PATTERN OF WARFARIN RELATED COMPLICATIONS AND ANTICOAGULATION PROFILE AMONG PATIENTS ON REGULAR WARFARIN THERAPY AT MUHIMBILI NATIONAL HOSPITAL

Buganda Leonard, B.Pharm

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By

Buganda Leonard

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

Muhimbili University of Health and Allied Sciences
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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled; **''Pattern of warfarin related complications and anticoagulation profile among patients on regular warfarin therapy at Muhimbili National Hospital'',** in (partial) fulfillment of the requirements for the degree of Master of Pharmacy (Hospital and Clinical Pharmacy) of Muhimbili University of Health and Allied Sciences.

_____

Prof. Omary Minzi

(Supervisor)

Date: _____

_____

Dr. Pilly Chillo

(Co-Supervisor)

Date: _____

_____

Dr. Mbonea Yonazi

(Co- Supervisor)

Date: _____

DECLARATION AND COPYRIGHT

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

Signature…….. **Date**……

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I'm so grateful to almighty God, because without him I could not have reached this far and to be able to complete this work. All glory, honor and praise belong to him who gives seed to the sower and bread for food. Certainly, I can do all things through him who gives me strength. His grace has always been sufficient through it all and he surely completes what he starts. Forever, I will worship him.

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DEDICATION

This dissertation is dedicated to my parents, my siblings and to all my friends. Thank you for your love, prayers and tireless support.

ABSTRACT

Background: Warfarin is a synthetic oral anticoagulant of choice in Tanzania and commonly used worldwide. Management of its anticoagulation effect remains a challenge due to anticoagulation shortfalls among patients on regular warfarin therapy. This study aimed to determine the anticoagulation profile, prevalence of complications associated with warfarin therapy and to study the reliability of INR measurements among patients on regular warfarin therapy attending hematology anticoagulation clinic at MNH.

Methodology: This was a cross sectional study, which included 190 patients on regular warfarin therapy, attending hematology anticoagulation clinic at MNH. Blood samples were taken from the recruited patients for laboratory tests which included INR measurements. Other clinical records were obtained from patients' medical records and from interviews. Data collected were coded and analyzed by Statistical Package for Social Sciences (SPSS) version 22 computer software. A Chi square test was used to test for associations between INR and the independent variables whereby a p-value of < 0.05 was regarded as a significant association.

Results: The commonest indication for anticoagulation was Mechanical Heart Valve Replacement (68.9%). Only 20% of the study participants had their INR within the therapeutic range. Out of all the study participants, 20.5% reported to have experienced warfarin induced bleeding whereas 3.2% reported to have experienced thromboembolic complications. There was no considerable noted influence of the studied risk factors on INR and warfarin related complications. Repeated INR measurements did not show significant variation.

Conclusion: Complications related to warfarin therapy are evident and poor anticoagulation profile was reflected by majority of the patients who didn't achieve the target INR. Having adhering patients to warfarin therapy yet showing non therapeutic INR indicates that though INR is presently indispensable, yet it should be used cautiously as a sole indicator and additional clinical assessments should be made in patients showing persistent non-therapeutic INR.

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LIST OF ACROYNMS

BMI	Body Mass Index
CRF	Case Report Form
DDI	Drug-Drug Interactions
Hb	Hemoglobin
HMIS	Health Management Information System
INR	International Normalization Ratio
MAMC	MUHAS Academic Medical Center
MMAS	Morisky Medication Adherence Scale
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
NACP	National AIDS Control Programme
PE	Pulmonary Embolism
SPSS	Statistical Package for Social Sciences
STG	Standard Treatment Guidelines
TEC	Thromboembolic Complications
TTR	Percentage of Time spent in the Therapeutic range
VKORC1	Vitamin K epoxide Reductase Complex subunit 1
VTE	Venous Thromboembolism
WHO	World Health Organization
WIT	Warfarin Induced Toxicity

DEFINITION OF TERMS

Anticoagulation: A process of hindering the clotting of blood through the use of anticoagulants. Anticoagulants are blood thinning agents used for treatment and prevention of various thromboembolic disorders.

Thromboembolism: Formation of a clot (thrombus) in a blood vessel that can be dislodged and carried by the blood stream to cause obstruction to another vessel. The clot may obstruct a vessel in the lungs (pulmonary embolism), brain (stroke), gastrointestinal tract, kidneys, or legs. It is a significant cause of morbidity and mortality especially in adults.

Prothrombin time (PT): A primary laboratory test used for monitoring of warfarin therapy. It measures how long it takes for blood plasma of an individual to clot. The reference range for prothrombin time depends on the analytical method used and results should always be interpreted using the reference range from the laboratory that performed the test.

International Normalization Ratio (INR): A calculation made to standardize the prothrombin time. INR permits patients on anticoagulation therapy to obtain comparable test results from any laboratory that performed the test.

Therapeutic INR – INR within the normal range sufficient to achieve the anticoagulation target. It is commonly considered to be between 2-3 for indications such as Deep Vein Thrombosis (DVT), Pulmonary Embolism and when warfarin is used as a prophylaxis whereas for Mechanical Heart Valves therapeutic INR is considered to be between 2.5-3.5.

Supra-therapeutic INR – INR level above therapeutic range.

Sub-therapeutic INR – INR level below therapeutic range.

Warfarin induced bleeding: Hemorrhage due to warfarin toxicity which can manifest as ecchymosis, sub-conjunctival hemorrhage, epistaxis, vaginal bleeding, bleeding gums, or hematuria. Warfarin induced bleeding could be severe and life threatening.

Morisky Medication Adherence Scale: A scale used to rank the degree of adherence/compliance to medications. Adherence/compliance describes the degree to which a patient correctly follows medical advice particularly on rational use of medications.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Warfarin is a coumarin derivative and a synthetic oral anticoagulant used for prophylaxis and treatment of arterial and venous thromboembolic disorders (1). It is the most commonly used oral anticoagulant in Tanzania and worldwide at large. Anticoagulation management with warfarin therapy is challenging due to its narrow therapeutic index and response variability which could lead to adverse effects among patients. Warfarin induced bleeding is the commonest adverse effect experienced among patients on regular use of warfarin. However, for many years warfarin still remains a dominant and widely used oral anticoagulant despite its limitations (2). The availability of newer oral anticoagulants with different mechanisms of action some of which requiring less monitoring, has not affected the continued use of this drug because of its affordability and ease to access (3).

1.2 Pharmacodynamics and pharmacokinetics

Warfarin achieves its action through inhibiting vitamin K epoxide reductase (VKOR), an enzyme that reduces vitamin K epoxide to vitamin K thus interfering with hepatic synthesis of vitamin K dependent clotting factors II, VII, IX, and X. Vitamin K and vitamin K epoxide are in reversible equilibrium which is disrupted by warfarin through inhibiting VKOR. Inhibition of VKOR results into a decrease in effective concentration of vitamin K and consequently impairs the synthesis of clotting factors. Along with inhibition of hepatic synthesis of clotting factors, warfarin also inhibits synthesis of the naturally occurring anticoagulants, protein C and protein S (4).

Warfarin is clinically available and administered as a racemic mixture of R- and S-warfarin, whereby the S-isomer appears to be more potent than its optical congener (5). The peak absorption of warfarin occurs in 1 to 2 hours with nearly 100% bioavailability following an oral administration. It takes about 5 to 7 days for warfarin to start showing its anticoagulation

effect (4). It has a narrow therapeutic index and highly bound to plasma proteins (99%) thus there is a potential for interaction when co-administered with other highly protein bound substances (6). Due to its extensive binding to plasma proteins, warfarin distributes into a small volume of distribution. (4).

Elimination of more than 98% of warfarin occurs via hepatic metabolism with elimination half-life of about 35 hours. Of the two enantiomers, S-warfarin is cleared faster than R-warfarin and since the volume of distribution for both enantiomers is same, R-enantiomer appears to have a longer half-life than that of the S-enantiomer (7). The R- and S- enantiomers are metabolized by different cytochrome P450 (CYP) isoenzymes causing their plasma concentrations, clearance and potency to be different relative to each other (8). S-warfarin is metabolized primarily by CYP2C9 to 7-hydroxywarfarin, comparatively, R-warfarin is metabolized primarily by CYP1A2 to 6- and 8-hydroxywarfarin and by CYP3A4 to 10-hydroxywarfarin (9).

Enantiomeric analysis is one of the tests that can indicate the performance of the metabolizing enzymes and predict how fast different patients metabolize warfarin enantiomers. It was found in some studies that majority of the subjects have S/R-warfarin ratio of about 1:2 which could be explained by the rapid clearance of S-warfarin relative to R-warfarin (10).

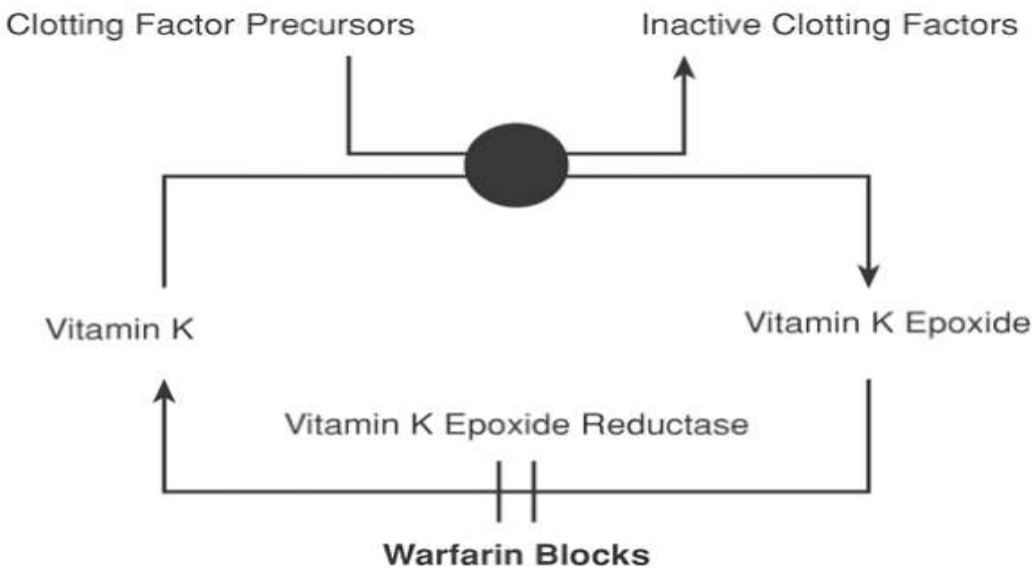


Figure 1: Mechanism of action of warfarin

Studies have reported inter-individual variability in warfarin metabolism and consequently in warfarin treatment response among patients. Single-nucleotide polymorphisms in CYP2C9 and vitamin K epoxide reductase (VKOR) have been found to cause significant variability in warfarin dose requirements and treatment response among patients (11). Studies have shown genetic variations of VKOR complex subunit protein 1 (VKORC1) have an influence on the maintenance dose requirements of warfarin among individuals (12). Different CYP2C9 variants have been identified across different ethnic groups which appear to influence variability among patients on warfarin therapy (5).

The two most common variants of CYP2C9 which influence warfarin response variability are CYP2C9*2 and CYP2C9*3. Dose requirement has been found to be high in individuals with CYP2C9 homozygous wild-type variant, compared to those with CYP2C9*2 and CYP2C9*3 variants (12). A decrease in warfarin metabolism which results into decreased clearance of S-warfarin and increased plasma level of S-warfarin could explain the increased warfarin response, bleeding episodes and prolongation of hospitalization in some patients. Genetic identification of patients before therapy may therefore be indicated in order to prevent adverse effects associated with warfarin toxicity during treatment (8).

1.3 Contraindications and interactions

1.3.1 Interactions

Patients on warfarin therapy may be exposed to drug interactions when given together with a number of drugs particularly those that induce or inhibit CYP2C9 isoenzyme (13). Since warfarin is extensively bound to plasma proteins, other high protein bound drugs can displace warfarin and increase the free plasma concentration of warfarin that can cause warfarin toxicity. Interactions that potentiate its anticoagulation effect may cause life threatening hemorrhagic events therefore drug interactions should be accounted for before concomitant administration of warfarin with other drugs.

Many drugs including co-trimoxazole, erthyromycin, fluconazole, metronidazole, amiodarone, propranolol, cimetidine, omeprazole and isoniazid have been reported to potentiate the anticoagulation effect of warfarin. Non-steroidal anti-inflammatory drugs (NSAIDs) can also prolong bleeding through inhibiting platelet function . However, it is sometimes clinically difficult to manage individual patient's warfarin drug interactions due to lack of information concerning concomitant use of both prescription and non-prescription medications, including herbal medicines (14).

Other documented potential interactions occur due to alcohol consumption and ingestion of increased amounts of vitamin K containing foods (15). Chronic ingestion of alcohol may induce the warfarin metabolizing enzymes resulting into a need of higher warfarin doses to achieve the therapeutic International Normalization Ratio (INR). On the other hand acute ingestion of large amounts of alcohol is associated with competitive inhibition of metabolizing enzymes leading to prolongation of prothrombin time and bleeding tendencies (4,16).

Dietary vitamin K is associated with fluctuations in treatment response to warfarin among patients. Ingestion of high vitamin K containing foods, is reported to cause warfarin resistance, decreased INR (15) and high doses of warfarin maybe needed to achieve the therapeutic INR range (17). Phylloquinone (vitamin K1) and menaquinones (K2 vitamins) are the two main forms of vitamin K that can be obtained from foods (16). Makubi et. al stated that irregular and variable intake of green leafy vegetables is associated with anticoagulation inadequacy,

whereby broccoli, spinach, cabbage and soybean were found to impair the anticoagulation activity when taken in variable amounts (17,18).

1.3.2 Risk factors for warfarin complications

The commonest warfarin related complication is warfarin induced bleeding; however, some patients may experience thromboembolic complications during treatment with warfarin. A study in South Africa reported the prevalence of hemorrhagic events due to warfarin was 14% while 2.2% were reported to have developed thromboembolic complications during treatment with warfarin (19) and somewhere else in East Africa the prevalence of warfarin induced bleeding was reported to be 16.5% (20).

Certain diseases may influence the effect of warfarin and potentiate its toxicity. Chronic kidney disease (CKD) is reported to affect hepatically cleared drugs including warfarin. This is because CKD is associated with decreased CYP2C9 activity hence decreased metabolism of warfarin (4). One study found that patients with CKD require lower doses of warfarin to maintain the therapeutic anticoagulation effect of warfarin as compared to patients without CKD. Moreover, it was found that CKD tends to decrease stability of warfarin anticoagulation and increase the need for therapeutic management of warfarin therapy (21).

Not only metabolism and clearance of warfarin occurs in the liver but also synthesis of clotting factors takes place in the liver. A liver disease can impair hemostasis and cause prolongation of prothrombin time hence, it can influence warfarin therapy response in such a way that, patients with liver disease are at increased risk of bleeding episodes than patients with a well functioning liver (22). Since the liver is responsible for synthesis of proteins, liver disease and several other factors can cause hypoalbuminemia including taking low protein diets. About 99% of warfarin is bound to plasma proteins (albumin). Patients with hypoalbuminemia are more likely to experience warfarin toxicity due to increased free warfarin plasma concentration, (23) and because of its high protein binding, warfarin is subjected to displacement by other high protein binding drugs (24).

1.3.3 Contraindications

According to the US Foods and Drugs Administration (FDA), warfarin use is contraindicated in pregnant women except in those with prosthetic heart valve who are at high risk of thromboembolic events, where warfarin benefits have been found to outweigh risks. Warfarin is associated with fewer maternal complications when compared to other anticoagulants, but on the other hand warfarin crosses the placenta and it is associated with the lowest live birth rates as well as warfarin-related embryopathy and fetopathy (25). Due to maternal complications associated with the considered alternative anticoagulants which are low molecular weight heparin and unfractionated heparin, researchers recommend prospective studies to determine the anticoagulant regimen for pregnant women that provides optimal and acceptable maternal and fetal outcomes (25).

Other potential contraindications for anticoagulation with warfarin therapy, include peptic ulcer disease, gastritis and duodenitis, other gastrointestinal bleeding, ataxia, cerebral hemorrhage, seizure disorder, benign or malignant central nervous system tumors, gastrointestinal and genitourinary tract malignancies, thrombocytopenia, hematuria and esophageal varices (26).

1.4 Initiation and monitoring of warfarin therapy

Warfarin is commonly initiated in a trial and error manner which is deemed to cause problems associated with inappropriate warfarin dosing (27). Such modality of warfarin therapy initiation could most of the time result into adverse effects of warfarin or under dosing of warfarin, therefore, genetic and environmental factors need to be accounted for during the induction and maintenance phases of treatment (28).

The primary laboratory test for monitoring of warfarin therapy is prothrombin time (PT) also expressed as International normalized ratio (INR). The safety and effectiveness of warfarin therapy depends on maintaining INR values within the therapeutic range of 2-3 (29) while for mechanical heart valves indications is 2.5-3.5. Giving low doses of warfarin decrease the risk

of bleeding but can increase the incidence of having INR values of less than 1.5 and increase the risk of new thrombus formation (22).

An increase in plasma concentration of warfarin tends to cause elevation of INR, (4) hence INR can be used as a substitute of plasma concentration for monitoring of warfarin therapy. However, some studies have reported poor correlation between INR and warfarin plasma concentration and recommend concentration monitoring for patient management (30).
Measurement of warfarin plasma concentration could help to assess drug metabolism, non-compliance and resistance to anticoagulation (31). Although the best way to monitor individual's response to warfarin therapy would be to measure warfarin levels, for this study INR measurements were used as per the current practice.

1.5 Problem Statement

Variability in response to treatment with warfarin therapy among patients is well documented and it has been found to be mainly associated with pharmacogenetic differences, demographic and environmental factors. It results into impairment of therapeutic effect of warfarin by either suppressing or enhancing the activity which could lead to adverse effects.

Initiation of warfarin therapy is empirical and involves titration of warfarin dose to achieve safe target INR values. According to the Tanzania standard treatment guideline (STG), the recommended starting dose of warfarin is 5mg for indication of various conditions. The guideline does not state factors to be considered before initiating warfarin treatment and it has not considered fluctuation in treatment response among patients on warfarin therapy. Factors like body weight and BMI are not considered during initiation and maintenance of warfarin therapy despite reports from some studies that there is a positive association between BMI and warfarin dose (32).

There have been cases where some individuals on warfarin therapy experience bleeding and thromboembolic complications during treatment with others having normal INR which makes the reliability of INR for monitoring of warfarin therapy and for dose adjustments questionable. It is recommended to genotype and/or measure plasma concentration of warfarin so as to be able to give individualized doses to patients, when doubts occur. Unfortunately, at the moment facilities for conducting genotyping and monitoring of warfarin plasma levels are expensive and are not yet established in Tanzania.

Therefore this study intended to determine the magnitude of warfarin related complications, anticoagulation profile as well as to assess the reliability of INR measurements.

1.6 Study Questions

i. What is the proportion of patients that experience warfarin induced bleeding while on warfarin therapy?
ii. What is the proportion of patients that experience thromboembolism while on warfarin therapy?
iii. What risk factors for warfarin complications (bleeding and thromboembolism) exist among patients on regular warfarin therapy?
iv. To what extent risk factors influence warfarin complications (bleeding and thromboembolism) among patients on warfarin therapy?
v. Do patients' warfarin dosages correlate well with INR measurements as per Clinician's intended anticoagulation effect?

1.7 Rationale of doing the study

Understanding the anticoagulation profile, pattern and the prevalence of complications associated with warfarin therapy, their associated risk factors as well as the correlation of warfarin dosing and INR measurements will help to optimize anticoagulation management with warfarin therapy in our setting. Findings of this study may also serve as basis to convince the government to introduce more rigorous facilities for warfarin therapy monitoring including measurement of warfarin plasma concentrations and genotyping of patients.

1.8 Study Objectives

1.8.1 Broad objective

To determine the anticoagulation profile, prevalence of complications associated with warfarin therapy, their associated risk factors and to study the reliability of INR measurements among patients on regular warfarin therapy attending hematology anticoagulation clinic at MNH.

1.8.2 Specific objectives

i. To determine the prevalence of warfarin induced bleeding complications among patients on regular warfarin therapy attending hematology anticoagulation clinic at MNH.
ii. To determine the prevalence of thromboembolism among patients on regular warfarin therapy attending hematology anticoagulation clinic at MNH.
iii. To determine the influence of risk factors on warfarin induced bleeding and thromboembolism, among patients on regular warfarin therapy attending hematology clinic at MNH.
vi. To study the correlation between warfarin dosing and INR measurements as per Clinician's intended anticoagulation effect.
iv. To assess the precision of INR measurement at the MNH laboratory.

CHAPTER TWO

2.0 LITERATURE REVIEW

A number of studies have reported variability of warfarin treatment response among patients on warfarin therapy. According to studies, variability of warfarin therapy response is associated with genetic variability involving CYP2C9 genotypes and VKORC1. One study conducted to assess the genetic determinants of response to warfarin during initial anticoagulation found that variability in the INR response to warfarin was more strongly associated with genetic variability in the pharmacologic target of warfarin, VKORC1, than with CYP2C9 (33). Similar studies have been conducted in different populations to ascertain the diversity in outcome and found significant variability in warfarin treatment response associated with genetic variability among different populations (34,35,36,37,38,39,40,41,42).

A prospective study that followed newly treated patients, aimed to estimate and explore the incidence of warfarin related bleeding in a representative sample of patients in the United Kingdom. Patients were followed for a period of 12 months and found the overall incidence of first-time, idiopathic bleeding was 15.2 per 100 patient-years of current warfarin exposure whereby the incidence of fatal/hospitalized and referred bleeding was 3.5 and 2.6 per 100 patient-years, respectively (43).

In US warfarin was reported to be among the top 10 drugs with the largest number of serious adverse events. It was reported that the number of deaths related to complications of anticoagulants ranked first in 2003 and 2004. Most visits due to bleeding complications were found to be associated with warfarin use whereby the bleeding frequencies were reported to be as high as 10% to 16%. Still warfarin was the most widely used anticoagulant with the number of dispensed outpatient prescriptions for warfarin reported to have increased by 45%, from 21 million in 1998 to nearly 31 million in 2004 (44).

A prospective observational study assessed the prevalence of drug-drug interactions and risk of bleeding among inpatients on warfarin therapy. Drug-drug interactions were significantly high with a prevalence of 92.2%. In that study bleeding complications due to warfarin were also reported to be high hence researchers recommended awareness of drug-drug interactions and INR monitoring as strategies to prevent bleeding complications (20).

A retrospective cohort study conducted to assess the risk of recurrent VTE among deep vein thrombosis and pulmonary embolism patients treated with warfarin found approximately 8% of patients experienced a recurrent VTE during follow up. The study reported most of the patients who experienced recurrent VTE had INR below the therapeutic range and that contributed to more than three-fold increased risk. Surprisingly, low platelet count was also found to be a predictor of recurrent VTE (45).

Findings of a retrospective cohort study conducted to assess the adequacy of anticoagulant control results among patients with mechanical heart valves attending the anticoagulation clinic at MNH reported high anticoagulation inadequacy. Anticoagulation inadequacy was justified by the prothrombin time results whereby most of the results were found to be out of therapeutic ranges. Researchers gave recommendations to MNH and to the ministry responsible for health towards improving the anticoagulation adequacy among patients on warfarin therapy (18).

Warfarin clearance is a major contributor to dose requirement and response as it has been reported in different studies. A study on clinical and genetic determinants of warfarin pharmacokinetics and pharmacodynamics during treatment initiation demonstrated that kidney function, gender, CYP2C9*2 and *3 genotype are major determinants of warfarin clearance. Similar study failed to observe correlation between age and warfarin clearance but gender was observed a significant independent contributor to warfarin clearance, with females having lower warfarin clearance than males (33).

A study that aimed to determine how CKD affects warfarin maintenance dose, anticoagulation stability and the proportion of clinic visits that necessitates a dose manipulation found that, CKD is associated with both decreased warfarin maintenance dose and decreased anticoagulation stability which, in turn, require more frequent and intensive anticoagulation clinic management (21). Another study pointed out that patients with severe CKD have a risk for major hemorrhage more than double the risk of patients with lesser degrees of renal dysfunction (46).

Dietary modification has been reported to affect stability of anticoagulation whereby subjects on chronic anticoagulation with warfarin are reported to be sensitive to fluctuating levels of dietary vitamin K. Vitamin K tends to interfere with warfarin metabolism pathway and increased intake of dietary vitamin K is reported to be sufficient to reduce anticoagulation response to warfarin while reduced intake can potentiate the anticoagulation response (29,47).

Studies report patients with liver disease are at higher risk of experiencing bleeding during warfarin therapy because hepatic dysfunction tends to potentiate the response to warfarin through impaired synthesis of coagulation factors (22,29). Moreover, conditions that tend to induce hypermetabolic states such as fever and hyperthyroidism, may increase warfarin responsiveness probably by increasing the catabolism of vitamin K–dependent clotting factors hence increasing risk of bleeding during treatment with warfarin therapy (29).

A retrospective study found association between BMI and warfarin dose. The study involved a total of 831 patients with a BMI range between 13.4 and 63.1 kg/^{m2}. Findings of this study reported a positive correlation between BMI and the total weekly warfarin dose. The association is speculated to have implication to both patients and prescribers that a higher dose of warfarin would be needed to maintain a therapeutic INR in patients with high BMI (32).

Observations of one study that investigated implications for safer anticoagulation in the elderly population, observed that, the commonly employed empiric warfarin starting dose of 5 mg/d can lead to over anticoagulation for the majority of the elderly patients, hence lower initiation and maintenance doses should be considered for the geriatric population (48).

Another study indicated the necessity of assessing over anticoagulation, warfarin discontinuation and its management in older patients since this population is at increased risk of warfarin toxicity (49).

A study on warfarin plasma concentration and its correlation with INR, found that, the correlation of warfarin dosage or concentration with INR is very poor. Investigators recommended monitoring of warfarin plasma concentration for accurate dosage adjustment especially when the ideal INR is difficult to target (30). Measuring of warfarin plasma concentration is useful for assessment of drug metabolism, non-compliance and resistance to anticoagulation (31).

The quality of anticoagulation management with warfarin was found to be suboptimal in a retrospective study done in Ethiopia. The suboptimal quality of anticoagulation management with warfarin was reflected by low Time in Therapeutic Range (TTR), longer than recommended INR monitoring frequency, and minimal actions taken to adjust warfarin dose after occurrences of non-therapeutic INRs. Study participants were adult patients who were treated with warfarin for various indications (50).

According to studies, education and re-education of patients on anticoagulation may assure a safer and more effective treatment. This may improve adherence and enable patients to take precautions especially on dietary modification and self-medication while on warfarin therapy. Special attention should be addressed to elderly patients and to those patients with low educational level and language barriers (51).

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study design

This was a cross sectional study that involved patients who were on regular warfarin therapy (regardless of the indication) for a period of not less than a month.

3.2 Study site

This study was conducted at MNH hematology anticoagulation clinic.

3.3 Target population

The target population was patients on regular warfarin therapy.

3.4 Study population

The study involved patients who were on regular warfarin therapy for a period of not less than a month, attending anticoagulation clinic at MNH.

3.5 Sampling method

Study participants were obtained using a consecutive sampling technique whereby patients who were on warfarin therapy attending the anticoagulation clinic at MNH were consecutively enrolled. Enrollment was done every Tuesday by means of which patients were interviewed for eligibility as they attended their regular scheduled clinics. Eligible patients were invited to participate in the study and asked to sign an informed consent.

3.6 Sample size

About 190 patients who met the inclusion criteria were included in this study. Sample size was calculated by using the formula $n=z2P(1-P)/\varepsilon 2$ whereby prevalence (P) = 16.5% (20), level of confidence of the study (z) =1.96 ≈ 2 for 95% confidence level and the margin of error(ε) =5%.

3.7 Participants inclusion criteria

i. Patient on warfarin therapy.
ii. Attending hematology anticoagulation clinic at MNH
iii. Patient on regular warfarin therapy for a period of ≥ 1 month.

3.8 Participants exclusion criteria

i. Patients who were unstable to be interviewed to provide the needed information.
ii. Missed warfarin doses for more than two consecutive days before clinic.

3.9 Data collection

The study was explained to the patients and those who consented and found to be eligible were recruited to take part in the study. Socio-demographic data were collected by interviewing the study participants and their past medical history was obtained through reviewing their medical records. Parents were involved in the interviews for their children who assented and involved in the study. A pre-tested structured questionnaire/case report form was used to record the required information.

Weight and height were measured by using a weighing scale and a standard height board respectively, with patients on bare feet. Weight in kilograms and height in meters square were used to determine the body mass index (BMI) in kg/m^2 of the study participants. BMI was classified in to the following classes; lower than 18.5, 18.5 – 24.9, 25 - 29.9 and above 30 which were defined as underweight, normal weight, overweight and obesity respectively.

Three blood samples were collected from the patients by phlebotomists at MNH outpatient department laboratory and tested for INR, full blood count and biochemistry at MNH Central Pathology Laboratory (CPL). Results for INR, full blood count, serum albumin, serum creatinine, blood urea nitrogen and liver transaminases were traced after the blood samples were analyzed. Full blood count was studied to ascertain the platelet count. Previous INR data were obtained from patients' booklets and records though HMIS.

Determination of the prevalence of warfarin induced bleeding and thromboembolism involved interviewing patients and reviewing their medical records. Patients were interviewed to recall incidences of warfarin associated complications (bleeding and thromboembolism) since they started taking warfarin. More information was traced from their records through HMIS.

Co-administered drugs during warfarin therapy were recorded for analysis and for identification of potential drug- drug interactions. This mainly involved asking patients if they were taking other medications together with warfarin. Patients, who reported to be taking other medications, were asked to mention the drugs. Some happened to have the drugs while being interviewed whereas some were called later through their mobile phones to confirm the drugs at home. Other information regarding the co-administered drugs were traced and obtained from patients' HMIS records.

Study participants were also interviewed regarding their lifestyles including the tendency of taking green vegetables and alcohol during treatment with warfarin therapy. Adherence to warfarin therapy was measured and assessed according to Morisky Medication Adherence Scale (MMAS-4)(52). This was a four questions tool which was included in the questionnaire/case report form (ANNEX 1).

Precision of INR measurements was assessed through determining the repeatability of INR results. This involved analyzing blood samples of six patients who were randomly obtained from among the study participants to obtain six INR readings intraday and repeated for three consecutive days to ascertain for intermediate precision. After every two hours, same blood samples from the six selected patients were analyzed until six intraday INR readings were obtained. The same procedures were carried out for three consecutive days to make a total of eighteen INR readings for each patient. Mean, standard deviation and coefficient of variation (CV) were determined.

3.10 Data analysis

Data collected were coded and analyzed by the Statistical Package for Social Sciences (SPSS) version 22 computer software. A Chi square test was used to test for associations between INR and the independent variables whereby a p-value of < 0.05 was regarded as a significant association. Adherence to warfarin therapy was measured according to Morisky Medication Adherence Scale (MMAS-4). Potential interactions of warfarin and co-administered drugs were identified using an online DDI checker.

3.11 Ethical clearance

Ethical clearance was sought from Muhimbili University of Health And Allied Sciences, Research and Publications Committee. Eligible study participants were given a description of the study and gave written informed consent before they were recruited. Parents of eligible pediatric patients were given a description of the study and gave written informed consent on behalf of their children. Older children gave assent to participate in the study in addition to their parents' informed consent. Patients were given identity numbers which ensured confidentiality of their information.

3.12 Study limitations

Nature of the study design and sample size included might have not captured enough information to be able to draw conclusion of the findings. This could be the reason why we couldn't find statistical association between INR and the studied independent variables because of a failure to establish a true cause and effect relationship due to the nature of the study design being cross sectional.

CHAPTER FOUR

4.0 RESULTS

This study included 190 patients who were on regular warfarin tablet therapy for a period of not less than a month and routinely attending the anticoagulation clinic at MNH. Their mean age was 41 ± 17 years with the majority being female (63.2%). The indications for warfarin use in these patients were various; with the majority (68.9%) having undergone Mechanical Heart Valve Replacement. Other common indications were as reflected in figure 2. The average daily dose of warfarin ranged from 2.5mg to 12.5mg (Median, 5 mg). The mean BMI was 24 ± 4.5 kg/m^2, whereby about 2/3 of the patients (66.3%) were having normal body weight. Moreover, BMI and INR showed a weak negative association (r = $^{-}$ 0.65). The mean platelet count was 267±80 (x 10^9/ liter) whereby majority 183 (96.3%) had normal platelet count. Table 1 and figure 2 summarize socio-demographic information and clinical characteristics of the studied patients.

Table 1: Socio-demographic and Clinical Characteristics of Study Participants

Socio-demographic characteristic	**n**	**%**
Age group (years)		
< 18	12	6.3
18-59	146	76.8
≥60	32	16.8
Gender		
Male	70	36.8
Female	120	63.2
Clinical characteristics		
Current INR		
Therapeutic INR	38	20
Supra- therapeutic INR	42	22.1
Sub- therapeutic INR	110	57.9
Body mass index, kg/m^2		
Over weight	41	21.6
Under-weight	5	2.6
Normal weight	126	66.3
Obese	18	9.5

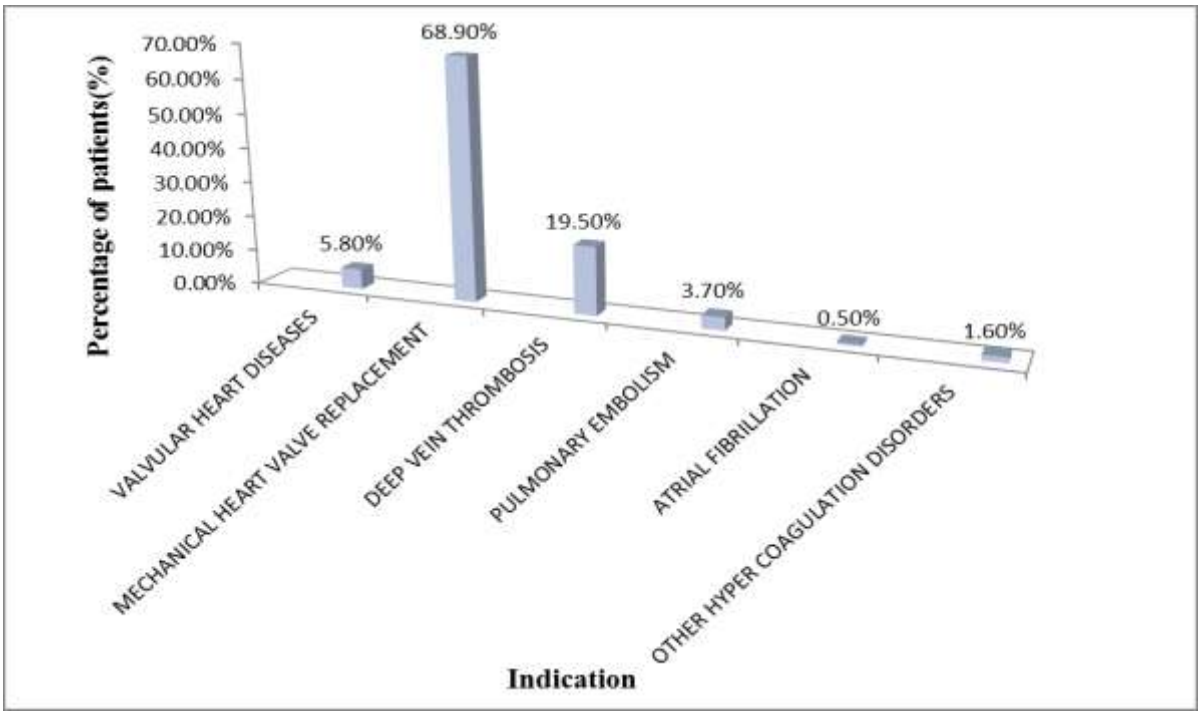


Figure 2: Proportion of studied patients per condition

Three blood samples were drawn on the day of clinic and were subsequently used for measurement of INR, full blood count, serum albumin as well as for renal function and liver function tests.

4.1 INR of the study participants

Patients were categorized per gender and from each category, the proportion that fell under therapeutic, supra or sub-therapeutic INR were determined. Results in table 2 show that there were poor anticoagulation outcomes whereby only 20% of the studied patients achieved target therapeutic INR and majority of the study participants (80%) had their INR values out of the target therapeutic range. In addition, association between gender status and INR level was determined and results indicated that there was no association between the two ($P = .432$). Details are reflected in table 2.

Table 2: Proportion of patients with therapeutic, supra-therapeutic and sub-therapeutic INR range (n=190).

		Patients' INR			*P-value*
		Therapeutic INR n (%)	**Supra-therapeutic INR n (%)**	**Sub-therapeutic INR n (%)**	
Gender	Male	11(15.7%)	18 (25.7%)	41(58.6%)	0.432
	Female	27 (22.5%)	24 (20%)	69 (57.5%)	
Total		38 (20%)	42 (22.1%)	110 (57.9%)	

4.2 INR of the study participants per renal function status, liver function status and serum albumin

Renal function status of the patients was tested and patients were categorized as those with normal renal function and renal insufficiency. Renal insufficiency was defined by elevated serum creatinine and blood urea nitrogen whereby majority of the patients 181(95.3%) had normal renal function. Liver function status was also tested and patients were categorized as those with normal liver function and those with elevated liver transaminases whereby it was found that majority of the patients 177 (93.2%) had normal liver function. Moreover, serum albumin of the patients was determined and categorized as normal serum albumin, hypoalbuminemia and hyperalbuminemia. Out of all the study participants, 182 (95.8%) had normal serum albumin levels. Proportions of patients that fell under therapeutic, supra or sub-therapeutic INR were determined per renal function status, liver function status and serum albumin levels. In addition, association between renal function status, liver function status, serum albumin level and INR was determined and results indicated that there was no association between INR and the variables. Details are reflected in table 3.

Table 3: Proportion of patients with therapeutic, supra-therapeutic and sub-therapeutic INR range per renal function status, liver function status and serum albumin (n=190).

	Patients' INR			*P-value*
	Therapeutic INR n = 38	**Supra-therapeutic INR n = 42**	**Sub-therapeutic INR n = 110**	
Elevated creatinine and BUN	2 (22.2%)	2 (22.2%)	5 (55.6%)	0.984
Elevated liver transaminases	2 (15.4%)	3 (23.1%)	8 (61.5%)	0.911
Hyperalbuminemia	0	0	1 (100%)	0.862
Hypoalbuminemia	1(14.3%)	1(14.3%)	5 (71.4%)	
Total	38 (20%)	42 (22.1%)	110 (57.9%	

4.3 Prevalence of warfarin induced bleeding and thromboembolism

As shown in figure 3, 39 (20.5%) of the study participants reported to have experienced bleeding complications after they started taking warfarin while 6 (3.2%) reported to have experienced thromboembolic complications despite the fact they were on warfarin therapy. Nevertheless, such information as well as their INR values were missing in the HMIS patients' files.

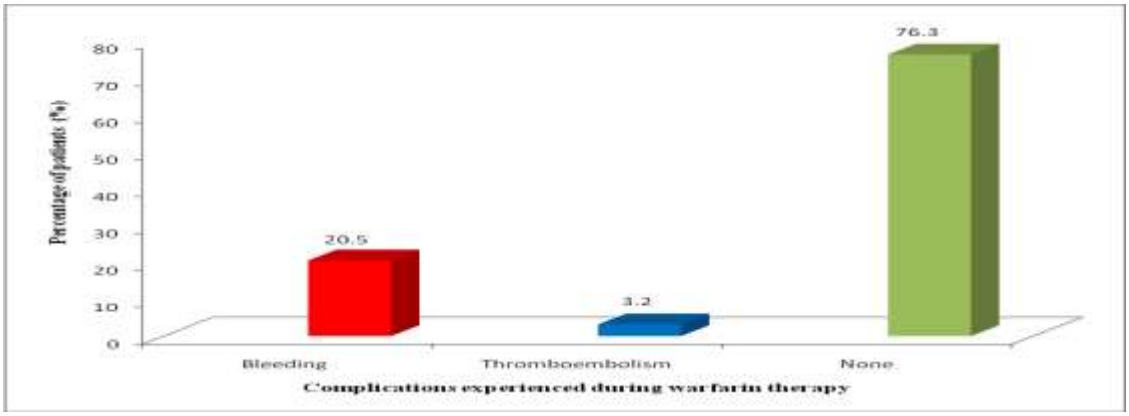


Figure 3: Proportion of patients reported to have experienced warfarin induced bleeding and thromboembolic complications.

4.4 Tendency of taking green vegetables

Of all the study participants, 127 (66.8%) patients reported to be taking green vegetables on a regular basis as directed by clinicians. Frequency of taking green vegetables per week was as indicated in figure 4. The rest reported not to be taking green vegetables altogether. Among the study participants that were regularly taking green vegetables, 72 (56.7%) and 29 (22.8%) had sub therapeutic and supra-therapeutic INR respectively. Among patients who were not taking green vegetables, 38 (60.3%) had sub therapeutic INR and 13 (20.6%) patients had supra therapeutic INR. Nevertheless, the difference observed had no statistical significance (*P=0 .891*).

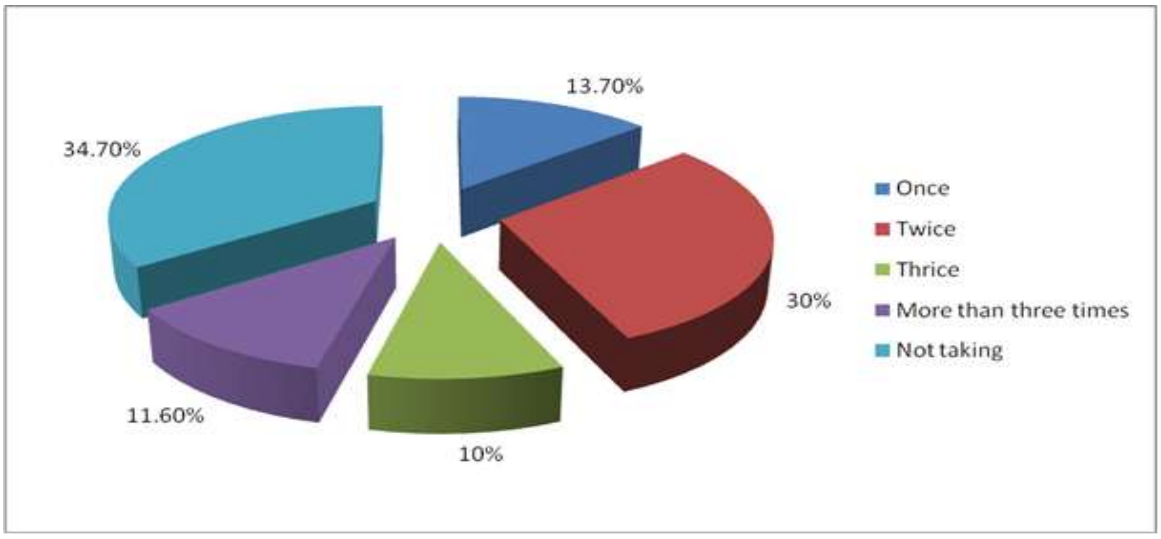


Figure 4: Percentage of frequency of taking green vegetables per week

4.5 Tendency of taking alcohol during treatment with warfarin therapy

Of all the study participants, only 6 (3.2%) reported to have tendency of taking alcohol while on regular treatment with warfarin whereas majority reported to be aware of the possible interaction between alcohol and warfarin. Of the 6 patients with tendency of taking alcohol, 1 patient had supra therapeutic INR and 3 patients had sub therapeutic INR. However, the frequency of alcohol taking was not ascertained and there was no statistical difference between patients with tendency of taking alcohol and patients who do not take alcohol (*P =0.705*).

4.6 Medication adherence

Medication adherence was measured by using Morisky Medication Adherence Scale. Majority of the patients 142 (74.7%) were found to have high adherence. 48 (25.3%) had medium adherence while none of them had low adherence.

Table 4: Proportion of patients with therapeutic, supra-therapeutic and sub-therapeutic INR range per medication adherence (N=190).

		Patients' INR			P-value
		Therapeutic INR n (%)	**Supra-therapeutic INR n (%)**	**Sub-therapeutic INR n (%)**	
Medication adherence	High adherence	26 (18.3%)	36 (25.4%)	80 (56.3%)	0.156
	Medium adherence	12 (25%)	6 (12.5%)	30 (62.5%)	
Total		38 (20%)	42 (22.1%)	110 (57.9%	

Table 4 shows that 81.7% of patients who had high medication adherence, had non therapeutic INR whereby 25.4% had supra therapeutic INR and majority 56.3% had sub therapeutic INR. Conversely, 75% of patients who had medium medication adherence, were found to have non therapeutic INR of which 12.5% had supra therapeutic INR and 62.5% had sub therapeutic INR. Nevertheless, the difference observed was not statistically significant (*P = 0.156*).

4.7 Co-administered medications

About 75 (39.5%) of the studied patients reported to be taking other medications together with warfarin. Using an online drug – drug interaction checker, 27 (47.4%) interactions were detected out of 57 combinations of warfarin and other medications that were being taken concomitantly. The detected interactions were identified as major and moderate interactions. Details are reflected in Table 5.

Table 5: List of drugs found interacting with warfarin

Drugs	Level of interactions	Drugs	Level of interactions
Amiodarone	Major	Mesalamine	Moderate
Amoxicillin	Moderate	Multivitamin	Moderate
Aspirin	Major	Omeprazole	Moderate
Carbamazepine	Moderate	Pantoprazole	Moderate
Cloxacillin	Moderate	Prednisolone	Moderate
Diclofenac	Major	Rabeprazole	Moderate
Efavirenz	Moderate	Sildenafil	Moderate
Esomeprazole	Moderate	Sulfamethoxazole	Major
Fluconazole	Major	Tamoxifen	Major
Glibenclamide	Moderate	Terbinafine	Moderate
Glimepiride	Moderate	Tramadol	Moderate
Ibuprofen	Major	Trimethoprim	Moderate
Levothyroxine	Moderate	Valproic acid	Moderate
Meloxicam	Major		

4.8 Correlation between warfarin dosing and INR measurements as per intended clinician's target.

Results from table 2 show that, only 20% of the study participants had their INR within therapeutic range. 80% of the studied patients had non therapeutic INR with most of them having sub-therapeutic INR (57.9%). INR records for their last previous visit were checked and found 56.3% of the study participants who had non therapeutic INR, also had non therapeutic INR during their last previous visit**.** Correlation coefficient between warfarin dosing and INR among the studied patients was determined and found that there was no correlation between the two as reflected in figure 5 below (r = 0.023).

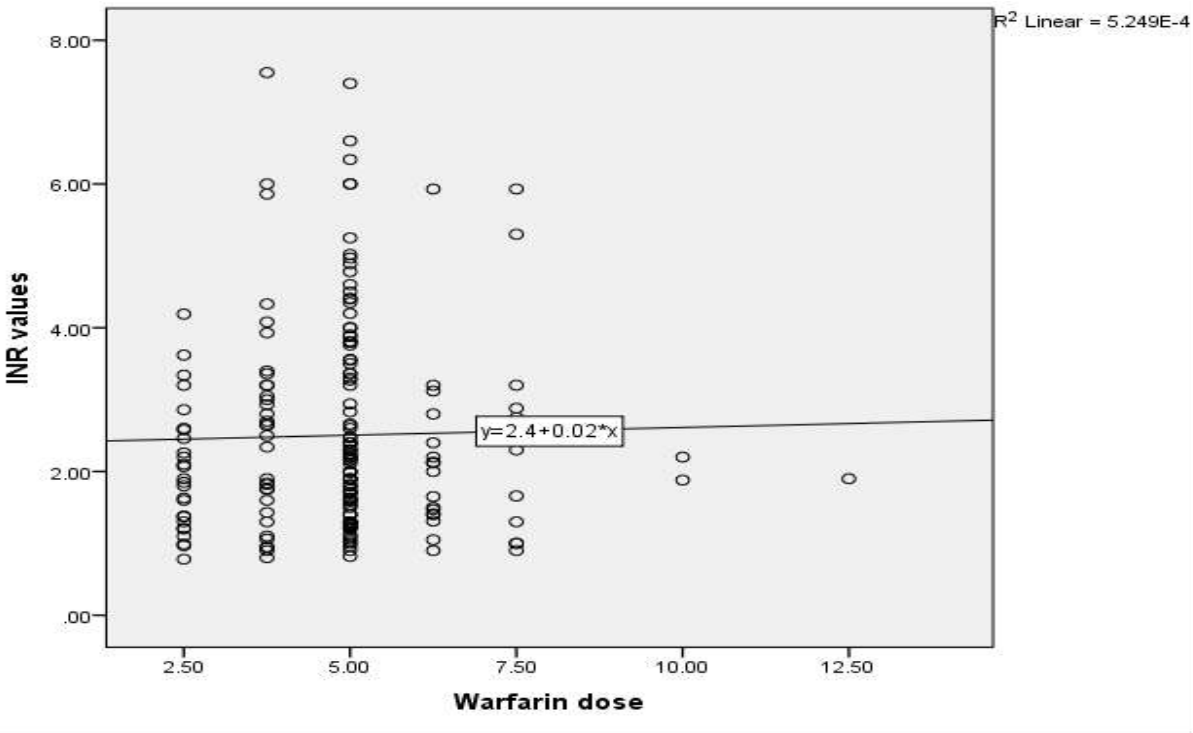


Figure 5: Correlation between warfarin dose and INR of the study participants

4.9 Precision of INR measurements

Blood samples from randomly selected six patients (N=190) were analyzed repeatedly six times intraday for three consecutive days to ascertain for intraday and intermediate precision of INR measurements. Mean, standard deviation and coefficient of variation were determined.

Results from table 6 show that there was high precision as indicated by low dispersion across the obtained results.

Table 6: Intraday and inter-day precision of INR results

		Mean	Standard deviation (**SD**)	Coefficient of variation (**CV%**)
Patient 1	Day 1	3.12	0.01	**0.18**
	Day 2	3.11	0.01	**0.43**
	Day 3	3.12	0.01	**0.26**
	Coefficient of variation **(CV %)**	**0.20**		
Patient 2	Day 1	1.43	0.001	**0.09**
	Day 2	1.43	0.012	**0.86**
	Day 3	1.43	0.004	**0.29**
	Coefficient of variation **(CV %)**	**0.19**		
Patient 3	Day 1	2.86	0.01	**0.57**
	Day 2	2.86	0	**0**
	Day 3	2.86	0	**0**
	Coefficient of variation **(CV %)**	**0.07**		
Patient 4	Day 1	1.76	0	**0**
	Day 2	1.77	0.02	**0.92**
	Day 3	1.76	0	**0**
	Coefficient of variation **(CV%)**	**0.22**		
Patient 5	Day 1	3.20	0	**0**
	Day 2	3.20	0.01	**0.26**
	Day 3	3.21	0.02	**0.76**
	Coefficient of variation **(CV%)**	**0.22**		
Patient 6	Day 1	1.50	0	**0**
	Day 2	1.49	0.04	**2.90**
	Day 3	1.49	0.012	**1.07**
	Coefficient of variation **(CV%)**	**0.45**		

CHAPTER FIVE

5.0 DISCUSSION

This study assessed the pattern of warfarin related complications and anticoagulation profile among patients attending hematology anticoagulation clinic at Muhimbili National Hospital in Dar Es Salaam, Tanzania. Prevalence of warfarin induced toxicity (WIT) as reflected by patient self report was 20.5% and manifested in a form of bleeding. Patients who reported to have experienced bleeding complications affirmed to have presented with ecchymosis, nasal bleeding, epistaxis, gum bleeding, hematuria and severe menstrual bleeding. All these patients reported to have required medical attention that included hospitalization and stoppage of warfarin therapy. The observed 20.5% prevalence has relevant clinical implications and portrays the magnitude of the problem. Our findings are comparable to what was reported elsewhere in East Africa (46). Warfarin works by inhibiting synthesis of vitamin K dependent clotting factors in the coagulation cascade and if proper dosing is not maintained, long term use of the drug could lead to bleeding as one of the side effects.

It is expected that warfarin would protect an individual from developing thromboembolic complications (TEC). However in this study, 3.2% of participants reported to have experienced stroke, pulmonary embolism and recurrent DVT. Similar findings were reported in South Africa (19). The reported prevalence of TEC draws attention for clinicians on the need to continuously monitor patients despite being on warfarin therapy. It was observed that majority (80%) of the patients had non-therapeutic INR and among them, (57.9%) had sub-therapeutic INR despite being adherent to warfarin therapy. This could be the reason to development of TEC to some patients. Having majority of the patients failing to attain therapeutic INR despite good adherence to warfarin entails that INR alone may not be an adequate surrogate marker for assessing safety profile of warfarin. Other factors such as genetics may have an effect on INR measurements (53).

Correlation between dose taken by patients and their INR values is illustrated by figure 5. There was no correlation between the two parameters though it was expected to have high INR in those patients who were taking higher doses of warfarin and vice versa. This underlines the importance of measuring warfarin plasma concentration and genotyping which could help in dose individualization among the patients. Patients on long term use of warfarin are likely to have variables which may be difficult to explain. Lack of correlation between the magnitude of dose and INR values entails that more factors must be considered when monitoring the performance and adjusting dosing of the drug. This is in consistency with what was reported in one of the studies (30). Nevertheless, based on the fact that this was a cross sectional study and also that most of the patients' information were not reflected in the HMIS, our findings on lack of reliability of INR for monitoring the use of Warfarin remain inconclusive.

This study found out that, diet as reflected by the tendency of taking green vegetables, sporadic alcohol intake, liver dysfunction, renal insufficiency, serum albumin level as well as medication adherence had no influence on INR (table 3-4). This is contrary to what is known in the literature (4,15,16,17,21). Within this study, only 9 (4.7%) patients were found to have renal insufficiency. Five (55.6%) patients among them had sub-therapeutic INR, notwithstanding they had renal insufficiency while 2 (22.2%) patients had supra-therapeutic and 2 (22.2%) patients had therapeutic INR respectively. Renal insufficiency is known to increase risk of warfarin induced bleeding due to impaired elimination of warfarin as well as decreased expression of CYP2C9 and consequently decreasing metabolism of warfarin hence causing WIT. This is contrary to results from other studies which reported WIT among patients with decreased renal function (4). This conflict could be due to the nature of the study design and the fact that there were only few patients with renal insufficiency as defined by elevated serum creatinine and blood urea nitrogen.

To ascertain the precision of INR measurements, internal control of machines and procedures for assessment of INR was performed whereby intra and inter day INR measurements were repeatedly determined and results are as reflected in table 6. Results did not show significant variation of INR measurements of the patients. As we have observed from table 2 that majority of the patients were out of therapeutic INR range, high precision of repeated INR measurements means that, the poor anticoagulation profile based on non therapeutic INR for majority of the patients have no connection with the method of measurements.

One of the most important factors in warfarin dosing is genetics of the patients. Studies have shown variability in response among patients on warfarin due to polymorphism of CYP2C9, an enzyme responsible for metabolism of warfarin whereby some patients tend to be fast metabolizers whereas some are slow metabolizers of warfarin due to polymorphism of CYP2C9 (5,11,12,35,36,37,38,39,40,41,42). Fast metabolizers are the ones that would have a sub-therapeutic INR due to high clearance of warfarin therefore need high doses of the drug; contrary to slow metabolizers who on the other hand would have supra-therapeutic INR due to accumulation of warfarin in the blood therefore need dose adjustment by lowering the dose. Therefore, measurement of warfarin plasma concentrations and genotyping could be helpful in determination of individual warfarin doses and as additional indicators to predict warfarin anticoagulation effects.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATION

6.1 Conclusion

Complications related to warfarin therapy are evident and poor anticoagulation profile was reflected by majority of the patients who didn't achieve the target INR. Having adhering patients to warfarin therapy yet showing non therapeutic INR indicates that though INR is presently indispensable, yet it should be used cautiously as a sole indicator for monitoring of warfarin therapy. Risk factors studied did not show significant influence on anticoagulation profile of the patients.

6.2 Recommendation

Additional clinical assessments should be made in patients showing persistent non-therapeutic INR and the patient should be discussed by team of practitioners to enable making proper dose adjustments. The government may introduce more rigorous therapeutic drug monitoring facilities and not to depend on INR alone for patients who are persistently out of the therapeutic target.

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APPENDICES

Appendix I: Questionnaire /Case Report Form (CRF)

RESEARCH TITLE: "PATTERN OF WARFARIN RELATED COMPLICATIONS AND ANTICOAGULATION PROFILE AMONG PATIENTS ON REGULAR WARFARIN THERAPY AT MUHIMBILI NATIONAL HOSPITAL"

SUBJECT INFORMATION

Identification

1. Date _____/____/___
2. Patient: ID_____
3. Address: _____Mobile No _____

Demography

4. Date of birth/Age: _____
5. Sex:_____

Physical Examination and vital signs

6. Temperature _____
7. Weight _____
8. Height _____
9. BMI _____

Indication for anticoagulation

10. Medical history

S/N	Medical illness	FROM	TO	Tick if active
1				☐
2				☐
3				☐
4				☐
5				☐

Hematology

11. INR results

Date						
INR value						

12. Platelet count_____

13. Serum albumin……

Medication history

14. Warfarin dose _____

1. Any other drug used by the patient _____
2. If yes specify drug(s),

SN	Drug name (Generic/common brand name)	Dose	Frequency	Tick if currently ongoing
1				
2				
3				
4				
5				

15. Diet
    i. Does the patient regularly take green vegetables? Yes_____ No_____
    ii. How frequent per week_____
    iii. What are the commonly taken vegetables? (tick if available in the following options)
        - Spinach (___)
        - Cabbage (___)
        - Broccoli (___)
        - Mention others: _____

16. Alcohol history
    i. Does the patient take alcohol during treatment?_____
    ii. How much alcohol does the patient take? _____

17. Symptoms and signs suggestive of warfarin associated complications?

Date	Presented signs

i. State the confirmed complication
    - Bleeding (____)
    - Thromboembolism (____)

ii. Frequency of occurrence _____

Warfarin adherence assessment tool (Morisky Medication Adherence Scale-4**)** **(**Tick the correct response)

Items	Yes = 1	No = 0
Do you ever forget to take your warfarin?		
Do you ever have problems remembering to take your warfarin?		
When you feel better, do you sometimes stop taking your warfarin?		
Sometimes if you feel worse when you take your warfarin, do you stop taking it?		

Appendix II: Fomu ya kibali cha kushiriki katika utafiti

UTAFITI JUU YA DAWA YA KUZUIA DAMU KUGANDA AINA YA WARFARIN

JINA LA MTAFITI: BUGANDA LEONARD

MFADHILI: CHUO KIKUU CHA AFYA NA SAYANSI SHIRIKISHI MUHIMBILI (CoE Project)

ANUANI:

P.O BOX 65001,

DAR-ES SALAAM.

Namba ya utambulisho: _____

Utambulisho:

Habari! Fomu hii inamaelezo juu ya utafiti uliotajwa hapo juu. Ili kuwa na uhakika unataarifa juu ya utafiti huu unaombwa kusoma au kusomewa maelezo ya fomu hii. Vile vile utaombwa kusaini au kuweka alama ya dole gumba mbele ya shahidi. Utapatiwa nakala ya fomu hii. Fomu hii inaweza kuwa na maelezo ambayo hujayaelewa, tafadhali uliza chochote ambacho utakuwa hujaelewa.

Madhumuni ya Utafiti

Utafiti huu una lengo la kufatilia maendeleo na matokeo ya ufanyaji kazi wa dawa aina ya warfarin inayotumiwa kuzuia damu kuganda. Utakua ukipatiwa huduma kama kawaida sawa sawa na tatizo lako na majibu ya baadhi ya vipimo vyako vinavyohusiana na dawa hii yatatumika kufanyia utafiti huu. Matokeo yatafiti hii yatasaidia kuboresha huduma zinazohusiana na matumizi ya dawa hii.

Hatari

Hatutarajii matatizo yoyote ya kiafya kukutokea sababu ya kushiriki katika utafiti huu.

Faida za kushiriki

Kama utakubali kushiriki kwenye utafiti huu itakuwa ni faraja na faida sababu wataalamu watapata kufahamu maendeleo yako yanayohusiana na dawa hii kila wanapokupima na kasha kukutibu ipasavyo. Pia utapata elimu zaidi ya namna ya kutumia dawa hii na jinsi ya kuepuka athari zozote zinazoweza kutokana na matumizi mabaya ya dawa hii. Pia maelezo utakayotoa yatasaidia kuchangia uboreshaji wa huduma kwako na kwa wenye matatizo kama yako na itashawishi serikali kuongeza nguvu kwenye sekta ya afya hususani kwa wagonjwa wenye shida kama ya kwako. Tunatumaini taarifa itakayopatikana itasaidia zaidi kupunguza madhara yanayoweza kutokea pindi mtu anapotumia dawa hii.

Haki ya kujitoa katika ushiriki

Kushiriki katika utafiti huu ni uamuzi wako. Unaweza kujitoa katika ushiriki muda wowote ule hata kama umeshaidhinisha kibali cha kushiriki. Kukataa kushiriki au kujitoa katika ushiriki hakutasababisha kuchukuliwa hatua yoyote.

Usiri

Maelezo yoyote yatakayotolewa yatatumika kwa faida ya utafiti huu tu, hakuna maelezo yoyote yatakayotolewa mahali popote bila idhini ya mshiriki.

Kama kuna tatizo au swali lolote wasiliana na: Buganda Leonard (Simu: 0716137574). Kama unahitaji msaada zaidi wasiliana na Prof. OMARY MINZI (0785892009) au Dr PILLY CHILLO (0713779781)ambao ni wasimamizi wa utafiti huu, Chuo Kikuu Cha Afya na Sayansi Shirikishi Muhimbili, S.L.P 65001, Dar es Salaam.

Sahihi

Je umekubali?Mshiriki amekubali.....

Mshiriki hajakubali.....

Mimi, _____ Nimesoma/kuambiwa maelezo yote yaliyopo kwenye fomu hii.Maswali yangu yote yamejibiwa.Nimekubali kushiriki katika utafiti huu.

Sahihi ya mshiriki _____

Sahihi ya mtafiti _____ Tarehe ya kutia sahihi ya kushiriki _____

Appendix III: Consent Form

RESEARCH ON WARFARIN THERAPY AN ORAL ANTICOAGULANT

NAME OF RESEARCHER: BUGANDA LEONARD

SPONSOR: MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCENCES (CoE project)

ADRESS

P.O BOX 65001,

DAR-ES SALAAM.

Identification number: _____

Preamble:

This form has instructions regarding the mentioned study. To be sure that you are well informed about the study, you are requested to read the contents in this form. Moreover, you will be required to sign this form before a witness. You will be given a copy of this form and please ask in case you don't understand the contents.

Purpose of the study

Findings of this study may serve to convince the government and policy makers to improve services pertaining to use of this medicine.

Risk

We do not expect any harm to happen to you.

Benefits

Your information will enable clinicians to understand your response and progress during treatment. You will also get more education on how to use this medicine properly so as to avoid harmful effects due to improper use of the medicine. Moreover, information from your

data will enable the government and policy makers to improve the services that will benefit you and other patients with similar conditions who happen to use this medicine.

Exit from study

You are not forced to participate in this study and once you are in, you can withdrawal from the study anytime you may wish to do so. You will not be counted responsible for anything if you decide to withdrawal from the study.

Confidentiality

All the information obtained from this study will remain confidential and will be used for the purpose.

Who to contact

If you ever have any questions about this study, you should contact the investigator Buganda Leonard (Phone: 0716137574). For more help and clarification you may call supervisors of this study Prof. OMARY MINZI (0785892009) or Dr PILLY CHILLO (0713779781) from Muhimbili University of Health and Allied Sciences, P.O BOX 65001, Dar es Salaam.

Signature

Are you willing to participate?.....

I, _____ have read the contents in this form. My questions have been answered and I agree to participate in this study.

Signature of participant _____

Signature of researcher or assistant _____

Date of a signed consent _____