH/UON-ERC – Kenyatta National Hospital/ University of Nairobi – Ethics and Review Committee

LMICs – Low- and Middle-Income Countries

MOPC – Medical Outpatient Clinic

MRPs – Medication Related Problems

NSAIDs – Non-Steroidal Anti-inflammatory Drugs

ORs – Odds Ratios

PE- Pulmonary Thromboembolism

PI – Principal Investigator

PPIs- Proton Pump Inhibitors

PT- Prothrombin time

PTE – Pulmonary Thromboembolism

SD- Standard Deviation

SOPC- Surgical Outpatient Clinic

TEDs- Thromboembolic Disorders

TTR- Time in Therapeutic Range

UK – The United Kingdom

USA – The United States of America

VTEs – Venous Thromboembolisms

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OPERATIONAL DEFINITION OF TERMS

Adherence – also known as compliance, refers to the extent by which a patient retains individual treatment according to the dose and interval of drug prescribed by a health practitioner.

Adverse Drug Reaction - an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.

Comorbidity- An underlying chronic or long-term illness that occur alongside a primary disease.

Dosage too high- In this case, the drug administered is the right one but the dosage administered is more than the recommended for the indication as such it can cause toxic effects in patients.

Dosage too low- In this category of drug therapy problems, the drug prescribed is the right one for the condition but the dose, duration and frequency of drug being administered is insufficient to cause desired outcome/ response.

Drug Interactions – refers to a change in the way a drug acts in the body when taken with certain other drugs, herbs, or foods, or when taken with patients with certain medical conditions. They may cause the drug to be more or less effective, or cause effects on the body that are not expected.

Drug Therapy Problems - any undesirable event experienced by a patient that involves, or is suspected to involve, drug therapy, and interferes with achieving the desired goals of therapy and requires professional judgment to resolve.

Medication Related Problem - an event or circumstance involving drug therapy that actually or potentially interferes with their desired outcome.

Polypharmacy – simultaneous use of three or more prescription drugs.

Poor Anticoagulation – refers to sub-optimal or supra-optimal ranges of INRs and PTs

Therapeutic Failure - a failure to accomplish the goals of treatment attributable to inadequate therapy, a drug-drug interaction that results in a subtherapeutic level for a drug, or medication nonadherence.

Thromboembolic Disorders – medical conditions caused by formation of blood clots in veins and arteries and the subsequent break and dissemination of the clot to distant sites within circulation.

Unnecessary Drug Therapy- refers to a situation whereby a drug is given without necessarily there being a medical indication. This includes use of medication to manage side effects that can be avoided. As such the drug is not necessary and only can lead to toxicity.

Untreated Indication- refers to any other medical condition/symptom that a patient could be having and they are not receiving treatment for them.

Wrong Choice of Medication- this arises when a patient receives a less effective medication when there are better alternatives or when they use a medication that cannot treat the illness or alleviate symptoms.

ABSTRACT

Background: Drug therapy problems are undesirable events experienced by patients that involve, or are suspected to involve medication being utilized. Studies assessing drug therapy problems among patients with thromboembolic disorders are scanty in resource limited areas.

Objective: To describe the pattern of drug therapy problems among adult patients with thromboembolic disorders at Kenyatta National Hospital.

Methodology: Convenient sampling was used to conduct a descriptive cross-sectional study that involved 113 adult patients with thromboembolic disorders at Kenyatta National Hospital outpatient clinics. Clinical data such as medications used, comorbidities and indication for drug therapy was abstracted from the files and recorded in the questionnaire while sociodemographic details were obtained through face-to-face interviews. Drug therapy problems were identified by asking patients questions to determine their adherence and how they were doing to gauge if they needed additional therapy, and checking their medications' use. Outcomes of drug therapy problems were assessed through establishment of anticoagulation profiles and adverse effects such as bleeding.

Data Management and Statistical Analysis: Raw data was entered into a pre-generated Microsoft Excel version 2023 spreadsheet and exported to STATA v.13 for statistical analysis. Descriptive statistics was done using both STATA v.13 and Ms. Excel. Bivariate analysis was conducted using Pearson's Chi test and Fischer Exact test. Predictor variables with statistically significant associations were further subjected to multivariate analysis and backwards stepwise elimination model was used to identify independent predictors of drug therapy problems.

Results: Majority of the participants were female (70.8%) and the median age was 51 years [IQR= 39, 62]. The main indication for antithrombotic therapy was for management of cardioembolic events (58.4%). The overall prevalence of drug therapy problems was 63.7% with the most common drug therapy problems being nonadherence (46.9%), additional therapy needed (35.4%), drug interactions (31%) and adverse drug reactions (14.4%). The major outcomes of these drug therapy problems were poor anticoagulation (28.4%) and bleeding events (3.5%). The independent predictors of drug therapy problems were the use of proton pump inhibitors [aOR=7.155, 95% CI: (0.861, 59.444), ***p***=0.029] and diuretics [aOR=2.689, 95% CI: (1.193, 6.059), ***p***=0.017], meaning that patients on these drugs had 7.155 times and 2.689 times chance of developing drug therapy

problems compared to those not on these drugs. Independent predictors of occurrence of drug interactions included polypharmacy [aOR=8.413, 95% CI: (2.761,25.641), ***p***=0.001] the use of proton pump inhibitors [aOR=10.116, 95% CI: (1.647, 62.103) ***p***=0.012] and vitamin supplements [aOR=41.322, 95% CI: (3.817, 447.288), ***p***=0.002]. The use of clopidogrel was a significant independent predictor for nonadherence, though this association was lost on logistic regression [aOR=7.531, 95% CI: (0.876, 64.751), ***p***=0.066]. The use of calcium channel blockers was an independent predictor of occurrence of adverse drug reactions [aOR=3.708, 95% CI: (0.968, 14.205), ***p***=0.046].

Conclusion: The prevalence of drug therapy problems among patients with thromboembolic disorders was mainly due to nonadherence. The high prevalence of drug therapy problems among patients on diuretics and proton pump inhibitors suggests that anticoagulation management should be intensified in patients receiving these medications. Despite nonadherence being the most prevalent drug therapy identified, only one medication related factor was identified as a significant independent predictor. Further qualitative research should be done to identify non-clinical and non-medical factors that influence non-adherence in patients with thromboembolic disorders.

CHAPTER ONE: INTRODUCTION

1.1 : Background

1.1.1: Burden of Thromboembolic Disorders

Thromboembolic disorders (TEDs) are the third largest type of cardiovascular diseases after stroke and myocardial infarction (1) with annual global incidences of between 1 to 2 cases per 1000 people (1,2). A large, 25-year retrospective cohort study conducted in the American population indicated the incidence of TEDs to be 117 cases per 100,000 person years, with majority of these being reported among males and older people (3). In addition, deep venous thrombosis (DVT) and pulmonary embolism(PE) were the major types of TEDs reported with rates of 48 cases per 100,000 person-years and 69 cases per 100,000 person-years respectively (1). Moreover, related studies indicate that nearly half a million Americans suffer or develop TEDs every year (4).

A meta-analysis of 21 studies in Africa revealed that the prevalence of venous thrombotic events and associated mortality is high especially among patients undergoing surgery, the pregnant and postpartum women(5). In this meta-analysis, the prevalence of DVT was between 2.4% and 9.6% in post-operative patients. In addition, the prevalence of DVT in pregnant and post-partum women was between 380-448 per 100,000 births per year(5). In Kenya, a study on venous thrombosis in pregnancy revealed a 5-year incidence of 1.8 per 1000 deliveries with DVT and PE accounting for 94.9% and 5.1% of all the VTEs respectively (6).

1.1.2: Drug Therapy Problems Among Patients with Thromboembolic Disorders

Drug therapy problem (DTP) is an event or circumstance involving medication use that actually or potentially interferes with desired health outcome. According to Cipolle and Strand, DTPs can be classified into seven classes, namely: unnecessary drug therapy, need for additional therapy, dosage too low, ineffective drug therapy, dosage too high, adverse drug reaction and nonadherence (7).

Several studies have been conducted on DTPs in TEDs among the western population. A study conducted among Americans on both anticancer treatment and anticoagulation therapy revealed an associated increase in bleeding events among patients on both anticoagulation and Burtons Tyrosine Kinase (BTK) Inhibitors (8). In addition, a large Danish cohort study assessed the impact of drug-drug interactions. Findings indicated that the concomitant use of anticoagulants and NSAIDs increased the absolute risk of bleeding among patients with atrial fibrillation (9). In the

same study, there were 11.4% and 13.0% occurrences of serious bleeding and thromboembolism, respectively. These studies indicated that probably the dosage of anticoagulants was too high or there were drug-drug interactions.

In one study conducted in Ethiopia, the burden of DTPs among patients with TEDs was evident. Majority of the patients had either subtherapeutic doses of anticoagulant (49.2%) or excess doses of anticoagulant (17.3%). Moreover, 37.4% of the patients with DVT had multiple drug interactions. In the same study, nonadherence (6.6%) and adverse drug reactions (9.0%) were also noted (10).

Locally, a study by Mariita *et al*. assessing the patient factors impacting on oral anticoagulation therapy among adult outpatients revealed that less than half of the patients had optimum anticoagulation which could be attributed to underdosing of the anticoagulants (11). Another study by Kamuren *et al*. revealed poor anticoagulation among patients with TEDs on warfarin therapy with only 14.8% of INRs being in range. Moreover, the study revealed significant drug interactions with over 52.0% of the patients having major drug interactions (12). Another study by Karuri *et al*. evaluating the quality of oral anticoagulation among patients on follow up at KNH revealed that 95% of the patients had drug interactions(13). Another local study by Iqbal *et al*. studying the effects of patient education on adherence to anticoagulants revealed that before education the nonadherence among patients at KNH was 71.1% which reduced to 33.3% after education (14).

Although there are numerous studies that have assessed the quality and adequacy of anticoagulation among patients with TEDs, there is limited published literature on DTPs among these patients, especially in resource-constrained settings. This study seeks to identify DTPs among patients being treated for TEDs at the KNH. It aims at identifying the DTPs, categorizing them so as to provide information about the nature of drug therapy problems currently being experienced so as to improve anticoagulation management.

1.2: Problem Statement

TEDs have a reported incidence of 1-2 cases per 1000 people(1,2). They also have high morbidity, mortality, poor quality of life and even financial costs (2,15,16). The management of TEDs pose a challenge because multiple drugs may be prescribed in addition to anticoagulants. This is because studies have suggested that these patients may have multiple comorbidities or other underlying

medical conditions(6,12,17). A local study revealed that patients on long term anticoagulation for instance, had an average of 7.5 drugs per patient with a range of 1 to 18 drugs (10,12).

The use of multiple drugs in patients with TEDs is likely to cause DTPs and probably poor therapeutic outcomes such as therapeutic failure, drug interactions and development of adverse drug reactions(10). The burden of DTPs is well documented and the adverse effects of drug therapy problems include increased hospitalization costs, increased medications cost, harm to the patients, increased unnecessary expenditure on healthcare by governments and health financiers and in some cases, death has been reported due to DTPs (18–20).

Most of the existing local and regional studies on TEDs have embarked onto the epidemiology of TEDs and adequacy of anticoagulation (6,11,12,14,17,21). However, studies focusing on characterization of DTPs among patients with TEDs are scarce, especially in low resource settings.

1.3: Research Questions

The study sought to answer the following research questions:

1 What are the types and prevalences of drug therapy problems identified among adult patients with thromboembolic disorders at KNH?
2 To what extent do drug therapy problems affect clinical outcomes in adult patients with TEDs at KNH?
3 What are the predictors of drug therapy problems among the adult patients with thromboembolic disorders at KNH?

1.4: Objectives

1.4.1: Broad Objective

To describe the pattern of drug therapy problems among adult patients with thromboembolic disorders at Kenyatta National Hospital (KNH).

1.4.2: Specific Objectives

1 To find out the types and prevalences of drug therapy problems among adult patients with thromboembolic disorders at KNH.
2 To determine the extent to which drug therapy problems affect clinical outcomes among adult patients with thromboembolic disorders at KNH.
3 To identify predictors of drug therapy problems among adult patients with thromboembolic disorders at KNH.

1.5: Study Justification

This study sought to identify the DTPs among the adult patients with TEDs. Further, it sought to identify significant factors associated with the identified DTPs in the patients. The study was also aiming at finding out the clinical outcomes associated with the identified DTPs. This information will be important in addressing the DTPs in terms of their prevention and mitigation. For instance, the information generated will provide patient counselling points to improve adherence and identify educational and training needs for caregivers which can lead to behavior change especially when prescribing and doing physical exams to consider holistic approach to address unattended symptoms/undermanaged conditions, all in an effort to minimize DTPs.

Whereas extensive studies have been conducted locally in the area of use of anticoagulants, the efficacy of anticoagulation, the epidemiology of some TEDs and clinical outcomes of TEDs, studies focusing on DTPs in TEDs are lacking (6,11,12,14,17,21). As such, this study was intended to fill the knowledge gap that exists locally on the DTPs among patients with TEDs and identify the factors associated with these DTPs and the clinical outcomes in patients with DTPs.

The results of this study could be important for all stakeholders as they can identify potential areas of action and can help in formulation of policies that would be potentially beneficial in mitigating DTPs among patients with TEDs. For the government and hospital management, the burden of DTPs and clinical outcomes of DTPs among patients with TEDs has been highlighted and programs can be put in place to address the causes of DTPs especially advocating for adherence among patients. For the caregivers, the study highlighted that polypharmacy is a leading cause of DTPs and some of the patients had additional symptoms that were not being addressed and undermanaged conditions. This could be a key action area as infrastructure and guidelines can be put in place to ensure patients are optimally managed, there is appropriate selection of medications and avoidance of unnecessary drug therapy. For the patients, nonadherence was high and as such, the caregivers can encourage adherence by counselling the patients to improve adherence.

1.6: Conceptual Framework

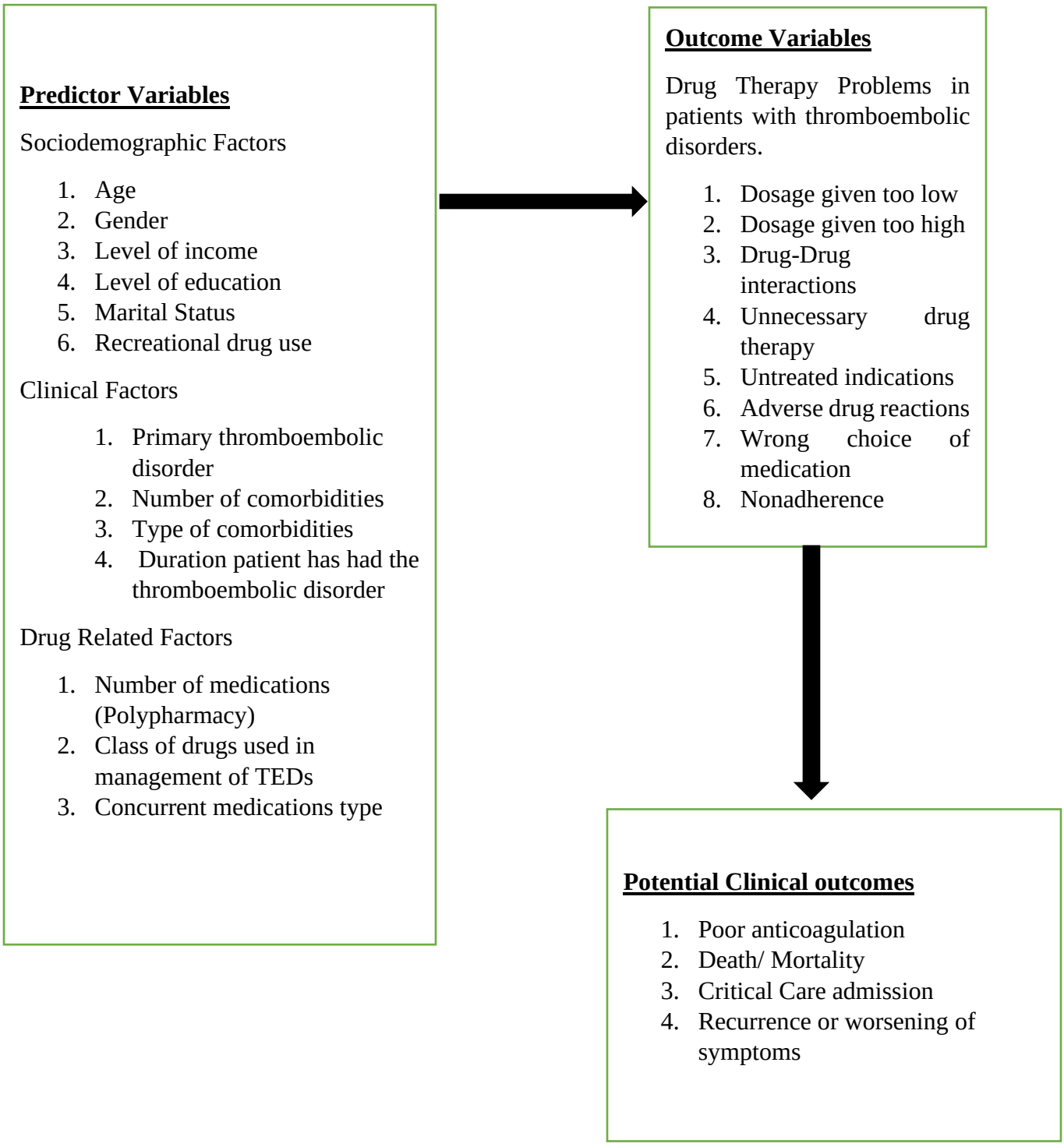


Figure 1: The conceptual framework of the study

1.7: Theoretical Framework

Sociodemographic factors are important predictors of drug therapy problems. Age is a risk factor for potential DTPs due to challenges in dosing of drugs, due to reduced organ function and comorbidities(22,23). Presence of comorbidities poses a challenge in provision of pharmaceutical care. Some comorbidities may require dosage adjustment of the drugs. For instance, in patients with renal disease or hepatic disease, dosage adjustments may be needed to optimize therapy and minimize development of adverse drug events. Failure to recognize these comorbidities and/or inappropriate dosage adjustments could lead to DTPs.

Generally elderly patients are at increased risk of development of hemorrhagic complications (24). Moreover, one study indicated that the DTP of non-adherence to warfarin anticoagulation was high among the young patients (25). Educational status and level of income also can predispose one to DTPs especially in a setting where they affect affordability of drugs and ability to understand warnings and precautions associated with use of drugs (26).

Drug related factors perhaps present the biggest contribution in terms of DTPs. Studies have demonstrated that the frequency of DTPs among different categories (ATC Classifications) of drugs differ (23,27). The use of more than one class of drugs due to comorbidities or due to the need for synergy also poses a risk for DTPs especially drug-drug interactions. For instance, an American Study demonstrated significant drug-drug interaction among patients receiving NSAIDs and anticoagulation(9). Another American study revealed significant interactions between anticoagulants and anticancer medications(8).

Ultimately, the possible clinical outcomes of these DTPs include poor coagulation, death/ Mortality, critical care admissions, requirement for additional monitoring, and recurrence or worsening of symptoms of thromboembolic disorders(10,28,29).

1.8: Delimitations

This study was conducted among adult patients (18 years and above) both male and female, who attended outpatient medical clinics at KNH. Only patients with thromboembolic disorders were recruited regardless of other comorbidities. Information bias was minimized by conducting both oral interviews and confirming information on the patient files.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter highlights the existing literature on DTPs among patients with TEDs. This included the epidemiology of DTPs in patients with TEDs, with focus on both the global burden and local burden of DTPs among patients with TEDs.

Further, different classes of DTPs among patients with TEDs are discussed in this chapter. Additionally, the gaps in existing local literature are discussed and how the study sought to fill some of those gaps.

2.2 Epidemiology of Thromboembolic Disorders

Thromboembolic disorders such as Venous thromboembolism (VTE) and its complication, Pulmonary Embolism (PE) are a great burden to public health, having a high mortality rate and a relatively high incidence. VTE affects 78 to 137 million people globally every year (1). Further, VTE is the third most common cardiovascular disease according to WHO, with an incidence of 1-2 new cases per 1000 people annually and accounting for over 17.5 million deaths annually as at 2012, with majority of these deaths (over three quarters) occurring in Low and Middle Income Countries (LMIC) (1,2).

In the USA, incidence rates vary with gender, age and race, with African Americans having the highest incidence rates and Asian Americans having the lowest incidences. A 35-year population-based study in the USA (1966-2000) revealed an overall age and sex adjusted incidence rate of 122 cases per 100,000 people-years per annum (30). Of these, DVT accounted for 56 cases while PE accounted for 66 cases per 100,000 person years. Moreover, the study further revealed that men had higher incidence rates compared to women (134 vs 115 cases per 100,000 person years).

Another population-based survey conducted in Worcester, Massachusetts by Huang et. al revealed that age and sex adjusted annual event rates for first time thrombotic events increased from 73 per 100,000 person years at the beginning of the study (1985/86) to 133 per 100,000 person years in 2009 at the conclusion of the study (31). A large survey conducted in Alberta, Canada over 10 years revealed the incidence rate of VTE to be 1.38 per 1000 person years. DVT accounted for majority of the cases (1.0 per 1000 person years with PE accounting for 0.3 per 1000 person years. The same study indicated that PE, predictably had highest case fatality compared to DVT. A 30-

day case fatality following DVT was 2% while the case fatality in this duration was almost double (3.9%) for PE. Further, the 1-year case fatality was 9.2% for DVT and 12.9% for PE (32).

In Europe, a study conducted in Norway by Nadia *et al*. using population data revealed an overall incidence rate of 188 per 100, 000 person-years. The study further revealed that most of the cases were due to DVT as compared to PE (108 vs 80 per 100,000 person years). Time trend analysis indicated increase in incidence over time. Further, comparing gender by age group, women of reproductive age had higher incidence rates compared to males of the same age groups (33). The annual incidence of PE in the UK is 7-8 per 10,000 people while that of DVT is significantly lower especially among the young (1 in 10,000) with higher rates among those ≥80 years of age (1 in 100) (34).

Studies have shown that people of Asian origin have less incidence rates of TEDs as compared to Caucasians. One Chinese study revealed relatively low prevalence and incidence of TEDs. This study by Cheuk *et al*. revealed annual incidences of PE and DVT to be 3.9 per 100,000 people and 17.1 per 100,000 people, respectively. Further, the study showed low incidence of DVT and PE following surgery, with incidences being 0.13 and 0.04% respectively (35).

In a study conducted in Saudi Arabia by Al Sheef *et al*. involving patients with suspected TEDs over 10 years in a registry system, just over 1000 patients were registered and of these, majority (73.2%) were women. Further, over half (58%) had unprovoked VTE. Of the cases of provoked VTE, most common causes of VTE were surgery (29.8%) and hospitalization (24.2%) (36). Findings from a study conducted in South Iran revealed a higher prevalence of Venous thromboembolism (61.6%) compared to arterial thromboembolism (38.4%). This study by Akbari *et al*. further revealed that females were the most affected by TEDs compared with males (52.5% vs 47.5%) (37).

A systematic review conducted by Danwang *et al*., focussing on the epidemiology of VTE in African setting, revealed that the prevalence of DVT following surgery was between 2.4 and 9.6%. The review further revealed that the cases of DVT following pregnancy were 380-448 per 100,000 births per year among pregnant and post-partum women. According to the same review, the prevalence of PE varied between 0.14-61.5% among medical patients with a mortality rate of between 40 and 69.5% (5).

In a study conducted in Nigeria by Adelaye *et al*., 2.4% of patients undergoing neurosurgery developed VTE with 60% of these ultimately dying (38). A hospital-based cross sectional study conducted by Njonnou *et al*. in Yaoundé, Cameroon among patients with suspected VTE revealed that majority of the patients had DVT (49.5%), 38.7% had PE while 11.8% had PE associated with DVT (39). Another study conducted in Cameroon among medical patients revealed an overall prevalence of TEDs to be 5.5%. Of these, majority had DVT (69.6%), 17.7% had PE, 11.4% had post-phlebitic syndrome and 0.1% had cerulae alba dolens (40). Studies conducted in Sudan involving pregnant and post-partum women indicated incidence of DVT to be 448 per 100,000 birth-years with majority of the events (93.8%) being diagnosed during post-partum period. A study conducted in Eritrea by Hagos *et al*. revealed a prevalence of DVT to be 8% among patients admitted to ICU (41).

In East Africa, some studies have been conducted in the field of TEDs and anticoagulation. One such study conducted in Uganda by Muleledhu *et al.* found out that the prevalence of DVT among patients undergoing major abdominal surgery to be 5.0%. Majority of those who developed DVT (75.0%) were female (42). A study by Mugeni *et al*. in Rwandan hospitals revealed a prevalence of DVT to be 5.5% in the study population with equal rates in both medical and obstetrics and gynaecology wards. Further, higher prevalence was noted in women (70%) (43).

Within the local Kenyan setting, some studies have been done as well involving different categories of patients in relation to TEDs. A study by Kamuren *et. al* at a referral hospital in Eldoret gave a prevalence of TEDs to be 4.5%. Of these events, females had a higher prevalence (57.1%) compared with males. According to the same study, the most common TEDs were DVT (65.1%) and atrial fibrillation (22.2%) (12). A study conducted by Micheni *et al*. involving pregnant and puerperium women over 5 years at KNH found a prevalence of TEDs to be 1.8 per 1000 deliveries with DVT accounting for majority of the TEDs at 94.9% while PE accounted for 5.1%. From the same study, majority of the thromboembolic events happened during the antenatal period (74.5%) whereas few (25.5%) occurred postnatally (6).

Another study conducted at KNH by Ogeng'o *et al*. involving patients with pulmonary thromboembolism (PTE) revealed that females were the most affected compared to males (ratio of 1.3: 1). The study further revealed that most of the patients who had developed PTE had

underlying history of DVT (36%). Moreover, 28.1% of the patients died while 72.1% survived with about a quarter developing cor pulmonale (17).

2.3 Drug Therapy Problems

As defined by Cipolle, Strand and Morley, a drug therapy problem is any undesirable event experienced by a patient that involves or is suspected to involve drug therapy and that event interferes with the achievement of the desired goals of therapy and thus requires professional judgement to solve (7). If DTPs are not solved, there will be clinical consequences, hence the need for good clinical judgement and resolution by relevant practitioners.

Whilst many formats have been developed for classifying DTPs and associated Medication Related Problems (MRPs), this study will focus on the classification developed by Cipolle *et al*. which classifies DTPs into seven classes as indicated in Table 1. The Cipolle-Strand-Morley classification covers all domains of drug related needs of patients including the effectiveness, indication, adherence and safety.

Table 1: Classification of drug therapy problems.

Serial No.	Class of drug therapy problem
1.	Unnecessary drug therapy
2.	Needs additional drug therapy
3.	Ineffective Drug
4.	Dosage too low
5.	Dosage too high
6.	Adverse drug reaction
7.	Adherence (Non-Compliance)

2.3.1 Unnecessary Drug Therapy

This DTP arises in the event a patient is using a drug which is unnecessary at the moment because the patient lacks the condition or symptoms that the drug could be used to manage or treat normally. Some of the common causes of this DTP include: using more than one medication to manage a condition that can be managed by one medication, using drugs to manage conditions that can be managed non-pharmacologically, using a drug to manage adverse effects of another drug

that can be avoided, no medical indication for a drug and use of drugs for recreational and addictive purposes (7).

2.3.2 Needs Additional Drug Therapy

This denotes that additional medication is required to manage untreated condition or relieve unaddressed symptoms or to prevent a condition or symptoms from developing. The causes of this DTP include: unaddressed medical condition that requires initiation of drug therapy, need for additional pharmacotherapy for the purpose of synergy or additive effects and the need for preventive therapy to reduce the risk of developing a new condition for instance the use of aspirin in patients with cardiovascular disease to prevent secondary heart attacks (7,44).

2.3.3 Ineffective Drug

This DTP denotes that the drug used is not producing the desired therapeutic outcome or response. Some of the causes of this include: use of an ineffective drug for the medical condition, use of a contraindicated drug for the condition/patient population, the medical condition being refractory to the drug, use of inappropriate dosage form and the drug being used not being the most effective for the condition.

2.3.4 Dosage Too Low

In this category of DTP, the drug prescribed is the right one for the condition but the dose, duration and frequency of drug being administered is too low to cause desired outcome/ response. Potential causes of this DTP include: too low dose, the dosing interval is too infrequent to attain good plasma concentrations, incorrect administration of the drug, incorrect storage of the drug, drug interactions that can cause low levels of the drug in plasma, short duration of administration to produce desired effect and needs for additional monitoring to determine if the dosage is too low.

2.3.5 Adverse Drug Reaction

Adverse drug reaction (ADR) refers to a negative reaction to a drug or drug product that is not dose related and often leads to substitution of the drug for a safer drug. Some of the causes of this DTP include: use of contraindicated drugs, drug product causing allergic reactions, incorrect administration of drug product, rapid administration or change of treatment regimen, drug interactions and based on the risk factors of the patient, a safer drug was required to begin with (7).

2.3.6 Dosage Too High

In this case, the dosage administered is too high to the extent it can cause toxic effects in patients. Common causes of this DTP include: drug interactions leading to high levels of the drug or metabolites, prolonged duration of therapy, too short frequency of administration, high dose of drug product and the need for additional monitoring to determine whether the dose is too high (7).

2.3.7 Adherence (Non-Compliance)

Noncompliance refers to the patient not being able or willing to take the drug as intended. Causes of noncompliance include: patient not being able to afford the drug, the patient willingly prefers not to take the drug, the patient does not understand the instructions on how to take the drug, forgetting to take the drug, the drug is not available and the patient cannot self-administer or swallow the drug appropriately.

2.4 Drug Therapy Problems Among Patients with Thromboembolic Disorders

A study conducted by Stafford *et al*. in Australia focussing on DTPs of post-discharge warfarin use in patients with DTPs revealed that out of the 109 reviews done, 157 DTPs were identified, an average of 1.4 DTPs per patient (45). A multicentre cross-sectional study conducted by Viprey *et al*. in Lyon, France involving patients on direct-acting oral anticoagulants (DOACs) for atrial fibrillation revealed an overall prevalence of DTPs to be 8.4%. The study also revealed that the most common DTPs were dosage too low (4.7%) and dosage too high (3.1%) (46).

In a study conducted in Lebanon by Bassam *et al*., the overall prevalence of DTPs in patients on anticoagulation for atrial fibrillation and stroke was 87.2%. In the study, patients were grouped into 3 categories, those receiving acenocoumarol, those receiving dabigatran and those on rivaroxaban. Excessive doses as a DTP were noted in 35.2% of the patients on acenocoumarol, 7% in dabigatran and 10.2% of those on rivaroxaban. Moreover, dose too low was documented in 22.2% of patients on acenocoumarol and 2.3% of patients on rivaroxaban. Potential drug interactions were reported for all the groups with the acenocoumarol group leading with 93.8%, followed by 69.8% in dabigatran and lastly 51.3% of patients on rivaroxaban had potential drug interactions (47).

A Nigerian study by Anakwue *et al*. revealed that effective anticoagulation was achieved in just 30.8% of the patients. Further, the DTP of “adverse drug reaction” was reported in 11.5% of the patients (48). Elsewhere, a study by Daba *et al*. in Ethiopia revealed that the most common DTPs

encountered in patients undergoing anticoagulation were dosage too low, dosage too high and potential drug interactions. In this study, dosage adjustments were done yet over half (51%) of the study participants did not attain therapeutic INRs (10). In the same study, 41.8% of the patients had potential drug interactions, non-adherence was reported in 8% of the study participants, mainly due to skipped doses of warfarin and lack of access to the drug. Further, about 9% of the patients experienced adverse drug reactions, mainly bleeding (10).

Locally, some studies have been conducted with different objectives that can reveal the burden of some of the DTPs in patients receiving anticoagulation. In a study conducted at Eldoret by Kamuren *et al*. assessing efficacy of anticoagulation, only 14.8% of the INRs were within range for the study duration. The causes for out-of-range INRs were attributed to drug interactions, too low or too high doses (12).

A study by Karuri *et al.* revealed that 95% of the patients on TEDs prophylaxis had significant drug interactions that can lead to DTPs. The study further revealed that almost half of the follow up time, patients had too low doses of warfarin leading to subtherapeutic INR (13). Another study by Nyamu *et al*. conducted at KNH focussing on adequacy of ambulatory anticoagulation revealed poor anticoagulation with only 27.5% percent of the study participants having adequate anticoagulation (49). The poor anticoagulation could be as a consequence of one or several DTPs which were not characterised.

A Pre-Post study by Sakina *et al*. assessing knowledge on anticoagulation among patients on warfarin revealed that the adherence to warfarin was low during the initial assessment (about 33%) but following education of the patients, the adherence improved to 67%. The study also revealed that there was poor anticoagulation control before the education, which improved following the education (30% to 50%) (14).

2.5 Risk Factors for DTPs in TEDs

Comorbidities play a great role in the development of DTPs. In the Lebanese study conducted by Bassam *et al.*, DTPs had a great association with comorbidities with out-of-range INRs being strongly associated with anaemia, renal disease and dialysis ($p=0.03$, $p=0.001$ and $p=0.020$, respectively). This translated to 64.1% of anaemic patients, 93.8% of patients on dialysis and 73.1% of those with renal disease having non-therapeutic INRs. Further the number of comorbidities was also a risk factor for uncontrolled aPTT ($p=0.013$) (47). A study conducted by

Kamuren *et al*. in a resource limited setting also concurred with this finding and strongly revealed that both the number and type of comorbidities affect anticoagulation control. In the study, the more the comorbidities, the poor the anticoagulation. Patients with underlying cardiovascular disease had the most uncontrolled INRs at 54.2%. Other classes with significant findings included patients with cancer, hepatic and renal disease (12).

Besides the underlying comorbidities, the study by Bassam *et al*. also revealed that the class of co-administered drugs also had an impact on the anticoagulation control. Renal disease and concomitant use of PPIs caused a 2-5-fold increase in the probability of having uncontrolled INR (OR=2.153). Renal disease and concomitant use of NSAIDs was associated with twofold increase in the probability of uncontrolled INR (OR=2.114). Further, the use of antiplatelet drugs was associated with uncontrolled aPTT in 29.6% of the patients (p=0.025) (47). In the study by Kamuren *et al.*, all of the patients were on concomitant drugs in addition to anticoagulants. Anti-infective and analgesics were the most co-prescribed drugs at 70% and 64%, respectively. Given their drug interactions with warfarin, the anti-infectives would have contributed to out-of-range INRs. Further other drugs with potential for drug interactions were administered including metronidazole (25%), cotrimoxazole (14%), rifampicin (8%) and diclofenac (8%). The number of drugs used concomitantly also had an association with the uncontrolled INRs (12). The findings were similar in an Ethiopian study by Daba *et al.* which revealed that 57.9% of the deranged INRs could be attributed to drug interactions between warfarin and co-prescribed medications of which majority were anti-infectives (61.6%) (10).

The choice and dose of the administered anticoagulants are also good predictors of DTPs. For instance, subtherapeutic doses of anticoagulants will lead to poor anticoagulation whereas excessive doses will lead to adverse events such as bleeding in warfarin overdose. In the study by Daba *et al*., the variation of the cumulative weekly dose of warfarin led to moderately linear relationship between the percentage of dose adjustment and consequent INR (10). In another study, the use of apixaban was associated with better adherence as compared to other anticoagulants (50).

Generally, age also has an impact on the success of anticoagulation. This is mainly because of the physiological changes that occur with aging. The elderly may be on more than one drug (polypharmacy) which can have unpredictable drug interactions with anticoagulants. Further, the elderly are susceptible to comorbidities and failing organ systems that can lead to drug toxicities.

Contrast to this, one American study reported better adherence in older patients compared to younger patients (50). Locally, poor anticoagulation has been reported among the elderly as compared to younger patients, with one study conducted by Nyamu *et al*. revealing that patients aged 60 years or more had poor anticoagulation (p=0.006) (49).

A study by Kizito *et al*. assessing patient factors impacting on oral anticoagulation therapy among adults in a referral hospital revealed that indication for the use of anticoagulants, female gender (OR=2.782, p=0.011) and lower education levels (OR=1.935, p=0.005) were good predictors of poor anticoagulation (11). Other significant predictors for DTPs in TEDs patients include: Smoking which was also associated with uncontrolled aPTT in the Lebanese study (OR=8.325) (47), the occupation of a patient which was found to be associated with adherence in the study conducted by Sakina *et al*. (14), race and ethnicity where African Americans were associated with low adherence to anticoagulants (p=0.006) (50).

2.6 Outcomes of DTPs Among Patients with TEDs

Poor anticoagulation as a result of DTPs among patients with TEDs is quite common. Pooled data from USA, China and Canada showed relatively better achievement of anticoagulation with a mean percentage of time within therapeutic range (%TTR) being 59.9% (Range of means 56.0-64.0%) (51). On the contrast, in Africa, the achievement of desired anticoagulation is relatively low, with one Nigerian study showing success rate of 39% (48), an Ethiopian study by Daba *et al.* showed a success rate of 49% (10), while a South African study showed successful anticoagulation in 32-58% of the patients (52). Locally, successful anticoagulation has been achieved in rates of between 7% to 43.5% (11,12,48,49).

Mortality is also an outcome of DTPs among patients with TEDs. In a Japanese study comparing the outcomes of underdose and standard dose rivaroxaban use among patients with VTEs, death due to PE or any other cause was higher in the group that received the underdose (10.9% per patient year) than the group that received standard dose (3.6 % per patient year), p=0.001 (29). Locally, a study by Micheni *et al.* targeting pregnant mothers reported a 5-year maternal mortality rate of 1.7% among pregnant mothers with TEDs who never achieved controlled anticoagulation (6). Higher mortality rates were reported in a study conducted by Kamuren *et al*. which was conducted in Eldoret. In this study, 28.6% of the study participants died. Majority of those who died were receiving anticoagulation for atrial fibrillation and DVT (12).

Aggravation or recurrence of symptoms is a possible outcome of the DTPs among patients with TEDs. In the study by Daisuke *et al*., recurrence of symptoms or aggravation was noted in 1.77% per patient-year on subtherapeutic doses of rivaroxaban and 3.35% per patient-year on standard doses. The incidence of worsening or recurrence of DVT symptoms was significantly different for patients with DVT in the underdose group relative to those in standard dose group (0.9% vs 2.8% per patient-year respectively), p=0.035. As much as the data portrayed the lower doses to have less incidences of recurrence or aggravation of DVT symptoms compared to standard doses, there was no statistical significance (29). A study comparing multimorbid patients vs nonmorbid patients revealed that the 3-year cumulative incidence of recurrent VTE was higher in multimorbid patients (16.8% vs 10.8%, p=0.056). This was attributed to poor anticoagulation in multimorbid patients (53).

Bleeding is a major side effect of anticoagulant use and both major and minor bleeding could indicate poor clinical outcome which could be due to one or more DTPs. Major bleeding was a significant outcome of poor anticoagulation in the study carried out by Lange *et al*. in Switzerland, with major bleeding being reported in both multimorbid and nonmorbid elderly patients (3-year cumulative incidence of 18.7% and 9.0% respectively (53). The Ethiopian study by Daba *et al*. revealed a 9% incidence of bleeding disorders following use of warfarin (10). In the local study by Kamuren *et al*., bleeding episodes were documented in 6.3% of the study participants (12).

Poor clinical outcomes could necessitate in-patient admissions to manage the complications brought about by DTPs. A study conducted in Bangkok by Paisansirikul *et al.* revealed that 10% of the study participants had to be admitted due to complications, mainly adverse drug reactions (54). The study by Kamuren *et al*. revealed that 1.6% of the study participant had to be admitted thrice during the study duration. Further, 9.5% were admitted twice during the study duration. The median duration of hospital stay was 9 days [IQR: 7.0, 16.5] with hospital stays ranging from 3 days to 104 days (12).

2.7 Gaps in Local Literature

Many studies have been conducted locally, both in referral hospitals and in other relatively smaller hospitals in the area of anticoagulation and TEDs. Most of these studies have explored the adequacy of anticoagulation, the characteristics of patients receiving anticoagulation, factors impeding attainment of effective anticoagulation, the prevalence of TEDs among different

categories of patients on anticoagulation, knowledge of patients regarding anticoagulation therapy, among other topics (6,11,12,14,17,49).

However, despite the rich local information generated from these studies, studies focussing on DTPs among patients receiving anticoagulation and DTPs among patients with TEDs are lacking. Some local studies have indicated the clinical outcomes of poor anticoagulation. Some of these studies have indicated death, bleeding, hospital admissions and worsening or recurrence of symptoms of TEDs to be the most common clinical outcomes.

There are no local studies giving information on the prevalence of different classes of DTPs in patients on anticoagulation at large and prevalence and classes of DTPs in patients with TEDs in particular. Further, no studies have been conducted to assess predictors and outcomes of DTPs among patients with TEDs. Therefore, this study aimed at filling these gaps.

CHAPTER THREE: METHODOLOGY

3.1: Perspective of Research Methodology

This chapter describes the methods and processes that were undertaken to ensure the data collected was as accurate as possible and of good quality. It also describes how the data was handled so as to ensure the study objectives were met while upholding research ethics.

This part also describes the study design, study population, eligibility criteria, ethical considerations, sampling technique, recruitment of study participants, data collection and handling. It also includes the data quality assurance and data management, all in an effort to come up with quality data that meets the study objectives.

3.2: Study Design

The study conducted was a descriptive cross-sectional study that was carried out among adult patients with TEDs visiting outpatient clinics at KNH. This study design was chosen because it can easily and simply give the prevalences of interest in the study. Further, it can be conducted over a lesser duration of time as both exposure and outcomes can be measured (observed) simultaneously and thus its relatively cheaper.

3.3: Study Area and Site

The study site was Kenyatta National Hospital (KNH) the largest referral hospital in Kenya, serving patients from Kenya, as well as East and Central Africa. The Hospital is located along Ngong Road approximately 3.5Km from Nairobi's Central Business District. The hospital was founded in 1901 and has a bed capacity of over 2000, with several Intensive Care Units (ICUs), 22 outpatient clinics, 24 theaters and 50 in patient wards.

Specifically, the study was carried out in the outpatient clinics where patients with TEDs are attended to, these included the Medical Outpatient Clinic (MOPC) and the Surgical Outpatient Clinic (SOPC) which provide services to patients with TEDs on Mondays, Wednesdays and Fridays.

3.4: Study Population

The study targeted adult patients (≥18 years of age) with a diagnosis of any thromboembolic disorder or with a thromboembolic disorder as a comorbid condition. These patients were attending the outpatient clinics for the management of the TEDs. This included patients with the following

conditions: deep venous thrombosis (DVT) with or without pulmonary embolism (PE), cerebral vein thrombosis (CVT), arterial thromboembolism, atrial fibrillation, post-operative patients seen in outpatient clinics and patients who have undergone surgery for implantation of prostheses.

3.5: Eligibility Criteria

3.5.1: Inclusion Criteria

1. Patients aged ≥ 18 years of age with TEDs
2. Patients with TEDs who were attending the outpatient clinics at KNH
3. Patients who gave informed consent to participate in the study
4. Patients who were available during the duration of the study, three months.

3.5.2: Exclusion criteria

1. Patients with cognitive impairment who could not give reliable information.
2. Patients who refused to give consent to participate in the study
3. Patients under the age of 18 years
4. Patients without a TED or lacking indication for anticoagulation therapy

3.6: Sample Size Estimation

In line with the study design, the Cochran Formula was used to estimate the sample size(55).

According to the Cochran Formula, the sample size was to be given by:

$$n_0 = \frac{z^2 pq}{e^2}$$

Where n_0= the estimated sample size

Z = desired confidence level (95%) corresponding to Z value of 1.96

p = estimated prevalence DTPs among patients with TEDs

q = (1− p)

e = desired level of precision (0.05)

Local data on prevalence of DTPs among patients with TEDs is lacking but several local studies assessing efficacy of anticoagulation have revealed low anticoagulation efficacy, probably due to DTPs. Based on this assumption, the prevalence of poor anticoagulation was used as an indirect

indicator of the prevalence of DTPs in these patients. A study by Karuri *et al.* revealed 95% of patients on warfarin had potential drug interactions that could lead to DTPs (13).

Further studies by Nyamu *et al*. (49) and Kamuren *et al*. (12) revealed poor anticoagulation with prevalence of uncontrolled INRs at 82.5% and 85.2%, respectively.

Based on the three studies, the average prevalence was determined to be 87.57%. Therefore, the sample size was calculated as follows:

$$n_0 = \frac{1.96^2 * 0.8757 * 0.1243}{0.05^2}$$

$$n_0 = 167$$

Adjusting for attrition or data loses, a 10% allowance was added. Thus, the definitive sample size was calculated to be:

(110*167) / 100= 184

However, the reached sample size was 113 study participants. This was mainly due to a lower-than-expected study population being reached, incomplete medical files and some of the patients meeting the inclusion criteria declining to give informed consent.

3.7: Sampling Method

Convenient sampling was used to attain the desired sample size. Adults with TEDs visiting outpatient clinics who met the inclusion criteria and gave informed consent were recruited for the study. Recruitments were done during clinic days for both medical and surgical clinics.

3.8: Participants Recruitment and Consenting Process

Prior to the clinic days, the principal investigator (PI) and/or the research assistant visited the records office and got a list of patients who met the inclusion criteria and with the help of the records office staff identified potential study participants who met the eligibility screening criteria (Appendix 1) based on the information on the patient files. Thereafter, preferably after seeing the clinician the next day, the PI and/or research assistant would approach the potential study participants and introduce themselves, explain the objectives of the study and give an overall overview of the study in the language that the patient understood as in Appendix 2 or 3. The PI and/or research assistant then addressed any questions and concerns that the patient was having

and then informed the patient on the voluntary nature of their participation. Upon satisfaction, and if the patient agreed to consent to be involved in the study, they would be recruited to be study participants by signing the consent declaration form (Appendix 2 or 3). Only patients meeting the inclusion criteria were considered for the study. Sampling and recruitment were done on clinic days, that is on Mondays, Wednesdays and Thursdays.

3.9: Research Instruments and Data Collection

An eligibility screening criterion (Appendix 1) was used to review files and identify patients who were to be considered for inclusion in the study. The informed consent form (Appendix 2A or 3A) was used to inform the prospective participants about the study in the language they best understood.

A data collection form (Appendix 4) was used to abstract medical data from the patient files and treatment sheets. This data collection tool was also used to interview the study participants to get information that may have not been captured in the medical files. This tool (Appendix 4) was extensive and able to capture as much information as possible.

3.10: Medical Record and Medication Chart Review

Medical records were reviewed by the PI and/or research assistant and critical information such as medications prescribed (drug, dose, route, duration and indication), laboratory parameters, vital signs and clinical status of the patient abstracted and recorded in the data collection tool (Appendix 4).

3.11: Quality Assurance, Validity and Reliability of the Collected Data

Quality assurance of the collected data was achieved by ensuring that the collected data was complete. Where medical files were not updated or missing some data, efforts were made to get objective information as much as possible from the study participants and caregivers. Further, data was entered onto the data collection tool as soon as it was obtained/ abstracted and then uploaded to a pre-generated spreadsheet to avoid forgetting entries. Prior to analysis, proper data cleaning and coding was done ho help in data analysis

Internal validity was ensured by the pretesting of the data collection tools so as to ensure that before the commencement of the study, the tools were able to deliver data that meets the objectives of the study. The use of objective data (from medical and treatment files) also ensured good

internal validity. Data on various variables was also collected to try explore relationships between variables.

External validity was assured by ensuring that as much as sampling was convenient, there was some sort of diversity, including patients of both gender, varied ages and of different diagnoses. By design KNH receives many referrals from across the nation and this gave great diversity which enhances external validity.

3.12: Study Variables

3.12.1: Predictor Variables

1. Age
2. Body Mass Index (BMI)
3. Medical diagnosis (indication)
4. Gender
5. Number of comorbidities
6. Type of comorbidities
7. Duration patient has had the thromboembolic disorder
8. Number of medications (Polypharmacy)
9. Class of drugs used in management of TEDs
10. Concurrent medications type.
11. Level of income
12. Level of education
13. Marital Status
14. Recreational drug use

3.12.2: Outcome Variables

1. Dosage given too low
2. Dosage given too high
3. Drug-Drug interactions
4. Unnecessary drug therapy
5. Untreated indications
6. Adverse drug reactions
7. Wrong choice of medication

8. Adherence (Non-compliance)

3.13: Data Management

3.13.1: Data Processing

Data was collected with the use the data collection tools which were mainly hardcopy. The collected data was then entered into an excel sheet as soon as possible (Ms. Excel® 2016). The entries were checked for completeness and saved. Categorical data was coded with codes reflecting different categories of data and a separate code book created to denote different categories of data. The code book was then saved and backed up separately. Both the data and codebook were saved both on a laptop and external hard drive.

The saved electronic data was password protected and patient details codified for the sake of confidentiality and this was backed up with an external storage disk. Regular back up was done every time the entries were updated. The hardcopy forms were stored under lock and key, only accessible to the PI. Data analysis was conducted using STATA v.13 and Ms. excel (mainly for data visualization).

3.13.2: Statistical Methods

3.13.2.1: Univariate Analyses

Univariate analysis was done using STATA v. 13 and Microsoft Excel. Descriptive statistics of sociodemographic and socio-economic variables was conducted (frequencies, percentages and measures of central tendencies) and results displayed both numerically and visually in graphs and charts plotted by Ms. Excel.

3.13.2.2: Bivariate Analyses

The strength of associations between various predictor variables and DTPs and other outcome variables was assessed using binomial logistic regression, chi test and Fisher's exact test (STATA). Significant associations were determined using a p-value of less than or equal to 0.05.

3.13.2.3: Multivariable Analyses

Multivariate logistic regression was conducted using STATA to identify independent predictor variables for occurrence of DTPs, and other outcomes of interest. Backward stepwise elimination model building was conducted to identify predictor variables that best predicted the outcomes. Predictor variables that had statistically significant associations with the outcome of interest after

bivariate analysis were further analyzed with multivariate analysis in order to come up with the most parsimonious model that can predict the outcomes of interest. Only predictor variables that had p-values of less than 0.05 were considered as the components of the most parsimonious model after multivariate analysis.

3.14: Ethical Considerations

3.14.1: Study Approvals

Before conducting the study, approval was sought from the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UON ERC). The study was approved prior to commencement vide study approval P74/01/2023 (Appendix 5).

Further approvals were sought from the Departments of General Surgery and Medicine to conduct the study in the outpatient clinics and they were approved as follows: Approval to conduct study at the Department of General Surgery: KNH/HOD/GEN-SURG/35/VOL.I (Appendix 6) and approval to conduct study at medical outpatient clinic: KNH/HOD-MED/37/VOL. II (Appendix 7).

3.14.2: Informed Consent

Eligible study participants were taken through an overview of the study including its objectives, potential risks and benefits of participating in the study. Questions and concerns from potential participants were addressed and the participants informed of their freedom to opt out if they felt like. Patient confidentiality and the privacy of their data was addressed and those consenting to be involved in the study were recruited and they signed a consent form acknowledging voluntary decision to participate in the study.

3.14.3: Confidentiality

After consenting to the study, the consent forms and any material that may reference to the identity of the study participants was stored under lock and key. Only the principal investigator had access to the forms. No obvious patient identifiers that could link collected data to specific patient were used from that point on. All enrolled patients were given unique serial numbers and under no phase of data processing and analysis was the identity of the patients revealed. Further, the electronic copies of data collected were password protected, only accessible to the PI.

3.14.4: Benefits from the Study

This was an observational descriptive study and the findings will play a role in mitigating future DTPs in this class of patients. Directly, patients did not gain anything financially. Significant observations that required medical intervention and where pharmacotherapy could be improved, the observations were communicated with the caregivers.

3.14.5: Risks from the Study

There was no risk of harm for participants involved in this study. The study relied mostly on oral interviews and in event laboratory data was required, it was abstracted form already existing records as such the participants did not need to undergo extra invasive procedures.

3.15: Dissemination Plan

The findings of the study shall be shared with relevant stakeholders through the KNH-UON conference. Findings will also be shared with the respective departments. Further, the findings will be published in a peer reviewed journal and possibly presented in an international conference as either an oral presentation or poster presentation.

CHAPTER 4: RESULTS

This chapter highlights the key findings of the study, ranging from the sociodemographic and the clinical characteristics of the study participants to the DTPs identified. Further, it shows the results of statistical associations between the dependent and independent variables of the study.

4.1 Participants' Recruitment and Characteristics

4.1.1 Participants Recruitment

Over the duration of the study, 139 potential study candidates met the inclusion criteria and were eligible for inclusion in the study. However, 15 of these did not have complete medical information, having vital medical information missing in their files and hence were not included in the study. A further eight potential candidates refused to give consent and as such were excluded from the study. Three of the potential study candidates were omitted due to language barrier as they could not express themselves coherently in either English or Swahili. Consequently, a total of 113 study participants were involved in the study.

4.1.2 Sociodemographic Characteristics

The sociodemographic characteristics of the study participants are tabulated in Table 2.

Table 2: Sociodemographic characteristics of study participants.

Parameter	Characteristic	Frequency (n)	Percentage (%)
Marital Status	Not married	18	15.9
	Married	78	**69.0**
	Widowed	12	10.6
	Divorced	5	4.4
Gender	Male	33	29.2
	Female	80	**70.8**
Religion	Christian	111	**98.2**
	Muslim	2	1.8
Employment Status	Unemployed	39	34.5
	Employed	46	**40.7**
	Retired	28	24.8
Salary Per Month	No Income	67	**59.3**
	Less than Ksh 20,000	25	22.1
	Ksh 20,001-74,999	21	18.6
Level of Education	Informal	7	6.2
	Primary Level	26	23.0
	Secondary level	54	**47.8**
	Tertiary Level	26	23.0
History of Smoking	Yes	3	2.6
	No	110	**97.4**
History of Alcohol Use	Yes	12	10.6
	No	101	**89.4**
Residence	Rural	56	49.6
	Urban	57	**50.4**
BMI Category	Normal weight	57	**50.4**
	Underweight	6	5.3
	Overweight	31	27.4
	Obese	19	16.8

Key: BMI- Body mass index

The median age of the participants was 51 years [IQR= 39, 62]. Median body weight was 70kg [IQR=60,80]. The average height for the study participants was 1.67m (SD=0.12) whereas the average BMI was 25.7 (SD= 6.4). Majority of the participants were of normal weight (50.4%), female (70.8%), married (69.0%) and Christian (98.2%) (Table 2).

4.2 Clinical Characteristics of the Participants

4.2.1 Indication for antithrombotic therapy

The medical conditions among the study participants that necessitated the use of antithrombotic drugs are illustrated in Figure 2.

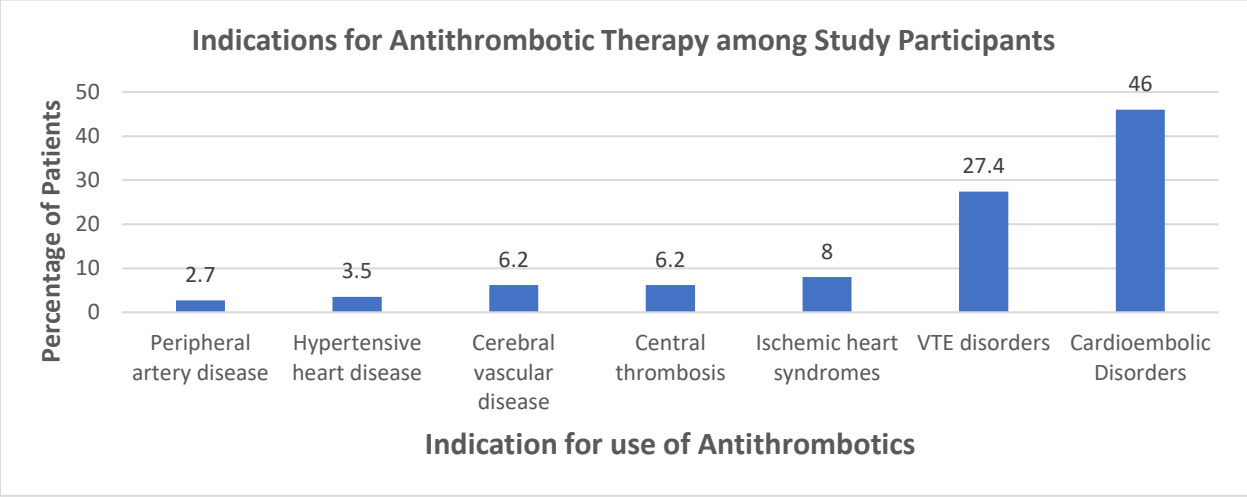


Figure 2: Indications for antithrombotic therapy among the study participants.

Almost half of the patients (52, 46.0%) were on treatment for cardioembolic events. These included: rheumatic heart disease (1, 0.9%), atrial fibrillation (12, 10.6%), secondary prophylaxis following valve replacement (17, 15.0%), prophylaxis in patients with heart failure (13, 11.5%), mural thrombosis (7, 6.2%) and dilated cardiomyopathy (2, 1.8%).

The second most common indication for antithrombotic therapy was for the management of venous thromboembolic disorders, with 31 patients (27.4%) being on antithrombotics for this indication. Majority of these patients (27, 23.9%) were being treated or on secondary prophylaxis following an event of DVT.

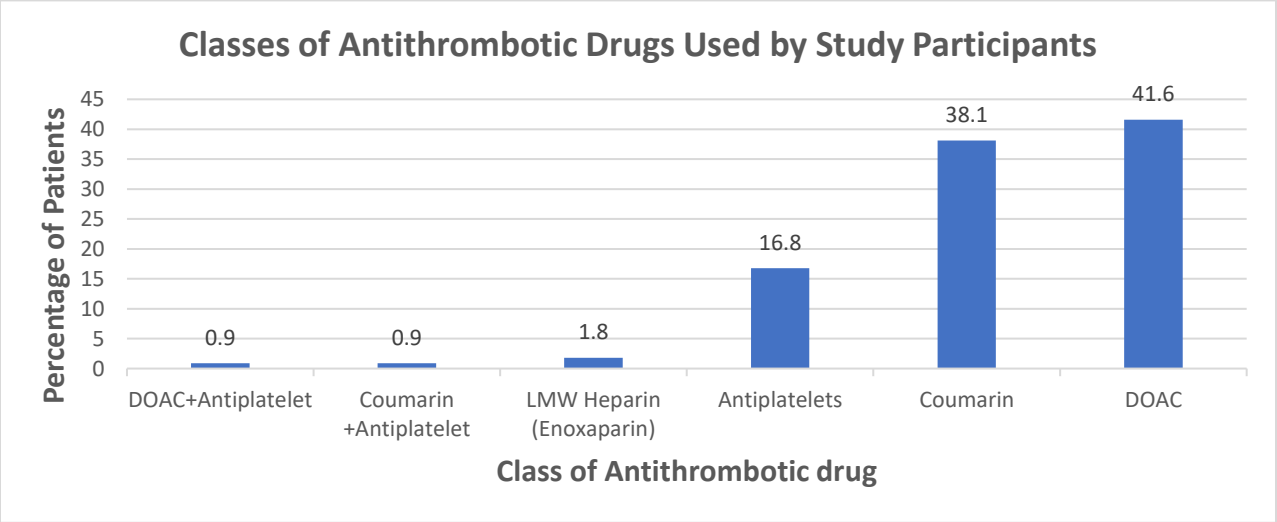
Ischemic heart syndromes were main indications for anticoagulation in 9 (8.0%) patients while both central thrombosis and history of stroke accounted for 7 (6.2%) cases each. Minor indications

for the use of antithrombotic therapy included hypertensive heart disease and peripheral artery disease with proportions of 3.5% and 2.7% (Figure 2).

4.2.2 Drugs Used to manage TEDs

Majority of the patients were on treatment with a single antithrombotic agent (100, 88.5%). Eleven (9.7%) were on treatment with two antithrombotic agents while two (1.8%) were on treatment with 3 agents.

Majority of the patients (47, 41.6%) were under treatment with a direct oral anticoagulant. The main DOACs prescribed included rivaroxaban (43, 38.1%) and apixaban (4, 3.5%). The second most prescribed anticoagulants were coumarins, with 43 (38.1%) patients being on warfarin. Further, 19 patients (16.8%) were on anticoagulation with antiplatelet agents, mainly aspirin and clopidogrel, with majority of them (13, 11.5%) being on dual aspirin and clopidogrel therapy). Two participants (1.8%) were on enoxaparin, a low molecular weight heparin and a further 2 (1.8%) were on dual therapy with either DOAC (rivaroxaban) and antiplatelets or coumarin (warfarin) and antiplatelets. This is illustrated in Figure 3.



Key: DOAC- Direct oral anticoagulant, LMW- Low molecular weight

Figure 3: Classes of antithrombotic drugs used by the study participants

4.2.3 Co-Administered Medications

Eighty-six (76.1%) of the study participants had another drug prescribed, in addition to the drugs targeting TEDs. The highest number of co-prescribed drugs was 12, whereas the least number was

1. Tables 3 and 4 summarize the frequencies and percentages of patients who had co-prescribed drugs.

Table 3: Frequency and percentages of number of co-administered drugs

Number of co-administered drugs	Frequency (n)	Percentage (%)
None	27	23.9
1	9	8.0
2	9	8.0
3	15	13.3
4	13	11.5
5	16	14.2
6	13	11.5
7	4	3.5
8	5	4.4
10	1	0.9
12	1	0.9

The patient on 12 medications had a diagnosis of dilated cardiomyopathy with consequent heart failure. The patient also had diabetes mellitus and hypertension as comorbid conditions in addition to other complaints. Consequently, the patient was on management with a potassium sparing diuretic, antibiotics, digoxin, PPIs, paracetamol, metformin, SGLT 2 Inhibitor and beta-blockers.

Table 4: Frequency and percentages of classes of co-administered drugs

Class of Drugs	Number of Patents (n)	Percentage (%)
Diuretics	55	48.7
Beta blockers	49	43.4
RAAS blockers	35	31.0
Glucose lowering agents	30	26.5
Antiarrhythmics	26	23.0
Lipid lowering agents	21	18.6
Calcium Channel blockers	12	10.6
Proton pump inhibitors	11	9.7
Vitamin Supplements	8	7.1
Antimicrobials	7	6.2
Phosphodiesterase inhibitors	7	6.2
Analgesics	6	5.3
Vasodilators	5	4.4
Inhibitors of platelet aggregation	5	4.4
Corticosteroids	2	1.8

Key: RAAS- Renin angiotensin aldosterone system.

Almost half of the patients (48.7%) were on diuretics. Further, 49 (43.4%) of the study participants were on beta blockers while RAAS blockers were the third most commonly co-prescribed drugs. Over a quarter of the patients (26.5 %) were on glucose lowering agents. Less commonly co-prescribed medications included corticosteroids (1.8%), vasodilators (4.4%) and analgesics (5.3%) (Table 4).

4.3 Drug Therapy Problems Identified

The overall prevalence of DTPs in the study participants was 63.7%, meaning that 72 out of the 113 participants had at least one drug therapy problem. The number of DTPs per patient was determined and the results are displayed in Figure 4. Majority of the patients (41.6%) had at least one DTP, while six (5.3%) had three DTPs.

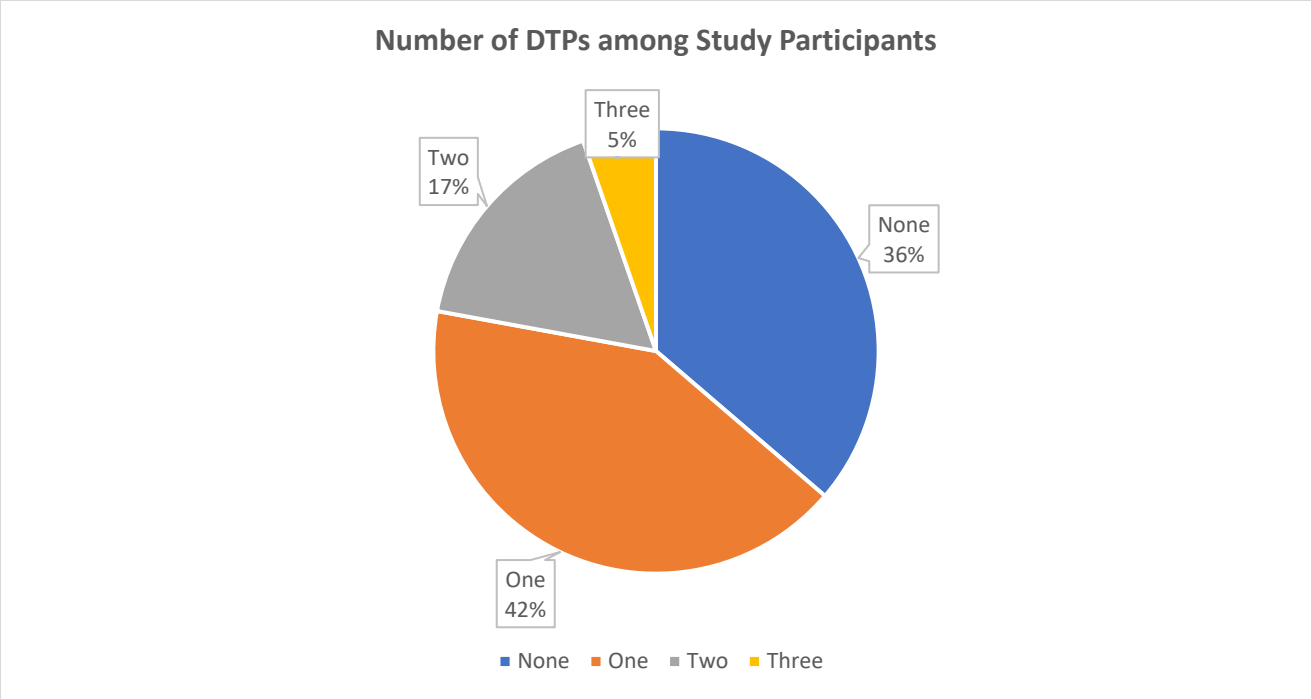


Figure 4: Prevalence of DTPs among the study participants.

Further, the prevalence of the various categories of DTPs and the contributing factors are summarized in Table 5 below.

Table 5: The Prevalence of drug therapy problems and their characteristics

Class of DTP	Characteristic	Frequency (n)	Percentage (%)
Non-adherence	Yes No	53 60	46.9 53.1
	Inability to afford medications	22	19.5
	Inconvenience taking medications	17	15.0
	Occasionally forget to take medication	28	24.8
	Intentionally skip medications when feeling well	4	3.5
	Confusion on what medication to take at what time	1	0.9
Additional therapy needed	Yes No	40 73	35.4 64.6
	Untreated medical conditions	26	23.0
	Synergism required to manage existing conditions	14	12.4
Adverse drug reactions	Yes No	16 97	14.4 85.6
	Drug product causing allergic reactions	4	3.5
	Safer drug required based on patient risk factors	3	2.7
	Drug interactions that can cause toxicity	9	8.0
Ineffective drug	Yes No	7 106	6.2 83.8
	Medication used not the most effective for condition due to drug interactions	6	4.4
	Condition being refractory to the drug used	1	0.9
Unnecessary drug therapy	Yes No	4 109	3.5 96.5
	Treating avoidable adverse effects of co-prescribed drugs	2	1.8
	Duplication of therapy	1	0.9
	No medical indication for drug prescribed	1	0.9
Dosage too low	Yes No	2 111	1.8 98.3
	Dose too low despite suboptimal anti coagulation	2	1.8
Dosage too high	Yes No	2 111	1.8 98.3
	Dose of anticoagulant too high despite supra-optimal anticoagulation	2	1.8

The most prevalent DTP was nonadherence, with almost half of the patients (46.9%) being nonadherent to their medications. The most common causes of non-adherence to medications included the inability to afford medications and the occasional forgetting to take prescribed medications, as reported by 19.5% and 24.8% of the patients. Interestingly, 4 (3.5%) of the patients reported that they avoid medications when they have symptomatic relief.

Most patients (23.0%) needed additional therapy because they had untreated medical conditions and symptoms that were yet to be addressed by caregivers. A further 12.4 % of the patients required additional therapy because the medical conditions they had were not being resolved with their current medications hence needed synergism to address their underlying medical conditions.

Adverse drug reactions were reported in 14.4% of the participants, and majority of these were related to drug interactions which precipitated ADRs (8.0%). Other significant contributors to ADRs were allergic reactions (3.5%) and patient related risk factors (2.7%). DTPs associated with wrong dosage of medications were identified in 4 (3.5%) of the patients, with doses being too high (2, 1.8%) or too low (2, 1.8%) in relation to the anticoagulation status of patients as reflected by the INR and/or PT (Table 5).

4.4 Outcomes of The DTPs

Adequate anticoagulation, as indicated by therapeutic ranges of the coagulation profile, was achieved in 81 patients (71.7%). Thirty-two patients (28.3%) had deranged anticoagulation with majority of them, 23 (20.4%) having supra-optimal INR and/or PTs while minority, nine (8%) having suboptimal INR and/or PT. This is summarized in Figure 6.

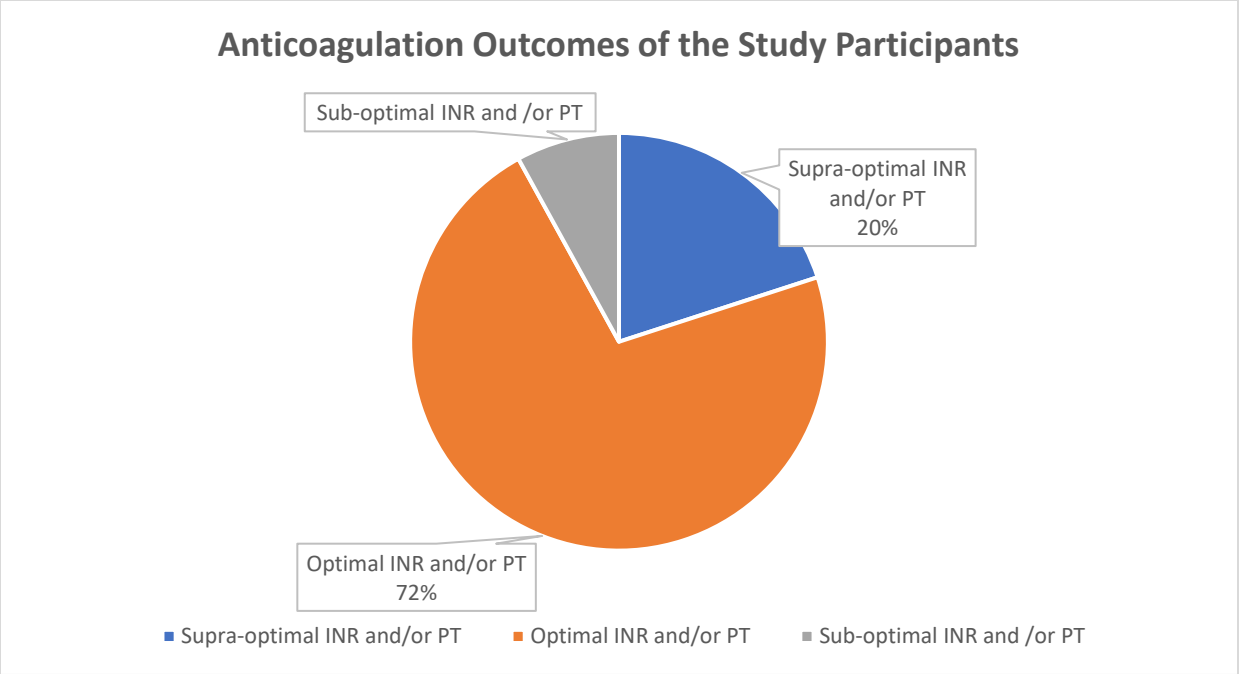


Figure 5: Anticoagulation outcomes of the study participants

Bleeding was noted in four (3.5%) patients who had supra-optimal INRs and/or PTs. These included hemoptysis, epistaxis, gum bleeding and menorrhagia.

4.5 Factors associated with DTPs

4.5.1 Risk factors for occurrence of DTPs

Bivariate analysis to identify predictor variables that influence the occurrence of DTPs was done using either chi square test or Fisher's exact chi test (for variables with levels having less than 5 observations). The results of bivariate analysis are tabulated in Tables 6, 7, 8 and 9.

Table 6: Association between sociodemographic factors with occurrence of DTPs

Variable	Category	Presence of DTPs (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Age in years	<35	11 (10.6)	6 (5.3)	0.927
	≥35	61 (53.1)	35 (31.0)	
BMI category	BMI >25	31 (27.4)	20 (17.7)	0.557
	BMI ≤25	41 (36.3)	21 (18.6)	
Gender	Male	22 (19.5)	11 (9.7)	0.916
	Female	50 (44.2)	30 (26.5)	
Religion	Christian	71 (62.8)	40 (35.4)	0.684
	Muslim	1 (0.9)	1 (0.9)	
Marital status	With spouse	49 (43.4)	29 (25.7)	0.767
	Without spouse	23 (20.4)	12 (10.6)	
Employment Status	Working	29 (25.7)	24 (21.2)	0.902
	Not working	43 (38.1)	17 (15.0)	
Monthly income	No income	43 (38.1)	24 (21.2)	0.551
	With income	29 (25.7)	17 (15.0)	
Level of education	Primary and below	20 (17.7)	12 (10.6)	0.866
	Secondary and above	52 (46.0)	29 (26.7)	
Residence	Urban	37 (32.7)	20 (17.7)	0.790
	Rural	35 (31.0)	21 (18.6)	
Physical activity	Active	43 (38.1)	30 (26.5)	0.151
	Inactive	29 (25.7)	11 (9.7)	
History of smoking	Yes	2 (1.8)	1 (0.9)	0.914
	No	70 (61.9)	40 (35.4)	
History of alcohol use	Yes	7 (6.2)	5 (4.4)	0.682
	No	65 (57.5)	36 (31.9)	

Key: BMI- body mass index

Following the bivariate analysis of sociodemographic characteristics, no variable was found to have statistically significant association with the occurrence of DTPs (Table 6).

Table 7: Association between indications for antithrombotic use and occurrence of DTPs

Variable	**Category**	**DTPs (n=113)**		**p-value**
		Present (n), (%)	**Absent (n), (%)**	
Hypertensive heart disease	Yes	2 (1.8)	1 (0.9)	0.914
	No	70 (61.9)	40 (35.4)	
Peripheral arterial disease	Yes	2 (1.8)	1 (0.9)	0.914
	No	70 (61.9)	40 (35.4)	
Cerebral vascular accident	Yes	3 (2.7)	3 (2.7)	0.473
	No	69 (61.1)	38 (33.6)	
Central thrombosis	Yes	4 (3.5)	2 (2.7)	0.877
	No	68 (60.2)	39 (34.5)	
Ischemic heart syndromes	Yes	7 (6.2)	1 (0.9)	0.147
	No	65 (57.5)	40 (35.4)	
Venous thromboembolic events	Yes	17 (15.0)	14 (12.4)	0.227
	No	55 (48.7)	27 (23.9)	
Cardioembolic events	Yes	34 (30.0)	18 (16.0)	0.734
	No	38 (33.6)	23 (20.4)	

Following bivariable analysis of the different indications to explore the associations with occurrence of DTPs, no indication was found to have significant association with occurrence of DTPs (Table 7).

Table 8: Associations between anticoagulant medications used and occurrence of DTPs

Variable	Category	DTPs (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Number of anticoagulants	One	66 (58.4)	34 (30.0)	0.372
	More than one	6 (5.3)	7 (6.2)	
Enoxaparin	Yes	2 (1.80	0 (0.0)	0.282
	No	70 (62.0)	41 (36.3)	
Apixaban	Yes	2 (1.8)	2 (1.8)	0.561
	No	70 (62.0)	39 (34.5)	
Clopidogrel	Yes	6 (5.3)	1 (0.9)	0.211
	No	66 (60.2)	40 (35.4)	
Aspirin + clopidogrel	Yes	6 (5.3)	7 (6.2)	0.162
	No	66 (60.2)	34 (30.0)	
Rivaroxaban	Yes	31 (27.4)	13 (11.5)	0.234
	No	41 (36.3)	28 (24.8)	
Warfarin	Yes	26 (23.0)	18 (16.0)	0.414
	No	46 (40.7)	23 (20.4)	

The number of antithrombotic drugs used for managing TEDs and type of antithrombotic drugs used did not have significant association with the occurrence of DTPs as all variables had p-values of >0.05 (Table 8).

Table 9: Associations between co-prescribed medications and occurrence of DTPs

Variable	Category	DTPs (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Number of co-administered drugs	>3	39 (34.5)	14 (12.4)	**0.040**
	≤3	33 (29.2)	27 (23.9)	
Corticosteroids	Yes	2 (1.8)	0 (0.0)	0.282
	No	70 (62.0)	41 (36.3)	
Inhibitors of platelet aggregation	Yes	4 (3.5)	1 (0.9)	0.439
	No	68 (60.2)	40 (35.4)	
Vitamin supplements	Yes	6 (5.30)	2 (1.8)	0.491
	No	66 (58.4)	39 (34.5)	
Analgesics	Yes	5 (4.4)	1 (0.9)	0.304
	No	67 (59.3)	40 (35.4)	
Vasodilators	Yes	4 (3.5)	1 (0.9)	0.439
	No	68 (60.2)	40 (35.4)	
Glucose lowering agents	Yes	21 (18.6)	9 (8.0)	0.404
	No	51 (45.1)	32 (28.3)	
Proton pump inhibitors	Yes	10 (8.8)	1 (0.9)	**0.048**
	No	62 (54.9)	40 (35.4)	
Antimicrobials	Yes	4 (3.5)	3 (2.7)	0.709
	No	68 (60.2)	38 (33.6)	
PDE 5 inhibitors	Yes	6 (5.3)	1 (0.9)	0.211
	No	66 (58.4)	40 (35.4)	
RAAS blockers	Yes	24 (21.2)	11 (9.7)	0.472
	No	38 (33.6)	30 (26.5)	
Calcium channel blockers	Yes	9 (8.0)	3 (2.7)	0.390
	No	63 (55.80	38 (33.6)	
Lipid lowering agents	Yes	13 (11.5)	7 (6.2)	0.895
	No	59 (52.2)	34 (30.0)	
Diuretics	Yes	41 (36.3)	14 (12.4)	**0.020**
	No	31 (27.4)	27 (23.9)	
Antiarrhythmics	Yes	18 (16.0)	8 (7.1)	0.505
	No	54 (47.80	33 (29.2)	
Beta blockers	Yes	32 (28.3)	17 (15.0)	0.759
	No	40 (35.4)	24 (21.2)	

Key: PDE- Phosphodiesterase, RAAS- renin-angiotensin-aldosterone system.

Significant associations with the occurrence of DTPs were detected with the use of diuretics (p=0.020), use of PPIs (p=0.048) and polypharmacy (p=0.040). The use of other co-administered drugs was not significantly associated with occurrence of DTPs (Table 9).

Following bivariate analysis, variables with p-values over 0.05 were omitted when doing multivariate logistic regression analysis and backwards stepwise elimination, in an effort to identify the most parsimonious model that predicts occurrence of DTPs. Significant variables following bivariate analysis included the use of diuretics, PPIs and coadministration of more than three medications. Results of this analysis are displayed in Table 10.

Table 10: Independent risk factors for occurrence of DTPs

	Bivariate analysis		**Multivariate analysis**	
Variable	**cOR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
>3 co-administered drugs	2.279 (1.023, 5.046)	0.040	-	
PPIs	6.452 (0.795, 52.354)	0.048	7.155 (0.861, 59.444)	0.029
Diuretics	2.550 (1.150, 5.656)	0.020	2.689 (1.193, 6.059)	0.017

Key: PPIs- proton pump inhibitors

On multivariate regression, only two variables had significant statistical association with the occurrence of DTPs. Treatment with PPIs and diuretics had the strongest association with occurrence of DTPs with aOR of 7.155 and 2.689, respectively. Patients using diuretics and PPIs were 7.155 and 2.689 times more likely to develop DTPs as compared to those not on these medications, respectively. Polypharmacy, though statistically significant on bivariate analysis, lost significance on multivariate analysis (Table 10).

4.5.2 Risk Factors for Occurrence of Drug Interactions

Associations between the occurrence of drug interactions and sociodemographic, clinical characteristics and medications used were explored using chi test and Fischer's exact chi test. Significant associations were signified by p-values of ≤0.05 and the results of bivariate analysis are summarized in Tables 11, 12, 13 and 14.

Table 11: Associations between sociodemographic factors and the occurrence of drug interactions

Variable	Category	Drug interactions (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Age in years	<35	4 (3.5)	13 (11.5)	0.471
	≥35	31 (27.4)	65 (57.5)	
BMI category	BMI >25	13 (11.5)	38 (33.6)	0.253
	BMI ≤25	22 (19.5)	40 (35.4)	
Gender	Male	13 (11.5)	20 (17.7)	0.214
	Female	22 (19.5)	58 951.3)	
Religion	Christian	35 (31.0)	76 (67.3)	0.339
	Muslim	0 (0.0)	2 (1.8)	
Marital status	With spouse	25 (22.1)	53 (47.9)	0.711
	Without spouse	10 (8.8)	25 (22.1)	
Employment Status	Working	15 (13.3)	31 (27.4)	0.755
	Not working	20 (17.7)	47 (41.6)	
Monthly income	No income	21 (18.6)	46 (40.7)	0.922
	With income	14 (12.4)	32 (28.3)	
Level of education	Primary and below	26 (23.0)	55 (48.7)	0.681
	Secondary and above	9 (8.0)	23 (20.4)	
Residence	Urban	20 (17.7)	37 (32.7)	0.340
	Rural	15 (13.3)	41 (36.3)	
Physical activity	Active	23 (20.4)	50 (44.2)	0.868
	Inactive	12 (10.6)	28 (24.8)	
History of smoking	Yes	1 (0.9)	2 (1.8)	0.929
	No	34 (30.0)	76 (67.3)	
History of alcohol use	Yes	3 (2.7)	9 (8.0)	0.636
	No	32 (28.3)	69 (61.1)	

Key: BMI- Body mass index

No sociodemographic character had a significant association with the development of drug interactions since all variables had p-values of >0.05 (Table 11).

Table 12: Association between indications for antithrombotic use and occurrence of drug interactions

Variable	**Category**	**Drug interactions (n=113)**		**p-value**
		Present (n), (%)	**Absent (n), (%)**	
Hypertensive heart disease	Yes	1 (0.9)	2 (1.8)	0.929
	No	34 (30.0)	76 (67.3	
Peripheral arterial disease	Yes	1 (0.9)	2 (1.8)	0.926
	No	34 (30.0)	76 (67.3	
Cerebral vascular accident	Yes	4 (3.5)	2 (1.8)	0.052
	No	31 (27.4)	76 (67.3)	
Central thrombosis	Yes	1 (0.9)	5 (4.4)	0.436
	No	34 (30.0)	73 (64.6)	
Ischemic heart syndromes	Yes	5 (4.4)	3 (2.7)	0.105
	No	30 (26.5)	75 (66.4)	
Venous thromboembolic events	Yes	5 (4.4)	26 (23.0)	**0.042**
	No	30 (26.5)	52 (46.0)	
Cardioembolic events	Yes	17 (15.0)	35 (31.0)	0.715
	No	18 (16.0)	43 (38.1)	

Bivariate analysis to identify any medical indication with significant association with occurrence of drug interactions revealed that venous thromboembolism had a significant association with the occurrence of drug interactions (Table 12).

Table 13: **Associations between anticoagulant medications used and drug interactions**

Variable	**Category**	**Drug interactions (n=113)**		**p-value**
		Present (n), (%)	**Absent (n), (%)**	
Number of anticoagulants	One	30 (26.5)	70 (61.9)	0.766
	More than one	5 (4.4)	8 (7.1)	
Enoxaparin	Yes	2 (1.8)	0 (0.0)	0.094
	No	33 (29.2)	78 (69.0)	
Apixaban	Yes	0 (0.0)	4 (3.5)	0.173
	No	35 (31.0)	74 (65.4)	
Clopidogrel	Yes	6 (5.3)	1 (0.9)	**0.003**
	No	29 (25.7)	77 (68.1)	
Aspirin + clopidogrel	Yes	5 (4.4)	8 (7.1)	0.535
	No	30 (26.5)	70 (61.9)	
Rivaroxaban	Yes	10 (8.8)	34 (30.0)	0.130
	No	25 (22.1)	44 (38.9)	
Warfarin	Yes	13 (11.5)	31 (27.4)	0.793
	No	22 (19.5)	47 (41.6)	

The use of clopidogrel as the main antithrombotic agent had a statistically significant association with the development of drug interactions (p=0.003). No other class of antithrombotics had a significant association with development of drug interactions. Similarly, the number of antithrombotic agents used was not significantly associated with drug interactions (Table 13).

Table 14: Associations between drug interactions and co-prescribed medications

Variable	Category	Drug interactions (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Number of co-administered drugs	>3	27 (23.9)	26 (23.0)	**0.0001**
	≤3	8 (7.1)	52 (46.0)	
Corticosteroids	Yes	2 (1.9)	0 (0.0)	0.094
	No	33 (28.7)	78 (69.0)	
Inhibitors of platelet aggregation	Yes	4 (3.5)	1 (0.9)	**0.031**
	No	31 (27.4)	77 (68.1)	
Vitamin supplements	Yes	7 (6.2)	1 (0.9)	**0.001**
	No	28 (24.8)	77 (68.1)	
Analgesics	Yes	4 (3.5)	2 (1.8)	0.073
	No	31 (27.4)	76 (67.3)	
Vasodilators	Yes	3 (2.7)	2 (1.8)	0.171
	No	32 (28.3)	76 (67.3)	
Glucose lowering agents	Yes	13 (11.5)	17 (15.0)	0.088
	No	22 (19.5)	61 (54.0)	
Proton pump inhibitors	Yes	9 (8.0)	2 (1.8)	**0.0001**
	No	26 (23.0)	76 (67.3)	
Antimicrobials	Yes	2 (1.9)	5 (4.4)	0.887
	No	33 (29.2)	73 (64.6)	
PDE 5 inhibitors	Yes	2 (1.8)	5 (4.4)	0.887
	No	33 (28.7)	73 (64.6)	
RAAS blockers	Yes	17 (15.0)	18 (15.9)	**0.007**
	No	18 (15.9)	60 (53.0)	
Calcium channel blockers	Yes	5 (4.4)	7 (6.2)	0.397
	No	30 (26.5)	71 (62.8)	
Lipid lowering agents	Yes	10 (8.8)	10 (8.8)	**0.048**
	No	25 (22.1)	68 (60.2)	
Diuretics	Yes	24 (21.2)	31 (27.4)	**0.005**
	No	11 (9.7)	47 (41.6)	
Antiarrhythmics	Yes	10 (8.8)	16 (14.2)	0.347
	No	25 (22.1)	62 (54.9)	
Beta blockers	Yes	21 (18.6)	28 (24.8)	**0.017**
	No	14 (12.4)	50 (44.2)	

Key: RAAS- renin angiotensin aldosterone system, PDE- Phosphodiesterase

Drug related factors associated with the occurrence of drug interactions following bivariate analysis included coadministration of beta blockers (p=0.017), diuretics (p=0.005), statins (p=0.048), PPIs (p=0.0001), platelet aggregation inhibitors (p=0.031), use of clopidogrel (0.003), vitamin supplements (p=0.001), RAAS blockers (p=0.007) and polypharmacy (p=0.0001) (Table 14 and 15).

Independent variables that had p-values of ≤0.05 upon bivariate analysis were further subjected to logistic multivariate analysis to come up with independent predictors of drug interactions. Backward stepwise elimination model was used, whereby variables were sequentially dropped, with variables with highest p-values being dropped sequentially from the multivariate regression model, so as to obtain the most parsimonious model in which all the variables remaining in the model had p-values of ≤0.05.

Table 15: Independent factors associated with occurrence of drug interactions

	Bivariate analysis		**Multivariate analysis**	
Variable	**cOR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
VTE Events	0.333 (0.116, 0.960)	0.042	-	-
>3 co-administered drugs	6.750 (2.693, 16.916)	0.0001	8.413 (2.761, 25.641)	0.0001
PPIs	13.154, (2.667, 64.863)	0.0001	10.116 (1.647, 62.103)	0.012
Diuretics	3.307 (1.420, 7.705)	0.005	-	-
Inhibitors of platelet aggregation	9.935 (1.068, 92.455)	0.031	-	-
Vitamin supplements	19.250 (2.2660, 163.525)	0.001	41.322 (3.817, 447.288)	0.002
RAAS blockers	3.148 (1.350, 7.341)	0.007	-	-
Clopidogrel	15.931 (1.838, 138.090)	0.003	-	-
Statins	2.720 (1.012, 7.314)	0.048	-	-
Beta blockers	2.678 (1.180, 6.077)	0.017	-	-

Key: RAAS- renin angiotensin aldosterone system, PPIs- proton pump inhibitors.

Despite having strong associations with the occurrence of drug interactions following bivariate analysis, VTE as an indication for use of antithrombotics, the use of diuretics, platelet aggregation inhibitors, RAAS blockers, clopidogrel, statins and betablockers lost the association upon multivariate logistic regression (Table 15).

Significant associations were observed between polypharmacy [aOR=8.413, 95% CI: (2.761, 25.641), p<0.0001], the use of PPIs [aOR=10.116, 95% CI: (1.647, 62.103), p=0.012] and the coadministration of vitamin supplements [aOR=41.322, 95% CI: (3.817, 447.288), p=0.002]. Patients who had more than 3 co-prescribed medications had an 8.413 higher chance of developing drug interactions than those receiving less than three. Further, patients on PPIs and vitamin supplements were 10.116 and 41.322 times more likely to experience drug interactions than those not receiving these medications, respectively.

4.5.3 Risk factors for non-adherence

Analysis was done to determine factors with significant associations with nonadherence. The results are tabulated in Tables 16, 17, 18 and 19.

Table 16: Association between sociodemographic factors and non-adherence

Variable	Category	Non-adherence (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Age in years	<35	4 (3.5)	13 (11.5)	0.063
	≥35	49 (43.4)	47 (41.60	
BMI category	BMI >25	25 (22.1)	26 (23.0)	0.683
	BMI ≤25	28 (24.8)	34 (30.0)	
Gender	Male	15 (13.3)	18 (15.9)	0.843
	Female	38 (33.6)	42 (37.2)	
Religion	Christian	53 (46.9)	56 (49.6)	0.497
	Muslim	0 (0.0)	2 (1.8)	
Marital status	With spouse	39 (34.5)	39 (34.5)	0.325
	Without spouse	14 (12.4)	21 (18.6)	
Employment Status	Working	25 (22.1)	21 (18.6)	0.189
	Not working	28 (24.8)	39 (34.5)	
Monthly income	No income	28 (24.8)	39 (34.5)	0.297
	With income	25 (22.1)	21 (18.6)	
Level of education	Primary and below	17 (15.0)	15 (13.3)	0.401
	Secondary and above	36 (31.9)	45 (39.8)	
Residence	Urban	30 (26.5)	27 (23.9)	0.219
	Rural	23 (20.4)	33 (29.2)	
Physical activity	Active	34 (30.0)	39 (34.5)	0.925
	Inactive	19 (16.8)	21 (18.6)	
History of smoking	Yes	1 (0.9)	2 (1.8)	0.999
	No	52 (46.00	53 (46.9)	
History of alcohol use	Yes	5 (4.4)	7 (6.2)	0.701
	No	48 (42.5)	53 (46.9)	

Key: BMI- body mass index.

All sociodemographic factors had insignificant association with nonadherence (Table 16).

Table 17: Association between indications for antithrombotic therapy and non-adherence

Variable	Category	Non-adherence (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Hypertensive heart disease	Yes	1 (0.9)	2 (1.8)	0.999
	No	52 (46.0)	58 (51.3)	
Peripheral arterial disease	Yes	1 (0.9)	2 (1.8)	0.999
	No	52 (46.0)	58 (51.3)	
Cerebral vascular accident	Yes	3 (2.7)	3 (2.7)	0.999
	No	50 (44.2)	57 (50.4)	
Central thrombosis	Yes	3 (2.7)	3 (2.7)	0.999
	No	50 (44.2)	57 (50.4)	
Ischemic heart syndromes	Yes	4 (3.5)	4 (3.5)	0.999
	No	49 (43.4)	56 (49.6)	
Venous thromboembolic events	Yes	14 (12.4)	17 (15.0)	0.820
	No	39 (34.5)	43 (38.1)	
Cardioembolic events	Yes	25 (22.1)	27 (23.9)	0.817
	No	28 (24.8)	33 (29.2)	

No clinical indication for the use of antithrombotic drugs was found to have a statistically significant association with nonadherence as all the associated p-values were above 0.05 (Table 17).

Table 18: Association between antithrombotic used and non-adherence

Variable	Category	non-adherence (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Number of anticoagulants	One	50 (44.2)	50 (44.2)	0.084
	More than one	3 (2.7)	10 (8.8)	
Enoxaparin	Yes	2 (1.8)	0 (0.0)	0.129
	No	51 (45.1)	60 (53.1)	
Apixaban	Yes	3 (2.7)	1 (0.9)	0.340
	No	50 (44.2)	59 (52.2)	
Clopidogrel	Yes	6 (5.3)	1 (0.9)	**0.050**
	No	47 (41.6)	59 (52.2)	
Aspirin + clopidogrel	Yes	3 (2.7)	10 (8.8)	0.082
	No	50 (44.2)	40 (35.4)	
Rivaroxaban	Yes	23 (20.4)	21 (18.6)	0.361
	No	30 (26.5)	39 (34.5)	
Warfarin	Yes	17 (15.0)	27 (23.9)	0.160
	No	36 (31.8)	33 (29.2)	

The use of clopidogrel to manage thromboembolic disorders was associated with nonadherence (p=0.050). The number of anticoagulants used and other classes of anticoagulants did not have statistically significant associations with nonadherence (Table 18).

Table 19: Association between co-prescribed drugs and non-adherence

Variable	Category	Non-adherence (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Number of co-administered drugs	>3	29 (25.7)	24 (21.2)	0.118
	≤3	24 (21.2)	36 (31.9)	
Corticosteroids	Yes	2 (1.8)	0 (0.0)	0.218
	No	51 (45.1)	60 (53.1)	
Inhibitors of platelet aggregation	Yes	3 (2.7)	2 (1.8)	0.664
	No	50 (44.2)	58 (51.3)	
Vitamin supplements	Yes	4 (3.5)	4 (3.5)	0.999
	No	59 (52.2)	56 (49.5)	
Analgesics	Yes	3 (2.7)	3 (2.7)	0.999
	No	50 (44.2)	57 (50.4)	
Vasodilators	Yes	4 (3.5)	1 (0.9)	0.185
	No	49 (43.4)	49 (43.4)	
Glucose lowering agents	Yes	15 (13.3)	15 (13.3)	0.831
	No	38 (33.6)	45 (39.8)	
Proton pump inhibitors	Yes	6 (5.3)	5 (4.4)	0.593
	No	47 (41.6)	55 (48.7)	
Antimicrobials	Yes	1 (0.9)	6 (5.3)	0.118
	No	52 (46.0)	54 (47.8)	
PDE 5 inhibitors	Yes	4 (3.5)	3 (2.7)	0.704
	No	49 (43.4)	57 (50.4)	
RAAS blockers	Yes	16 (14.2)	19 (16.8)	0.865
	No	37 (32.7)	41 (36.3)	
Calcium channel blockers	Yes	9 (8.0)	3 (2.7)	0.064
	No	44 (38.9)	57 (50.4)	
Lipid lowering agents	Yes	10 (8.8)	10 (8.8)	0.808
	No	43 (38.1)	50 (44.2)	
Diuretics	Yes	30 (26.5)	25 (22.1)	0.113
	No	23 (20.4)	35 (31.0)	
Antiarrhythmics	Yes	14 (12.4)	12 (10.6)	0.419
	No	39 (34.5)	48 (42.5)	
Beta blockers	Yes	27 (23.9)	22 (19.5)	0.126
	No	26 (23.0)	38 (33.6)	

Key: RAAS- renin angiotensin aldosterone system, PDE- phosphodiesterase.

Bivariate analysis to determine if there are associations between class and number of drugs co-prescribed revealed that there were no significant associations. As such, the class and type of co-administered medications were not good predictors of nonadherence (Table19).

Following bivariable analysis, only the use of clopidogrel had a significant association with the outcome of nonadherence [OR=7.531, 95% CI: (0.876, 64.751) p=0.050].

4.5.4 Risk Factors for ADRs

A significant number (16, 14.2%) of the study participants reported having experienced adverse drug reactions. As such, analysis was done to identify risk factors for occurrence of ADRs among the study participants. The results of bivariate analysis are shown in Tables 20,21,22 and 23.

Table 20:**Association between sociodemographic factors and occurrence of ADRs**

Variable	Category	Adverse drug reactions (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Age in years	<35	3 (2.7)	14 (12.4)	0.706
	≥35	13 (11.5)	83 (73.5)	
BMI category	BMI >25	6 (5.3)	45 (39.8)	0.508
	BMI ≤25	10 (8.8)	52 (46.0)	
Gender	Male	7 (6.2)	26 (23.0)	0.167
	Female	9 (8.0)	71 (62.8)	
Religion	Christian	16 (14.2)	95 (84.1	0.999
	Muslim	0 (0.0)	2 (1.8)	
Marital status	With spouse	11 (9.7)	67 (59.3)	0.979
	Without spouse	5 (4.44)	30 (26.5)	
Employment Status	Working	5 (4.4)	41 (36.3)	0.406
	Not working	11 (9.7)	56 (49.6)	
Monthly income	No income	11 (9.7)	56 (49.6)	0.688
	With income	5 (4.4)	41 (36.2)	
Level of education	Primary and below	5 (4.4)	27 (23.9)	0.779
	Secondary and above	11 (9.7)	70 (61.9)	
Residence	Urban	8 (7.1)	49 (43.4)	0.970
	Rural	8 (7.1)	48 (42.5)	
Physical activity	Active	12 (10.6)	61 (54.0)	0.410
	Inactive	4 (3.5)	36 (31.9)	
History of smoking	Yes	0 (0.0)	3 (2.7)	0.999
	No	16 (14.2)	96 (85.0)	
History of alcohol use	Yes	1 (0.9)	11 (9.7)	0.999
	No	15 (13.3)	86 (76.1)	

Key: BMI- body mass index.

None of the sociodemographic factors was a predictor of ADRs occurring as there were no significant associations (Table 20).

Table 21: **Association between indications for antithrombotic therapy and occurrence of ADRs**

Variable	**Category**	**ADRs (n=113)**		**p-value**
		Present (n), (%)	**Absent (n), (%)**	
Hypertensive heart disease	Yes	0 (0.0)	3 (2.7)	0.999
	No	16 (14.2)	94 (83.2)	
Peripheral arterial disease	Yes	0 (0.0)	3 (2.7)	0.999
	No	16 (14.2)	94 (83.2)	
Cerebral vascular accident	Yes	0 (0.0)	6 (5.3)	0.592
	No	16 (14.2)	91 (80.5)	
Central thrombosis	Yes	1 (0.9)	5 (4.4)	0.999
	No	15 (13.3)	92 (79.6)	
Ischemic heart syndromes	Yes	2 (1.8)	6 (5.3)	0.316
	No	14 (12.4)	91 (80.5)	
Venous thromboembolic events	Yes	3 (2.7)	28 (24.8)	0.550
	No	13 (11.5)	69 (61.1)	
Cardioembolic events	Yes	10 (8.8)	42 (37.2)	0.153
	No	6 (5.3)	55 (48.7)	

None of the clinical indications was a predictor for the occurrence of adverse drug reactions as the associations were statistically insignificant (Table 21).

Table 22:Association between anticoagulants used and development of ADRs

Variable	Category	ADRs (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Number of anticoagulants	One	16 (14.2)	84 (74.3)	0.529
	More than one	0 (0.0)	13 (11.5)	
Enoxaparin	Yes	0 (0.0)	2 (1.8)	0.999
	No	16 (14.2)	95 (84.1)	
Apixaban	Yes	1 (0.9)	3 (2.7)	0.462
	No	15 (13.3)	94 (83.2)	
Clopidogrel	Yes	2 (1.8)	5 (4.4)	0.258
	No	14 (12.4)	92 (81.4)	
Aspirin + clopidogrel	Yes	0 (0.0)	13 (11.5)	0.209
	No	16 (14.2)	84 (74.3)	
Rivaroxaban	Yes	7 (6.2)	37 (32.7)	0.670
	No	9 (8.0)	60 (53.1)	
Warfarin	Yes	6 (5.3)	38 (33.6)	0.899
	No	10 (8.8)	59 (52.2)	

All the classes of anticoagulants used had no statistically significant associations with development of ADRs. The number of anticoagulants used also had no statistically significant association with occurrence of ADRs (Table 22).

Table 23: Association between co-prescribed drugs and adverse drug reactions

Variable	Category	ADRs (n=113)		p-value
		Present (n), (%)	Absent (n), (%)	
Number of co-administered drugs	>3	10 (8.8)	43 (38.1)	0.177
	≤3	6 (5.3)	54 (47.8)	
Corticosteroids	Yes	1 (0.9)	1 (0.9)	0.264
	No	15 (13.3)	96 (85.0)	
Inhibitors of platelet aggregation	Yes	1 (0.9)	4 (3.5)	0.541
	No	15 (13.3)	94 (83.2)	
Vitamin supplements	Yes	1 (0.9)	7 (6.2)	0.999
	No	15 (13.3)	90 (79.6)	
Analgesics	Yes	0 (0.0)	6 (5.3)	0.592
	No	16 (14.2)	91 (80.5)	
Vasodilators	Yes	0 (0.0)	5 (4.4)	0.999
	No	16 (14.2)	92 (81.4)	
Glucose lowering agents	Yes	5 (4.4)	25 (22.1)	0.646
	No	11 (9.7)	72 (63.7)	
Proton pump inhibitors	Yes	3 (2.7)	8 (7.1)	0.188
	No	13 (11.5)	89 (78.8)	
Antimicrobials	Yes	0 (0.0)	7 (6.2)	0.591
	No	16 (14.2)	90 (79.6)	
PDE 5 inhibitors	Yes	2 (1.8)	5 (4.4)	0.258
	No	14 (12.4)	92 (81.4)	
RAAS blockers	Yes	7 (6.2)	28 (24.7)	0.233
	No	9 (8.0)	63 (55.8)	
Calcium channel blockers	Yes	4 (3.5)	8 (7.1)	**0.044***
	No	12 (10.6)	89 (78.8)	
Lipid lowering agents	Yes	1 (0.9)	19 (16.8)	0.297
	No	15 (13.3)	78 (69.0)	
Diuretics	Yes	11 (9.7)	44 (38.9)	0.083
	No	5 (4.4)	53 (46.9)	
Antiarrhythmics	Yes	2 (1.8)	24 (21.2)	0.355
	No	14 (12.4)	73 (64.6)	
Beta blockers	Yes	7 (6.2	42 (37.2)	0.973
	No	9 (8.0)	55 (48.7)	

Key: RAAS- renin angiotensin aldosterone system, PDE- phosphodiesterase.

Only the use of calcium channel blockers was found to have significant statistical association with the development of ADRs. Other co-prescribed medications did not have statistically significant association with occurrence of ADRs (Table 23).

The use of calcium channel blockers was the only variable that had significant association with the occurrence of ADRs upon bivariable analysis [OR=3.708, 95% CI: (0.968, 14.205), p= 0.044]. Patients with thromboembolic disorders who are co-prescribed calcium channel blockers were 3.708 times more likely to develop ADRs than those not on calcium channel blockers (Table 23).

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

Introduction

This chapter summarizes the key findings of the study and explores how the findings compare with similar studies conducted elsewhere. It also highlights the study limitations and recommendations for further research and for policy and practice.

5.1 Discussion

DTPs carry significant impact on medications use, affecting the outcome of medications use and can potentially lead to serious complications such as development of side effects and adverse drug reactions that can hinder the uptake of medications. Their financial impact has been assessed and found to be quite high, with studies from the USA documenting that a lot of money is being spent on addressing DTPs that are avoidable. There are also indirect costs associated with DTPs such as lost productivity and prolonged hospitalizations (53).

The present study characterized the DTP among patients with TEDs in the largest referral centre in East Africa and found that prevalence rate at 63.7%, with majority of the participants (41.6%) having one DTP. The results may be comparable to local studies which have documented poor anticoagulation in 5—90% of the patients with TEDs (12,14,21,49,56). In comparison to a study conducted in Australia by Stafford *et al*., the prevalence rates in our study were lower compared those in the Australian study, as the study revealed 100% prevalence rates and at least each participant had 1.4 DTPs (45). Similarly higher prevalence rates of DTPs were reported in other studies conducted in Lebanon and Ethiopia with prevalences of 87.2% and 99.2%, respectively (47,57). The higher prevalence rates in the Australian study could be attributed to the fact that the study involved older people (mean age 76years ± 6) who had comorbidities and were exclusively on warfarin which is subject to a lot of drug interactions. The high prevalence rates in Lebanese study could be attributed to the effect of comorbidities, larger sample size and longer duration of study(47).

In contrast, a low prevalence rate of DTPs (8.4%) was reported in a multicenter study focused on patients with TEDs conducted in France (46). This observation can be explained by the fact that the study was a multicenter hospital-based study focusing on patients on DOACs which are associated with fewer DTPs. Further the study excluded patients who had some comorbidities such as renal failure. Generally, DOACs have a better safety and interactions profile compared to

coumarins and given that these patients were in-patients, they had regular monitoring and frequent contact with care givers and thus some potential DTPs could be mitigated before they occur.

The study comprised majorly of adults with a median age of 51 years of age [IQR= 39,62]. Most of the study participants were female (70.8%) and married (69%). This is consistent with findings from other studies conducted locally that have revealed that majority of patients on anticoagulation are female (60-85%) and majority are in above the age of 40 years (11,14,21,49,56) and elsewhere (57–59). However, a study carried out in France revealed contrasting findings, with participants having a median age of 71 years [IQR 14-98] and almost equal distribution among both gender (females 52.7%, males 47.3%) (46). The higher median age was also reported in another study conducted in Canada (59). This is a critical finding since it implies that the burden and morbidity is high in pre-retirees and this could affect their productivity and turn them to be dependent on others.

The most common indication for the use of antithrombotic drugs among the study participants was for management of cardioembolic events (52, 46.0%), followed by the management of venous thromboembolism (31, 27.4%). The findings are consistent with some studies which had findings that the individual components of cardioembolic events or a combination of one or two of the events were the most common indications for antithrombotic therapy. Two separate studies had revealed that majority of patients with TEDs had been prescribed anticoagulants to manage atrial fibrillation with proportions of 48.8% (47) and 67.0% (59). However, some studies revealed that venous thromboembolism events were the most prevalent indications for the use of antithrombotic drugs including a majority of local studies (10,12,21,49,56–58). The study by Daba *et al.* was solely focused on patients with DVT (10) while the study by Kamuren *et al.* was a retrospective study conducted on patients who had had acute worsening of TEDs and this VTEs are bound to predominate other TEDs (12).

Majority of the patients (100, 88.5%) were on treatment with a single antithrombotic agent, a finding that is consistent with many studies (10–12,21,49,56,59) that revealed that 100% of the patients were on single agent of coumarin therapy. Further, in a study comparing efficacy of coumarins and new oral anticoagulants, all the patients were on single agent treatment with majority (68.2%) being on warfarin and 32.8% being on a direct oral anticoagulant (47). The most commonly used class of drugs for anticoagulation among the study participants was the direct oral

anticoagulants (47, 41.6%) with majority being on rivaroxaban (43, 38.0%). These are higher rates of use of DOAC than previously documented locally. Local studies are lacking on the use of DOACs since the uptake of DOACs has been hindered by cost issues, despite having equal or better efficacy than warfarin and better safety profile (60). The only local study on DOACs was a study conducted at MTRH in 2021 which assessed the risk of bleeding among outpatients on rivaroxaban (61). Meta analyses done elsewhere in Africa recommended the use of DOACs and in response to this KNH guidelines were changed to make DOACs the drug of choice in some TEDs in line with American College of Chest Physicians (ACCP guidelines) (60). The second most commonly used antithrombotic was warfarin, with 43 (38.0%) being on treatment with this drug.

Majority of the study participants (76.1%) had other drugs co-administered. The average number of co-administered medications was 4.3 drugs per patient. This finding was different from the findings of the study conducted at MTRH which revealed that 100% of the patients had at least one co-administered drug. In the study, the average number of co-administered medications per patient was 7.5±1.9 with a range of 1-18 (12). The study by Karuri *et al.* revealed that over 95% of the participants were on concurrent medications (13). The Ethiopian study by Fekede *et al*. revealed that all the patients (100%) had co-administered drugs, with majority (60.4%) having more than three co-administered drugs (10). Another Ethiopian study by Gebrehiwot *et al*. revealed that all the participants had at least one co-prescribed drug, with an average of six drugs per patient (57). Our findings suggest that patients with TEDs are likely to require multiple medications to manage other diseases.

Among the co-prescribed medications, diuretics were the most co-prescribed drugs, with 55 patients (48.7%) having been prescribed these drugs. In second place and third place were beta blockers and RAAS blockers, being co-prescribed in 49 (43.4%) and 35 patients (31.0%) respectively. This is in tandem with the finding that most of the patients had cardiovascular disorders as comorbid conditions. Contrast to the findings of this study, the study by Karuri *et al.* had antimicrobials being the most co-administered medications (with antibacterials being administered in 37.4% of the patients, antivirals in 12.6% of the patients and antifungals in 2.5%), followed by opioids (27.8%) and antiarrhythmics at 17% (13). Findings from the MTRH study conducted by Kamuren *et al*. showed that the most common co-administered drugs were

antimicrobials (70%), antiemetics (65%) and cardiovascular medications (50%). This finding has an association with the comorbidities as 43.1% of the patients had infections which are managed by anti-infective agents, further, 15.9% had gastrointestinal disorders and 12.7% had neoplasms, conditions which may require antiemetics in their management (12). In the Ethiopian study by Teklay *et al*., findings were similar to our findings, with majority of the patients being on cardiovascular drugs as up to 60% of the patients had cardiovascular diseases as comorbidities (57).

Among the DTPs identified, the most prevalent DTPs was nonadherence (46.9%). Other DTPs with high prevalences included additional therapy needed (35.4%) and adverse drug reactions (14.4%). Few patients had DTPs of ineffective drug (6.2%), unnecessary therapy (3.5) dosage too low (1.7%) and dosage too high (1.7%).

Nonadherence negatively affects the patients' ability to attain their therapeutic goals. Several factors affect adherence, key of which include development of side effects, inability to afford medication, medication unavailability and in some cases polypharmacy (24,62,63). Adherence has a major impact on health care as the lack of adherence interferes with the therapeutic benefits of medication leading to increases in the severity of the disease, risk for death and health costs (24,64,65). In the study, 46.9% of the patients were nonadherent, meaning that just over half are compliant to their medications. These findings were incomparable to results of a meta-analysis conducted in Canada which had relatively lower rates of nonadherence with 71%±17 being adherent (66). Several studies reported nonadherence to anticoagulation to be in the range of 22-58% and our findings are consistent with the findings from those studies (24,67,68). Local studies yielded similar results, with a study conducted by Kizito *et al*. revealing that nonadherence in the participants was 47.6% (11). However, a study conducted in Ethiopia revealed high rates of adherence with only 6.6% of the study participants being noncompliant (10). A local study also had lower rates of non-adherence, with 39% of patients being nonadherent (56). A pre-post by Sakina *et al*. reported low rates of adherence (33%) which improved to 67% after patient education (14). The main reasons for non-adherence as reported by the patients were as follows: inability to afford the medications sometimes (19.5%), inconvenience (15%), some forget to take the medications at times (24.8%), some intentionally skip doses when they feel well (3.5%) and some

(0.9%) reported that they get confused on what medications they should take and when, because of polypharmacy.

Adverse drug reactions present a challenging and expensive public health problem. They account for up to a quarter of hospital admissions, prolong hospital stays and increase morbidity and mortality. Factors that can lead to adverse drug reactions include Anatomical Therapeutic Class (ATC) of medications, polypharmacy, drug interactions, pharmacokinetic and pharmacodynamic changes that come with age and compliance. Findings from our study indicated that 14.4% of the patients developed ADRs which were due to either the antithrombotic drug used or the co-administered drugs. Comparable results were obtained by Fekede *et al*. and Anakwue *et al*. with prevalences of adverse events being 9% and 11.5% respectively (10,48). Bleeding events occurred in 3.5% of the study participants. This was significantly lower compared to findings from other similar studies which have documented up to 35% of patients having bleeding disorders when on anticoagulants (10,12,53). The reasons for the higher prevalence of bleeding disorders is due to the type of anticoagulant used, as all these other studies reported only the use of warfarin. Further, drug interactions contributed to supra-optimal INRs that increases the chance of bleeding (12,21,49,57).

Drug interactions present a challenge in achieving anticoagulation, especially for patients on warfarin. Warfarin has a narrow therapeutic index and window, has a variable dose-response relationship and is prone to many drug-drug and drug-food interactions. As such, any interactions can drastically compromise the efficacy and safety of warfarin. DOACs have a relatively better interaction profile but they are not free of significant interactions. Thirty-one percent of the study participants had significant drug-drug interactions. Almost a quarter (23.9%) of the study participants had interactions that can affect the concentration of antithrombotic drugs. The findings were comparable to those of a study conducted by Kibiru *et al*. that documented a 21% prevalence of drug interactions affecting anticoagulants (56).

The findings, however, were incomparable to most studies that have been conducted locally and regionally. Two Ethiopian studies revealed that majority of the patients (99.2% and 92.1%) on anticoagulation had drug-drug interactions (10,57). Another study revealed that 79% of patients were prescribed medications that interacted with anticoagulants (59). Findings from a studies conducted by Karuri *et al*. and Kamuren *et al*. also revealed high percentage of patients (over 95%)

on anticoagulation being co-prescribed medicines that interacted with anticoagulants (12,13). The high prevalence of drug interactions was also a finding in a study conducted in Lebanon, with 83.3% of the patients having drug interactions (47). The high prevalence of drug interactions can be attributed to multiple comorbidities among the participants in these studies and the fact that patients in these studies were mainly on warfarin.

Poor anticoagulation is the most common outcome of DTPs among patients on anticoagulant therapy. This can present as deranged INR, percentage of time outside therapeutic range of INR, bleeding disorders and deranged clotting parameters such as prothrombin time (PT) and aPTT. Essentially poor anticoagulation can be a result of many factors, key of which include poor compliance, drug interactions, deranged organ function, improper dosages and even food-drug interactions especially for patients on coumarins (47,61,69,70).

Effective anticoagulation was documented in 71.7% of the study participants, as evidenced by normal results of the coagulation profile. This was a contrast to findings from several local studies that have consistently reported poor anticoagulation, with effective anticoagulation being achieved in 7-43.5% of the patients (11,14,21,49,56). The findings of poor anticoagulation have also been reported elsewhere in Africa, with studies in Nigeria and Ethiopia revealing effective anticoagulation in 39% and 49% of patients respectively (10,48). The higher rates of effective anticoagulation can, in part, be explained by the fact that majority of the patients were on DOACs. Compared to warfarin, which was the main drug being used in other compared results therein, DOACs have a favorable interaction profile and relatively wider therapeutic window thus variations in diet and even some drug interactions expected with warfarin will not affect the safety and efficacy of DOACs(71). Higher rates of effective anticoagulation were documented in a study conducted by Manji *et al.*, with success rates of 63.5%. Even though the main drug used among the study patients in this study was warfarin, it was an interventional study evaluating outcomes of pharmacy led anticoagulation clinics (72). Notably, of the 28.4% patients who had poor anticoagulation, majority (20.4%) had elevated INR and/or PT indicating excess anticoagulation, while 8% had low INR and/or PT indicating inadequate anticoagulation. This was a finding that contradicted some studies that had documented most patients being under-anticoagulated (10,12,14,21,56).

In this study, significant predictors for the occurrence of DTPs included the use of PPIs and diuretics. Upon bivariable analysis, polypharmacy, in addition to the use of diuretics and PPIs was a good predictor of the occurrence of DTPs among the study participants. Upon multivariable analysis, the use of PPIs [aOR=7.155, 95% CI: (0.861, 59.444), p=0.029] and the use of diuretics [aOR=2.689 95% CI: (1.193, 6.050), p=0.017] were the only strongest predictors of occurrence of DTPs. The observation that use of PPIs in patients with TEDs increase the risk of developing DTPs was a finding documented by an earlier study which documented that the use of PPIs was associated with an almost 2.5 fold increase in the risk of having deranged INR [aOR = 2.487, 95% CI: (1.139, 5.430)] (47). This could possibly be due to the drug interactions between PPIs and anticoagulants, especially warfarin. PPIs can inhibit metabolism of warfarin leading to high INRs and increasing the risk of lower gastric bleeding (73). Various factors are associated with the occurrence of DTPs. In literature, several factors have been found to have an association with the occurrence of DTPs. Key of these include drug interactions, classes of drugs administered, number and type of comorbid conditions and sociodemographic characteristics such as age (9–12,22,23,47).

Risk factors for drug interactions identified among the study participants upon bivariable analysis included patients with venous thromboembolic events, polypharmacy, the use of PPIs, diuretics, inhibitors of platelet aggregation, vitamin supplements, RAAS blockers, clopidogrel, statins and beta blockers. However, upon multivariate analysis, most of these variables lost significance and only polypharmacy [aOR=8.413, 95% CI: (2.761, 25.641), p=0.0001], the use of PPIs [aOR=10.116, 95% CI: (1.647, 62.103), p=0.012] and the use of vitamin supplements [aOR=41.322, 95% CI: (3.817, 447.288), p=0.002] retained the associations.

Most of the patients had comorbidities and thus were on multiple drugs. As the number of co-prescribed drugs increase, the chances of developing drug interactions increase. Comorbid conditions may affect the pharmacokinetics and pharmacodynamics of administered medications which could lead to development of drug interactions. The coadministration of vitamin supplements poses risk of drug interactions since some of the supplements have many components that could have unpredictable interaction profiles. Similarly, the use of PPIs could induce or inhibit metabolism of some drugs, leading to loss of efficacy or development of toxicity and ADRs (74).

Non-adherence was the most prevalent DTP. The use of clopidogrel was the only significant factor that was associated with nonadherence. However, upon regression, the association was lost. Despite many patients revealing they do not adhere to medications because of inability to afford the medications and forgetfulness, sociodemographic factors that have a bearing on these factors (income levels, income and age) did not show any significant associations with nonadherence. Another reason given for nonadherence was related to the pill burden but there was no significant statistical association with polypharmacy.

The only variable that had an association with development of ADRs was the use of CCBs [aOR=3.708, 95% CI: (0.968, 14.205), p= 0.046]. This observation is consistent with findings from a study conducted among patients with atrial fibrillation in Canada where CCBs were associated with development of ADRs [aOR = 1.93, 95% CI: (1.88, 1.97), p = 0.002) (59). The findings are consistent with the observation that some of the reported ADRs by patients are common side effects of CCBs (headache and dizziness). Polypharmacy and drug interactions could potentially lead to ADRs but findings from this study did not show significant associations.

5.2 Strengths, Weaknesses and Study limitations

Information bias could have been a key limitation in the study, especially participants wanting to refrain from disclosing information on some of the questions asked such as the use of alcohol and smoking or even giving exaggerated information when responding to questions asked to determine their adherence. To minimize this, participants were assured of their confidence and the privacy of the data collected.

The study was not able to assess other patient factors that may affect medication use and thus influence the occurrence of DTPs such as genetics and diet.

5.3 Conclusion

The prevalence of DTPs among patients with TEDs was high at 63.7% with non-adherence being the most prevalent DTP. Significant outcomes of the DTPs included deranged coagulation, with majority of the study participants having supra-optimal anticoagulation. Independent predictors for the occurrence of DTPs in these patients included the use of PPIs and diuretics. Independent predictors of occurrence of drug interactions included polypharmacy, the use of PPIs and coadministration of vitamin supplements. The use of clopidogrel was a significant independent

predictor for nonadherence and the use of calcium channel blockers was associated with occurrence of adverse drug reactions.

5.4 Recommendations

5.4.1 Recommendations for Policy and Practice

The high prevalence of DTPs and their association with PPIs as well as diuretics suggests that clinicians should intensify the anticoagulation management in patients receiving these agents.

Non-adherence was the most prevalent DTP and as such patient education and counselling should emphasized so as to optimize the uptake of antithrombotic drugs among these patients.

Polypharmacy was a key factor in developing some DTPs, with some patients having been prescribed drugs they do not have a medical indication for. Caregivers should do comprehensive medication reconciliation and thorough review of patients to avoid prescribing unnecessary drugs.

5.4.2 Recommendations for Research

Further large studies should assess other factors such as provider related determinants and hospital contextual predictors that may contribute to a huge prevalence of DTPs among patients with TEDs.

Large prospective cohort studies can also be conducted to determine the long-term outcomes and health and financial impacts of DTPs among patients with TEDs.

Studies can be done to generate more information on the prevalence rates of DTPs and associated risk factors among hospitalized patients with TEDs in order to build on the information generated from this study.

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APPENDICES

APPENDIX 1: ELIGIBILITY SCREENING FORM

KENYATTA NATIONAL HOSPITAL OUTPATIENT CLINICS **OUTPATIENT NUMBER:** **DATE:** **UNIQUE STUDY NUMBER ALLOCATED:**	
CRITERION	**REMARK (YES OR NO)**
Is the patient aged 18 years old or above?	
Does the patient have a diagnosis of thromboembolic disorder?	
Is the patient on medical treatment for thromboembolic disorder and thus on follow up at KNH?	
No obvious record of mental and psychiatric illness.	
No record of current pregnancy.	

Patients whose medical files answer all the above questions with a YES will be eligible for inclusion into the study pending signing of informed consent form.

Decision: included into study/ not included?

Reason for exclusion?

APPENDIX 2: INFORMED CONSENT ENGLISH VERSION

TITLE OF THE STUDY: DRUG THERAPY PROBLEMS AMONG ADULT PATIENTS WITH THROMBOEMBOLIC DISORDERS AT KENYATTA NATIONAL HOSPITAL

PRINCIPAL INVESTIGATOR AND AFFILIATIATION: The principal investigator is Dr. David Nyaundi Kimonge, a registered Pharmacist and currently a student at the University of Nairobi, School of Pharmacy, currently pursuing a course leading to the award of a degree in Master of Pharmacy in Clinical Pharmacy.

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INTRODUCTION

My name is David Nyaundi Kimonge. I am a pharmacist by training currently pursuing my postgraduate studies at the University of Nairobi. I am in my final year, undertaking a course leading to the award of a degree in Master of Pharmacy in Clinical Pharmacy.

I am undertaking a study titled “DRUG THERAPY PROBLEMS AMONG ADULT PATIENTS WITH THROMBOEMBOLIC DISORDERS AT KENYATTA NATIONAL HOSPITAL”. I am requesting for the permission to talk to you about this study and if agreeable to you, your participation in the study as well.

You are free to ask questions related to the study such as, what will happen to you as a participant, the potential risks, or benefits, the rights you have as a participant or any other information. When you feel satisfied with the study, you are free to enroll into the study by giving your consent. The name of this process is 'informed consent.' When you understand and decide to join in the study, you will sign your name on this form as proof of consent.

Some of the universal principles that in medical research, which apply to participants are:

i) Participation in this study is totally voluntary

ii) At any point in this study, you are free to withdraw without necessarily explaining your withdrawal

iii) In case you decline to be a participant in the research, you will still enjoy all the normal services you are entitled to.

May I continue? **YES / NO**

The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee has approved this study via protocol No._____

WHAT IS THE STUDY ABOUT?

The management of most medical conditions especially those requiring the use of more than one medication is often challenging due to complex factors surrounding the use of more than one drugs. This is especially so in patients with chronic diseases. Factors surrounding the use of medications in such populations may lead to events called drug therapy problems. These drug therapy problems will adversely affect the outcomes of treatments.

This study aims to identify some of the drug therapy problems which patients with thromboembolic disorders experience. Through the review of your medical files and oral interviews, I am going to identify some of these and this information will come in handy in coming up with some approaches to mitigate them.

WHAT WILL HAPPEN IF YOU AGREE TO PARTICIPATE?

Should you agree to participate in the study, I will take extensive time to study your medical file to try to identify some of these drug therapy problems from the medical files. This information will be supplemented by an oral interview that shall not be more than 20 minutes long in a private office room. In event you do to wish to respond to any question, your choice shall be respected and the interview will be at your convenience. All the information gathered shall be confidential and your privacy will be respected.

VOLUNTARY PARTICIPATION

Just like any other biomedical research, participating in this research is voluntary. You have the option to decline to participate or to withdraw from this study at any point without suffering any injustice or losing any benefits and services usually enjoyed at the hospital.

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

From this study, you may suffer a loss of privacy. However, all the information collected from your file will be kept confidential. In this study, a code number will be used to refer to you in computer database that is password-protected, and all paper records will be kept in a well-secured cabinet. However, it could still be possible that someone gains access to the study records and finds out that you were one of the participants since no data storage system can be absolutely secure.

The study will not involve any invasive procedures or additional medications.

Realistically, the study may consume some more of your time beyond the stated 20 minutes although I will try my level best to avoid this.

ARE THERE ANY BENEFITS TO BEING IN THIS STUDY?

You may benefit by being part of this study. If problems are detected, the doctor will be informed and this will be of benefit to you. Also, the results of this study will be useful for improving the quality of care received by you and future patients.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

Participating in this study will not cost you any money. **Data will be collected only when you come to the clinic and therefore you will not incur additional transportation fees**.

WILL YOU GET A RENUMERATION?

Since there is no foreseeable expenditure for participating in this study, there will be no compensation arising from being a participant. Further, no gifts nor incentives shall be given to those who opt to enroll in the study

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

In case you have any additional concerns and questions about being part of this study, please send a text message, or call the Principal Investigator on the following number:

Dr David Nyaundi Kimonge

Phone Number: 0715027584.

Email: ddepark@gmail.com

If you need additional information about your rights as a research participant, please contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee through the telephone number 2726300 Ext. 44102 or the email address: uonknh_erc@uonbi.ac.ke

Having gone through the consent form, I now humbly request you to give consent to participate in the study by signing the Consent Declaration Form attached.

CONSENT DECLARATION FORM ENGLISH VERSION
PARTICIPANT'S STATEMENT

This is to confirm that I have read the consent information and/or it has been read and explained to me in the language I understand best. I have discussed with the investigator in details about this research, and my questions have been addressed in a language that I understand.

I am aware of the benefits and risks of being one of the participants. It is clear to me that my participation is voluntary, and at any given point in this study, I am free to withdraw. Therefore, I have agreed to participate in this study freely.

I have been assured that the research staff will make all efforts possible to maintain the confidentiality and privacy of my personal records and identity. I understand that by consenting to this study, I have not foregone my legal rights, which I am entitled to as a study participant.

I therefore give consent to be interviewed and I give the principal investigator the freedom to review my medical files and records.

Signature……..... **Date**: …….

Witness Name and Signature…….... **Date**: ……

RESEARCHER'S STATEMENT

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

Researcher's Name: …….

Date: …….

Signature: …….

Role in the study: ……

APPENDIX 3: MAELEZO KUHUSU KUSHIRIKI KATIKA UTAFITI

MADA YA UTAFITI: KUTATHMINI SHIDA ZA MATIBABU ZINAZOWEZA KUTOKEA KWA WAGONJWA AMBAO WAKO NA THROMBOSI ZA VINA VYA MISHIPA MIONGONI MWA WAGONJWA AMBAO WANAPATA MATIBABU KATIKA HOSPITALI YA RUFAA YA KENYATTA.

MCHUNGUZI MKUU NA USHIRIKA WA TAASISI

Mchunguzi mkuu katika utafiti huu ni Dkt. David Nyaundi Kimonge ambaye ni mwanafunzi katika chuo kikuu cha Nairobi katika shule ya Famasia. Dkt David Nyaundi Kimonge amesajiliwa katika taifa la Kenya kama daktari mwanafamasia na kwa sasa hivi ako katika mwaka wake wa mwisho wa masomo ya upeoni akiwa anafanya masomo ambayo hatimaye yatampa fursa ya kuhitimu katika somo la Clinical Pharmacy.

WASIMAMIZI / WACHUNGUZI WA USHIRIKIANO NA USHIRIKA WA KITAASISI

1. Dkt. David G. Nyamu

   Idara ya Pharmacology, Clinical Pharmacy na Pharmacy Practice

   Shule ya Famasia

   Chuo Kikuu cha Nairobi

2. Dkt. Peter Njogu

   Idara ya Pharmaceutical Chemistry, Pharmaceutics na Pharmacognosy

   Shule ya Famasia

   Chuo Kikuu cha Nairobi

UTANGULIZI

Jina langu ni Dkt. David Nyaundi Kimonge, mwanafunzi wa shahada ya uzamifu katika kitengo cha “Clinical Pharmacy” katika chuo kikuu cha Nairobi.

Nina nia ya kufanya utafiti katika eneo la “KUTATHMINI SHIDA ZA MATIBABU ZINAZOWEZA KUTOKEA KWA WAGONJWA AMBAO WAKO NA THROMBOSI ZA VINA VYA MISHIPA MIONGONI MWA WAGONJWA AMBAO WANAPATA MATIBABU KATIKA HOSPITALI YA RUFAA YA KENYATTA” naomba fursa ya kuongea nawe kuhusu utafiti huu na ikiwezekana unipe fursa ya kukujumulisha kwa utafiti huu.

Kuwa huru kuniuliza swali lolote ambalo unaweza kuwa nalo kuhusu utafiti huu wakati wowote ukisoma hii nakala ama nikiwa katika hali ya kukuelezezea kuhusu huu utafiti ama hata baada ya ukisoma. Baada ya ukisoma nakala hii ama hata baada ya kukuelezea ana kwa ana kuhusu utafiti huu, ukiridhika nakusihi ujisajili kuwa mmoja wa watakaoshiriki katika huu utafiti. Kuna nakala baada ya hii ambayo utajaza kuonyesha kwamba umeelezewa kuhusu utafiti huu na umekubali kuwa mhusika katika hii utafiti

Kabla tundelee, yafaa ujue kwamba kuhusika katika utafiti wowote ni kwa hiari na hakuna mtu atakulazimisha kinyume na hiari yako. Pili, hata baada ya kujisajili kuwa mhusika katika utafiti wowote, uko na haki ya kujiuzulu kutoka kwa utafiti wakati wowote bila kujieleza. Tatu, hata ukikataa kuwa mhusika katita utafiti huu, hautanyimwa haki zako zozote na utapata matibabu yako kama tu wengine bile ubaguzi.

Je, tuendelee? **NDIO / LA**

Utafiti huu umeidhinishwa na Kamati ya Kitaifa ya Hospitali ya Maadili na Utafiti ya Kenya ya Kenyatta na Chuo Kikuu cha Nairobi kupitia itifaki nambari. _____

JE UTAFITI HUU NI KUHUSU NINI?

Wagonjwa wengi hutibiwa na madawa. Baadhi ya wagonjwa hutumia zaidi ya dawa moja kwa minajili ya kutibu hali zao. Hii huwa sanasana kwa wagonjwa wenye magonjwa ambayo hayatibiki kikamilifu kwa muda mchache. Utumizi wa madawa zaidi ya moja au utumizi wa madawa kwa wagonjwa ambao wako na magonjwa ya kudumu. Matatizo ambayo hutokea wakati wagonjwa hawa wanatumia hizi madawa yanaweza changia hali kuwa mbaya zaidi, kudhoofika kwa afya na mara kwa mara inachangia wagonjwa kutopata afueni.

Utafiti huu una nia ya kuchunguza baadhi ya shida za matumizi ya dawa ambazo wagonjwa wa thrombosi ya vina vya mishipa hupata mara kwa mara wanapotumia dawa kutibu shida hii. Kwa kupitia rekodi zako za hospitali na kuongea na wewe ana kwa ana nina nia ya kutambua haya matatizo. Matokeo ya utafiti huu yatasaidia pakubwa kupambana na haya matatizo na kusaidia washiriki kutambua mbinu za kuzuia hayo matatizo kutokea tena kwako na kwa wengine.

NI NINI KITATOKEA IKIWA UTAAMUA KUWA KATIKA UTAFITI HUU?

Ikiwa utakubali kuwa sehemu ya utafiti huu, mhojiwa atapata habari kutoka kwa faili yako ya matibabu inayohusiana na historia yako ya kijamii, matibabu, na dawa. Kando na hayo, ntakuuliza maswali kuhusu matumizi yako ya dawa na taarifa yoyote ambayo itasaidia katika utafiti huu.

USHIRIKI WA KUJITOLEA

Kushiriki katika utafiti huu ni kwa hiari yako na kujitolea kwako. Sio lazima ushiriki katika utafiti huu. Ikiwa utaamua kwamba hutaki kushiriki, hakutakuwa na ubaguzi wowote katika matibabu yako. Utahudumiwa tu kama kawaida na utatibiwa sawa na wengine bila ubaguzi. Ikiwa utakubali kuwa mhusika katika utafiti huu na ifike mahali uamue kujitoa kwa utafiti, una huru wa kufanya hivyo.

JE! KUNA HATARI YOYOTE AU HUDHURU USUMBUFU UNAOHUSISHWA NA UTAFITI HUU?

Kutoka kwa utafiti huu, unaeza kupoteza faragha. Walakini, habari yote itayokusanywa kutoka kwa faili yako itahifadhiwa kwa siri. Katika utafiti huu, nambari ya kisiri itatumiwa kukurejelea kwenye hifadhidata ya kompyuta ambayo inalindwa na nenosiri, na rekodi zote za karatasi zitahifadhiwa kwenye baraza la mawaziri lenye usalama. Tafadhali kumbuka kuwa bado inaweza kuwa mtu anaweza kupata rekodi za utafiti na kugundua kuwa wewe ni mmoja wa washiriki kwani hakuna mfumo wa kuhifadhi data ambao unaweza kuwa salama kabisa. Utafiti huu hahutahitaji mshirika kutumia madawa za ziada na operesheni za kudhuru mwili wa mshirika hazitatumika.

JE! KUNA FAIDA YOYOTE KUWA KATIKA UTAFITI HUU?

Unaweza kufaidika kwa kuwa sehemu ya utafiti huu. Ikiwa shida yoyote itagunduliwa, daktari atajulishwa na hii itakuwa ya faida kwako. Pia, matokeo ya utafiti huu yatakuwa muhimu kwa kuboresha ubora wa huduma unayoipokea wewe na wagonjwa wa baadaye.

JE! KUWA KATIKA UTAFITI HUU KUTAGHARIMU CHOCHOTE?

kushiriki katika utafiti huu hakutakugharimu pesa yoyote. **Hutahitaji kutumia pesa kwa usafiri kwa minajili ya utafiti huu. Data yote itakusanywa siku za kiliniki.**

JE! UTAPATA MAREJESHO YA PESA YOYOTE ILIYOTUMIWA KAMA SEHEMU YA UTAFITI HUU?

Kwa kuwa hakuna matumizi ya kuonekana kwa kushiriki katika utafiti huu, hakutakuwa na Fidia inayotokana na kuwa mshiriki katika utafiti huu.

JE! IKIWA UNA MASWALI KATIKA SIKU ZIJAZO?

Ikiwa una wasiwasi zaidi kuhusu kuwa sehemu ya utafiti huu, tafadhali tuma ujumbe mfupi, au piga simu kwa mchunguzi kwa nambari ifuatayo:

Dkt. David Nyaundi Kimonge

Nambari ya simu: 0715027584.

Barua pepe: ddepark@gmail.com

Ikiwa unahitaji habari zaidi kuhusu haki yako kama mshiriki wa utafiti, tafadhali wasiliana na Katibu / Mwenyekiti, Hospitali ya Kitaifa ya Kenyatta-Kamati ya Maadili na Utafiti ya Chuo Kikuu cha Nairobi kupitia:

nambari ya simu 2726300 Ext. 44102 au

anwani ya barua pepe: uonknh_erc@uonbi.ac.ke

Utafiti huu una idhini ya kimaadili kutoka kwa chombo hiki.

Baada ya kupitia fomu hii ya idhini, kama umeridhika na unataka kushiriki katika utafiti huu, tafadhali idhinisha Fomu ya Ridhaa inayofuata.

FOMU YA RIDHAA (KUKUBALI KUSHIRIKI)

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 uhuru.

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.

Mshiriki: ……. Tarehe: ……...

Shahidi: …… 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: ……. ……

Tarehe: ……..

Sahihi: ……

APPENDIX 4: DATA COLLECTION TOOL
Patient Identifier: ……

Data Collector: ……

Date: ……....

PART I: PATIENT SOCIODEMOGRAPHICS

1. Patient age in Years: ……
2. Patient Weight in Kg: ……...
3. Patient Height in Meters…….....
4. Body Mass Index: …….
5. Patient Gender (0=female, 1=male): …….
6. Marital Status (0=Not Married, 1=Married, 2=widowed, 3=divorced): …….
7. Religion (0=other, 1= Christian, 2=Muslim, 3=Hinduism) …….
8. Employment Status (0=Unemployed, 1=Employed): …….
9. If employed, what is your average monthly salary?.....

Average Salary	**Code**
Below Ksh 20,000	1
Ksh. 20,001-74,999	2
Above Ksh. 75,000	3

10. Education Level: …….

Education Level	**Code**
Informal	0
Primary Level	1
Secondary Level	2
Tertiary Level and Above	3

11. History of Smoking (0=No, 1=Yes): ……

    If yes, how many years have you smoked cigarettes?

    Less than 10 years ☐

10 – 19 years ☐
20 years or more ☐

12. History of Alcohol Use (0=No, 1=Yes): ……...

    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 ☐

13. Do you regularly exercise/ are you involved in physical activities at least 30 minutes per day for at least 4 days a week? (0=No, 1=Yes) ……...
14. Where do you live? Rural or Urban area? (Rural=0, Urban area=1) .....

PART II: CLINICAL PROFILE

1. What is the clinical diagnosis of the patient, the exact thromboembolic disorder?

   DVT ☐

   History of DVT ☐

   History of PE ☐

   Atrial Fibrillation ☐

   Cerebral Artery Thrombosis☐

   Post-Op following implant of prosthesis ☐

   Other, please specify……
2. For how long has the patient had the TED/ When was the diagnosis made?.....months.
3. For how long has the patient been on treatment? ……. months.
4. Does the patient have any comorbidities? (0=No, 1= Yes) ……
5. If yes to number 2 above, what are comorbid conditions the patient has.

6. Does the patient have any known drug allergies? 0=No, 1=Yes
7. If yes to 5 above, what drug (s) is the patient allergic to?

MEDICATIONS HISTORY

Currently what medications is the patient on? Both prescribed and herbal remedies.

Drug	Indication	Duration	Comments

PART III: DTPS AS REPORTED BY THE PATIENT

1. In the course of taking your medication, have you had any other symptoms? (0=No, 1=Yes). ……
   If you have, what are these symptoms and when was that?

2. While taking your medications, does any of them make you feel sick or unwell compared to when you are not taking/have not taken them? (0=No, 1=Yes). ……
   If yes, how do you feel after taking the drug? Can you identify the drug which makes you feel unwell?

3. Do you have any symptoms that you have not told the doctor about? (0=No, 1=Yes). …..
   If yes, what is the symptom (s)?

   Why have you not told the doctor about it?

4. Do you feel like your medications are too expensive to buy? (0=No, 1=Yes)
5.

THE MORISKY MEDICATION ADHERENCE SCALE (MMAS-8) TO MEASURE ADHERENCE.

No.	Question	(Yes or No)
1.	Do you sometimes forget to take your medication?	
2.	In the past 2 weeks is there a day you forgot to take your medication?	
3.	Have you ever stopped taking your medication or took a less dose because you felt worse without consulting your doctor?	
4.	When you travel or leave the house, do you sometimes forget to carry or take your medication?	
5.	Did you take your medication yesterday?	
6.	Sometimes when you feel better do you stop taking your medication?	
7.	Taking medicines everyday can be quite an inconvenience and challenging. Do you feel like that's a challenge and its difficult to stick to the treatment plan?	
8.	How often do you find it difficult remembering to take your medicine? a. Rarely/ Never b. Once in a while c. Sometimes d. Usually e. All the time	

For Questions 1-7, a response of "yes" scores one point, a score of "no" scores zero points.

For question 8, if the response is "a", the score is zero points, any other score is 1 point.

Based on the score, adherence will be categorized as follows:

Score	Level of Adherence	Code
0	High adherence/ Low non-adherence	2
1-2	Medium Adherence	1
Above 2	Low Adherence/High Non-adherence	0

Based on this, the patient is: ……

PART IV: ABSTRACTING MEDICAL INFORMATION FROM FILES

1. LABORATORY TESTS AND RELEVANT INVESTIGATIONS

In this section, significant lab parameters such as organ function tests, coagulation and vital signs will be recorded.

Date	Parameter	Normal Values	Test Values	Comments

2. MEDICATIONS CHART

Patient is currently on the following medications.

Medication	Dose, frequency and Route	Start and Stop Date	Indication	Comments

3. CLINICAL STATUS OF THE PATIENT

During the current visit, how is the patient doing, any new complaints?

PART V: IDENTIFICATION OF DTPS AND ASSOCIATED MEDICATIONS

By analyzing Parts II to IV, is there any DTP noted? What is the implicated drug? What is the probable cause?

a. Is there unnecessary drug therapy? (0=No, 1=Yes) _____
   If yes, what is the implicated drug? _____
   What is the possible cause? Duplicate therapy (0), No medical Indication for drug (1), treating avoidable adverse reaction (2), non-drug therapy more appropriate (3), addiction/recreational drug use (4).
b. Does the patient need additional drug therapy? (0=1, 1=Yes) _____
   If yes, why? Preventive therapy (0), untreated condition (1), need for synergism (2)
c. Is there ineffective drug therapy in the patient? (0=No, 1=Yes) _____
   What drug is implicated? _____
   Why? More effective drug available (0), condition refractory to the drug (1), dosage form inappropriate (2), existing contraindication (3), drug not indicated for condition (4)
d. Is there any drug in the regimen whose dose is too low? (0=No, 1=Yes) _____
   Implicated drug? _____
   What is the possible cause? Wrong frequency (0), Ineffective dose (1), drug interactions (2), small dose prescribed (3)
e. Is there any drug causing or has a potential for causing adverse drug reactions? (0=No, 1=Yes) _____

What drug is implicated? _____

What is the potential cause of this? Undesirable non-dose related drug effect (0), unsafe in the patient due to patient risk factors (1), drug interactions (2), allergic reaction (3)

f. Is there any drug in the regimen whose dose is too large? (0=No, 1=Yes) _____

What drug is implicated? _____

What is the potential cause of this? Large dose prescribed (0), frequency too short (1), duration too long (2), drug interactions leading to toxic doses (3)

g. Is the patient non-compliant to TED drugs? (0=No, 1=Yes) _____

If yes, what drug is the patient non-compliant to? _____

Potential reasons for noncompliance? Patient doesn't understand instructions on how to take the drug (0), patient cannot afford the drug (1), forgets to take medication (2), medication not available (3), can't take medication (4)

h. In the prescribed drugs, are there drug interactions? (0=No, 1=Yes) _____

Interacting drugs? _____

Effect of the interactions on TED drugs? Decrease dose of TED drugs (1), increase dose of TED drugs (2).

APPENDIX 5 ERC 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/199

16th May, 2023

David Nyaundi Kimonge
Reg No. U56/38075/2020
Dept. of Pharmacy
Faculty of Health Sciences
University of Nairobi

APPROVED
16 MAY 2023

Dear David,

ETHICAL APPROVAL-RESEARCH PROPOSAL: DRUG THERAPY PROBLEMS AMONG ADULT PATIENTS WITH THROMBOEMBOLIC DISORDERS AT KENYATTA NATIONAL HOSPITAL (P74/01/2023)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P74/01/2023.** The approval period is 16th May 2023 – 15th May 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 Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept., KNH
The Chair, Dept. of Pharmacy, UoN
Supervisors: Dr. Davis G Nyamu, Dept. of Pharmacy UoN
Dr. Peter M Njogu, Dept. of Pharmacy, UoN

Appendix 6 GENERAL SURGERY APPROVAL

appendix

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

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

Ref: KNH/HOD/GEN-SURG/35/VOL.I **Date: 13th June, 2023**

David Nyaundi Kimonge
Reg. NO. U56/38075/2020
Department of Pharmacy
Faculty of Health sciences
University of Nairobi

Dear David,

RE: APPROVAL TO COLLECT DATA FROM - GENERAL SURGERY AT KNH

We acknowledge your request on the above, together with a study registration form and a KNH/UON ERC approval letter on the study titled ***"DRUG THERAPY PROBLEMS AMONG ADULT PATIENTS WITH THROMBOEMBOLIC DISORDERS AT KENYATTA NATIONAL HOSPITAL."***

Approval has been granted for you to collect data from General Surgery at Kenyatta National Hospital. Kindly liaise with the SACN In-charge, General Surgery.

Note, we would like you to forward a copy of the study report to the undersigned after completion of the study.

Dr. Gibson Musila
HOD GENERAL SURGERY

Copy to: SACN Level 5
ACN Clinic 24

APPENDIX 7 MEDICINE DEPARTMENT APPROVAL

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: 2nd June 2023**

David Nyakundi Kimonge
Reg No. U56/38075/2020
Dept. of Pharmacy
Faculty of Health Sciences
University of Nairobi

Dear David,

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 among adult patients with thromboembolic disorders at Kenyatta National Hospital."***

By a copy of this letter, **DCN- Medical** 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

DCN - Medical

Dr G. Nyamu

12/10/2023

DRUG THERAPY PROBLEMS AMONG ADULT PATIENTS WITH THROMBOEMBOLIC DISORDERS AT KENYATTA NATIONAL HOSPITAL

ORIGINALITY REPORT

13%	11%	8%	2%
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