QUALITY OF ORAL ANTICOAGULATION MANAGEMENT AMONG PATIENTS ON FOLLOW UP AT KENYATTA NATIONAL HOSPITAL

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A dissertation submitted in partial fulfillment of the requirements for the award of the Degree of Master of Pharmacy in Clinical pharmacy at the School of Pharmacy of the University of Nairobi.

NOVEMBER 2016

DECLARATION

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DEDICATION

I dedicate this dissertation to my husband Lawrence and our sons Micah and Lucca Agufa for their prayers, love and support throughout my studies.

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I am grateful to God without whom I would not have made it this far. Thank you for strength, wisdom and understanding throughout my studies.

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LIST OF ABBREVIATIONS

ACCP:	American College of Chest Physicians
CDC:	Centers for Disease Control and Prevention
CI:	Confidence Intervals
CVA:	Cerebral Vascular Accident
DVT:	Deep Venous Thrombosis
HIV:	Human Immunodeficiency Virus
INR:	International Normalized Ratio
IQR:	Interquartile range
KNH:	Kenyatta National Hospital
MTRH:	Moi Teaching and Referral Hospital
NSAIDS:	Non-Steroidal Anti-Inflammatory Drugs
OAC:	Oral Anticoagulation
PE:	Pulmonary embolism
RCT:	Randomized Control Trial
SIGN:	Scottish Intercollegiate Guidelines Network
IBM SPSS:	Statistical Package for Social Sciences
TTR:	Time in Therapeutic Range
TB:	Tuberculosis
UK:	United Kingdom
UON:	University of Nairobi
USA:	United States of America
VKA:	Vitamin K Antagonists
VTE:	Venous thromboembolism

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DEFINITION OF TERMS

Anticoagulant: An agent that is used to prevent the formation of blood clots or treat disorders characterized by abnormal blood clots and emboli.

Anticoagulation: The process of hindering the clotting of blood especially by treatment with an anticoagulant.

Therapeutic INR: INR values between 2.0 to 3.0 or to 3.5 in the case of prosthetic valves

Thromboembolism: Obstruction of a blood vessel by a blood clot that has become dislodged from another site in the circulation.

Thromboprophylaxis: Medication taken to reduce the likelihood of formation of a thrombus or clot.

Sub-therapeutic INR: INR below lower range of therapeutic INR (<2.0).

Supra-therapeutic INR: INR above the upper range of therapeutic INR for a particular indication (mainly > 3.0 or >3.5 for prosthetic valves).

ABSTRACT

Background: Oral anticoagulation with warfarin for various indications is challenging given that it has a narrow therapeutic index. Quality management of patients on warfarin is therefore important to minimize the complications of bleeding and thrombosis associated with warfarin therapy. Published literature on the quality of oral anticoagulation management in Kenyatta National Hospital is scanty hence this study sought to fill this gap.

Objective: The objective of this study was to describe the quality of oral anticoagulation among patients who are on follow-up at Kenyatta National Hospital.

Methods: A retrospective cross-sectional study design which analyzed data for eligible participants treated between January 2014 and June 2016 was carried out at Kenyatta National Hospital. Four hundred and six files of all age-groups of patients on warfarin anticoagulation who met the study inclusion criteria were reviewed. A pre-designed structured data collection form was used to extract data from patient files on socio-demographics, indications and duration of warfarin therapy, comorbidities, concomitant medicines and International Normalized Ratio values and the dates the tests were taken. The percentage of follow-up time spent in therapeutic range was computed by Rosendaal Linear Interpolation method. The data was analyzed using IBM Statistical Package for Social Sciences version 22.0. Multivariate linear regression was used to identify independent predictors of poor anticoagulation control. Statistical significance was determined at 95% confidence level.

Results: Female to male ratio was 3:1 and the mean age of the study population was 43 years. Venous thromboembolism was the main indication for warfarin use. Percentage of time spent in therapeutic anticoagulation control was 31.1% and a fifth of the patients had therapeutic International Normalized Ratio for 50% or more of their follow-up time. The median frequency of monitoring was 18.5 days [interquartile range 9.5-34.7]. Proportion of time that International Normalized Ratio was in therapeutic range was associated with renal dysfunction (β = -13.3, p = 0.038). Independent predictors of time outside therapeutic levels were deep venous thrombosis (β= 15.0, p < 0.001), atrial fibrillation

(β= 17.0, p = 0.001), prosthetic valves (β = 27.7, p < 0.001), the use of corticosteroids (β= 18.2, p = 0.026), Islam religion (β = 21.2, p = 0.013) and lower education level (β=5.5, p = 0.037). Congestive heart failure was associated with poor anticoagulation control (p=0.047) whereas valvular heart disease and long duration of anticoagulation were predictors of decreased frequency of monitoring (β =8.6, p = 0.042 and β = 18.0, p<0.001 respectively).

Conclusion: The quality of oral anticoagulation with warfarin in Kenyatta National Hospital is poor especially among patients with renal dysfunction, congestive heart failure and concomitant therapy suggesting that better management and monitoring of patients with these conditions need to be emphasized. Larger studies to determine the reasons for the poor quality and find association between time in therapeutic range and outcomes of warfarin therapy should be conducted.

CHAPTER ONE: INTRODUCTION

1.1 Background

Thromboembolism is a major public health concern that causes substantial morbidity and mortality. Anticoagulants are used to manage patients with thromboembolism and warfarin is the most widely prescribed anticoagulant in the world (1). In Kenya for instance, 94% of patients with various forms of thromboembolic disorders are prescribed warfarin (2).

Due to the narrow therapeutic window of warfarin, its use is associated with increased risk of under-anticoagulation leading to clotting or bleeding due to over-anticoagulation, both of which are serious but avoidable complications. Consequently, patients on warfarin require regular monitoring of International Normalized Ratio (INR) to allow adjustments to be made to the dose to minimize the associated risk (3,4). The INR goal, dose and duration of anticoagulation with warfarin differs depending on the diagnosis and risk of thromboembolism whereas the intensity of monitoring varies depending on the stability of the patient's INR (5).

Quality prescribing of a drug should aim at maximizing its effectiveness, minimizing the risks and costs, and respecting the patient's choices. On the other hand, effective medication monitoring can help to identify drug-related problems before they result in serious patient harm. Studies have shown that inadequate monitoring of patients accounts for about a quarter of preventable medication-related hospital admissions (6,7).

Determination of the quality of warfarin therapy is important for the safety and effectiveness of warfarin anticoagulation. It is commonly measured using Time in Therapeutic Range (TTR) which is strongly associated with outcomes such as the incidence of thrombosis and bleeding (7).

There is scant published literature on quality of oral anticoagulation therapy management at Kenyatta National Hospital thus the impetus for this study.

1.2 Problem statement

Managing patients on warfarin is still a challenge despite it being in use for many years. Thrombosis and bleeding events associated with warfarin therapy are serious and can potentially lead to increased morbidity and mortality (8). In Kenyatta National Hospital for instance, the prevalence of bleeding associated with warfarin anticoagulation has been estimated to be approximately 35% (9). The propensity for drug-drug and food-drug interactions further complicate its use (10).

Other studies in KNH have revealed inadequate control of anticoagulation with 69% of patients having their INR out of therapeutic range and 38% of patients with prosthetic valves and on warfarin presenting with bleeding and thrombotic complications (11,12). Another study showed that only 6.9% of patients after heart valve surgery were able to maintain adequate anticoagulation for 50% or more of their follow up time (1). Furthermore, among the orthopedic surgery patients, thromboprophylaxis was found to be underutilized partly due to lack of guidelines detailing evidence-based recommendations that should be followed by all practitioners (13).

Warfarin is the most commonly prescribed oral anticoagulant and therefore, there is need to ensure quality management to maximize its efficacy and minimize the risks associated with it. The purpose of this study was to determine the quality of oral anticoagulation management at Kenyatta National Hospital.

1.3 Research questions

1. What percentage of time do patients on warfarin spend in therapeutic INR range in KNH?
2. What proportion of patients have INR in therapeutic range on 50% or more of their follow-up time in KNH?
3. What is the frequency of INR monitoring among patients on follow-up at KNH?
4. What factors are associated with quality of anticoagulation control among patients on follow-up at KNH?

1.4 Justification

Although provision of high-quality health care that is affordable is an increasingly difficult challenge (14) it is the right of every Kenyan to have access the highest attainable standard of health according to the Kenya Health Policy 2012 (15).

Quality oral anticoagulation management reduces the complications associated with warfarin therapy hence decrease morbidity, mortality and even cost (8) not only to the patient but also to the institution providing the services. Although studies have shown that adequate control of anticoagulation with warfarin is a challenge despite employing several clinical strategies, warfarin still remains efficacious and cost effective for majority of patients when optimally managed (16).

There being limited published literature on the quality of oral anticoagulation management in KNH, there was need for it to be determined. The findings and recommendations of this study may serve as a benchmark for improvement in the quality of care of patients on warfarin hence better clinical outcomes.

1.5 Study objectives

1.5.1 General objective

The main objective of this study was to determine the quality of oral anticoagulation management in patients on follow-up at Kenyatta National Hospital.

1.5.2 Specific objectives

1. To determine the percentage of time patients spent in the therapeutic INR range.
2. To determine the proportion of patients with INR in therapeutic range on 50% or more of their follow-up time.
3. To determine the frequency of INR monitoring among patients on follow-up at KNH.
4. To identify the factors associated with quality of anticoagulation control

1.6 Delimitations

This study was limited to patients attending Kenyatta National Hospital for treatment and follow-up. The quality of oral anticoagulation management was in terms of time that INR

values are in therapeutic range, proportion of patients with INR in therapeutic range on 50% or more of their follow-up time and the frequency of INR monitoring.

1.7 Conceptual framework

Figure 1 shows patient and clinical factors affecting anticoagulation control and the effect quality of warfarin therapy has on the patient and the institution providing the care.

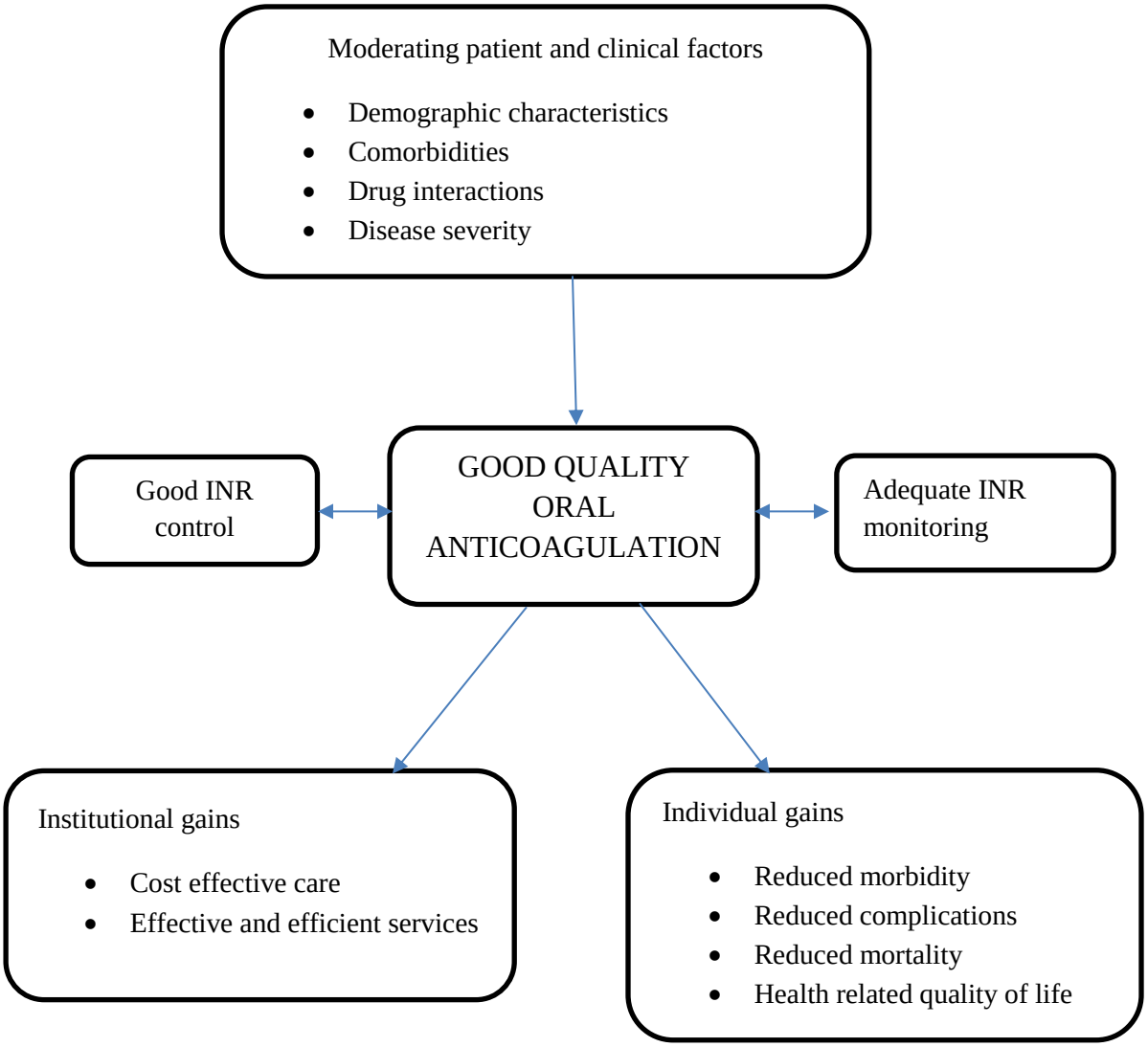

Figure 1: Conceptual framework for quality of anticoagulation control

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Many patients have conditions such as deep venous thrombosis (DVT), pulmonary embolism (PE), atrial fibrillation, mechanical heart valves and dilated cardiomyopathies that increase risk of thromboembolism. Venous thromboembolic (VTE) events cause a major burden of disease in low-, middle-, and high-income countries. For instance, it is estimated that in European Union countries, the total number of symptomatic non-fatal VTE events annually, is over 465,000 and 295,000 cases for DVT and PE respectively, whereas VTE-related deaths are over 370,000. In addition, it was found that the incidence is higher in the African American population than in whites (17). In the USA, Centers for Disease Control and Prevention (CDC) estimated that there were about half a million VTE-related adult hospitalizations between 2007-2009 (18).

In low and middle income countries the incidence of VTE is about 3% in hospitalized patients (18). A study in Nigeria found that the prevalence of PE was 2.9%. In KNH, approximately 250 patients are diagnosed with various forms of VTE diseases annually and 37 patients were diagnosed with atrial fibrillation between January and September 2014 (19).

At present, warfarin is the most widely used oral medicine for long-term management of thromboembolism. High quality management of patients on warfarin is essential for achieving good clinical outcomes hence the increasing need to determine its level (4,8).

2.2 Time spent in therapeutic INR range

Time in Therapeutic Range (TTR) has been used as a measure of quality of anticoagulation in many settings. TTR computes the average duration of time that the patient spends in therapeutic INR range usually 2.0 to 3.0 or 2.5 to 3.5 for those with prosthetic heart valves. Despite its limitations, TTR is a validated and recommended way for measuring quality of warfarin use (20–23); although it is challenging to maintain anticoagulation within therapeutic range (24). The average TTR for patients on warfarin has been reported to be approximately 60% by several studies (25,26). This low

proportion is related to genetic polymorphisms, numerous dietary and medication interactions, issues with patient compliance and variation in the skill and experience of clinicians (24,27). In addition, comorbidities such as renal disease, heart failure, previous heart valve surgery, cancer, diabetes, hypertension, COPD, and higher risk for bleeding, or stroke, further complicate this challenge and is associated with lower TTR (28–30).

2.2.1 Calculating time in therapeutic range

There are three different methodologies for calculating TTR. They have been compared and there is still no consensus on which method is recommended as each of them has different attributes, advantages and limitations. These methods are Rosendaal linear interpolation method, percent of INRs in therapeutic range and cross-section of the files method (20).

The percent of INRs that are in range method simply divides the number of INRs within range by the overall number of INRs for all patients during a specific time. Results are however affected by how frequent INR is monitored and it does not analyze individual patients. In contrast, the cross-section of files method selects a specific point in time and assumes that it represents of the rest of the time. The number of INRs within range are then divided by the total number of INR values at that specific point in time. The Rosendaal interpolation method on the other hand is the only method that considers time. It assumes that a linear relationship exists between two consecutive INR values and allocates a specific INR value to each day between the two consecutive tests for each patient. Furthermore, incidence rates associated with therapy like bleeding and thrombosis can be calculated (31).

Although TTR results can differ depending on the method used, there is no consensus on which methodology is better (26). It is also not clear whether the accuracy in prediction of an outcome is affected by the choice of methodology. One study by Barbui *et al.* to assess the organization and the quality of care in the anticoagulation clinic, the structure, the process of laboratory control and the clinical outcome found no difference between TTR calculated by either fraction or Rosendaal interpolation in patients who experienced bleeding and thrombotic complications. The choice of which methodology to use therefore, should be determined by the size of the clinic, desired information and

available resources (20). Some of the advantages and limitations of each methodology are outlined in the Table 1 below.

Table 1: Advantages and disadvantages of methods to obtain TTR

Methodology	Advantage	Disadvantage
Fraction of INR	Simple to calculate Requires only one INR value per patient Not influenced by extent of INR out-of-range	More frequent testing in unstable patients may bias overall results (underestimation of TTR) Does not consider actual days within target range Does not consider individual patients
Cross-section-of-the-files	Simple to calculate Considers individual patients Not influenced by extent of INR out-of-range results	Does not consider actual days within target range Only considers one point in time
Rosendaal linear interpolation	Considers actual days in target range Incidence rates of adverse events that are INR specific can be calculated	More difficult to calculate Makes assumptions about INR between actual tests Does not consider individual patients Extreme out-of-range results may bias overall results

Source: Schmitt L, Speckman J, Ansell J. Quality assessment of anticoagulation dose management: comparative evaluation of measures of time-in-therapeutic range. *J Thromb Thrombolysis*.2003; 15(3):213–6.

In this study, the Rosendaal Linear interpolation method will be used to determine TTR as it is the only method that incorporates time and takes into account the actual days the INR is in target range (20).

2.2.2 Quality of warfarin therapy in different settings

Several studies have been done to evaluate the quality of warfarin use by measuring TTR. For instance, a study done in Sweden among patients on warfarin found quality

anticoagulation control with a high TTR of 76.2% and consequently a low prevalence of complications. These results were attributed to the well-organized anticoagulation services across all centers in Sweden (32).

Another study in Japan found that although their patients had a high TTR, there was variation between the various institutions (33). In Italy, a prospective study at centers for anticoagulation also found a high TTR of above 60% among geriatric patients (34). On the other hand, a study done in Ontario recorded suboptimal warfarin control with significant variation in adequacy of anticoagulation control between physicians in five long-term care facilities (27). Similarly, suboptimal anticoagulation control was recorded in a recent study in the United States of America (USA) among patients with atrial fibrillation (28).

A study to evaluate the prescribing and monitoring quality among patients on warfarin in Veterans Affairs nursing homes found that their practice was of good quality with INRs within therapeutic range for more than half of the follow-up time (7). A prospective RCT study in the Chinese population similarly recorded a high TTR of about 60%. Further in this study, anticoagulation management by pharmacists was found to be more effective than those by physicians (35). A similar high figure of TTR was also recorded in Portugal in a retrospective study and those outside the therapeutic range were at risk of thrombosis. (36).

Studies to determine quality management in atrial fibrillation patients who are on warfarin have found that a TTR of $\geq$ 58% is a validated threshold at which warfarin has benefit over aspirin, while TTR < 40% may cause net harm due to hemorrhage (37,38). Moreover, the findings of an observational study in the UK showed that warfarin therapy with TTR of less than 40% does not offer significant mortality benefit over no warfarin at all (30).

In Africa, the level of anticoagulation control is suboptimal as evidenced by studies done in KNH, Nigeria and South Africa (1,12,39). In contrast however, a study done in Moi Teaching and Referral Hospital, Eldoret (MTRH) recorded a high TTR of 64% among their patients which is comparable to many resource-rich countries (40).

2.3 Proportion of patients with therapeutic INR on 50% or more of their follow-up time

The proportion of follow-up days that a patient has been in therapeutic INR range during treatment is also a good indicator of quality of anticoagulation therapy. For example, one study done in Veterans Affairs Nursing homes found that approximately half of their patients had INRs in target range for 50% or more of their person-days. This was found to be more likely in patients on chronic warfarin therapy than newly initiated patients. Those with a history of stroke were found to be less likely to have therapeutic INRs for more than 50% of their days (7). A local study in KNH among patients with prosthetic valves found that approximately 7% of the patients had adequate anticoagulation control for 50% or more of the follow up time (1).

2.4 Frequency of monitoring INR

The frequency of monitoring INR may be used as a measure of quality of warfarin therapy (41). This is because, to ensure a patient maintains INR in therapeutic range continually, frequent INR monitoring is necessary as there are many factors that can alter warfarin pharmacokinetics such as concurrent medications, diet and comorbidities. The optimal frequency of long-term INR monitoring is influenced by patient adherence, variations in the severity of comorbidities, concurrent medications, changes in diet, the nature of dose-adjustment, and patient response to therapy (4,16).

It is recommended that INR monitoring of hospitalized patients be done daily until their target INR is achieved and maintained for at least two consecutive days. For outpatients, monitoring once every few days initially is adequate until a stable INR is achieved after which it can be reduced to every 4 to 6 weeks or longer in stable patients (4,42). However, for medically unstable patients or those who are not adherent to medication, follow up should be every 1 to 2 weeks (43).

There is evidence suggesting that increasing INR testing frequency can improve TTR (44,45). The frequency of INR measurement is strongly associated with the overall quality of anticoagulation (46). For instance, one large study that looked at more than 250,000 INRs of chronic atrial fibrillation patients, found an increase in TTR as the testing interval decreased (31). Another study by Horstkotte *et al.* found that for patients

with mechanical heart valves, the percentage of INRs within target range increased significantly when INR monitoring was increased to an average of every four days by home self-testing (47). In addition, the findings of a study in Veterans Affairs Nursing Homes revealed that 99% of the INR tests were done at 4 weeks intervals and reported high quality therapy with warfarin (7).

Furthermore, a study in a national cohort of Veterans Health Administration found that although there was a wide variation in frequency of monitoring INR, females as well as patients with INR values that were outside the therapeutic range were more frequently monitored (41). Recommended frequencies of INR monitoring and patient assessment during warfarin therapy is outlined in Table 2 (43).

Table 2: Frequency of INR Monitoring and Patient Assessment during Warfarin Therapy

Warfarin therapy	**Frequency of monitoring**
Initiation therapy	
Inpatient initiation	Daily
Outpatient flexible initiation method	Daily until day 4, then within 3-5 days
Outpatient average daily dosing method	Within 3-5 days then within 1 week
After hospital discharge	If stable, within 3-5 days If unstable, within 1-3 days
First month of therapy	Every 1-4 days until therapeutic, then weekly
Maintenance therapy	
Medically stable inpatients	Every 1-3 days
Medically unstable inpatients	Daily
After hospitalization discharge	If stable, within 3-5 days If unstable, every 1-3 days
Routine follow-up in medically stable	Every 4-6 weeks
Routine follow-up in medically unstable or unreliable patients	Every 1-2 weeks
Dose held for significant over-anticoagulation	In 1-2 days
Dose change	Within 1-2 weeks

Source*:* Wittkowsky A, A NE. Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs. Lippincott Williams & Wilkins; 2012;(16) 345-368 .

CHAPTER THREE: METHODS

3.1 Study design

A descriptive cross-sectional study design between January 2014 and June 2016 was used.

3.2 Study setting

The study setting was in Kenyatta National Hospital (KNH). It is the largest referral and teaching hospital in the country, located in Nairobi County. The hospital has 50 Wards and a bed capacity of 2000, with over 200 beds for the Private Wing. It also has 22 out-patient clinics, 24 theaters (16 specialized) and an accident & emergency department. Outpatient clinics manage patients on anticoagulants and an average of 70 patients on each clinic day is seen. These are the cardiac, hemato-oncology and cardiothoracic clinics. Approximately 200 patients requiring warfarin treatment are seen per month.

3.3 Target population

The target population was all patients on warfarin for the various indications for anticoagulation on follow-up at Kenyatta National Hospital between January 2014 and June 2016.

3.3.1 Inclusion criteria

Patient files included were those for patients who were on warfarin for more than one month, were on follow-up between January 2014 and June 2016, and had at least two INR readings.

3.3.2 Exclusion criteria

Patients files excluded were those for patients with no warfarin for their thromboembolic disorder, those with less than two INR tests recorded during the study period and those with a contraindication to warfarin but receiving the same.

3.4 Sample size

The primary end-point of this study is the duration of time INR was within therapeutic range which was evaluated against the quality of anticoagulation. The findings of meta-

analysis studies revealed the average rate of INRs in therapeutic range for patients on warfarin is approximately 60% (26), hence a prevalence of 0.6 was used to estimate the sample size for this study.

Using the Fisher's Formula (48):

$$N=\frac{Z^2\{P(1-P)\}}{d^2}$$

Where:

N is the Sample size

Z is the standard normal deviation corresponding to 95 % confidence level, Z-value (1.96)

P is Prevalence (60% = 0.60)

The desired precision of confidence interval (5% = 0.05)

Hence:

$$N=\frac{(1.96)^2\{0.6(1-0.6)\}}{(0.05)^2}=368.7936$$

= 369 files

Therefore, a minimum of 369 files were required.

3.5 Sampling method

Universal sampling method was used. A list of all the indications requiring anticoagulation with warfarin was recorded and provided to the medical records department at KNH with a request for retrieval of the files in the period between January 2014 to June 2016. A list of patients was generated from the health records database and a total of 1009 files retrieved. These were then examined and 413 patient files met the inclusion criteria. 7 files were excluded as the INR results did not have dates. A total of four hundred and six (406) files were separated, assigned a unique study number and used in the study.

3.6 Data collection

A pre-designed structured data collection form (Appendix 2) was used to collect data from patient files on demographic characteristics, indication for anticoagulation, duration of warfarin therapy, date of INR test and corresponding INR results. In addition, comorbidities and drugs concomitantly prescribed with warfarin that affect INR were also recorded (49). One trained research assistant helped in data collection. The principal investigator ascertained that all the relevant information had been accurately captured in the data collection form daily.

3.6.1 Variables

The dependent variable was TTR whereas predictor variables included demographic characteristics, indication for anticoagulation, duration of warfarin therapy, comorbidities, concurrent use of drugs that interact with warfarin and frequency of monitoring INR.

3.7 Quality assurance

All aspects of quality assurance were adhered to. Piloting of the data collection tool before the study commenced ensured all the relevant information was captured and there was no ambiguity. External validity was ensured through adequate sample size and non-biased selection of the study participants. To ensure all relevant clinical data was collected, a pharmacist research assistant was used. All the data collection tools were kept under lock and key while the keyed information was stored in a password protected computer database.

3.8 Data management

The mean percentage of days INR was in therapeutic range was calculated using the Rosendaal linear interpolation method (50) whereby the change between two consecutive INRs over the time interval was assumed to be linear. Percentage of time below and above therapeutic INR were calculated in the same way. These were computed using Rosendaal TTR Microsoft Excel® (Appendix 3).

From the calculated TTR for each patient, the proportion of patients spending 50% or more of their follow time in therapeutic INR range was then determined. This figure

(50%) was chosen as it is the midpoint between 60%, the target TTR for patients on warfarin therapy and 40% which is poor anticoagulation control (26,30).

The frequency of INR monitoring per patient was calculated by dividing the total number of days the patient was on warfarin during the study period by the number of tests done. For instance, if 5 tests were done in 365 days for a given patient, then the frequency of INR monitoring was every 73 days. This meant monitoring INR every 73 days.

All the data was then keyed into IBM SPSS Statistics (version 22) for analysis. Data entry was counterchecked by the principal investigator using the hard copy forms to ensure completeness and accuracy. This was then backed up into a password protected external hard drive that was kept safely under lock and key.

3.9 Statistical analysis

Data analysis was performed using IBM SPSS Statistics (version 22) software. Socio-demographic and clinical characteristics were summarized into percentages for categorical data and continuous data into means and standard deviation. Quality of oral anticoagulation was determined by calculating the mean percentage follow up time in the therapeutic, sub-therapeutic and supra-therapeutic ranges. Proportion of patients in therapeutic range on 50% or more of their follow up time was calculated and presented as a percentage of all study participants. Frequency of INR monitoring was calculated and presented a median number of days with interquartile range. The mean percentages of follow up time in therapeutic, sub-therapeutic and supra-therapeutic ranges were compared between groups using the unpaired Student's T and ANOVA tests for two and more groups respectively. The mean percentage follow-up times (in therapeutic, sub- or supra therapeutic range) with 95% confidence intervals which were distinct from each other (not overlapping) within the same group of patients and did not include the value of zero effect were statistically significant. Proportions of patients who spent 50% of their follow up time in the therapeutic range was analyzed using Chi square test of associations. Odds ratios were calculated to estimate the relative risks associated with each of the independent variables. Mean frequencies of monitoring INR were compared across different categories of patients using Student's T test and ANOVA to compare means in two and more groups respectively. All the factors associated with percentage

time in the INR ranges and those associated with frequency of monitoring INR were analyzed in multiple linear regression models to determine independent predictors of each of the outcomes. All statistical tests were interpreted at 5% level of significance.

3.10 Ethical consideration

Ethical approval and authorization to carry out the study in KNH was granted by the KNH/UON Ethics and Research Committee (ERC P65/02/2016) (Appendix 4) and the KNH records department (Appendix 5) respectively.

Information from patient files was held in confidence and only details relevant to the study were extracted after which the files were immediately returned for storage and for use by the patients in the clinics. The data collections forms did not have any patient identifiers. Instead, unique study numbers were used in place of patient names or hospital numbers.

There were no direct risks or benefits to the patients whose files were used during the study as there was no direct contact. However, findings and recommendations made may be used to guide future decisions in KNH that may result in improved quality of care to the patients.

CHAPTER FOUR: RESULTS

4.1 Introduction

One thousand and nine files were retrieved for the study. However, data were analyzed from 406 files because the rest were excluded due to various reasons (Figure 2).

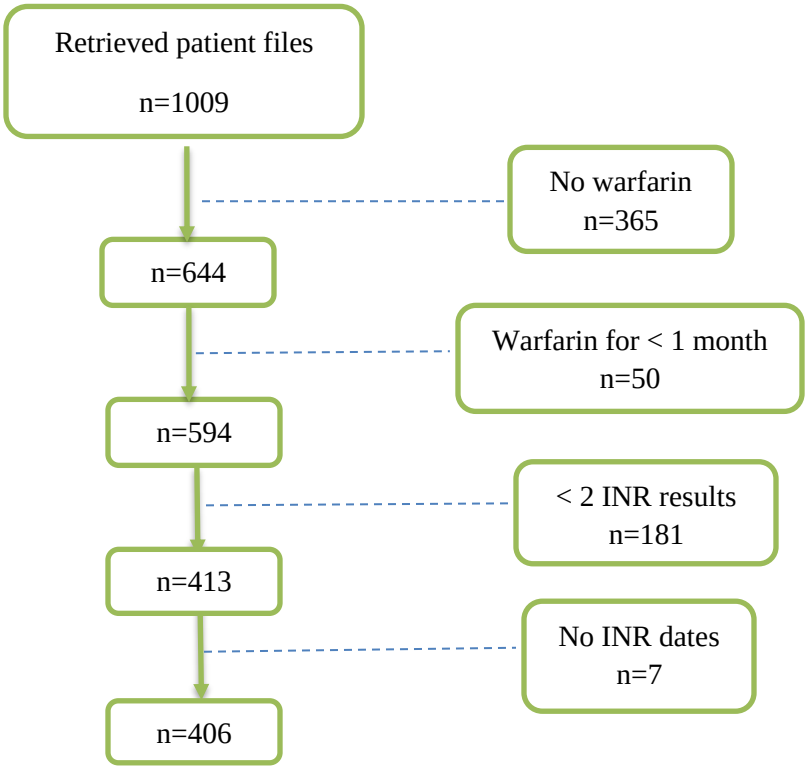

Figure 2: Consort diagram showing patients eligibility and reasons for exclusion

4.2 Social demographic characteristics of the study participants

Table 3 summarizes the socio-demographic characteristics of the study patients. Majority of the participants were female 301(74.1%). The mean age (SD) was 42.7 years (16.9). About half of the patients were aged between 36-65 years. Those that were married were the majority at 56.4%. Approximately 90% of the participants had attained at least primary level of education and a similar proportion did not consume ethanol.

Table 3: Social demographic characteristics of study participants

Variable	Category	n (%)
Age	0-18 Years	27 (6.7)
	19-35 years	120 (29.6)
	36-65 years	221 (54.4)
	>65 years	38 (9.4)
Gender	Male	105 (25.9)
	Female	301 (74.1)
Marital status	Married	229 (56.4)
	Single	110 (27.1)
	Divorced	5 (1.2)
	Separated	17 (4.2)
	Widowed	45 (11.1)
Occupation status	Salaried	92 (22.7)
	Self-Employed	181 (44.6)
	Unemployed	100 (24.6)
	Student	33 (8.1)
Level of education	Undocumented	1 (0.2)
	Informal	37 (9.1)
	Primary	175 (43.1)
	Secondary	133 (32.8)
	College and above	60 (14.8)
Religion	Christian	396 (97.5)
	Muslim	10 (2.5)
Alcohol consumption	Yes	45 (11.1)
	No	361 (88.9)
Age Mean (SD): 42.7 (16.9) years		

KEY: SD-Standard deviation

4.3 Clinical characteristics of study participants on warfarin therapy at KNH

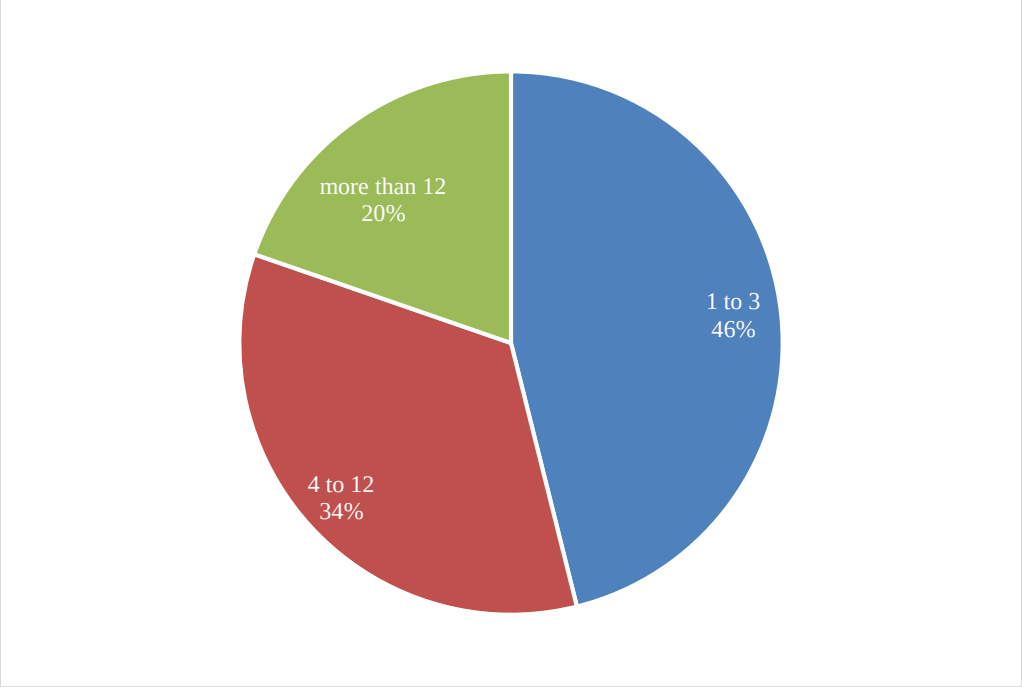

Figure 3: Duration of oral anticoagulation use in months

The mean duration on anticoagulants was about 9 months with a standard deviation of 12.7 months. About 80% of the patients had used warfarin for less than a year as shown in Figure 3.

The most prevalent indication for anticoagulation was DVT (72.4%). About 80% of the patients on oral anticoagulation had VTE (DVT and PE) whereas 7.6% required anticoagulation due to prosthetic valves (Figure 4).

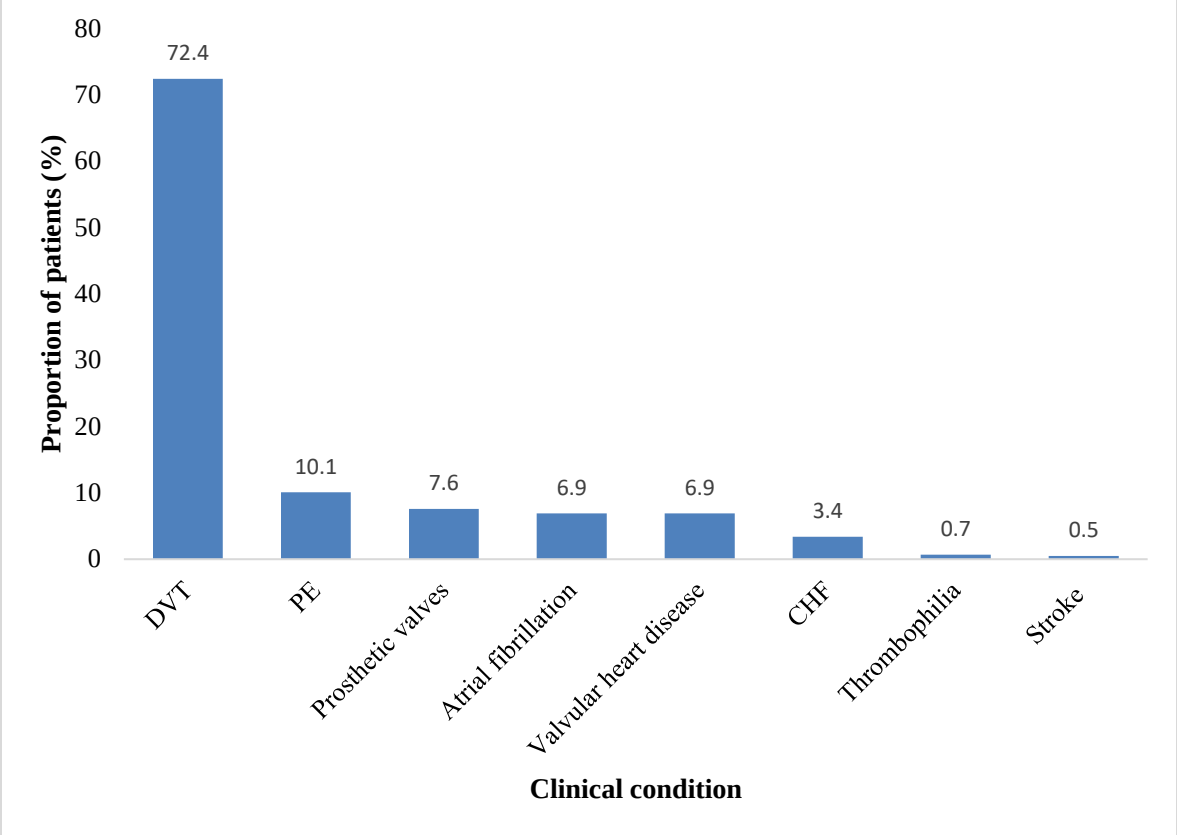

Figure 4: Clinical indication for oral anticoagulation for study participants

Key: DVT-Deep Venous Thrombosis; PE- Pulmonary Embolism; VHD: Valvular Heart Disease, AF: Atrial Fibrillation; CHF: Congestive Heart Failure

About 40% of the study participants had comorbidities that may have an influence on the INR value. HIV was the most prevalent comorbidity (15.5%) followed by hypertension (14.3%) and cancer (10.3%) as shown in Figure 5.

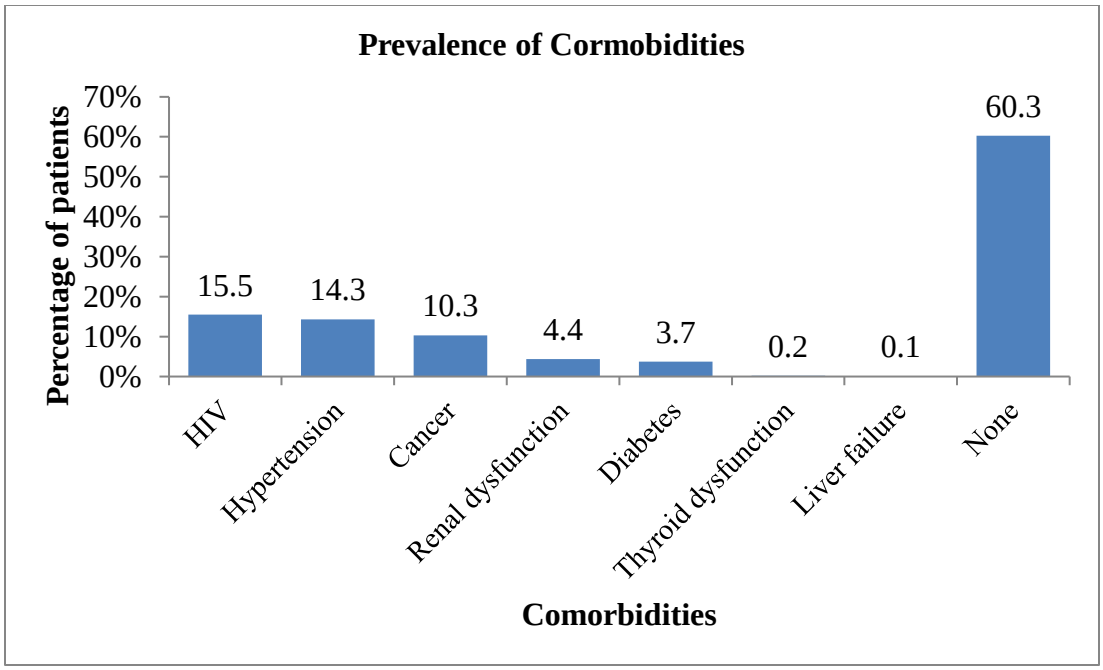

Figure 5: Comorbidities that may influence anticoagulation control

Key: HIV: Human Immunodeficiency Virus

Figure 6 shows that 95% of the participants were taking one other medicine known to interact with warfarin while a third of them had at least two other medicines.

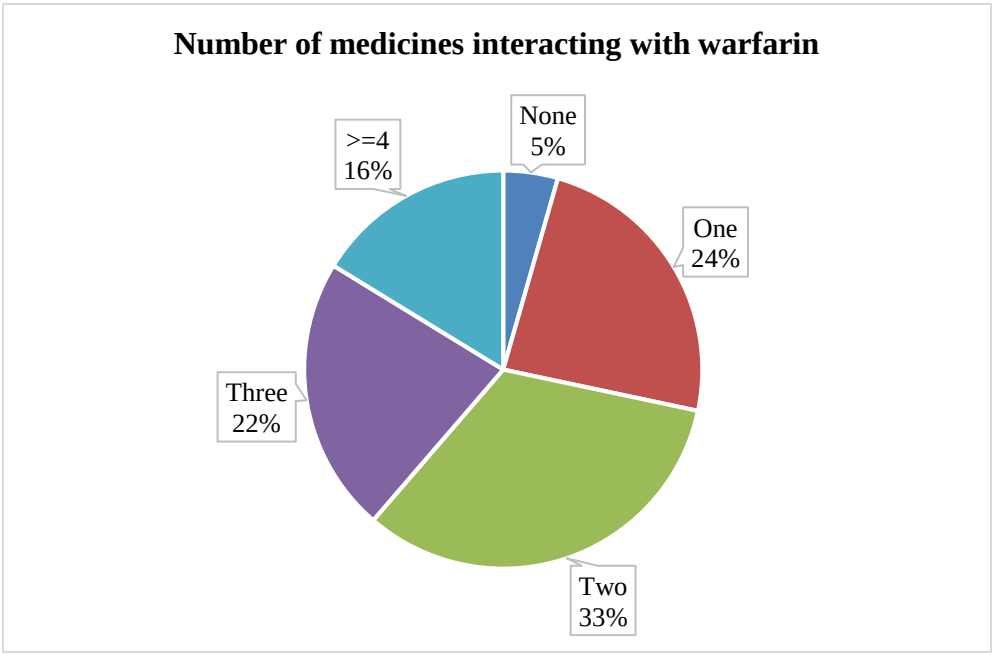

Figure 6: Number of medicines interacting with warfarin

Antithrombotics (Appendix 6) were the most widely used drug (78.3%), followed by antimicrobials (39.2%) and analgesics (35.2%) as shown in Table 4.

Table 4: Concurrent drugs interacting with warfarin

Group	Group frequency n (%)	Class	Class Frequency n(%)
Antimicrobials	159 (39.2)	Antibacterial	152 (37.4)
		Antifungal	10 (2.5)
		Antiviral	51 (12.6)
Analgesics	143 (35.2)	NSAIDS	49 (12.1)
		Opioids	113 (27.8)
		Paracetamol	2 (0.5)
CNS drugs	11 (2.7)	Anticonvulsants	11 (2.7)
		Antidepressant	1 (0.2)
Cardiovascular drugs	83 (20.4)	Antiarrhythmics	69 (17.0)
		Statins	20 (4.9
Antithrombotics	318 (78.3)	Anticoagulants	317 (78.1)
		Antiplatelets	14 (3.4)
Immunosuppressant	17 (4.2)	Corticosteroids	17 (4.2)
Gastrointestinal	103 (25.4)	Proton pump inhibitors	103 (25.4)

Key: CNS: Central Nervous System; NSAIDS: Non-Steroidal Anti-inflammatory Drugs

4.4 Quality of oral anticoagulation

4.4.1 Time spent in therapeutic INR Range (TTR)

TTR is the percentage of follow-up time that participants spent in therapeutic INR range. The proportion of time that participants spent in therapeutic, sub-therapeutic or supra-therapeutic INR are presented in Figure 7.

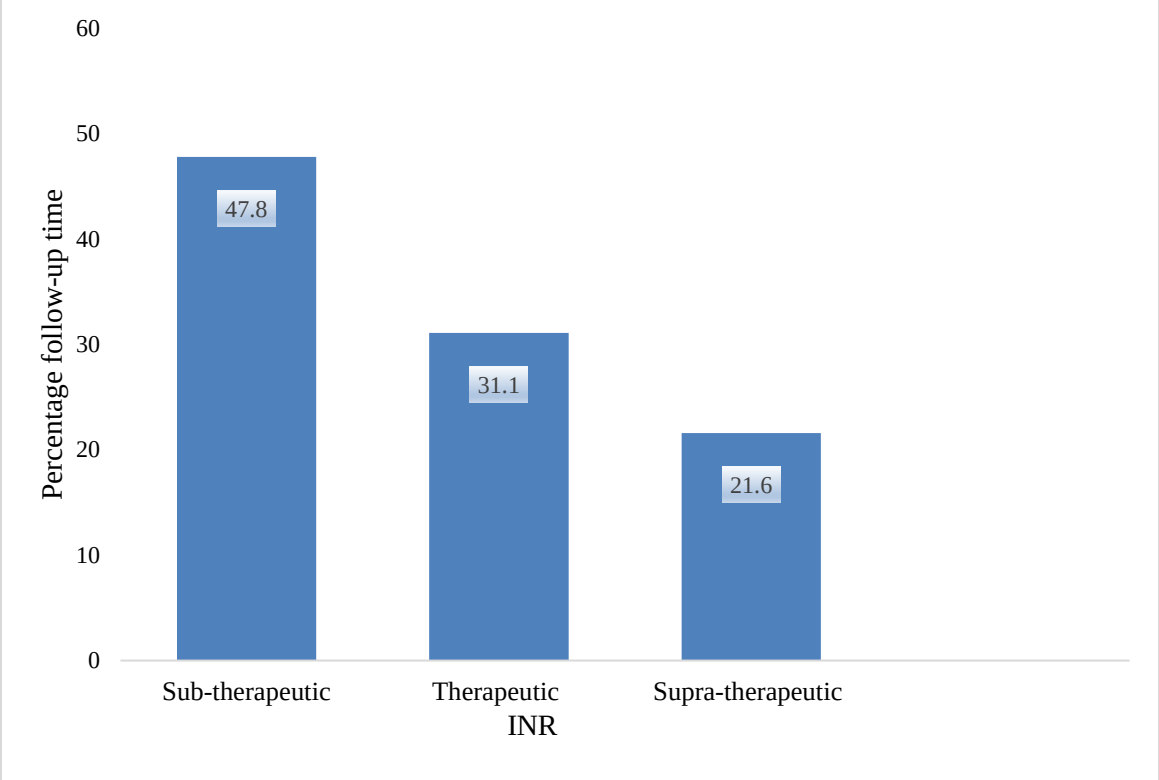

Figure 7: Level of INR control for study participants

The percentage follow-up time study participants spent in therapeutic INR was 31.1% with a Standard Deviation of 26.7%. Almost half of the follow-up time was spent in sub-therapeutic INR.

The time in therapeutic range with the corresponding proportion of patients is illustrated in the Figure 8.

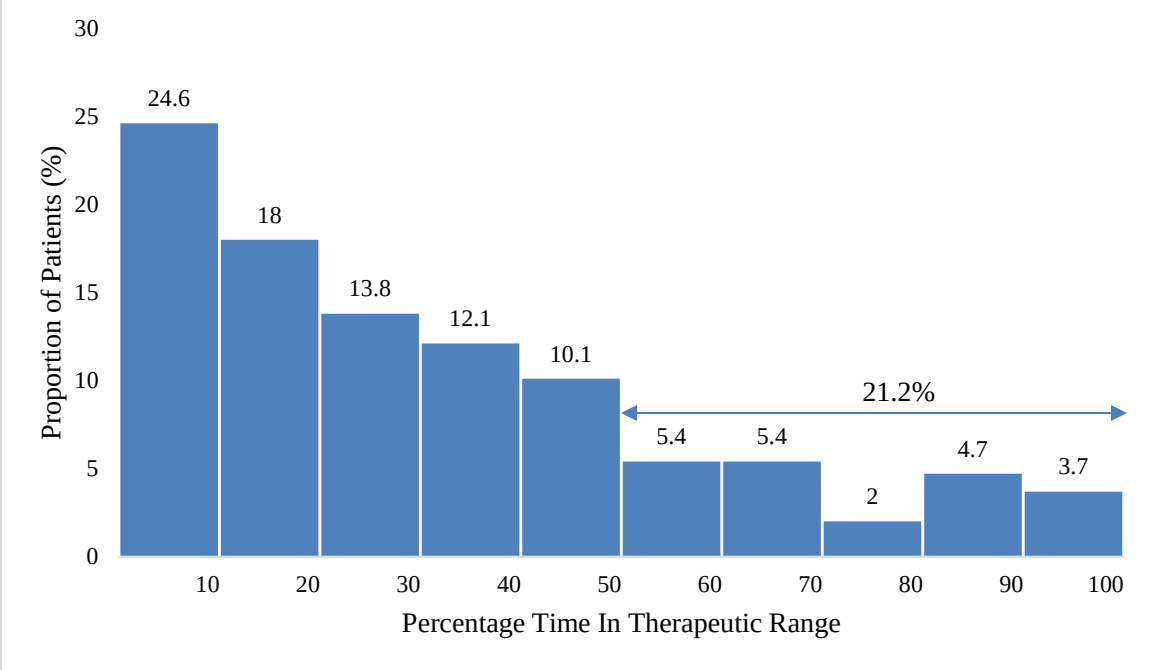

Figure 8: Percentage time in therapeutic INR vs proportion of patients

About a quarter of the patients were in therapeutic range for only 0-10% of follow-up time. A small proportion of about 10% of patients were in therapeutic range for more than 70% of their follow-up time. Only about a fifth of the patients spent 50% or more of their time in therapeutic INR.

4.4.2 Frequency of monitoring INR

The median frequency of monitoring INR for the patients was 18.5 days (IQR = 9.5-34.7). Figure 9 shows the proportion of patients with their corresponding frequency of INR monitoring during follow-up.

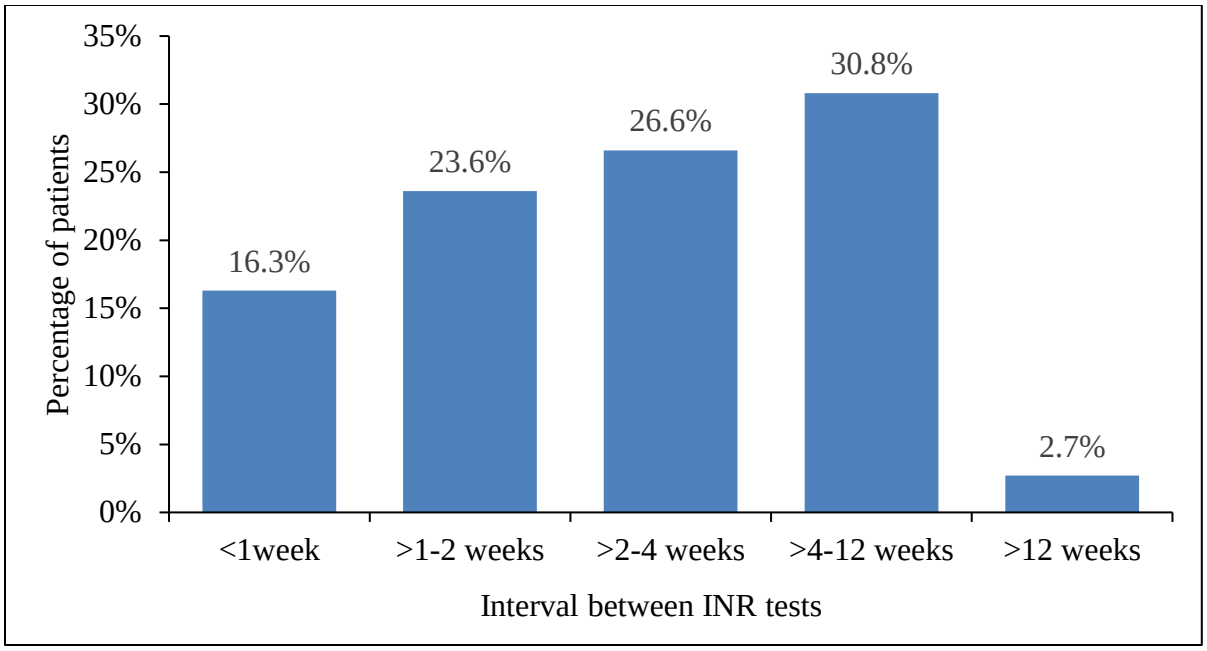

Figure 9: Frequency of monitoring International Normalized Ratio

Key: INR: International Normalized Ratio

Monitoring of INR was mostly done after every 4-12 weeks followed by every 2-4weeks during the patient follow up. Monitoring was infrequent every week and was rarely done after every 3 months.

4.5 Factors associated with anticoagulation control

4.5.1 Relationship between time spent in the INR ranges and sociodemographic characteristics of study participants

The relationship between socio-demographic characteristics of the study participants and INR control was determined as presented in Table 5.

Table 5: Proportion of follow-up time spent in INR ranges vs socio-demographic characteristics of study participants

Variable			INR range					
			Therapeutic		Sub-therapeutic		Supra-therapeutic	
		n	Mean (%)	95% CI	Mean (%)	95% CI	Mean (%)	95% CI
Age in years	0-18	27	32.3	21.4-43.1	51.7	38.2-65.2	16.1	6.2-25.9
	19-35	120	29.3	24.3-34.4	52.7	46.4-59.0	18.3	13.6-23.1
	36-65	221	31.8	28.3-35.2	46.2	41.9-50.5	22.7	19.2-26.2
	>65	38	32.0	23.0-41.0	39.4	28.7-50.0	29.2	18.7-39.6
P-value			0.861		0.120		0.099	
Gender	Male	105	29.5	24.8-34.2	47.6	41.2-54.0	24.0	18.5-29.4
	Female	301	31.7	28.5-34.8	47.9	44.1-51.8	20.8	17.8-23.8
P-value			0.480		0.928		0.297	
Marital status	Married	229	32.1	28.6-35.6	48.2	43.8-52.5	20.5	17.2-23.8
	Unmarried	177	29.8	25.8-33.7	47.4	42.6-52.6	23.0	18.6-27.2
P-value			0.406		0.829		0.368	
Employ-ment status	Employed	273	32.4	29.1-35.6	46.1	42.2-50.1	22.3	19.1-25.6
	Unemployed	133	28.5	23.9-32.9	51.4	45.7-57.4	20.1	15.5-24.5
P-value			0.177		0.141		0.440	
Religion	Christian	396	31.2	28.5-33.8	48.3	45.1-51.7	21.1	18.4-23.7
	Muslim	10	29.1	10.2-48.0	28.4	4.7-52.1	42.5	15.7-69.2
P-value			0.815		0.063		**0.013**	
Education level	≤Primary	212	29.9	26.4-33.4	46.1	41.5-50.7	24.3	20.5-28.2
	≥Secondary	193	32.3	28.4-36.3	49.9	45.3-54.6	18.5	15.0-22.1
P-value			0.365		0.251		**0.030**	
Alcohol consumption	Yes	45	31.0	23.6-38.4	48.8	38.4-59.3	20.6	13.0-28.3
	No	361	31.1	28.3-33.9	47.7	44.3-51.3	21.7	18.9-24.5
P-value			0.983		0.836		0.796	

Key: INR: International Normalized Ratio

Table 5 shows that the mean percentage of follow-time participants spent in therapeutic range was not significantly different in relation to their sociodemographic characteristics ($p>0.05$). However, Muslims and those with primary education and below spent significantly higher percentage of follow-up time in supra-therapeutic INR than their counterparts ($p=0.013$ and 0.030 respectively). In addition, all participants spent significantly higher percentage of follow-up time in sub-therapeutic range regardless of

their sex, marital status, employment status, education level and alcohol consumption status. Whereas patients 65 years of age and below spent a significantly higher percentage of their follow up time in sub-therapeutic range than in therapeutic and supra-therapeutic range, the percentage follow up time spent in any of the three INR ranges was not significantly different for patients older than 65 years.

4.5.2 Relationship between time spent in the INR ranges and clinical characteristics of study participants

Table 6 shows relationship between clinical characteristics of the patients and time spent in therapeutic sub- and supra-therapeutic INR levels.

Table 6: Percentage of follow-up time in the INR ranges vs clinical characteristics of study participants

Variable			INR range					
			Therapeutic		Sub-therapeutic		Supra-therapeutic	
		n	Mean (%)	95% CI	Mean (%)	95% CI	Mean (%)	95% CI
DVT	Yes	294	29.7	26.7-32.8	50.1	46.3-54.0	20.6	17.6-23.5
	No	110	35.0	30.0-40.0	41.6	35.4-47.9	24.2	18.6-29.8
P-value			0.079		**0.023**		0.231	
PE	Yes	41	39.3	30.2-48.5	39.8	29.7-49.9	21.8	14.0-29.5
	No	365	30.2	27.5-33.0	48.8	45.2-52.2	21.6	18.7-24.4
P-value			**0.038**		0.104		0.967	
Valvular heart disease	Yes	28	39.8	27.8-51.8	30.9	18.3-43.4	29.3	15.8-42.9
	No	376	30.5	27.9-33.2	49.1	45.7-52.4	21.0	18.3-23.6
P-value			0.074		**0.005**		0.115	
Atrial fibrillation	Yes	28	31.6	20.1-43.0	33.6	19.3-47.9	38.1	23.2-52.9
	No	376	31.1	28.4-33.8	48.9	45.5-52.2	20.3	17.8-23.9
P-value			0.923		**0.020**		**0.001**	
CHF	Yes	14	25.1	17.2-32.9	43.5	22.6-64.3	38.0	17.0-59.0
	No	390	31.4	28.7-34.1	48.0	44.6-51.3	21.0	18.4-23.6
P-value			0.389		0.618		**0.020**	
Prosthetic valves	Yes	31	28.8	21.2-36.3	61.8	52.6-70.9	9.5	4.4-14.5
	No	373	31.4	28.6-34.1	46.6	43.2-50.1	22.6	19.8-25.4
P-value			0.613		**0.016**		**0.009**	
Duration OAC in months	1-3	187	30.2	25.9-34.4	45.3	40.0-50.6	25.0	20.5-29.5
	4-12	139	29.9	25.8-34.1	50.8	45.4-56.3	20.0	15.9-24.2
	>12	80	35.3	30.2-40.4	48.6	42.7-54.6	16.3	12.4-20.3
P-value			0.294		0.330		**0.038**	
Frequency of monitoring in weeks	≤1	66	21.4	15.7-27.2	54.5	45.2-63.9	24.5	16.7-32.3
	>1 to 2	96	33.5	27.0-40.1	42.6	35.4-49.8	23.9	17.7-30.0
	>2 to 4	108	32.4	27.5-37.2	45.0	39.0-51.1	23.1	18.0-28.3
	>4 to 12	125	33.1	28.8-37.4	50.5	45.1-56.0	17.4	13.7-21.1
	>12	11	33.1	20.2-45.9	50.4	31.6-69.2	16.5	1.5-31.5
P-value			**0.034**		0.157		0.265	

Key: INR: International Normalized Ratio, DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism, CHF: Congestive Heart Failure, OAC: Oral Anticoagulation,

As shown in Table 6, participants with pulmonary embolism spent a higher percentage of follow-up time in therapeutic range (p=0.038) whereas those with DVT were in sub-therapeutic range most of their follow-up time (p=0.023). On the other hand, participants who had valvular heart disease and atrial fibrillation spent significantly lower percentage of follow up time in sub-therapeutic range than those without valvular heart disease or atrial fibrillation (p=0.005 and 0.020 respectively). In addition, those with atrial fibrillation and congestive heart failure spent more time in supra-therapeutic than those without (p=0.001 and 0.020 respectively). Conversely, participants with prosthetic valves spent a significantly higher percentage follow up time (61.8%, p=0.016) in sub-therapeutic range but lower time in the supra-therapeutic range (9.5%, p=0.009) than their counterparts spent in sub-therapeutic and supra-therapeutic ranges (46.6% and 22.6% respectively). Those on warfarin therapy for more than a year spent a significantly lower percentage of follow-up time in supra-therapeutic range than those on therapy for less than a year (p=0.038).

4.5.3 Relationship between time spent in INR ranges and comorbidities of study participants

Table 7 shows the relationship between INR control and comorbidities of study participants.

Table 7: Percentage of follow-up time in the INR ranges versus comorbidities of study participants

Comorbidities			INR range					
			Therapeutic		Sub-therapeutic		Supra-therapeutic	
		N	Mean (%)	95% CI	Mean (%)	95% CI	Mean (%)	95% CI
Diabetes	No	391	31.1	28.4-33.7	47.8	44.5-51.2	21.7	19.0-24.3
	Yes	15	31.7	17.6-45.8	48.3	30.3-66.3	19.8	6.0-33.7
P-value			0.912		0.960		0.229	
Hypertension	No	348	30.8	28.0-33.7	48.5	44.9-52.0	20.9	18.1-23.7
	Yes	58	32.6	25.3-39.9	44.2	35.2-53.1	25.6	18.0-33.1
P-value			0.642		0.367		0.226	
Renal dysfunction	No	388	31.7	29.1-34.4	47.4	44.0-50.7	21.1	18.5-23.8
	Yes	18	17.5	6.8-28.2	58.5	38.7-78.3	31.6	13.7-49.4
P-value			**0.027**		0.169		0.108	
Cancer	No	364	31.4	28.7-34.2	47.7	44.3-51.2	21.4	18.6-24.2
	Yes	42	28.1	20.5-35.8	48.9	38.1-59.6	22.9	14.9-31.0
P-value			0.447		0.837		0.732	
HIV	No	343	31.5	28.7-34.3	46.9	43.3-50.4	22.3	19.4-25.2
	Yes	63	29.1	21.9-36.4	53.1	44.7-61.4	17.8	11.7-24.0
P-value			0.521		0.178		0.226	

Key: INR: International Normalized Ratio

Participants with renal dysfunction spent significantly lower percentage of follow up time (17.5%) in therapeutic range compared their counterparts (31.7%, p=0.027). In addition, all participants with comorbidities except diabetes spent a significantly higher percentage of follow-up time in sub-therapeutic level than therapeutic or supra-therapeutic range.

4.5.4 Relationship between time spent in INR ranges and concurrent drugs

Table 8 shows the relationship between INR control and types of concurrent medicines used.

Table 8: Percentage of follow-up time in the INR ranges versus concurrent drugs used by study participants

Drugs			INR range					
			Therapeutic		Sub-therapeutic		Supra-therapeutic	
		n	Mean (%)	95% CI	Mean (%)	95% CI	Mean (%)	95% CI
Antibacterial	No	254	31.3	28.1-34.5	46.1	41.9-50.2	23.3	19.9-26.8
	Yes	152	30.7	26.3-35.2	50.9	45.5-56.2	18.7	14.6-22.7
p-value			0.830		0.162		0.089	
Antifungal	No	396	31.4	28.7-34.0	47.5	44.2-50.8	21.7	19.0-24.4
	Yes	10	20.5	3.5-37.5	62.4	38.1-86.7	17.1	0.0-34.4
p-value			0.206		0.165		0.594	
Antiviral	No	355	31.2	28.4-34.0	47.8	44.2-51.3	21.6	18.8-24.4
	Yes	51	30.3	22.4-38.3	48.5	39.4-57.6	21.5	14.5-28.6
p-value			0.829		0.883		0.989	
NSAIDS	No	357	31.9	29.1-34.8	46.9	43.4-50.4	21.8	19.0-24.6
	Yes	49	25.1	19.2-31.0	54.8	45.5-64.0	20.1	13.1-27.2
p-value			0.093		0.122		0.688	
Opioids	No	293	31.5	28.3-34.7	47.6	43.6-51.6	21.2	18.0-24.3
	Yes	113	30.0	25.5-34.5	48.5	42.8-54.2	22.7	17.8-27.6
p-value			0.610		0.815		0.605	
Anticonvulsants	No	395	31.4	28.7-34.1	47.2	43.9-50.5	21.9	19.3-24.6
	Yes	11	20.2	6.9-33.5	70.4	50.7-90.2	9.4	0.0-21.5
p-value			0.170		**0.023**		0.127	
Antiarrhythmics	No	337	31.0	28.1-33.9	48.9	45.3-52.4	20.5	17.8-23.2
	Yes	69	31.8	25.6-38.0	42.8	34.4-51.1	26.8	18.7-34.9
p-value			0.822		0.166		0.079	
Statins	No	386	31.1	28.4-33.8	47.8	44.5-51.2	21.6	18.9-24.4
	Yes	20	31.4	19.3-43.5	48.0	31.0-65.1	20.6	8.8-32.4
p-value			0.960		0.980		0.863	
Anticoagulants	No	89	28.4	23.7-33.2	48.4	41.6-55.2	24.1	18.1-30.2
	Yes	317	31.9	28.8-34.9	47.7	43.9-51.4	20.9	18.0-23.8
p-value			0.286		0.857		0.314	
Antiplatelets	No	392	31.0	28.4-33.7	47.6	44.2-50.9	21.9	19.2-24.6
	Yes	14	32.6	19.1-46.0	55.4	39.7-71.1	12.1	4.5-19.6
p-value			0.837		0.392		0.178	
Corticosteroids	No	389	31.5	28.8-34.2	47.0	43.6-50.3	22.1	19.4-24.8
	Yes	17	21.5	9.7-33.2	67.9	51.9-83.9	10.7	2.9-18.4
p-value			0.128		**0.012**		0.088	
Proton pump inhibitors	No	303	31.9	29.0-34.9	47.0	43.2-50.8	21.5	18.5-24.6
	Yes	103	28.6	23.3-34.0	50.4	43.8-57.0	21.7	16.4-27.0
p-value			0.279		0.374		0.949	

Patients on anticonvulsants and corticosteroids spent a significantly higher percentage of their follow up time in the sub-therapeutic range compared to those who were not using these drugs (p=0.023 and 0.012 respectively).

4.6 Factors associated with spending less than 50% of follow-up time in therapeutic range

The proportions of those who spent less than 50% of their follow up time in therapeutic INR range and associated factors was determined (Appendix 7). Congestive heart failure was significantly associated with spending less than 50% of follow-up time in therapeutic INR (p=0.047).

4.7 Factors affecting frequency of INR monitoring among study participants

4.7.1 Association between interval of INR monitoring and sociodemographic characteristics of the study participants

Table 9 shows association between frequency of INR monitoring and sociodemographic characteristics.

Table 9: Interval of monitoring INR and sociodemographic characteristics of study participants

Variable			Interval of monitoring (days)	
		n (%)	Mean	p-value
Age (years)	0-18 Years	27(6.7)	25.5	0.332
	19-35 years	120(29.6)	27.4	
	36-65 years	221(54.4)	25.7	
	>65years	38(9.4)	19.7	
Gender	Male	105(25.9)	26.0	0.836
	Female	301(74.1)	25.5	
Marital status	Married	229(56.4)	26.4	0.418
	Unmarried	177(43.6)	24.6	
Employment status	Employed	273(67.2)	24.8	0.296
	Unemployed	133(32.8)	27.3	
Education level	Primary and below	213(52.5)	25.3	0.698
	Secondary and above	193(47.5)	26.2	
Alcohol consumption	Yes	45(11.1)	26.4	0.809
	No	361(88.9)	25.5	

Table 9 shows that those above the age of 65 years were the most frequently monitored with 20 days between tests. This was however not statistically different from other age group sections.

4.7.2 Association between interval of INR monitoring and clinical characteristics of the study participants

The association between frequency of monitoring INR and clinical characteristics of the participants is presented in Table 10.

Table 10: Interval of INR monitoring and clinical characteristics of the study participants

Variable			Interval of monitoring (days)	
		n (%)	Mean	p-value
Indication for OAC				
DVT	Yes	294(72.4)	22.2	**<0.001**
	No	112(27.6)	35.1	
PE	Yes	41(10.1)	19.5	0.064
	No	365(89.9)	26.3	
Valvular heart disease	Yes	28(6.9)	46.6	**<0.001**
	No	378(93.1)	24.1	
Atrial fibrillation	Yes	28(6.9)	31.6	0.146
	No	378(93.1)	25.2	
Congestive Heart Failure	Yes	14(3.4)	36.5	0.067
	No	392(96.6)	25.3	
Thrombophilia	Yes	3(0.7)	13.3	0.343
	No	403(99.3)	25.7	
Prosthetic valves	Yes	31(7.6)	40.7	**<0.001**
	No	375(92.4)	24.4	
Stroke	Yes	2(0.5)	7.6	0.259
	No	404(99.5)	25.7	
Duration of OAC	1-3 months	187(46.1)	11.0	**<0.001**
	4-12 months	139(34.2)	31.9	
	>12 months	80(19.7)	49.0	

Key: OAC: oral anticoagulation

Participants with stroke had the shortest interval of monitoring INR. DVT and short duration on warfarin of between 1-3months was associated with more frequent monitoring whereas valvular heart disease, prosthetic valves and long duration on

warfarin (more than 1 year) was associated with less frequent monitoring ($p < 0.001$). As duration on anticoagulants increased the interval of monitoring INR increased.

Further, the relationship between comorbidities and frequency of monitoring INR was determined as shown in Table 11.

Table 11: Interval of monitoring INR and comorbidities of study participants

Comorbidity			Interval of monitoring (days)	
		n (%)	Mean	p-value
Diabetes	No	391(96.3)	25.5	0.425
	Yes	15(3.7)	30.2	
Hypertension	No	348(85.7)	25.9	0.404
	Yes	58(14.3)	23.9	
Thyroid dysfunction	No	405(99.8)	25.6	0.133
	Yes	1(0.2)	59.6	
Liver failure	No	405(99.8)	25.6	0.371
	Yes	1(0.2)	45.9	
Renal dysfunction	No	388(95.6)	26.1	0.075
	Yes	18(4.4)	16.4	
Cancer	No	364(89.7)	26.8	**0.002**
	Yes	42(10.3)	15.4	
HIV	No	343(84.5)	26.7	**0.022**
	Yes	63(15.5)	19.7	

More frequent monitoring of INR among the participants was associated with cancer and HIV comorbidities ($p= 0.002$ and 0.022 respectively).

The relationship between concurrent use of medicines and the frequency of monitoring INR is illustrated in Table 12. Antiarrhythmics concurrently used with warfarin was associated with less frequent monitoring whereas concurrent use of anticoagulants was associated with more frequent INR monitoring ($p < 0.001$).

Table 12: Interval of monitoring INR and concurrent medicines used by study participants

Drug		Interval of monitoring INR (days)		
		n (%)	Mean	p-value
Antibacterial	No	254 (62.6)	26.4	0.374
	Yes	152 (37.4)	24.4	
Antifungal	No	396 (97.5)	25.9	0.208
	Yes	10 (2.5)	16.8	
Antiviral	No	355 (87.4)	26.2	0.197
	Yes	51 (12.6)	21.8	
NSAIDS	No	357 (87.9)	25.5	0.722
	Yes	49 (12.1)	26.7	
Opioids	No	293 (72.2)	26.4	0.253
	Yes	113 (27.8)	23.6	
Paracetamol	No	404 (99.5)	25.7	0.430
	Yes	2 (0.5)	13.1	
Anticonvulsants	No	395 (97.3)	25.6	0.644
	Yes	11 (2.7)	28.8	
Antiarrhythmics	No	337 (83.0)	22.9	**<0.001**
	Yes	69 (17.0)	38.9	
Statins	No	386 (95.1)	25.3	0.206
	Yes	20 (4.9)	31.9	
Anticoagulants	No	89 (21.9)	34.3	**<0.001**
	Yes	317 (78.1)	23.2	
Antiplatelets	No	392 (96.6)	25.4	0.175
	Yes	14 (3.4)	33.7	
Corticosteroids	No	389 (95.8)	25.5	0.495
	Yes	17 (4.2)	29.3	
Proton pump inhibitors	No	303 (74.6)	26.3	0.351
	Yes	103 (25.4)	23.8	

Key: NSAIDS: Non-Steroidal Anti-inflammatory Drugs

4.8 Independent factors associated with therapeutic, sub-therapeutic, supra-therapeutic INR levels and frequency of monitoring among study participants

Multilinear regression analysis using backward stepwise method was done to determine the independent predictors of therapeutic, sub-therapeutic and supra-therapeutic INR as well as reduced frequency of monitoring INR (Table 13).

Table 13: Predictors of therapeutic, sub-therapeutic, supra-therapeutic INR and frequency of monitoring INR among study participants

	Variable	β co-efficient	95% CI	p-value
Predictors of TTR	PE	8.4	0.2, 17.1	0.054
	Renal dysfunction	-13.3	-25.9, -0.8	**0.038**
Predictors of sub-therapeutic INR	DVT	15.0	6.9, 23.2	**<0.001**
	Prosthetic valves	27.7	14.1, 41.3	**<0.001**
	Anticonvulsants	17.4	-2.3, 37.2	0.083
	Corticosteroids	18.2	2.2, 34.2	**0.026**
Predictors of supra-therapeutic INR	Islam Religion	21.2	4.5, 37.6	**0.013**
	Education level above secondary	-5.5	-10.6, -0.3	**0.037**
	Prosthetic valves	-13.3	-23.1, -3.5	**0.008**
	Atrial fibrillation	17.0	6.9, 27.1	**0.001**
Predictors of decreased monitoring frequency	DVT	-2.6	-8.2, 2.9	0.350
	Valvular heart disease	8.6	0.3, 16.9	**0.042**
	Prosthetic Valves	-0.7	-9.0, 7.6	0.866
	Duration of OAC	18.0	15.9, 20.3	**<0.001**
	Cancer	-2.4	-7.9, 3.0	0.378
	HIV	-0.9	-5.4, 3.7	0.707
	Antiarrhythmics	2.9	-3.5, 9.3	0.374
	Anticoagulants	-3.7	-8.3, 1.0	0.120

Key: DVT: Deep Venous Thrombosis, OAC: Oral Anticoagulation, HIV: Human Immunodeficiency Virus.

Presence of renal dysfunction reduced time in therapeutic range by 13.3% (p= 0.038). DVT, prosthetic valves and concurrent use of corticosteroids increased the percentage time in sub-therapeutic range by 15%, 27.7% and 18.2% respectively. (p<0.001, <0.001 and 0.026 respectively). Islam religion and atrial fibrillation were associated with 21.2% and 17% increase in the percentage time in the supra-therapeutic range (p= 0.013 and 0.037 respectively) whereas level of education above secondary school and prosthetic valves were associated with 5.5% and 13.3% reduction in the percentage time in the supra-therapeutic range. Presence of valvular heart disease was associated with 8-fold decrease in frequency of monitoring (p= 0.042) whereas, a unit increase in the duration of OAC decreased frequency of monitoring by18-fold (p<0.001).

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

The study comprised mostly of married adults with a mean age of 43 years. Majority of them were females (74%). This is consistent with other studies done in KNH (12,19). This female predominance is comparable to studies done elsewhere (39,27,19,51). Conversely, several studies in the USA, UK and Portugal have recorded a male majority (29,30,37,53).

Warfarin is used in the clinical setting for both prophylaxis and treatment of various thromboembolic disorders in patients with VTEs, atrial fibrillation and prosthetic or mechanical valves, among others (10). The major indication for anticoagulation in this study was deep venous thrombosis (72%) similar to other studies done in Kenya and Nigeria where VTEs predominated (39,19,40). In contrast, in different populations in other regions of the world like UK, USA, Portugal and China the most common indication for oral anticoagulation is atrial fibrillation (30,52,36,35). This variation is expected in different regions and populations as disease burden is varied.

The duration of time a patient has been on oral anticoagulation has an effect on the stability of INR as found in several studies (52,53). This study found that majority of the patients (80%) had been on oral anticoagulation for less than a year. This could be because a large proportion of the study participants had VTEs that required treatment for 3-6 months according to ACCP guidelines (4). These findings contrast a previous study done in KNH where about 70% had been on oral anticoagulants for more than a year (19). This difference could be attributed to the study methodology used. Our study, being retrospective, relied heavily on documented information, whereas the previous study was a cross-sectional study that interviewed ambulatory patients seen at the clinic. Poor documentation of vital information to this study such as initial and follow-up visits could have affected these results which would probably not be the case if this information was sought directly from the patients.

Some comorbidities further complicate the management of patients on warfarin as they influence INR (28–30). Moreover, these conditions increase the pill burden leading to pharmacodynamic and pharmacokinetic interactions with warfarin; thus posing a challenge to maintaining anticoagulation within therapeutic range (10). About 40% of the patients had comorbidities that would influence INR; the most prevalent comorbidity being HIV (16%) similar to a study done at MTRH (40). This was followed by hypertension (14%) and about 10% had cancer. In Ethiopia (51), majority (75%) of their patients on warfarin had comorbidities, the most prevalent being infectious diseases including HIV and TB (68%) followed by cardiovascular diseases (45%). This shows that both non-communicable and infectious diseases such as HIV continue to be a burden in our region. The higher disease burden among patients on warfarin in Ethiopia could be due to a difference in the study design which was a prospective cohort study on in-patients who are more likely to have several comorbidities than their counterpart outpatients who are ambulatory and more stable. On the other hand, a cohort study in the USA found the four most common comorbidities were hypertension (80%), diabetes (37%), heart failure (26%) and cancer (10%). It is evident that non-communicable diseases are the major burden in this region.

Drug interactions should be considered when co-prescribing medicines with warfarin as it is one of the common factors that affects INR control (27,30,54). About 95% of the participants were prescribed concurrent medications with the potential of interacting with warfarin. This high prevalence compares unfavorably with a previous study done in KNH by Kibiru *et al.* that found that only 21% were on medicines that could lead to interaction with warfarin (12). This marked disparity could be explained by a larger sample size in our study as well as participants that were both in-patients and outpatients compared to participants that were ambulatory, hence more stable in that previous study. Similar findings of extensive use of warfarin-interacting medicines was reported in Ethiopia, 99% (51) and Canada,79% (27). The most common concurrent medicines used were anticoagulants at 78%, followed by antibiotics (39%). This is expected as these anticoagulants are used in the initial management of thrombotic disorders to bridge warfarin therapy whereas concurrent antimicrobials could be explained by their common use in both the in-patient and outpatient setting for various infections including HIV

related opportunistic infections. Similarly, in Ethiopia antibiotics were the most prevalent concurrent medications (37%), followed by anticoagulants (24%) (51). In contrast, analgesics were the most commonly prescribed in Canada (40%) followed by antidepressants (25%) (27). In practice, clinicians should be aware of these interactions while prescribing to adequately counsel the patients to ensure safety and effectiveness of warfarin therapy.

The time in therapeutic INR as a measure of quality of anticoagulation has been used as a surrogate measure of outcomes such as thromboembolic and bleeding complications (7). The study participants maintained therapeutic INR levels 31% of the follow-up time. Similar figures that demonstrate suboptimal level of anticoagulation were found in studies in KNH (12), Nigeria and South Africa (39). One recent study in KNH that used the cross-section-of-files method of TTR determination recorded a slightly higher TTR of about 44% (19). Our study however, used the Rosendaal interpolation method which considers the follow-up time. Another study by Ogendo *et al*. on the other hand, recorded a much lower TTR (18%) (1). The differences in TTR could be because of implementation of recommendations made to improve the anticoagulation services in KNH. In contrast, patients followed up at Eldoret, Kenya attained better anticoagulation control comparable to many resource-rich countries with TTR levels of about 65% (40). This difference could be attributed to the presence of a dedicated anticoagulation clinic managed by pharmacists hence better patient care as compared to usual physician follow-up clinics in our setting. Studies done in similar follow-up clinics have comparable results (35,55). In these anticoagulation clinics patients are followed up more intensely, taken through detailed patient education counselling and standardized management protocols availed for dosage adjustment (40,35).

As in many studies with sub-optimal anticoagulation control (1,12) we found that patients were under-anticoagulated most of their follow-up time hence they are more predisposed to thromboembolic complications. This could be because clinicians are more concerned about the safety of warfarin (7) to avoid over-anticoagulation as bleeding is the most common complication of warfarin therapy, occurring in about 35% of the patients in KNH (9,11). These figures compare unfavorably with other studies where patients spent a

smaller proportion of follow-up time under-anticoagulated reflecting better quality of warfarin therapy in those centers (7,30,36). On the other extreme, one study done in Ethiopia found that more than half of the patients were over-anticoagulated while only about 13% had sub-therapeutic INR (51). However, the methodological differences could account for this disparity. The nearest INR values at the time of screening for drug interactions or bleeding were used to determine these proportions whereas the Rosendaal interpolation method was used in our study. The poor level of anticoagulation control in our setting illustrates the need for closer monitoring, better dosage adjustment and more intense patient education counselling so that there is maximum benefit from anticoagulation with minimal risk of thromboembolic and bleeding complications.

Only a fifth of the patients maintained an adequate anticoagulation level for 50% or more of their follow up time. Higher patient proportions were recorded elsewhere (7,56). A previous study in KNH on patients who have undergone heart valve surgery showed that only approximately 7% of them could maintain therapeutic INR for 50% or more of their follow-up time (1). In our study, the proportion of patients with prosthetic valves who were in therapeutic INR for 50% or more of their follow-up time was 12.9%. Although this proportion of patients is still low, it illustrates an improvement from the previous study. However, this further highlights the need to improve the anticoagulation control in all the patients as most them are at risk of thromboembolic and bleeding complications.

The recommended monitoring frequency for stable patients on VKA is every 4-6 weeks or longer whereas more frequent monitoring is required for those with complications and those in the initial phase of therapy according to the American College of Chest Physicians (ACCP) guidelines (4). Several studies have shown that frequent monitoring is associated with better TTR and improved safety and effectiveness of therapy with warfarin. In accordance with these guidelines, the cardiac unit of the KNH recommended monitoring at intervals of 6-8 weeks for patients whose INR is well controlled (1). However, the monitoring frequency for majority of the patients was inadequate just like in a previous study done in the same hospital (1). The median monitoring frequency among the participants was 18.5 days with monitoring mostly being done every 4-12 weeks. Although this is adequate monitoring for stable patients, our patients being in sub-

therapeutic INR levels most of the time, indicates the need for more frequent monitoring to stabilize their INR in therapeutic level. These findings contrast with those of patients at MTRH who had their INR monitored every 14 to 20 days and recorded better anticoagulation control, which was also attributed to their dedicated staff and institutional financial support (40). Frequent INR monitoring poses a great challenge to our population. The associated financial cost may not be within the reach of many (1,19) resulting in longer intervals between clinic visits, some lost to follow-ups and even defaulters. Setting up of anticoagulation clinics in the different County hospitals could improve monitoring of these patients, as costs such as transport and accommodation would be greatly reduced for those who live far.

Several factors are associated with poor INR control and these include younger age (29,30,52), female gender (19,30,36,52), comorbidities (7,52), interacting medicines (27,30), selected indications for anticoagulation (40) and shorter duration of OAC therapy (30,40).

Age below 65years was significantly associated with spending more time in sub-therapeutic INR levels while there was no significant difference in terms of adequacy of INR control for those 65 years of age and above. Comparable findings of younger age being associated with poor INR control has been demonstrated in several studies (29,30,52). However, the cut-off ages in these studies varied from below 45 to 65years. This was hypothesized to be related to poor medication compliance in one study (30). We did not find any association between poor anticoagulation and female gender contrary to several other studies (19,29,36,52).

There are conflicting results on the adequacy of INR control among the Muslim community. They significantly spent more time being over-anticoagulated compared to the Christians. Similarly, one study found an increased risk of supra-therapeutic INR levels among stable Muslim patients especially during the fasting month (57). On the contrary, another study concluded that fasting does not unfavorably affect the safety and efficacy of warfarin anticoagulation (58). Although the effect of diet change during fasting is varied, it is however important for those who are fasting to be more cautious

during these months to avoid the complications of over-anticoagulation especially among those that may not be medically stable.

The level of education significantly affected anticoagulation control. Those with secondary education and above spent significantly less time in supra-therapeutic level by 5.5%. This is comparable to the findings of one study which revealed better anticoagulation control in those with higher levels of education due to better understanding of the signs of poor INR control as well as drug interactions that could affect warfarin therapy compared to those with a lower level of education (19).

Renal dysfunction interferes with systemic clearance of warfarin hence patients with kidney disease are more likely to be out of therapeutic range (59). As compared to other studies (7,52), patients with renal dysfunction were less likely to be in therapeutic range during follow-up. Closer monitoring of these patients and appropriate dosage adjustment is therefore important to minimize risk of bleeding. Different studies have shown a variation in the comorbidities that affect anticoagulation including COPD, heart failure, cancer (30) liver dysfunction, diarrhea, fever (60) and HIV (40). Therefore, due to this variation there is need for closer follow-up of any patient with comorbidities to ensure they remain within therapeutic range.

Patients with DVT, prosthetic valves as well as those on anticonvulsants and corticosteroids significantly spent more of their follow-up time being under-anticoagulated. The independent predictors of sub-therapeutic INR levels after linear regression, were DVT, prosthetic valves and concurrent use of corticosteroids. Patients with DVT are therefore more likely to have recurring thrombosis due to poor INR control as found in one study (61) hence better INR control should be emphasized in this group. Patients with prosthetic valves did not significantly have better INR control than other patients but rather they increased their percentage time in sub-therapeutic level by 27.7% and decreased time in supra-therapeutic level by 13.3%. In contrast, other local studies revealed that patients with prosthetic valves had better anticoagulation control than other patients, and achieved higher TTR levels as they were found to be more knowledgeable, have a more stable disease and less interacting medicines (19,40). This disparity could be due to a difference in the cut-off therapeutic INR range. While they used a target range of

2-3 for those with prosthetic valves, we used 2.5-3.5 for this population hence affecting the proportion of patients within the therapeutic range.

Concurrent use of corticosteroids with warfarin significantly increased time in sub-therapeutic level by 18.2%. On the contrary, the findings of one study that evaluated the interaction between oral corticosteroids and warfarin showed that a majority of their patients were over-anticoagulated following corticosteroid administration (62). There is however little comparability with this study because their patients had good anticoagulation control and they excluded patients on any other drugs that could potentially interact with warfarin. Corticosteroids have the potential to increase the coagulability of blood (63,64) and depending on the nature of interaction, they can either increase or reduce the INR of patients on warfarin. While several studies (12,40,51) found no significant relationship between interacting drugs and anticoagulation control, others found different classes of drugs were associated with poor anticoagulation control including analgesics, lipid lowering drugs (30), beta blockers and calcium channel blockers (29). These variations could be due to different patient responses to medicines, emphasizing the need for adequate individualized patient education and counselling, careful assessment of concurrent drugs and appropriate prescribing and monitoring to minimize complications and adverse drug reactions.

Majority of the patients were outside the therapeutic range for more than 50% of the follow up time and this was significantly associated with congestive heart failure. CHF is a risk factor for over-anticoagulation as it interferes with the distribution of warfarin (65,60). Additionally, it activates the coagulation cascade and causes endothelial dysfunction by activating the neuroendocrine system (66). The proportion of patients less likely to be in therapeutic range on 50% or more of their follow-up time at Nursing Homes in the USA had a history of stroke (7). However, the comparability of these two studies is limited as their patient population was much older and were mainly on rehabilitation or long-term care.

The frequency of monitoring INR was significantly associated with the indication of warfarin therapy, duration on it, comorbidities and concurrent medicines. Patients who were more frequently monitored were DVT patients, those on short duration of warfarin

therapy (1-3 months), those with cancer, HIV and those on concurrent anticoagulants. On the other hand, those with valvular heart disease, prosthetic valves, on OAC for more than 12 months and concurrently on antiarrhythmics were significantly less frequently monitored. However, after linear regression, independent predictors of decreased frequency of monitoring were only valvular heart disease and duration of OAC. This finding is probably because after the initial period of warfarin therapy which is associated with both under-anticoagulation (67) and increased risk of bleeding (68), patients stabilize and need less frequent monitoring. This is further evidenced by the less frequent monitoring of patients with valvular heart disease which requires long-term warfarin therapy. This finding compares favorably with one local study at MTRH (40) that found that patients on warfarin for a longer duration were monitored less frequently. Another study (7) found that those on warfarin for longer duration were more likely to be in therapeutic range on 50% or more of their person days than those who were new to warfarin indicating stability of this group of patients.

5.2 Study limitations

There was risk of information bias as this was a retrospective study relying on information in patient files. Verification of the accuracy of the documented information was not possible. Also, it was prone to missing patient information if they had sought care outside KNH that was not documented.

Only the files that could be traced and were retrieved were analyzed. Hence eligible files that were not accessed could have had useful information for this study. However, this was minimized by taking a large sample size.

It was also not possible to assess other patient factors that may affect anticoagulation such as adherence to medication, diet, physical activity and genetic variability.

We used the Rosendaal Linear interpolation method that assumes a linear relationship between two consecutive results to determine TTR and is prone to underestimation of the overall results where extreme out-of-range results exist.

5.3 Conclusion

Anticoagulation control of patients followed up at KNH is sub-optimal. Time spent in therapeutic range for the patients was low with majority of them being under-anticoagulated most of the follow-up time. Renal dysfunction was associated with lower TTR values. Independent predictors of sub-therapeutic INR were DVT, prosthetic valves and concurrent use of corticosteroids whereas Muslims and those with primary education and below spent more time being over-anticoagulated than Christians and those with higher education level respectively.

Majority of the patients spent less than 50% of their follow-up time in therapeutic range and this was more likely in patients with congestive heart failure.

The frequency of monitoring INR was sub-optimal. Decreased frequency of monitoring was associated with valvular heart disease and long duration of anticoagulation

Therefore, there is need for closer monitoring of patients especially for those who are new to warfarin therapy, those with comorbidities as well as on other concurrent medications so that there is maximum benefit from warfarin anticoagulation with minimal risk of thromboembolic and bleeding complications.

5.4 Recommendations

5.4.1 Recommendations for policy and practice

Poor anticoagulation control was associated with those new to warfarin therapy, those with congestive heart failure and renal dysfunction, those on concomitant medicines, Muslim patients as well as those with lower level of education. More frequent monitoring and closer management should be done especially for these patients to ensure they are in therapeutic range most of their follow-up time.

One of the limitations was missing of clinical information in the patient files. In addition, some eligible files could not be traced. Documentation and filing system in KNH should be improved to ensure that the accuracy of results and findings of future retrospective studies is not compromised.

5.4.2 Recommendations for research

Further research to show the relationship between TTR and outcomes of warfarin therapy should be done for all indications of warfarin to establish the effect of TTR values on outcomes.

Research on provider and institutional factors associated with poor anticoagulation as well as the effect of genetic variability on anticoagulation control should be conducted as this was outside the scope of the current study.

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APPENDICES

Appendix 1: Eligibility criteria assessment form

Criteria	Yes=1 No=2
On warfarin therapy	
On warfarin for more than one month	
Has at least two INR readings	

If any of the above parameter is marked 2, the patient is not eligible for the study.

Appendix 2: Data collection form

Quality of oral anticoagulation management among patients followed up at Kenyatta National Hospital

1. Patient socio-demographics

Study serial number……..date [dd/mm/yy]……..

1.1) Age (years)……..

1.2) Weight (kg)…….

1.3) Sex……1.Male [ ] 2.Female [ ]

1.4) Marital status…. 1.Married [ ] 2. Single [ ] 3. Divorced [ ] 4. Separated [ ] 5. Widowed [ ]

1.5) Employment status…1. Employed [ ] 2. Self-employed [ ] 3.Unemployed [ ] 4. Student [ ]

1.6) Religion……1. Christian [ ] 2. Muslim [ ] 3. Other [ ] (specify)……

1.7) Education level……1.Informal [ ] 2. Primary [ ] 3. Secondary [ ] 4. College and above [ ]

1.8) Alcohol consumption…. 1. Yes [ ] 2. No [ ]

2. To determine the clinical characteristics of the patient (tick as appropriate)

2.1 Date started on anticoagulation……..

2.2 Indication for anticoagulation……. 1.DVT [ ] 2.PE [ ] 3. Thrombophilia [ ] 4.Valvular heart disease [ ] 5. Atrial fibrillation/flutter [ ] 6.Congestive Heart Failure [ ] 7. Stroke or CVA [ ] 8.Prosthetic Valve [ ] 9.Other [ ] (specify)……

2.3 Indicate in the table below if patient has comorbidities that may influence INR

Disease	Tick as appropriate	Duration of illness
[1] Diabetes Mellitus		
[2] Hypertension		
[3] Thyroid dysfunction		
[4] Liver failure		
[5] Renal dysfunction		
[6] Cancer		
[7] HIV		
[8] Other (specify)……		

3. Drug-drug interactions: Indicate in the table below if the patient has ever used/is using any of the mentioned drugs that may interact with warfarin

Drug class	Tick if used/using	Specify drug name(s)	Daily dose (mg)	Duration of use(days)
Antimicrobials				
[1] Antibacterials				
[2] Antifungal				
[3] Antivirals				
Analgsesics				
[4] NSAIDS				
[5] Opioids				
[6] Other (specify)				
CNS drugs				
[7] Anticonvulsants				
[8] Other (specify)				
Cardio.Drugs				
[9] Antiarhythmics				
[10] Statins				
[11]Fibric acid derivative				
[12] Bile acid sequestrant				
[13] Other (specify)				
Antithrombotics				
[14] Thrombolytics				
[15] Anticoagulants				
[16] Antiplatelets				
Immune-suppresant				
[17] Corticosteroids				
Metabolic and endocrine				
[18] Antithyroid				

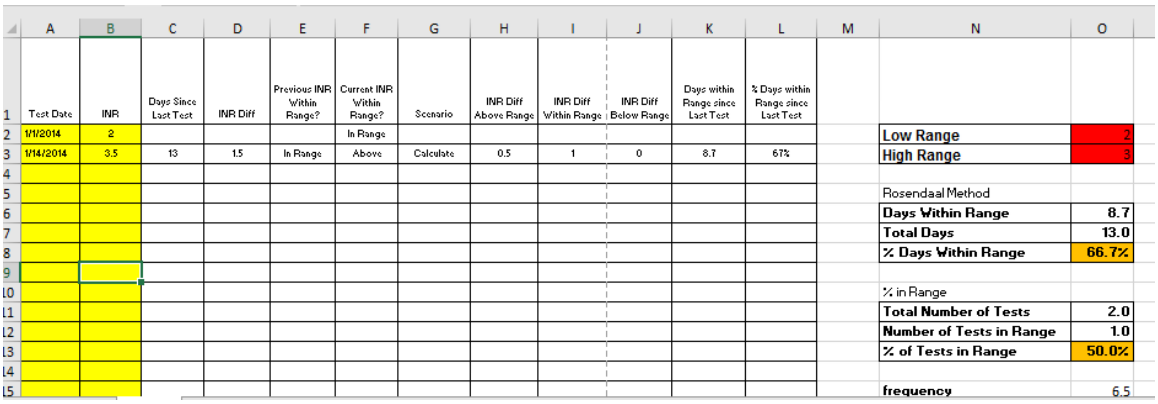
Gastrointestinal				
[19]Proton pump inhibitor				

4. To determine the duration of time spent in therapeutic INR and frequency of INR monitoring.

Indicate the date the INR test was done and the value between the period January 2014 and June 2016

INR reading	Date	INR value
Reading 1		
Reading 2		
Reading 3		
Reading 4		
Reading 5		
Reading 6		
Reading 7		
Reading 8		
Reading 9		
Reading 10		
Reading 11		
Reading 12		
Reading 13		
Reading 14		
Reading 15		

Appendix 3: Rosendaal Method for TTR computation.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	Test Date	INR	Days Since Last Test	INR Diff	Previous INR Within Range?	Current INR Within Range?	Scenario	INR Diff Above Range	INR Diff Within Range	INR Diff Below Range	Days within Range since Last Test	% Days within Range since Last Test			
2	1/1/2014	2				In Range								Low Range	2
3	1/14/2014	3.5	13	1.5	In Range	Above	Calculate	0.5	1	0	8.7	67%		High Range	3
4															
5														Rosendaal Method	
6														Days Within Range	8.7
7														Total Days	13.0
8														% Days Within Range	66.7%
9															
10														% in Range	
11														Total Number of Tests	2.0
12														Number of Tests in Range	1.0
13														% of Tests in Range	50.0%
14															
15														frequency	6.5

Steps

1. Enter the therapeutic INR target depending on the patient and indication for anticoagulation in the red cells: both the low range and high range
2. Enter the INR test dates for each INR and the result in the yellow cells
3. Calculate amount of the total shift (2.0 to 3.5 = 1.5 increase) that is within the therapeutic range (1.0 of shift is within range, [3.0 - 2.0 = 1.0])
4. Calculate percent of total shift within therapeutic range (L) (1/1.5 = 66.7%)
5. Estimate number of days since last visit that were within range (K) (66.7% x 13 days since last visit = 0.667 x 13 = 8.67= 9 days within range, 4 days out of range) (L*C) Percentage for that time period is 66.7% in range, and 9 total days in range.
6. Calculate overall % in range (TTR): add total days in range for each time period, and divide by total therapeutic days (sum K/sum C): 8.67/13= 66.7%

Appendix 4: Ethical approval letter

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
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Ref: KNH-ERC/A/123

8th April, 2016

KENYATTA NATIONAL HOSPITAL APPROVED 08 APR 2016 KNH/UoN-ERC P.O. Box 20723-00202 NAIROBI

Salome Wanjiru Karuri
Reg. No. U56/75585/2014
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Salome,

Revised Research Proposal: Quality of Oral Anticoagulation Management among Patients Followed up At Kenyatta National Hospital (P65/02/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and approved your above proposal. The approval period is from 8th April 2016 – 7th April 2017.

This approval is subject to compliance with the following requirements:

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

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

Yours sincerely,

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

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. David G. Nyamu, Dr. Sylvia A. Opanga, Dr. Tom B. Menge

Appendix 5: Institutional letter of authorization.

INTERNAL MEMO
KENYATTA NATIONAL HOSPITAL

OFFICE OF THE ASSISTANT DIRECTOR - HEALTH INFORMATION

Ref: KNH/HI/20/VOL.1 Thursday, March 17, 2016

TO: KNH/ERC

Dear Prof. Chindia,

PERMISSION FOR DR. SALOME WANJIRU KARURI TO USE DATA FROM KNH RECORDS DEPARTMENT

Your letter Ref: KNH-ERC/RR/168 dated 3rd March, 2016,

This is to certify that Dr Karuri will be allowed to use our data in KNH Records Department to carry out a study titled "Quality of oral anticoagulation management among patients followed up at Kenyatta National Hospital",

Dr Karuri will only be allowed to use the data after she has acquired the necessary ethical approval.

Yours Sincerely,

Gachoka Kiongo
For AD- Health Information Services

Appendix 6: List of concomitant drugs

Drug	n	Percentage
Antibiotics		
Cotrimoxazole	47	11.6
Ceftriaxone	22	5.4
Augmentin	19	4.7
Cefuroxime	15	3.7
Flucloxacillin	11	2.7
Rifampicin/Isoniazid/ Pyrizinamide/Ethambutol	10	2.5
Clarithromycin	6	1.5
Benzathine penicillin	4	1.0
Ciprofloxacin	4	1.0
Clindamycin	3	0.7
Levofloxacin	2	0.5
Meropenem	2	0.5
Metronidazole	2	0.5
Rifampicin/Isoniazid	2	0.5
Amoxicillin	1	0.2
Cefotaxime	1	0.2
Ceftazidime	1	0.2
Vancomycin	1	0.2
Nitrofurantoin	1	0.2
Antifungals		
Fluconazole	8	2.0
Itraconazole	1	0.2
Nystatin drops	1	0.2
Antivirals		
TDF/3TC/EFV	25	6.2
AZT/3TC/NVP	12	3.0
AZT/3TC/EFV	5	1.2
TDF/3TC/NVP	5	1.2
Acyclovir	3	0.7
ABC/3TC/EFV	2	0.5
Analgesics		
Tramadol	89	21.9
Diclofenac	43	10.6
DF118	20	4.9
Ibuprofen	3	0.7
Morphine	3	0.7
Meloxicam	2	0.5
Celecoxib	1	0.2

Methadone	1	0.2
Pethidine	1	0.2
PCM	1	0.2
Anticonvulsants		
Carbamazepine	5	1.2
Phenytoin	5	1.2
Diazepam	1	0.2
Antidepressants		
Amitriptyline	1	0.2
Antiarrhythmics		
Digoxin	67	16.5
Amiodarone	2	0.5
Lipid-lowering agents		
Atorvastatin	20	4.9
Antithrombotics		
Enoxaparin	172	42.4
Heparin	144	35.5
Junior Aspirin	12	3.0
Clopidogrel	2	0.5
Rivaroxaban	1	0.2
Corticosteroids		
Prednisolone	12	3.0
Dexamethasone	5	1.2
Proton Pump Inhibitors		
Omeprazole	103	25.4

Appendix 7: Factors associated with spending less than 50% of follow up time in therapeutic INR

Variable	Patient proportion			
	TTR<50% of time n (%)	**TTR>=50% of time n (%)**	**OR (95% CI)**	**P value**
Age				
0-18 Years	20 (74.1)	7 (25.9)	0.9 (0.3-28)	0.836
19-35 years	96 (80.0)	24 (20.0)	1.2 (0.5-3.0)	0.627
36-65 years	174 (78.7)	47 (21.3)	1.2 (0.5-2.6)	0.738
>65years	29 (76.3)	9 (23.7)	1.0	
Gender				
Male	84 (80.0)	21 (20.0)	1.1 (0.6-2.0	0.679
Marital status				
Married	178 (77.7)	51 (22.3)	0.9 (0.6-1.4)	0.891
Employment status				
Employed	210 (76.9)	63 (23.1)	0.7 (0.4-1.2)	0.247
Religion				
Christian	311 (78.5)	85 (21.5)	0.9 (0.2-4.4)	0.911
Educational level				
Primary and below	173 (81.6)	39 (18.4)	1.5 (0.9-2.4)	0.114
Alcohol consumption	35 (77.8)	10 (22.2)	1.0 (0.5-2.0)	0.891
DVT	232 (78.9)	62 (21. 1)	1.1 (0.7-1.9)	0.721
PE	29 (70.7)	12 (29.3)	0.6 (0.3-1.3)	0.197
Valvular heart disease	19 (67.9)	9 (32.1)	0.5 (0.2-1.3)	0.230
Atrial fibrillation	21 (75.0)	7 (25.0)	0.8 (0.3-2.0)	0.633
Congestive Heart Failure	14 (100.0)	0	-	**0.047**
Thrombophilia	3 (100.0)	0	-	1.000
Prosthetic valves	27 (87.1)	4 (12.9)	1.9 (0.6-5.6)	0.229
Stroke	1 (50.0)	1 (50.0)	0.3 (0-4.4)	0.383

Duration of OAC use				
1-3 months	147 (78.6)	40 (21.4)	1.1 (0.6-2.0)	0.840
4-12 months	110 (78.1)	29 (20.9)	1.1 (0.6-2.1)	0.776
>12 months	62 (77.5)	18 (22.5)	1.0	
Frequency of monitoring				
<7 Days	57 (93.4)	4 (6.6)	2.4 (0.2-24.8)	0.470
7-14 days	78 (75.0)	26 (25.0)	0.5 (0.1-4.3)	0.530
15-30 Days	87 (73.7)	31 (26.3)	0.5 (0.1-4.0)	0.490
31-90 Days	91 (78.4)	25 (21.6)	0.6 (0.1-5.3)	0.651
91-180 Days	6 (85.7)	1 (14.3)	1.0	
Comorbidities				
Diabetes	5 (33.3)	10 (66.7)	1.9 (0.6-5.7)	0.331
Hypertension	13 (22.4)	45 (77.6)	1.1 (0.6-2.1)	0.863
Thyroid dysfunction	0	1 (100.0)	-	1.000
Liver failure	0	1 (100.0)	-	1.000
Renal dysfunction	1 (5.6)	17 (94.4)	0.2 (0-1.6)	0.139
Cancer	8 (19.0)	34 (81.0)	0.9 (0.4-1.9)	0.843
HIV	16 (25.4)	47 (74.6)	1.3 (0.7-2.4)	0.406
Others	1 (16.7)	5 (83.3)	0.7 (0.1-6.3)	1.000
Concurrent medicines				
Antibacterial	35 (23.0)	117 (77.0)	1.2 (0.7-1.9)	0.544
Antifungal	2 (20.0)	8 (80.0)	0.9 (0.2-4.4)	0.911
Antiviral	12 (23.5)	39 (76.5)	1.2 (0.6-2.3)	0.696
NSAIDS	7 (14.3)	42 (85.7)	0.6 (0.3-1.3)	0.194
Opioids	23 (20.4)	90 (79.6)	0.9 (0.5-1.6)	0.743
Paracetamol	0	2 (100.0)	-	0.459
Anticonvulsants	1 (9.1)	10 (90.9)	0.4 (0.1-2.9)	0.312
Antidepressants	0	1 (100.0)	-	1.000
Antiarrhythmics	13 (18.8)	56 (81.2)	0.8 (0.4-1.6)	0.565
Statins	3 (15.0)	17 (85.0)	0.6 (0.2-2.2)	0.472
Anticoagulants	73 (23.0)	244 (77.0)	1.6 (0.9-3.0)	0.138
Antiplatelets	2 (14.3)	12 (85.7)	0.6 (0.1-2.7)	0.743