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WARFARIN MANAGEMENT PRACTICES AND OUTCOMES IN AMBULATORY PATIENTS AT KENYATTA NATIONAL HOSPITAL

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STUDENT'S DECLARATION

I hereby confirm that this is my original work and to the best of my knowledge has not been submitted elsewhere for examination. All resources and materials used or quoted have been indicated and acknowledged by means of reference.

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DEDICATION

I lovingly dedicate this work to my husband, Duncan Mwanzia and my daughter Hailey Mueni Mwanzia. Special dedication goes to my parents Mr. Francis Kibathi and Dr. Mary Kiarie, my sisters Irene Kibathi and Dr. Grace Kibathi who have stood by me through prayer and have been a great source of encouragement.

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LIST OF ABBREVIATIONS

OAT	Oral anticoagulant
AMS	Anticoagulation Management Services
VKA	Vitamin K Antagonist
INR	International Normalized Ratio
AF	Atrial Fibrillation
DVT	Deep Venous Thrombosis
PE	Pulmonary Embolism
VTE	Venous Thromboembolism
KNH	Kenyatta National Hospital
TTR	Time in Therapeutic Range
ISTH	International Society of Thrombosis and hemostasis
ACCP	American College of Chest Physicians
BSH	British Society of Hematology
PI	Principal investigator

ABSTRACT

Background: Thrombosis is a major public health problem that is associated with considerable morbidity and mortality. Warfarin is one of the most frequently used oral anticoagulants in Kenya to manage and prevent thrombosis [1]. Warfarin safety and efficacy depend on proper dosing, careful monitoring, patient education and maintaining INR within an optimal therapeutic range. Improvement in quality of warfarin management requires understanding of management practices and outcomes which this study set out to explore.

Objectives: The objective of this study was to determine the adequacy of anticoagulation control using time in therapeutic range (TTR). The study also aimed to describe warfarin management practices, their association with TTR and to determine the relationship between TTR and thrombotic and bleeding complications in ambulatory patients at Kenyatta National Hospital (KNH).

Methods: This study was a retrospective cohort study of warfarin-treated patients in the calendar year 2019 at cardiology, hematology and cardiothoracic clinics at KNH. The study had 2 sources of data; data on INR values, frequency of monitoring and dose adjustment were extracted from patient files and data on knowledge and complications was captured from interviewing patients. All these retrospective data was collected between August 2021 and October 2021. Data analysis was done using SPSS version 23.0. Statistical significance was interpreted at 5% level of significance.

Results: We recruited 146 patients. Majority (67.8%) were female with mean age of 46.6 years. Most common indication of warfarin therapy was VTE at 41%. The mean TTR was 43.6% with 71.2% of patients maintaining TTR of <60%. Median monitoring frequency was 73 days. Majority (54.1%) had inappropriate dosage adjustment. Only 19.2% had adequate knowledge on anticoagulation. The most common complication was bleeding at 34.2% while thrombosis occurred in 12.3%. Patients who had poor control were 2.9 times more likely to bleed than those with good control. Patients who had inappropriate dosage adjustment were 2.4 times more likely to have poor anticoagulation control.

Conclusion: Majority of patients on warfarin had poor anticoagulation control. Patients had inadequate monitoring frequency and poor knowledge on warfarin. Inappropriate dosage adjustment was a predictor of poor anticoagulation control. Bleeding complications were the most common complication of warfarin therapy and this was significantly associated with poor anticoagulation control.

1.0 CHAPTER ONE: INTRODUCTION

1.1 Background

Thromboembolism prevention is an important health issue. Thrombotic conditions namely, deep vein thrombosis (DVT) and pulmonary embolism (PE), affect a large proportion of the population. Thromboembolic conditions were estimated to account for 1 in 4 deaths globally according to the Global Burden of Disease study 2010 [2].

Atrial fibrillation (AF) and prosthetic heart valves that predispose patients to stroke and systemic embolism also have a high incidence. Globally, AF has a yearly incidence rate of 77.5 per 100,000 in males and 59.5 per 100,000 in females [2]. A study done in South Africa showed AF annual incidence rate of 5.6 cases/100,000 population [3]. There is a four to fivefold increase in stroke risk in patients with AF [4].

Rheumatic valvular heart disease has a higher prevalence in Africa with several patients requiring valve replacement surgery [5]. They often develop AF as a complication and have increased risk of thromboembolism. Without anticoagulation, patients with AF have a thrombosis risk of approximately 23% annually. With effective anticoagulation, there is reduction of risk to 1–2% [6]. For prevention of embolism in prosthetic heart valves and AF patients, warfarin is commonly used [7,8].

Patients with venous thromboembolism (VTE) similarly require anticoagulation to minimize the risk of complications. Global incidence rate of VTE is 115-269 per 100 000 annually [2].

In Kenya, warfarin is the most widely available and affordable anticoagulant [1] that is utilized for management of VTE [9], AF and following cardiac valve surgery[1]. Certain patient populations still need warfarin even with the advent of direct oral anticoagulants (DOACs). These include patients who have; AF as a complication of moderate or severe mitral stenosis, mechanical heart valves[10], end-stage renal disease with or without dialysis [11] and/or cannot afford the higher cost of the DOACs.

Warfarin remains an effective anticoagulation option despite a wide interpatient dosing variability, narrow therapeutic index, frequent monitoring and tendency to drug and dietary interactions [12].

Bleeding risk increases by spending more time above therapeutic range while thromboembolic complication risk increases by spending more time below the INR therapeutic range. In a large UK study in 2004, warfarin was ranked third among medications that result in hospital admissions due to their harmful effects on their utilization [13].

Optimum management of patients on warfarin is vital in minimizing the complications of bleeding and under-treatment. Improvement in quality of warfarin management requires understanding of current management practices and outcomes. Significant outcome measures for patients on anticoagulation are bleeding [14] and clinically verified venous or arterial thrombosis.

A measure of warfarin management quality is used to determine how well a certain system is effectively offering care [8,15]. The Rosendaal method is frequently used to calculate TTR, that is, an INR therapeutic range between 2.0 and 3.0 for AF and VTE and 2.5-3.5 for prosthetic heart valves [16]. TTR is a vital measure to assess efficacious warfarin therapy [17–19]. Maximizing TTR plays the greatest role in preventing stroke, thromboembolism, hemorrhage, or death [16,20].

The American College of Chest Physicians (ACCP) gave recommendations and guidelines on initiation, adjusting of dose and warfarin monitoring in the ambulatory setting [6,8,21,22]. Strategies and recommendations are provided in the guidelines to assist providers to develop warfarin management plans. Key guidance includes, recommendations for target INR ranges depending on indication, dose of warfarin depending on individual INR response, dietary and drug interactions. It further recommends use of standardized and validated decision support tools in warfarin dosing. Use of standardized guidelines and dosing decision support tools is associated with better anticoagulation control and outcomes [8].

The British Society of Hematology (BSH) also provides similar guidelines on indications for warfarin, target INR for the various indications, guidelines for management of supra-therapeutic and sub- therapeutic INR, vitamin K uses, doses and indications [23].

Even with these guidelines, management of warfarin therapy is suboptimal in many cases [24–26]. Despite proven benefits of adhering to guidelines, there is wide variability in dose adjustment and frequency of INR monitoring [24]. Furthermore, patients' knowledge of warfarin is scanty. This may have affected the anticoagulation control at Kenyatta National Hospital (KNH) [27] . For most favorable management, it is recommended that anticoagulation be instituted via anticoagulation clinics which is lacking at KNH.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 Thrombosis Burden

Atrial fibrillation (AF), the global arrhythmia epidemic [28], is associated with considerable mortality and morbidity, due to heightened risk of systemic embolism and ischemic stroke [29,30]. The prevalence of AF in Africa is high due to a double burden of valvular and non-valvular AF [31]. In a Kenyan study, patients who had non-valvular and valvular AF had annual stroke rates of 5% [32]. According to unpublished KNH morbidity data, approximately 380 patients had AF diagnosis in the past 5years (2015-2019).

Warfarin is commonly used in AF for prevention of systemic embolism and ischemic stroke. In clinical trials, warfarin was shown to reduce the yearly risk of ischaemic stroke and mortality by 70% and 33% respectively while increasing yearly bleeding risk slightly (from 1.0% to 1.3%) [33,34]. During warfarin therapy for AF, the stroke risk is dependent on INR. Stroke risk increases exponentially with an INR below 2.0 [35].

Venous thromboembolism (VTE) includes two serious medical conditions, DVT and PE with annual incidence rate of 1-2 per 1000 individuals globally. One in four deaths globally is due to VTE [36] . According to KNH unpublished morbidity data, approximately 1360 patients had a diagnosis of DVT and 520 had PE in the period 2015 to 2019.

Despite anticoagulant therapy, VTE frequently recurs at a rate of 7% during the initial 6 months following the first event [37]. Pulmonary embolism accounts for 14.2% of cardiovascular deaths in Kenya [38]. Warfarin is commonly used in management of these patients with INR target of 2.0.

Anticoagulation also forms an essential part in prosthetic heart valves management. Rheumatic heart disease, the predominant etiology necessitating valve surgery, has a high prevalence in Africa [39].

2.2 Warfarin Management Guidelines

The ACCP in 2012 and updates in 2016 provided guidelines for managing warfarin therapy [8,12,21,22]. These guidelines are consistent with the previous recommendations of the British Society of Hematology(BSH), 2011 [23].

The guidelines provide recommendations for initiation, dose adjustment and warfarin therapy monitoring in the ambulatory setting.

The objective of the guidelines was to standardize warfarin therapy management while offering individualized assessment. The guidelines are meant to guide clinicians in developing warfarin management strategies [12].

In the ACCP guidelines, warfarin is recommended first line in valvular AF and mechanical heart valves. In VTE and non-valvular AF patients, DOACs are recommended over warfarin [22]. However, due to the prohibitive costs of DOACs, it is likely that warfarin use will continue in resource limited settings and the requirement for proper warfarin monitoring and dosing will persist [40].

2.3 Warfarin Dosing Considerations

Guidelines recommend use of validated warfarin dosing decision support tools and dosing algorithms as opposed to no decision support [12]. Therapeutic anticoagulation for the various indications according to the ACCP guidelines and consistent with BSH guidelines is as shown in Table 1;

Table 1: Indications for Warfarin, INR Ranges, and Duration of Therapy

Indication	INR (Range)	Duration	Comments
Atrial fibrillation CHA2DS2VASc>1 Intermediate/high stroke risk	**2.5 (2-3)**	Chronic	
Thromboembolism (DVT,PE)			
Provoked VTE event	2.5(2-3)	3 Months	
Unprovoked 1st VTE event			
Proximal or distal DVT	2.5 (2-3)	3 Months	After 3 months evaluate risk benefit of extended therapy
PE	2.5 (2-3)	>3months	After 3 months evaluate risk benefit of extended therapy
Unprovoked 2nd VTE event			
DVT or PE	2.5 (2-3)	Chronic	
With malignancy	2.5 (2-3)	>3 months	LMWH preferred over warfarin. Consider chronic
Acute upper extremity DVT	2.5 (2-3)	3 months	
Valvular disease			
Rheumatic mitral valve disease			
-Left atrial diameter <55mm	None		
-with AF, left atrial thrombus, or left atrial diameter > 55mm	2.5 (2-3)	Chronic	
Valve replacement- Mechanical			
Aortic	2.5(2-3)	Chronic	
Mitral	3(2.5-3.5)	Chronic	
Dual Aortic and Mitral Valve	3(2.5-3.5)	Chronic	

Based largely on the ACCP guidelines and consistent with current recommendations of the BSH [22,23].

Table 2 shows an example of a dosing adjustment algorithm that shows use of one tablet strength and alternating multiples or fractions of it on certain days of the week [41]. Warfarin doses can be adjusted by adding or subtracting 5 to 20% to the cumulative weekly dose and distributing that evenly over the week [41]. Weekly dosage changes algorithms to achieve an INR of 2-3 are presented in Table 3 and INR 2.5-3.5 in Table 4 [12].

Table 2:Warfarin Dosing Adjustment Algorithm using One Tablet Strength (5mg)[41]

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Total weekly dosage	Approximate adjustment (%)
1 tablet	0.5 tablet	1 tablet	0.5 tablet	1 tablet	0.5 tablet	1 tablet	27.5 mg	–20
1 tablet	0.5 tablet	1 tablet	1 tablet	1 tablet	0.5 tablet	1 tablet	30 mg	–15
1 tablet	0.5 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	32.5 mg	–5
1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	35 mg	0
1 tablet	1.5 tablets	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	37.5 mg	+5
1 tablet	1.5 tablets	1 tablet	1 tablet	1 tablet	1.5 tablets	1 tablet	40 mg	+15
1 tablet	1.5 tablets	1 tablet	1.5 tablets	1 tablet	1.5 tablets	1 tablet	42.5 mg	+20

Warfarin dose adjustment is based on INR readings, symptoms of bleeding or clotting and consideration of any drug and dietary interactions, missed doses and recent INR trends [8,12].

Table 3: Warfarin Maintenance Dosing Protocol with INR Goal 2-3 [6,8]

INR<1.5	**INR 1.5-1.9**	**INR 2.0-3.0**	**INR 3.1-4.0**	**INR 4.1-5.0;no significant bleeding**	**INR 5.1-9.0; no significant bleeding**	**INR >9; No significant bleeding**
-Extra Dose -Increase weekly dose 10-20% -More frequent monitoring	-Increase weekly dose 5-10% -More frequent monitoring	**No change**	Decrease weekly dose 5-10%	-Hold 1 dose -Monitor more frequently -Decrease weekly dose 10%	Consider: -Hold 2 doses -Monitor more frequently -Decrease weekly dose 10-20% -Suggest against routine use of vitamin K If at increased risk of bleeding, give Vitamin K 1-2.5mg PO.	-Hold Warfarin Therapy -give Vitamin K 2.5-5mg PO -Monitor more frequently -resume therapy at an appropriately adjusted dose when INR is therapeutic.

Table 4. **Warfarin Maintenance Dosing Protocol with INR Goal 2.5-3.5** [6,8]

INR<1.9	**INR 1.9-2.4**	**INR 2.5-3.5**	**INR 3.6-4.5**	**INR 4.6-5.0**	**INR 5.1-9.0**	**INR>9.0**
Extra dose Increase weekly dose 10-20%	Increase weekly dose 5-10%	No change	Decrease weekly dose 5-10%	Hold 1 dose Decrease weekly dose 10%	Consider : Hold 2 doses Decrease weekly dose 10-20%	-Hold Warfarin Therapy -give Vitamin K 2.5-5mg PO -Monitor more frequently -resume therapy at an appropriately adjusted dose when INR is therapeutic.

Proper management of the doses is required to reach and sustain a therapeutic INR range [6,42]. Fenta et al in Ethiopia found the quality of warfarin dosing to be suboptimal. In only 50% of cases in patients with target INR of 2.0-3.0 and 36.9% in patients with target of 2.5-3.5, were warfarin doses adjusted for the days following occurrence of out of range INR [24].

The association between TTR, warfarin dosing practices and clinical outcomes was analyzed in Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial. Adherence to doing algorithms predicted improved TTR [43].

In a study done in an American institution, educating primary care physicians on evidence-based warfarin management guidelines and use of dosing algorithms resulted in a reduction in warfarin related adverse drug reactions from 3.8 to 0.98% ($p < 0.0001$) and an increase in TTR from 56% to 65% [44]. There was also reduction in total and average cost associated with severe adverse drug reactions associated with warfarin therapy by 57.6% and 20.3% respectively.

Yet another study to determine how warfarin dose management patterns contributed to TTR showed that, patients whose doses were adjusted appropriately achieved the best INR control [45].

2.4 INR Monitoring

Managing patients on warfarin therapy requires close monitoring using INR to maintain anticoagulation within the therapeutic range.

Table 5 and 6 shows recommendations for INR monitoring when initiating warfarin therapy and during warfarin maintenance therapy, respectively.

Table 5: Frequency of INR monitoring after initiation of warfarin [12]

INR Check	
Every 2-3 days	Until INR within therapeutic range on 2 consecutive INR checks
Then every week	Until INR within therapeutic range on 2 consecutive INR checks
Then every 2 weeks	Until INR within therapeutic range on 2 consecutive INR checks
Then every 4 weeks	When dose is stable check monthly

Table 6: Frequency of INR Monitoring for Maintenance of Warfarin [12]

INR Check	
After 1 week	If start/ stop interacting medication, change in diet, change in activity level or other change that could affect INR
Every 1-2 weeks	If dose needed adjustment by 5-10%
Every 4 weeks	If patient maintained on same stable dose < 6 months
Every 12 weeks	If patient maintained on same stable dose for at least 6 months

The INR monitoring frequency is influenced by the dosage-adjustment quality, adherence, use of or stopping of interacting drugs, diet adjustments and whether the patient has had stable INRs [6,45,46].

A study done in Ethiopia by Fenta et al in 2017 found that the quality of warfarin management was suboptimal due to longer than recommended INR monitoring frequency [24].

2.5 Patient Education

Warfarin can cause serious adverse effects when patient's knowledge on warfarin therapy is inadequate [47].

A patient's warfarin knowledge level plays a crucial role in successful warfarin use. According to the Joint Commission International (JCI) National patient Safety Goal (NPSG) 2014 guidelines, educating patients taking oral anticoagulants was found to be an important factor [48]. Important elements that form the basis of a detailed warfarin education program are listed in Table 7 [49].

Table 7: Key elements of patient education regarding warfarin[49]

- Purpose of therapy
- Expected duration of therapy
- Dosing and administration
- What to do in case of missed dose
- INR monitoring importance
- Recognition of symptoms and signs of bleeding
- Recognition of symptoms and signs of thromboembolism
- What to do if bleeding or thromboembolism happens
- Recognition of symptoms and signs of disease states that influence warfarin dosing requirements
- Potential for interaction with prescription and OTC medications and herbal products
- Dietary considerations and alcohol use
- Significance of informing other healthcare providers that warfarin has been prescribed
- When, where and with whom follow up will be done

Educating patients on the above elements of warfarin therapy is an important aspect of management and has been shown to reduce adverse events and improve TTR, thus reducing hospitalizations [50,51]. In a local study, inadequate knowledge was reported in 80% of patients on warfarin therapy [51].

A positive relationship has been reported in studies between INR in the therapeutic range and patients' warfarin knowledge [52–54]. One study found a correlation between bleeding risk and inadequate warfarin education [55]. Providing sufficient warfarin education reduces potential complications and improves patients' attitude and medication adherence [56].

According to ACCP guidelines, patients and care givers should be educated on use of warfarin at therapy initiation and periodically after that [12,57].

Educating the patient is one of the most important responsibilities of the clinician. With the aim of assessing patient education levels on warfarin therapy and investigating whether a patient's education may potentially affect anticoagulation control, a questionnaire on Oral Anticoagulation Knowledge (OAK) Test will be used [58]. This will bring awareness to knowledge gaps among patients.

Few validated anticoagulation knowledge tests exist for assessing patient knowledge on warfarin therapy [58–60]. The OAK test is a reliable and validated tool to assess anticoagulation knowledge in routine clinical practice. It has been used in other similar studies and has been found to be suitable in identifying gaps in patient education [58]. In one study, 62% of patients with overall score of at least 75% in the OAK test, which was considered satisfactory, had therapeutic INR in comparison to 20% of those having inadequate knowledge [53].

Anticoagulation knowledge will be assessed using fifteen multiple choice questions derived from the OAK test [58] as has been done in a similar local study [9].

2.6 Bleeding and Thrombotic Complications in Relation to TTR

In a UK study, warfarin was ranked in third place amongst the medications leading to hospital admissions due to their deleterious consequences on their use [13]. Bleeding stands as the commonest complication of warfarin treatment, occurring in 6-39% of patients yearly [7,61]. Bleeding incidence is associated with the anticoagulation intensity. In one study in patients on warfarin, time spent in supratherapeutic range caused 26% of the bleeding events [62].

Thrombotic complications can occur during warfarin therapy if target anticoagulation control is not achieved. Recurrent VTEs occurred at a rate of 10.7% in one study [63] and 11% in another study in patients managed with warfarin [62]. In another study, cumulative incidence of thromboembolic events while on anticoagulant therapy at 1,3,12 and 24 months was 2.3%, 5.0%, 7.4% and 13.1% respectively [64].

Factors influencing the rate of bleeding and thrombotic complications while on warfarin include; intensity of anticoagulation, duration of therapy, indication for anticoagulation, concomitant drug therapy and the quality of dose management [12].

Table 8 shows studies that have been done showing the association between bleeding and thrombotic outcomes and TTR.

Table 8: Summary of studies on bleeding and thrombotic outcomes in relation to TTR

Study	Study design	Study participants	Findings
Van Walraven et al [62]	Retrospective cohort study	10,020 patients on warfarin	Time spent above target INR range (14.2%) accounted for 26% of hemorrhagic events and time below the target range (26.7%) accounted for 11% of thromboembolic events.
An Jaejin et al [65]	Retrospective cohort study	32,074 NVAF patients	The lowest TTR quartile (< 46%) was associated with a 3 times higher risk of stroke or systemic embolism and a 2 times higher risk of major bleeding compared with the highest TTR quartile (≥ 73%).
White HD et al [66]	SPORTIF III-open label SPORTIF V-double blind RCT	3587, AF patients randomized to receive warfarin	Patients with poorest INR control (48% of time in range) had twice the rate of stroke, myocardial infarction, major bleeding, and death as did the one-third with the best INR control (83% of time in range).
Willey VJ et al [63]	Retrospective cohort study	2090 VTE patients	Patients maintained TTR of 37.7%. Recurrent VTE events and bleeding requiring hospitalization-were experienced by 10.7% and 5.8% of patients, respectively.

2.7 Time in Therapeutic Range (TTR)

The association between anticoagulation intensity and risk of bleeding and thrombosis has been assessed by examining the rate of such complications as a function of the TTR [42,66,67]. A robust association between frequency of thrombotic and bleeding events and TTR has been found in many studies [35,68–70].

It is recommended that TTR be used as a measure of warfarin management outcomes and efficiency of anticoagulation clinics [6,71]. The BSH and ACCP guidelines recommend that TTR should be at least 60% for optimal anticoagulation [6,23].

TTR may be derived using three methodologies, so comparing studies may be hard [71] The three methodologies commonly used to calculate TTR are; fractions of INRs in range, Rosendaal method and point prevalence.

Rosendaal method assumes that a linear relationship exists between two INR values and allocates a specific INR value to each day between tests for each patient.

Advantages and disadvantages exist for each approach [71].

Table 9: Advantages and Disadvantages of Methods to derive TTR

Method	Advantages	Disadvantages
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-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 days in target range -Incidence rates of INR specific adverse events can be calculated	-Difficult to calculate -Makes assumption about INR between tests -Overall results may be biased by extreme out of range INRs

Source : Schmitt at al [71]

Rosendaal method is the most commonly used and will be applied in this study. It is the only method which includes time plus considers the actual days the INR was in the range targeted.

2.8 Anticoagulation Management Services

For most favorable management, it is recommended that anticoagulation be instituted via Anticoagulation management services (AMS) which includes detailed patient education, dedicated multidisciplinary team, proper dose decisions and systematic INR monitoring [6,68,72]. Numerous studies have established that pharmacist-managed anticoagulation clinics had better INR control and more successful than conventional management [73–76].

A multicenter, cross-sectional study done in patients with chronic non-valvular atrial fibrillation, receiving oral anticoagulation therapy (OAT) for stroke prophylaxis, was carried out in Canada, USA, Spain, France and Italy based on their model of care [Anticoagulation Clinic care (ACC) or routine medical care (RMC)]. The objectives were to describe the features of the local model of care and to determine anticoagulation control using TTR. TTR was higher in ACC (69.5% and 64.9% for Italy and Spain, respectively) as compared to RMC (58.1%, 62.8% and 59.3% for the US, Canada and France, respectively)[74].

In a study by Manji et al in Eldoret to assess the viability of an AMS in a resource-limited rural setting compared to published metrics from resource-rich setting clinics, the AMS was found to be non-inferior [68].

The ACCP Guidelines committee made a best practice statement where they suggested that clinicians managing OAT should do that in a coordinated way, involving educating patients, timely INR testing and appropriate dosing decisions [8].

2.9 Problem Statement and Study Justification

Globally, the management of warfarin therapy represents a significant challenge [77]. Largely because warfarin has a narrow therapeutic index and optimum control depends on numerous factors including dosage adjustment pattern, frequency of monitoring, comorbidities, drugs and food interactions and compliance of the patient [12]. Warfarin management requires frequent INR testing, proper dosage adjustments, identifying and treating bleeding and thrombotic events [8]. Evidence suggests that inappropriate management in addition to other patient factors are crucial factors in morbidity and mortality in patients on OAT [78,79].

The implications of inadequate anticoagulation control are of great consequence to both the patient and clinician. Complications due to anticoagulants are associated with more frequent hospitalization, emergency visits and can result in death or permanent disability. These consequences ultimately increase the economic burden on the patient and the health sector.

Despite proven benefits of adhering to guidelines, there is wide variability in dose adjustment and frequency of INR monitoring [24]. This has affected the anticoagulation control at KNH [27] .

A KNH study found that anticoagulation quality with warfarin was low [80] with study participants having mean TTR of 31%. This is very low in comparison to the 60% recommended in the guidelines.

On the contrary, patients managed at Eldoret anticoagulation clinic achieved better TTR of 65% [68]. The variation is due to the presence of a clinic dedicated to anticoagulation management instead of usual physician follow up clinics. Use of AMS is recommended for optimal management [6,68,72].

Patient factors affecting anticoagulation control with warfarin at the KNH have been studied[27]. Eighty-five (85%) of the study population in that study had low TTRs of less than 60% as determined by the Rosendaal method denoting low anticoagulation levels. Poor adherence to warfarin, use of a concurrent interacting medicine and use of variable amounts of vegetables was noted in 39%, 21% and 60% of study participants respectively. However, there was no association between these factors and the TTR [27].

Kenyan studies on warfarin have focused on the anticoagulation adequacy [1,27] and patient factors impacting anticoagulation management [80]. The available local anticoagulant therapy studies have assessed adequacy of anticoagulation without consideration of warfarin dosing and monitoring practices. Furthermore, it is important that centres that run anticoagulation clinics periodically assess the adequacy of anticoagulation, using TTR, on their patients.

There is scarcity of local data on warfarin management practices and their relationship with anticoagulation outcomes including TTR, bleeding and thrombotic outcomes. This study's findings and recommendations will contribute to better quality of care of patients taking warfarin.

2.11 Research Question

What are the warfarin management practices and how do they influence anticoagulation outcomes among ambulatory patients at Kenyatta National Hospital?

2.12 Objectives

2.12.1 Broad Objective

To describe warfarin management practices, their association with anticoagulation control and to determine the relationship between TTR and clinical outcomes in ambulatory patients on warfarin at Kenyatta National Hospital.

2.12.2 Primary Objective

a) To determine the proportion of patients who are poorly anticoagulated with warfarin using TTR at Kenyatta National Hospital

b) To determine the frequency of INR monitoring and the dosage adjustment appropriateness in ambulatory patients on warfarin at Kenyatta National Hospital

c) To determine the adequacy of patient education on warfarin therapy as received from the provider at Kenyatta National Hospital

2.12.3 Secondary Objectives

a) To determine the frequency of bleeding and thrombotic events in ambulatory patients on warfarin at Kenyatta National Hospital.

b) To describe the relationship between TTR and bleeding and thrombotic events.

c) To explore the relationship between the management practices (dosage adjustments, frequency of monitoring, and educating patients) and anticoagulation control.

3.0 CHAPTER THREE: STUDY METHODOLOGY

3.1 Study Design

The study was a retrospective treatment cohort study of warfarin treated patients in the calendar year 2019 at cardiology, hematology and cardiothoracic clinics at KNH. The study had 2 sources of data; data on INR values, frequency of monitoring and dose adjustment were extracted from patient files and data on knowledge and complications was captured from interviewing patients. All these data from events that occurred in 2019 was collected between August 2021 and October 2021.

3.2 Study Site

The study was carried out at the Kenyatta National Hospital (KNH), the largest teaching and referral facility in Kenya, with an 1800 bed capacity serving patients from Nairobi County and its environs. The study was carried out in cardiology, hematology and cardiothoracic clinics of this facility. These 3 clinics are each run once a week by consultants, residents and nurses. They offer anticoagulation services to more than 500 patients per year with the AF, DVT, PE and mechanical heart valves who are on warfarin, and thus the reason for selecting them as study sites. In these clinics, patient INR results are reviewed, warfarin doses adjusted and follow up clinics scheduled for continued INR and adverse events monitoring.

3.3 Study Population

The study population included patients on warfarin due to AF attending cardiology clinic, patients on warfarin due to mechanical heart valves attending cardiothoracic and cardiology clinics and those on warfarin due to VTE attending hematology clinic at The Kenyatta National hospital.

3.4 Inclusion Criteria

Patients included in the study were those that meet the following criteria:

- **a)** Adult patients aged 18 years and above on warfarin for AF, VTE and mechanical heart valves between January 2019 and December 2019
- **b)** Patients on warfarin therapy for at least 1 month and must have been reviewed in clinic more than twice during the study period
- **c)** Patient with at least two INR readings
- **d)** Patients who gave informed consent to be included in the study

3.5 Exclusion Criteria

Pregnant women- due to the need for anticoagulant changes from warfarin to heparin in first and third trimester to avoid teratogenicity and fetal intracranial hemorrhage.

3.6 Sample Size Determination

Based on 2 studies done in Kenya, the percentage of patients achieving adequate control would be at least 15% of the study population [27,80]. Adequate control is TTR above the ACCP and BSH recommended TTR of 60%. According to health records estimates in KNH, 536 patients on warfarin were seen in the target clinics in 2019. A representative sample was drawn from this finite population and sample size was determined as follows [81]:

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

Where

n' = sample size with finite population correction,

N = size of the target population = 536

Z = Z statistic for 95% level of confidence = 1.96

P = expected proportion of patient using warfarin who are adequately anticoagulated = 15%

d = margin of error = 5%

$$n = \frac{536 \times 1.96^2 \times 0.15 \times 0.85}{0.05^2 (536-1) + 1.96^2 \times 0.15 \times 0.85}$$

n =144

A total of 146 patients were sampled to determine outcomes within 5% level of precision.

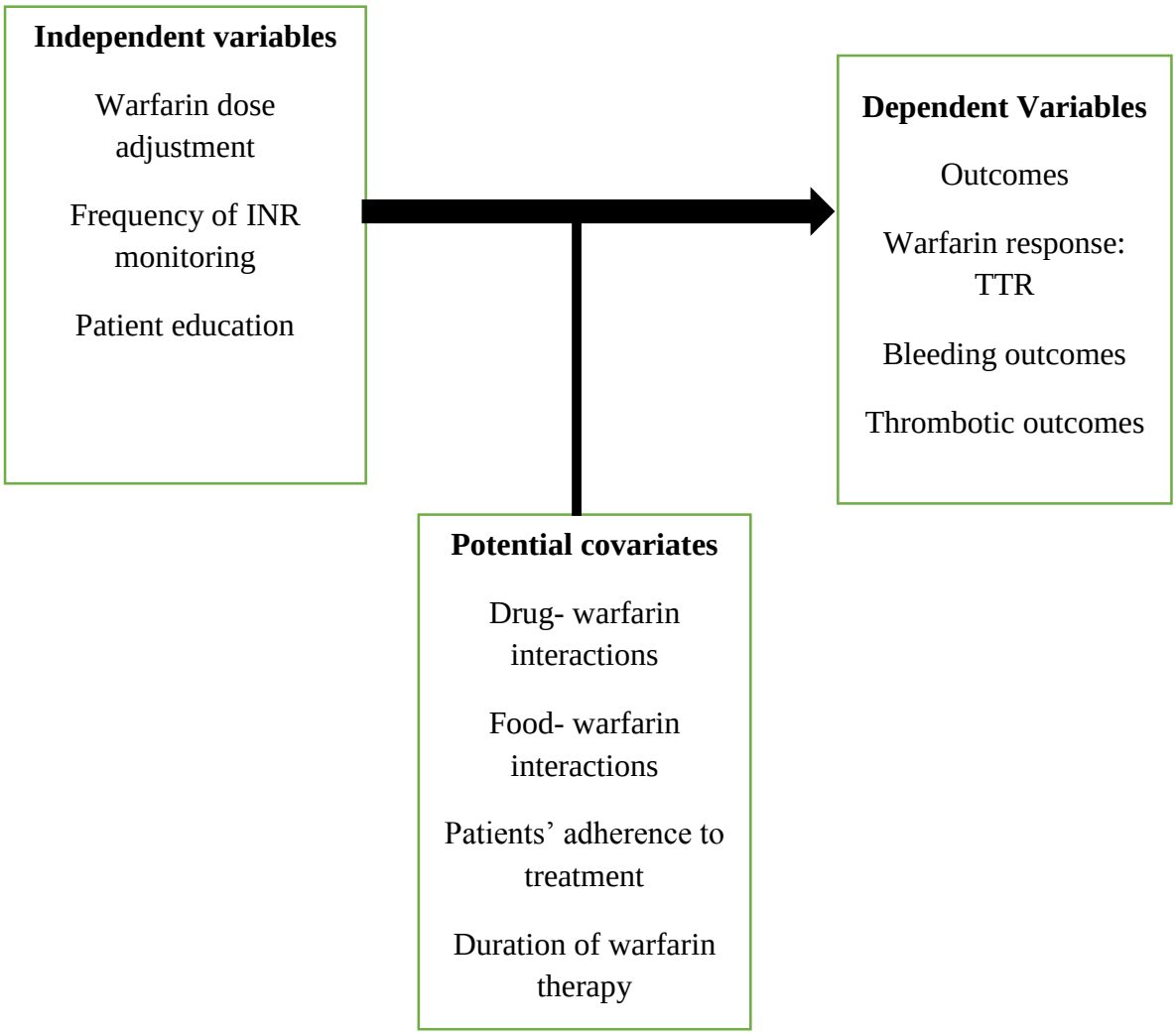

Figure 1: Conceptual Framework of the Study

3.7 Description of Study Variables

Warfarin dosage adjustment quality was determined by how out of range INRs were managed; decreasing, increasing or omitting warfarin dose and this was compared to guideline recommendations [12,21,22]. The number of patients in whom warfarin dose was adjusted appropriately according to guidelines was expressed as a percentage of the total. The quality was expressed as appropriate or inappropriate management.

INR monitoring frequency was derived by dividing the total number of days the patient was on warfarin during the study period (2019) by the number of tests done.

Patient education and understanding was assessed using questions included in the data collection form (Appendix 6) that are from a validated OAK test [58]. The performance of patients on the OAK was expressed as adequate if patient scored ≥75% and inadequate if patient scored <75% as it has been done in other studies. [9]

Time spent in therapeutic range (TTR) was derived by use of the Rosendaal linear interpolation method which estimates proportion of time in which a patient was in the target range. We used 2.0-3.0 as INR target range for VTE and AF and 2.5-3.5 as INR target range for mechanical heart valves. The percentage of time in supratherapeutic and subtherapeutic INR range were calculated in the same way. A simple Excel template, in which patient's test dates, INR values and INR target ranges are entered to automatically calculate Rosendaal method was used (Appendix 7) [82]. The formula is as follows;

$$\text{TTR} = \frac{\text{The number of days in range}}{\text{Total number of monitored days}}$$

In the Rosendaal linear interpolation method, the change in 2 consecutive INRs is assumed to be linear over the time interval. Patients were stratified based on their TTR with TTR>60% being good anticoagulation control and TTR<60% being poor anticoagulation control.

Clinical outcomes of warfarin therapy

The International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool are useful for standardized reporting of symptoms of bleeding and was used in this study to assess bleeding complications [83].

Major bleeding was defined as

1. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome.

and/or

2. Bleeding causing a drop in haemoglobin level of 2 g/dL or more, or leading to two or more units of whole blood or red cells transfusion.

Minor bleeding was defined as: All non-major bleeds were considered minor bleeds.

Recurrent thromboembolism defined as the development of new onset of a stroke, a transient ischemic attack, systemic embolism, PE and DVT while on treatment.

Stroke diagnosis was confirmed from the clinical notes based on typical symptoms and CT brain diagnosis of ischemic stroke.

Systemic embolism was defined as any acute onset arterial thromboembolic event such acute limb ischemia, splenic infarct or renal infarct.

VTE was defined as DVT or PE diagnosed with compression ultrasound and computed tomography pulmonary angiogram respectively.

3.8 Sampling, Screening and Recruitment

Random sampling was utilized to select patients for enrollment into the study. The sampling frame consisted of a list of patients in year 2019 on warfarin therapy attending the designated clinics which was established from pharmacy records. The sampling frame was serialized then random numbers were generated from Microsoft excel which were used to randomly select patients. Files were retrieved and screened for eligibility using an eligibility checklist form (Appendix 5). If eligible, they were invited to be study participants and taken through the consenting process (Appendix 2).

The patients were informed of the risks, benefits and confidentiality issues and that they could withdraw at any time from the study without any consequences. Patients who signed the informed consent form (Appendix 3) were recruited into the study. Patients whose scheduled clinic appointment were not within the study period were called and their transport was reimbursed. On each recruitment day, the same procedure was repeated until attainment of the desired sample size.

3.9 Data Collection

A pre-designed data collection form (Appendix 4) was utilized which had seven main parts. The first part was used to extract data from patient on socio-demographic characteristics such as age, sex, marital status, employment status, level of education and whether or not patient consumes alcohol.

The second part included patient clinical characteristics including indication and duration of warfarin therapy, comorbidities and concurrent medications.

The third part had questions from the Oral Anticoagulation Knowledge (OAK) Test, to assess whether patients had been educated on various aspects of warfarin therapy [58]. Fifteen multiple choice questions from the OAK were used as has been done in other studies. [9,51] The questions capture the knowledge on INR monitoring, food and drug interactions, effects of a missed dose, interaction with alcohol among other things.

The fourth part was utilized to collect data from files of participants on dosage adjustments. The fifth part was utilized to collect data from files of participants on INR readings as well as INR measurement dates to determine monitoring frequency and TTR. The sixth and seventh parts were used to collect data on bleeding using the ISTH standardized reporting of bleeding tool and thrombotic complications (recurrent VTE, systemic embolism or stroke). A research assistant was trained and assisted with collection of data. The PI ascertained daily that relevant data had been captured accurately.

3.10 Validity and Reliability of Data Collection Tools

The OAK test is a validated and standardized tool for testing knowledge in patients on anticoagulation therapy. It consists of 15 questions (each with 1 correct answer and 3 distractors), worded at seventh-grade level and have been evaluated for test-retest reliability and internal consistency. The ISTH standardized reporting of bleeding tool is valuable for standardized reporting of symptoms of bleeding and was used in this study to assess bleeding complications [83].

3.11 Data Management and Analysis

Data was entered and managed in Microsoft Excel 2016 data entry sheet. The data was cleaned and exported to SPSS version 23.0 for statistical analysis. The study population was described using the socio-demographic and clinical characteristics. Categorical variables such as gender, education level, indications of warfarin use, comorbidities and adherence to therapy were summarized into percentages.

Continuous data such as age of the patients and duration of warfarin therapy were summarized into means and standard deviations for normally distributed data or medians and interquartile ranges for data with non-normal distributions. Quality of warfarin dosage adjustments was categorized based on appropriateness and expressed as a percentage of patients studied. The INR monitoring frequency was calculated and the mean and median for the study population presented.

In addition, patients' knowledge was assessed and presented as percentage of patients with adequate education on warfarin therapy. TTR was calculated and summarized into mean and the number of patients with TTR above 60% was percentage of the study population. The mean percentage time in subtherapeutic and supratherapeutic ranges were also calculated in a similar way using Rosendaal method. Complications of warfarin therapy, which included bleeding and thromboembolic events, were described. The frequency of bleeding complications and clinically confirmed arterial and venous thrombosis were expressed as percentages and number of events per patient years.

Bivariate analysis was used to determine the relationship between the various independent and dependent variables. Warfarin response using TTR was associated with quality of warfarin dosage adjustments, patients' education on warfarin therapy and bleeding and thrombotic events using chi square test of associations while median frequency of INR monitoring was compared using Mann Whitney U test. TTR, time in subtherapeutic and supratherapeutic ranges were also associated with bleeding and thrombotic outcomes using independent t test. Odds ratios was calculated to estimate the risk of inadequate TTR associated with the quality of dosage adjustment, patient education scores and INR monitoring frequency.

Statistical significance was interpreted at 5% level of significance. Tables and graphs were used to present the findings.

3.12 Quality Control and Assurance

To maintain consistency, data from file reviews was based on a standardized data abstraction format. Appraisal of the research assistant on data abstraction process was done before starting the project. Counterchecking of data entry completeness and accuracy was done by the PI using hard copy forms. External validity was guaranteed through non-biased selection of study participants and adequate sample size.

3.13 Ethical Consideration

Enrollment of patients was on voluntary basis after obtaining informed consent. Study participants had assigned identification enrollment numbers. Confidentiality was upheld and anonymity ensured, patients identified only by study number. No additional cost was incurred by the patient by participating in the study. All hard copies of data were under lock and key, while digital data was password protected accessible only to study personnel. This ensured that data was safe from inappropriate use, unauthorized access and modification.

The study was conducted after approval by the department of clinical medicine and therapeutics and the Kenyatta National Hospital / University of Nairobi Ethics and research committee.

4.0 CHAPTER FOUR: RESULTS

Data collection was done between August 2021 to October 2021. A total of 228 files of patients on warfarin in the study period of January 2019 to December 2019 from the various target outpatient clinics at KNH were screened. Of these, 82 were excluded from the study (Figure 2). 17 were changed from warfarin to other anticoagulants, 4 were pregnant at some point during the study period, 34 had missing INR values, 19 had been on follow up for less than 1 month and had less than 2 INR readings documented during the study period and 8 patients eventually declined to give consent and were thus excluded. 146 patients were included in the study.

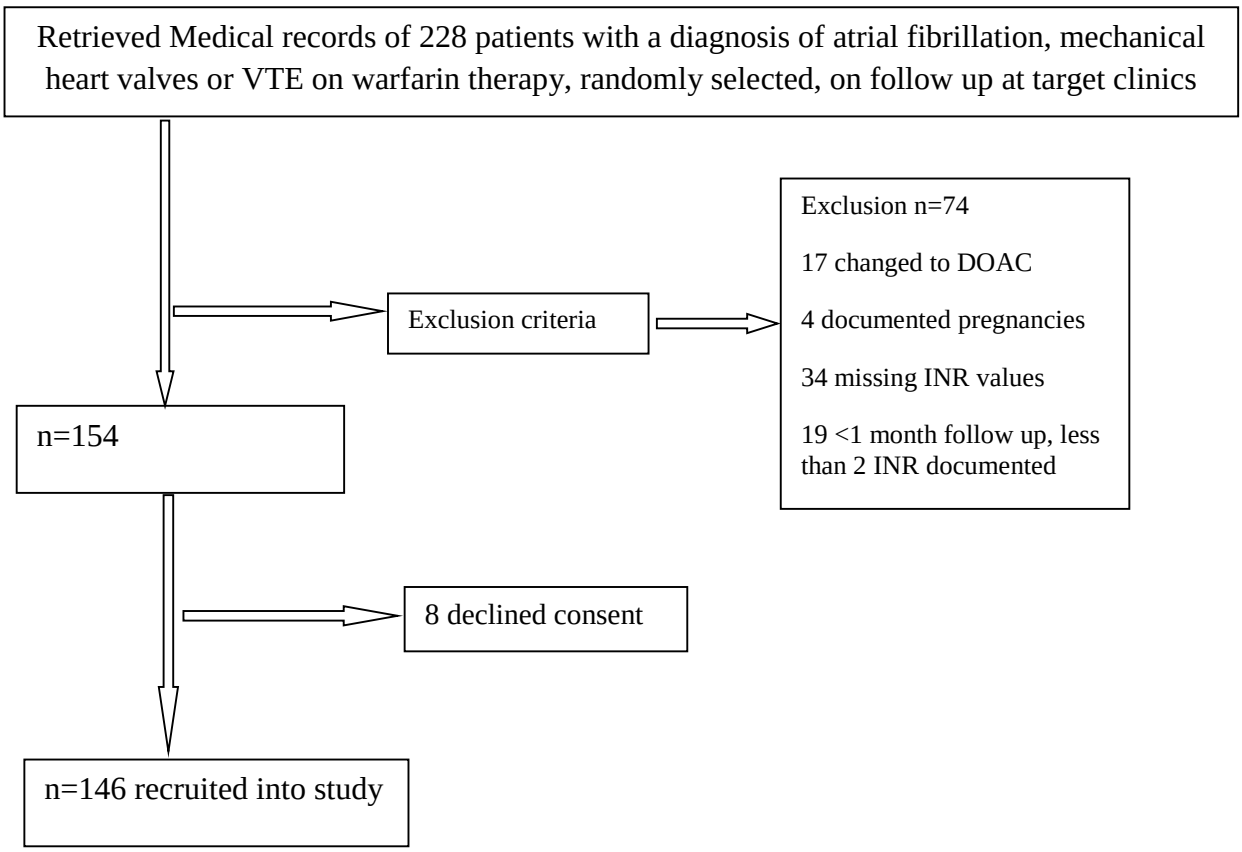

Figure 2:Patient recruitment flow diagram

4.1 Sociodemographic Characteristics

Of the 146 patients, 99 (67.8%) were female. The mean age of the study participants was 46.6 (SD 13.6) years with a minimum age of 18 years and a maximum age of 82 years. Majority of the patients (63.7%) had some form of employment- self-employed or employed. Approximately 97% of the participants had attained at least primary level education and 93.8% of the patients did not consume alcohol (Table 10).

Table 10: Demographic characteristics of patients on warfarin at KNH

Variable	Frequency (%)
Age in years	
Mean (SD)	46.6 (13.6)
Min –max	18-82
Sex	
Male	47 (32.2)
Female	99 (67.8)
Marital status	
Married	103 (70.5)
Single	27 (18.5)
Divorced	5 (3.4)
Widowed	11 (7.5)
Employment status	
Employed	32 (21.9)
Self-employed	61 (41.8)
Unemployed	51 (34.9)
Student	2 (1.4)
Education level	
Informal	4 (2.7)
Primary	41 (28.1)
Secondary	65 (44.5)
College and above	36 (24.7)
Alcohol consumption	
Yes	9 (6.2)
No	137 (93.8)

4.2 Clinical Characteristics

Majority of the patients were on warfarin therapy for VTE 60 (41%); in 50 (34.2%) the indication was DVT and 10 (6.8%) for PE. The other indications for warfarin use were atrial fibrillation 52 (35%) due to valvular and non-valvular disease; and mechanical heart valve 34 (23%).

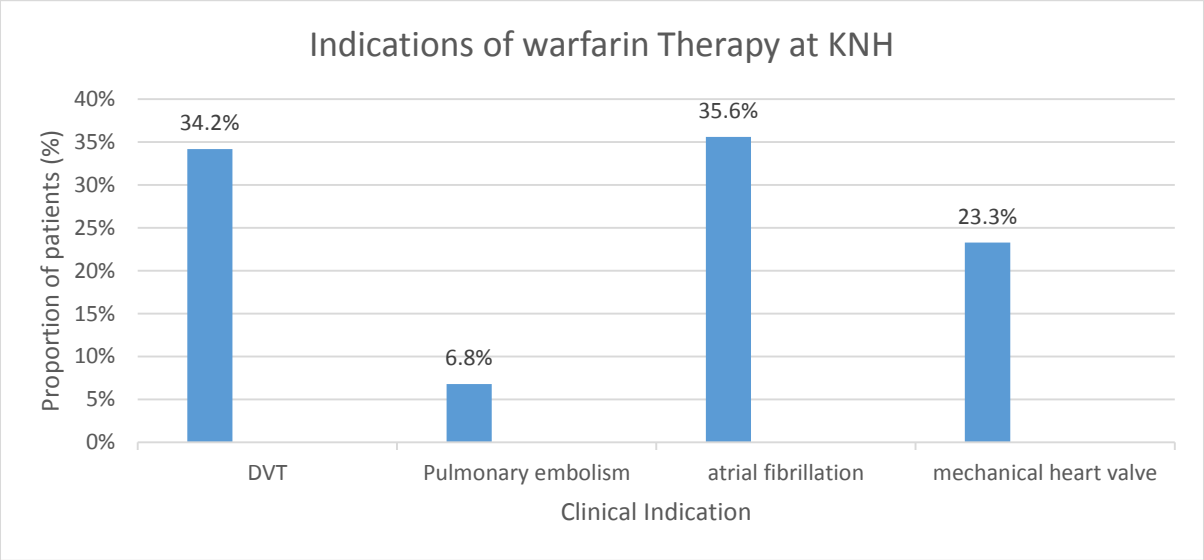

Figure 3:Indications of warfarin therapy

The INR target ranges for pulmonary embolism, DVT and atrial fibrillation was 2-3. Whereas INR target of 2.5–3.5 was used for mechanical valve replacement in mitral position, and for dual aortic and mitral mechanical valve replacement. All the patients with mechanical heart valves in this study had either mitral valve replacement or dual aortic and mitral valve replacement. One hundred and forty (95.9%) of the patients were on chronic warfarin use for >12 months.

Majority of the patients 102 (69.8%) had comorbidities with the commonest being: congestive cardiac failure 49 (33.6%), rheumatic heart disease 38 (26%) and hypertension 34 (23.3%). Twenty-nine (19.8%) had other comorbidities that included ischemic heart disease, Cor pulmonale, osteoarthritis, dyslipidemia, asthma, uterine fibroids, hypo or hyperthyroidism, tuberculosis, systemic lupus erythematosus, cerebral venous sinus thrombosis and sickle cell disease.

Almost half of the patients (47.9%) had 1 or 2 comorbidities in addition to the primary indication for warfarin therapy while 20.5% had more than 3 comorbidities.

Table 11 : Comorbidities in patients on warfarin at KNH

Variable	Frequency (%)
Diabetes mellitus	11 (7.5)
Hypertension	34 (23.3)
Congestive cardiac failure	49 (33.6)
Rheumatic heart disease	38 (26)
Renal dysfunction	3 (2.1)
HIV	11 (7.5)
Cancer	3 (2.1)
Other	29 (19.8)
3 or more comorbidities	30 (20.5)
2 or less comorbities	70 (47.9)
None	46 (31.5)

4.3 Adequacy of Anticoagulation Control Using Time in Therapeutic Range (TTR)

Using the Rosendaal method, which utilized at least 2 INR values to calculate TTR, our study found that the percentage of follow up time in therapeutic INR was 43.6% (SD 30.5). Patients who had poor anticoagulation control which was considered to be TTR less than 60% were 104 (71.2%). (Table 12)

Table 12:Time spent in therapeutic range (TTR) and adequacy of anticoagulation control

Variable	Frequency (%)
TTR	
Mean (SD)	43.6 (30.5)
Median (IQR)	40.2 (22.3-65.1)
Min –max	0-100
Anticoagulation control	
Good	42 (28.8)
Poor	104 (71.2)

The proportion of time that participants spent in therapeutic, subtherapeutic and supratherapeutic INR range also calculated using Rosendaal tool as further INR outcome variables are presented in Figure 4.

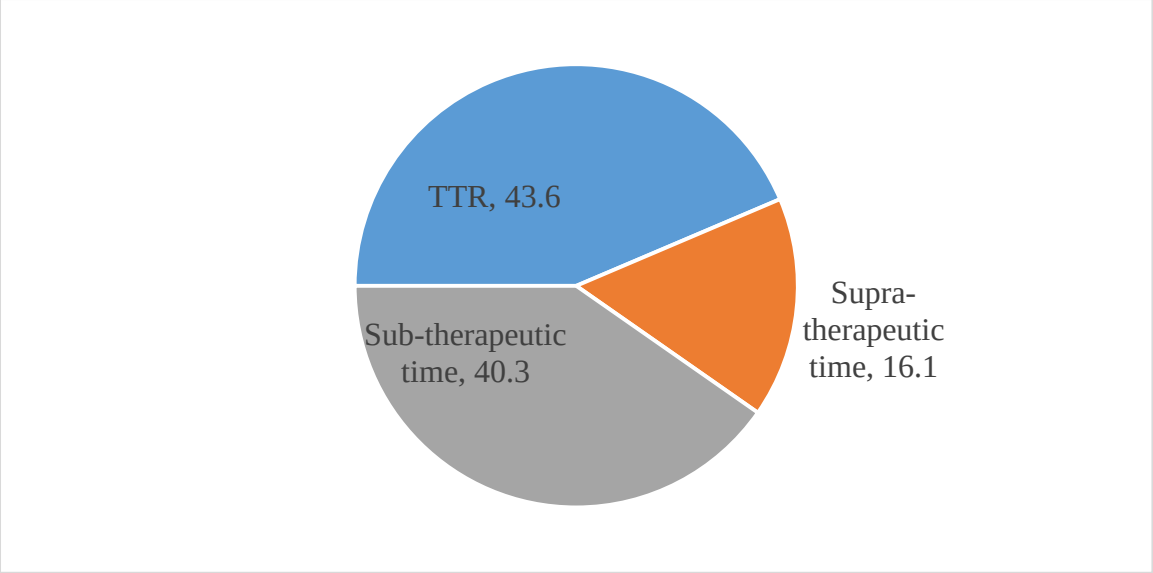

Figure 4:Level of INR control for study participants

4.4 Frequency of Monitoring and Dosage Adjustment

The median frequency of INR monitoring was 73 days (IQR 50.7-104.3). Monitoring ranged from 17 days to 182.5 days. Eighty-two patients (56.2%) had optimal monitoring, that is, their INRs monitored at an interval of 12 weeks or less according to ACCP 2012 guideline recommendations while 64 (43.8%) patients had monitoring frequency of more than 12 weeks. Majority of the patients 73 (54.1%) had inappropriate dosage adjustments, that is, their warfarin dose was either increased, decreased or retained inappropriately depending on their out-of-range INR values.

Table 13:Frequency of INR monitoring and the dosage adjustment patterns in patients on warfarin at KNH

INR monitoring Frequency	**Days**
Mean (SD) **Median (IQR)** **Min-Max**	81.6 (41.7) 73.0 (50.7-104.3) 17-182.5
Variable	**Frequency (%)**
Adequacy of INR monitoring, n (%) Adequate (<= 12 weeks) Inadequate (>12 weeks)	 82 (56.2) 64 (43.8)
Dosage adjustment, n (%) Appropriate Inappropriate	 62 (45.9) 73 (54.1)

4.5 Patient Education

Patients performed poorly in the oral anticoagulation knowledge test with 118 (80.8%) having inadequate knowledge as they scored <75% in the OAK test.

Table 14:Adequacy of patient education on warfarin therapy

Variable	Frequency (%)
Oral anticoagulation knowledge (OAK) percent score	
Mean (SD)	57.3 (21.5)
Category, n (%)	
Adequate (OAK score≥75%)	28 (19.2)
Inadequate (OAK score<75%)	118 (80.8)

4.6 Bleeding and Thrombotic Outcomes

A total of 50 patients (34.2%) experienced bleeding complications while on warfarin therapy majority having experienced minor bleeding episodes. As shown in Figure 5, (4.1%) patients had major bleeds while 44 (30.1%) patients experienced minor bleeds. Most reported minor bleeds were menorrhagia and epistaxis. A total of 18 patients (12.3%) had thromboembolic complications while on warfarin therapy:- 3 had stroke, 15 had DVT and 1 had PE/DVT. None of the patients had both bleeding and thrombotic complications during the study period.

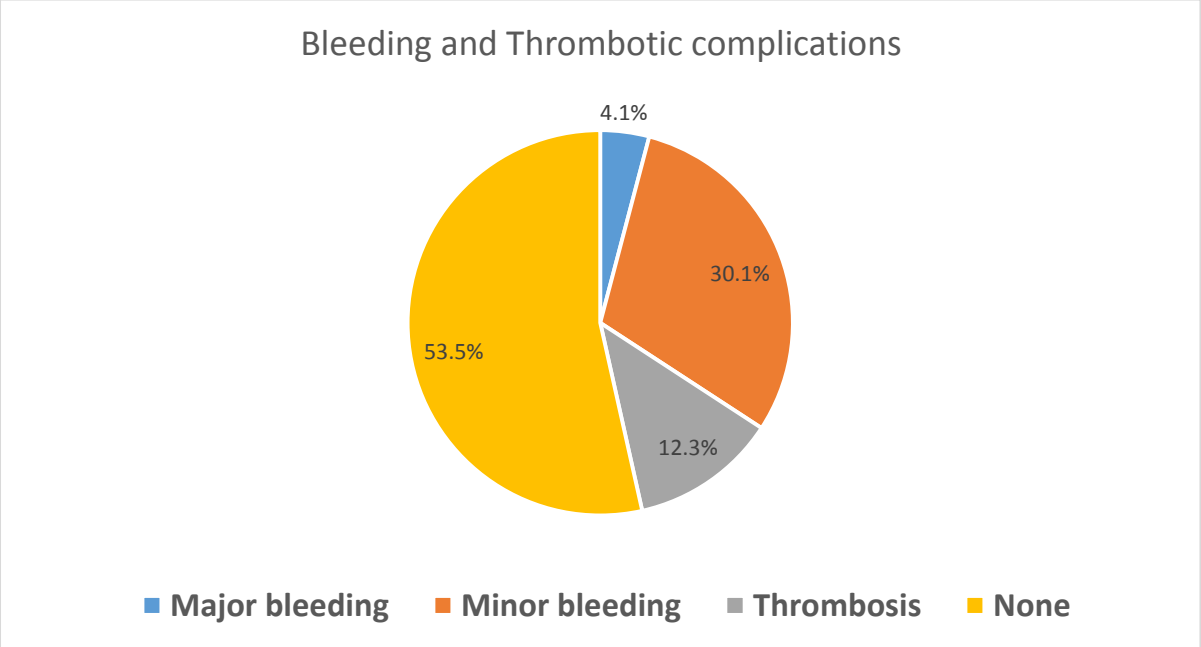

Figure 5:Proportion of patients with bleeding and thrombotic complications

Table 15:Complications of warfarin therapy at KNH

Bleeding	Frequency (%)	95% CI
Major	6 (4.1)	0.9-7.3
Minor	44 (30.1)	22.7-37.6
Thrombosis	18 (12.3)	7.0-17.7
No bleed	78 (53.5)	45.3-61.5

With a total duration of follow up of 120.7 years, bleeding events occurred at a rate of 41 events per 100 patient years while thrombotic events occurred at a rate of 15 events per 100 patient years. These were over a 12-month period of study thus frequency is higher as opposed to if it were spread out over cumulative years of warfarin exposure.

4.7 Bivariate Analysis

4.7.1 Relationship Between TTR, Bleeding and Thrombotic Events

There was a statistically significant association between poor anticoagulation control and bleeding complications with patients who had poor control being 2.9 times more likely to bleed than those with good control, OR 2.9 (1.2-6.8); p=0.014. In this respect, 42 patients (40.3%) who had poor anticoagulation control experienced bleeding complications as compared to only 8 patients (19%) who had good anticoagulation control. Only 18 patients (12.3%) had thrombotic complications with 12 out of the 18 having poor anticoagulation control although this was not statistically significant, OR 0.8 (0.3-2.2); p value=0.648.

Table 16:Relationship between TTR and bleeding and thrombotic events

Variable	Poor (n=104)	Good (n=42)	OR (95% CI)	OR
Bleeding complications				
Yes	**42 (40.3)**	**8 (19.0)**	**2.9 (1.2-6.8)**	**0.014**
No	62 (59.7)	34 (81.0)	1.0	
Thrombotic complications				
Yes	12 (11.5)	6 (14.3)	0.8 (0.3-2.2)	0.648
No	92 (88.5)	36 (85.7)	1.0	

To better define the relationship between time spent in the INR ranges and bleeding and thrombotic events, bivariate analysis using independent t-test was done (Table 17). There was a statistically significant association between time spent in supratherapeutic range and bleeding outcome. Spending more mean days in supratherapeutic range was a predictor of bleeding outcomes with a significant p value of 0.024.

However, there was no statistically significant association between thrombotic outcomes and spending more time in subtherapeutic range; p=0.923.

Table 17: Relationship between time spent in the INR ranges and bleeding and Thrombotic Outcomes

Variable		TTR		Supra-therapeutic time		Sub-therapeutic time	
Events	**n**	**Mean % days**	**P value**	**Mean % days**	**P value**	**Mean % days**	**P value**
Bleeding							
Yes	50	41.8	0.889	23.6	**0.024**	34.6	0.182
No	90	42.5		14.8		42.7	
Thrombotic							
Yes	18	45.6	0.767	13.3	0.600	41.0	0.923
No	128	43.4		16.5		40.2	

4.7.2 Relationship Between Management Practices and Anticoagulation Control (TTR)

Dosage adjustment was significantly associated with anticoagulation control, with patients who had inappropriate dosage adjustment being 2.4 times more likely to have poor anticoagulation control, p=0.032.

Patients who did not require dosage adjustments were less likely to have poor anticoagulation control, OR 0.2, p=0.015.

Participants in the study had a median INR monitoring frequency of 73 days. Patients who achieved good anticoagulation control were monitored a median of 91.3 days while those that had poor anticoagulation control were monitored a median of 73 days. Frequency of INR monitoring, whether less than 12 weeks or more than 12 weeks, was however not associated with anticoagulation control.

More patients who had inadequate knowledge (76.9%) had poor anticoagulation control compared to those that had adequate knowledge (23.1%). However, this was not statistically significant, OR 0.4 (0.1-1.1); p value=0.060. (Table 18)

Table 18: Relationship between the management practices and anticoagulation control

Variable	Anticoagulation outcome		OR (95% CI)	P value
	Poor (n=104)	**Good (n=42)**		
Dose adjustments				
Appropriate	41 (39.4)	21 (50.0)	1.0	
Inappropriate	60 (57.7)	13 (31.0)	**2.4 (1.1-5.2)**	**0.032**
No adjustment required	3 (2.9)	8 (19.0)	**0.2 (0.05-0.8)**	**0.015**
INR monitoring frequency				
Median (IQR)	73.0 (52.1-92.6)	91.3 (43.2-121.7)	-	0.656
Category, n (%)				
Adequate (<= 90 days)	63 (60.6)	19 (45.2)	1.0	
Inadequate (>90 days)	41 (39.4)	23 (54.8)	0.5 (0.3-1.1)	0.091
OAK score				
Adequate	24 (23.1)	4 (9.5)	1.0	
Inadequate	80 (76.9)	38 (90.5)	0.4 (0.1-1.1)	0.060

5.0 CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

The present study was designed to look at the warfarin management practices and outcomes in ambulatory patients at KNH.

In our study, a large proportion of patients had poor anticoagulation control with 71.2% of them achieving TTR of less than 60% and only 28.8% achieving good anticoagulation control. This study showed slightly better anticoagulation control compared to a previous study at KNH in a similar but smaller study population of 100 patients by Kibiru et al in 2012 that looked at quality of anticoagulation and found that 85% of patients had poor anticoagulation control [27]. Another study in prosthetic heart valve patients by Ogendo et al found that, during the study period 93.1% had poor anticoagulation control [1]. However, this study used a lower TTR cut off of 50% as opposed to the TTR cut off of 60% used in our study. In the past, there was lack of consensus on the benchmark TTR in assessing anticoagulation thus prior studies used different cut offs. A TTR of 60% has been found to confer the maximum benefit and the least adverse effects while on warfarin therapy and is thus recommended by ACCP 2012 and BSH guidelines. One of the reasons that contributed to poor anticoagulation among prosthetic heart valve patients in the study by Ogendo may have been lack of escalation of warfarin doses especially because heart valve patients have higher INR target of 2.5-3.5 [1].

In contrast to our study, Manji et al in 2011, using Rosendaal method for TTR calculation, found that patients on follow up in Eldoret achieved better anticoagulation control, with TTR levels of about 65%, comparable to other resource rich countries [84]. The difference with our study being due to the presence of dedicated anticoagulation clinic in Eldoret where anticoagulation is managed through a specialized anticoagulation management services which provides comprehensive protocol-based INR monitoring services as opposed to usual physician follow up clinics.

The difficulty in maintaining INR within therapeutic range has also been seen in other studies globally. A study done in USA assessing anticoagulation using Rosendaal method in 100 sites found that TTR ranged from as low as 38% to 69% [85]. The sites with lowest TTR were noted to have high poverty indices and patients were more elderly with mean age of 72 years with more comorbidities. Our study is comparable to this study's study sites with lowest TTRs as it was conducted in a resource limited setting but differs in that our study had much younger study participants with mean age of 46.6 years.

The ISAM study [74], which assessed anticoagulation in 5 countries; Italy, Spain, USA, Canada and France found that countries that utilized anticoagulation clinics had higher TTRs as opposed to those that used routine medical care. Use of routine medical care in our setting might have played a role in the achievement of lower TTR.

Our study found a mean TTR of 43.6% meaning that patients were in therapeutic range less than half of the time. This is less than the ACCP 2012 guideline recommended TTR of 60% at which patients would reap the benefits from warfarin therapy and reduce adverse effects. ACCP guidelines recommend that centers that manage anticoagulation keep track of patients' anticoagulation control by measuring TTR annually. Previous studies done at KNH that measured TTR as one of their objectives have found lower TTRs in their study population than our study. These include TTR of 18% in 2000 by Ogendo et al, 33.8% in 2012 by Kibiru et al and 31.1% in 2016 by Karuri et al [1,27,80]. The study by Ogendo et al only studied 103 post heart valve replacement patients and also used a different method to calculate TTR whereas we used Rosendaal method which might explain the difference in the findings [1]. Studies done by Kibiru et al and Karuri et al both utilized Rosendaal method and had similar study population [27,80]. The slight improvement in TTRs might be due to recommended measures put in place after the respective studies were done. For example, patients who had prosthetic heart valves on warfarin were issued with an advice book/diary in 2010 in which they would record their INRs, dosage adjustment and gave advice on frequent INR checks, adherence on warfarin, avoidance of alcohol, drugs to avoid while on warfarin, keeping a regular diet while on warfarin among other things. This was a good strategy to educate patients and assist them in keeping track of their anticoagulation control. However, this practice seems to have been abandoned along the way for unknown reason.

We found that patients spent 40.3% of time in supratherapeutic range and 16.1% in supratherapeutic range. In a study by Karuri et al at KNH among 406 patients, 47.8% of the time on follow up was spent in subtherapeutic range which is similar to our study findings [80]. This was related to the fact that clinicians were more worried about warfarin safety to prevent over anticoagulation as the commonest complication of warfarin is bleeding [80] .

ACCP in 2012 updated their guidelines and recommended that frequency of monitoring should be once every 4 weeks if patient is on same dose for <6 months or every 12 weeks if on same dose for at least 6 months [12]. More frequent INR monitoring is recommended if dosage adjustments are done. The median INR monitoring interval was 73 days (IQR 50.7-104.3). As our study did not only recruit stable patients with stable INRs, generalizing the guideline recommended frequency of monitoring overestimates good monitoring practices. To maintain

good anticoagulation control, 73 days may be too long an interval between visits to clinic in patients not on a stable dose for > 6 months considering our study had a majority of patients (71.2%) with poor anticoagulation control. In addition, patients in our study spent 40.3% and 16.1% of the time in subtherapeutic and supratherapeutic ranges, thus 73 days may be too long a period to monitor their INRs

Study by Kibiru et al in 2012 in a similar study population found a frequency of monitoring of 43.5 days [27]. In that study, only 19% had optimal monitoring which was considered as INR monitoring every 4 weeks or less according to the previous ACCP guidelines of 2008.

The reasons noted for the hindrance in frequent monitoring in that study were clinic bookings which were 3-6 monthly, financial constraints and inaccessibility to a health institution that can monitor INRs.

Fenta et al in Ethiopia in 2012 found that the quality of warfarin management was suboptimal due to longer than recommended frequency of INR monitoring. The mean interval between 2 INR tests per patient was 63 days in follow up patients at hematology and cardiology clinics of a large university teaching hospital in Ethiopia proving very prolonged even for patients on stable warfarin dose [24]. This Ethiopia study also considered optimal monitoring to be every 4 weeks.

This situation is a common economic reality in our set up as making frequent visits is hard for many patients. Most patients face problems of affording travelling costs to hospital plus the consultation and laboratory fees subsequently. For this reason, some patients even request long clinic intervals. A partial solution to this problem would be setting up of anticoagulation clinics in the various counties outside Nairobi.

Majority of the patients 73 (54.1%) had inappropriate dosing adjustments. Fenta et al in Ethiopia in 2012 had similar findings of 56% having inappropriate dosage adjustment [24]. In that study, some of the noted reasons for poor response by clinicians on adjusting warfarin dose was; lack of protocol for standard warfarin dosage management and using other alternative actions such as managing warfarin interacting drugs and recommending non- pharmacological actions. Findings from our study contrast a USA study by Aspinall et al which found that warfarin was prescribed effectively in 75% using dosing algorithms [86].

To manage out of therapeutic range INR readings, ACCP guidelines recommend use of dosing algorithms for warfarin. Use of standardized guidelines and dosing decision support tools is associated with better anticoagulation control and outcomes[8].

Patients performed poorly in the oral anticoagulation knowledge test with 80.8% having inadequate knowledge reflecting insufficient warfarin therapy education. In a local study by Iqbal et al, prior to educating patients and in a study by Matalaqah et al in Malaysia (2013), 73% and 88% respectively, had inadequate knowledge [51,87].

Both studies found similar patterns to our study where the least understood aspects were in nature more scientific and without them being explained in a structured way, through warfarin education or booklets, the patients may not understand. The aspects included drug and dietary interaction, effects of alcohol, time to take medications that interact with warfarin and effects of out-of-range INR.

Iqbal et al, after educating patients and administering the OAK test found that only 15.6% had inadequate knowledge; signifying the importance of education programs [51].

Our study had a high rate of complications with almost half (46.5%) having complications.

Bleeding complications were the most common occurring in 50 patients (34.2%) while 18 patients (12.3%) had thromboembolic complications while on warfarin therapy. This is consistent with other studies that found bleeding complications to be the commonest complication of warfarin therapy [27,62,63].

Of the patients who had bleeding events, 4.1% had major bleeds and 30.1% had minor bleeds. In a study done at KNH in 2013 by Kibiru et al, out of the 100 study participants, 22 (22%) had a minor bleed while on warfarin with no major bleed reported [27]. The slight difference might be due to the smaller sample size of 100 patients and shorter study period of 6 months used in that study. In a retrospective study done in Ontario in 2007 by Van Walvaren et al in 10,020 patients on warfarin with 6,400 patient years of warfarin exposure, 26% had hemorrhagic events and 11% had thromboembolic events [62] .This is similar to our study findings of both bleeding and thrombotic complications.

In another retrospective study by Willey et al in USA in 2004 to describe warfarin management patterns and outcomes in 2090 VTE patients, found that recurrent VTE events and major bleeding events, occurred in 10.7% and 5.8% of patients, respectively [63]. Our study had similar findings as major bleeding events occurred in 4.1% of our study participants.

Suboptimal INR control has important clinical implications. There was a statistically significant association between poor anticoagulation control and bleeding complications with patients who had poor control being 2.9 times more likely to bleed than those with good control. In addition, there was a statistically significant association between bleeding outcomes and time spent in supratherapeutic range and bleeding where spending more mean days in supratherapeutic range was a predictor of bleeding complications. In a study in Ontario by Van

Walvaren et al, patients spent 14.2% of the time with extremely high anticoagulation intensity and this explained the 25.6% of the hemorrhages experienced [62].

Only 18 patients (12.3%) in our study had thrombotic complications with 12 out of the 18 having poor anticoagulation control although this had no statistical significance. We also found no significant association between thrombotic outcomes and spending more time in subtherapeutic range. This differed from a study by Van Walvaren et al in Ontario that found that excessively low anticoagulation intensity explained 11.1% of thromboembolic events [62].

Consistent with other global and local study findings, TTR was found to be a predictor of bleeding outcomes. However, the association between thrombotic outcomes and TTR was not statistically significant. This could be due to our smaller sample size with few thrombotic complications as compared to other studies that actually found TTR to be a predictor of thrombotic outcomes. However, this was a secondary analysis and therefore not definitive.

In a large study of 32,074 NVAF patients by An Jaejin et al, the lowest TTR quartile (< 46%) was associated with a 3 fold increased risk of stroke or systemic embolism and a 2 fold increased risk of major bleeding compared with the highest TTR quartile (≥ 73%) [65].

In SPORTIF III-open label and SPORTIF V- double blind RCT, the patients with the poorest INR control (TTR of 48%) among the 3587 patients randomized to receive warfarin, had two-fold stroke rate, major bleeding and death as did the one-third with the good INR control (TTR of 83%) [66].

In yet another retrospective cohort study by Willey VJ et al, patients maintained poor TTR of 37.7% and this resulted in bleeding and recurrent VTE events requiring hospitalization in 5.8% and 10.7% of patients [63].

The association between anticoagulation control and dosage adjustment was statistically significant with patients who had inappropriate dosage adjustment being 2.4 times more probable to have poor anticoagulation control.

This is a similar finding with other studies that found that provider varying decisions to adjust warfarin dose affects INR control. The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial found that adherence to doing algorithms predicted improved TTR [43].

In addition, study by Rose et al, USA in 3961 patients found that patients whose dose adjustments were according to the guideline recommendations maintained the best INR control (mean TTR 70.1%); while patients with bigger deviations of their dose adjustments from guideline recommendations had lower TTR (65.8% and 62.0% for fewer and more dose changes than expected, respectively) [45].

In a study done in an American institution, educating primary care physicians on use of dosing algorithms resulted in a reduction in warfarin related adverse drug reactions from 3.8 to 0.98% ($p < 0.0001$) and an increase in TTR from 56% to 65% [44]. There was also reduction in total and average cost associated with severe adverse drug reactions associated with warfarin therapy by 57.6% and 20.3% respectively [44].

Clinicians are more likely to vary in their likelihood to adjust warfarin dose particularly with a minimally out of range value. Studies have found that use of standardized computer-based algorithms to manage warfarin doses results in better TTR than without assistance of computers [45,88]. Stability of INR control has been shown to improve with reduction in variation of warfarin dose management even without use of computer programs.

Participants in our study had a median INR monitoring frequency of 73 days. Patients who achieved good anticoagulation control were monitored for a median of 91.3 days while those that had poor anticoagulation control were monitored a median of 73 days. In this study where a majority of the patients (71.2%) had TTR <60%, it would be expected that the patients would have had a more frequent monitoring frequency. The poorly controlled patients in our study most likely needed more frequent monitoring to try and stabilize their anticoagulation control compared to their counterparts who had good control.

Frequency of INR monitoring, whether less than 12 weeks or more than 12 weeks, was however not associated with anticoagulation control. In the study by Aspinall et al, increased monitoring did not seem to improve the amount of TTR like in our study [86]. However, this finding differs from other studies that found association between higher frequency of monitoring and good anticoagulation control. A study by Shalev et al in Israel in 4408 patients found an increase in TTR with decreased testing interval with TTR of 45% at 4 weeks testing intervals and 41% at 5 weeks testing intervals [89].

The difference might be due to patients in our study who had consistently out of range INRs probably required more frequent monitoring as compared to those that had more time in therapeutic range. In addition, the longer monitoring frequency of 12 weeks is recommended in patients who have been on stable doses of warfarin for more than 6 months and thus patients who would be monitored after longer intervals would be those that are stable and with good TTR. This analysis is however limited as not all patients in our study had stable INR control.

Other confounding factors might also have affected their anticoagulation control that required more frequent monitoring. These might include drug and food interactions, adherence to

warfarin therapy, quality of warfarin dose adjustment among others. There could be a point where increased monitoring does not result in spending more time in goal INR range [86].

Anticoagulation knowledge was not significantly associated with anticoagulation control. However, this being a secondary analysis, it is not definitive.

Previous studies that have explored the association between knowledge and anticoagulation control have found a positive association between knowledge and number of INRs in range [42,52,54].

A study by Iqbal et al in Kenya in 2017, to examine the effect of a warfarin centered patient education program on control of anticoagulation found that good anticoagulation control was achieved by 30% and 50% of the patients at pre and post-tests, respectively [51].

Overall, adequate knowledge on warfarin therapy seems to be a predictor of good anticoagulation control as seen in many studies with this association as primary objective [53–55].

5.2 Conclusion

Majority of patients on warfarin therapy at KNH had poor anticoagulation control. Patients had inadequate monitoring frequency and poor knowledge on warfarin therapy though this were not related to anticoagulation control. Majority had inappropriate dose adjustment which was a predictor of poor anticoagulation control. Bleeding complications were the commonest complication of warfarin therapy and these were significantly associated with poor anticoagulation control and spending more time in supratherapeutic range.

5.3 Recommendations

There is need for anticoagulation clinics due to the difficulty of managing warfarin. The ACCP Guidelines committee made a best practice statement where they suggested that clinicians managing warfarin therapy should do that in a coordinated way, involving educating patients, timely INR testing and appropriate dosing decisions [8].

These anticoagulation clinics should be established at KNH and even in peripheral centres where patients can easily access them. This would result in better outcomes of patients including better anticoagulation control, reduced hospital admissions for avoidable bleeding, embolism, or treatment of thrombosis.

Warfarin dosing decision support tools may be a future opportunity to additionally increase TTR as dosing adjustment practices was found to be associated with anticoagulation control.

An audit to evaluate progress regularly, assess the consequent improvement, if any, and assess annual anticoagulation control using TTR and patient outcomes will also be of much benefit to patient care.

Patients with TTRs<60% and find it difficult to maintain optimal TTR despite good education, proper dosage adjustments and frequent interventions and implementation of other patient factors should be considered for direct oral anticoagulants (DOACs).

Future studies to further investigate these challenging patients and to evaluate outcomes from different treatment options would be beneficial. On the other hand, there were also groups of patients whose TTRs were ≥60% and who did not require frequent interventions. These stable patients could still be good candidates for continuing warfarin therapy.

Reintroduction of warfarin diary that was previously used in post heart valve replacement patients would also be of great benefit to the patients.

5.4 Study Limitations

In the retrospective arm of the study, there were some information such as INR readings that were missing from patients' files. In addition, confirmation of the correctness of all the information might not have been possible. However, this limitation was partly mitigated by the qualitative aspect of the study where patients could give some of the information themselves e.g., if they had sought treatment outside KNH etc.

The Rosendaal Linear interpolation method was utilized to derive the TTR and is likely to underestimate the overall results where extreme out of range INRs exist.

Study sample size was chosen for a descriptive study hence the secondary analysis is not definitive.

The study was retrospective for the year 2019 that coincided with beginning of Covid pandemic hence might have interfered with some study findings- the extent of which cannot be determined.

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APPENDICES

Appendix I: Participants Information Sheet

Study Title- Warfarin Management practices and outcomes in ambulatory patients at Kenyatta National Hospital.

Name of investigator and institution- Dr. Catherine Njeri Kibathi

Name of sponsor: Self

Introduction

You are invited to participate in the study because you are on treatment with warfarin. It is important that you understand why the research is being done and what it will involve. Please take time to read through and consider the information carefully before you make your decision. Please feel free to enquire from the study staff if anything is unclear or if you need additional information. Once you are satisfied that you have understood the information given and you wish to take part in the study, you must sign the consent form. To take part in the study you may be required to provide information on your health history. Your participation in this study is voluntary. You may decline to answer the questions that you do not want to answer. If you volunteer for the study, you may withdraw at any time but the information you have given will still be used for the study. Your refusal to participate or withdrawal from the study will not affect medical services or benefits to which you are otherwise entitled.

Purpose of the study

The purpose of the study is to find out how warfarin is managed at this clinic and the outcomes of management with warfarin. This information will be used to improve the quality of care given to patients on warfarin therapy. A total of 144 other patients in Kenyatta National Hospital will also participate like you. The study is expected to take 4 months but your participation in the study will take a day.

Benefits for the participant

The information gathered will be shared with your doctor to aid in better treatment of your condition.

Risks: You will be required to answer a few questions which may be personal but this will help in strengthening the study. The information obtained from your file regarding your condition and management will be kept confidential.

Procedure

If you agree to participate in the study you will be asked a few questions and your file will be used to access information about your condition.

Confidentiality

The information we obtain from you will be treated with utmost confidentiality. You will be identified by an assigned unique study number. Thus, your name and file number will not appear on any data form.

If you have any questions you can contact: -

The Chairman, KNH/UON – Ethics and Research Committee
P.O BOX 20723-00202, Nairobi or Tel. 020 2726300 ext. 44355
Dr. Catherine Njeri Kibathi
P.O BOX 33249-00600, Nairobi or Tel 0725664822

Appendix II: Consent to Participate in the Study

I have read and understood the information in the consent form and it has been explained to me. My questions and concerns have been addressed. I am also aware that participation is voluntary and I can withdraw from the study at any time without consequences. I have agreed to participate in the study.

Name of the participant / guardian_____

Date_____

Signature of Participant/Guardian_____

I confirm that I have explained the details of the research to the participant.

Researcher's Name _____

Date _____

Signature of Researcher_____

Appendix III: Fomu ya Habari kwa Wanao Shiriki

Utafiti: Utafiti kuhusu mifumo ya usimamizi wa dawa ya Warfarin na matokeo katika hospitali kuu ya Kenyatta.

Mtafiti: Dr. Catherine Njeri Kibathi

Mfadhili: mtafiti atagharamia mahitaji ya utafiti huu.

Utangulizi

Umekaribishwa kujihusisha kwa utafiti huu kwa sababu unatibiwa na dawa ya warfarin kwenye hospitali kuu ya Kenyatta. Ni muhimu uelewe utafiti huu unahusu nini na nini itafanyika. Tafadhali chukua muda kusoma kwa utaratibu mpaka uelewe kabla ya kufanya uamuzi iwapo utajihusisha na utafiti huu. Uliza wasaidizi wa utafiti iwapo kuna jambo usilolielewa ama unahitaji maelezo zaidi. Iwapo umeelewa na umekubali kujiunga na utafiti huu, utahitajika kutia sahihi fomu ya idhini. Tunahitaji maelezo kuhusu hali yako ya afya ambayo lazima yawe ya kweli. Kujiunga na utafiti huu ni kwa hiari yako wala hakuna kulazimishwa. Una ruhusa kukataa au kujiondoa wakati wowote. Unapojiondoa, kumbuka kwamba maelezo yako bado yatatumiwa kwa manufaa ya utafiti huu. Kwa kujiondoa kwa utafiti utazidi kupata matibabu kama unavyostahili.

Utaratibu

Kupata takwimu za kijamii, kutoka kwako na kutumia stakabadhi zako kuangalia matibabu uliyopata na dawa ya warfarin katika hospitali ya Kenyatta.

Faida

Maarifa yatakayotokana na utafiti huu yanaweza kuboresha matibabu ya wagonjwa siku zijazo. Matokeo yatawasilishwa kwa daktari wako na rufaa mwafaka itafanyika iwapo kuna haja. Washiriki hawatapata fidia yoyote ya kifedha kwa kushiriki katika utafiti huu.

Hatari

Ushiriki wako katika utafiti huu una hatari chache. Utaweza kuhisi kwamba unasumbuliwa utakapokua unajibu maswali kuhusu maisha yako ya kibinafsi.

Usiri

Habari zote utakazotoa zitabaki kua ni siri. Vidodosi vitawekwa kwenye eneo salama ambapo ni wale tu wanahusika na utafiti huu moja kwa moja ndio watakaozipata.

Kushiriki

Kushiriki kwa utafiti huu ni kwa hiari na uko na uhuru wa kujitoa katika hatua yoyote ama kukataa kushiriki bila ya maonevu.

Maswali kuhusu utafiti

Kama una maswali yoyote tafadhali wasiliana nami kwa nambari hii ya simu: 0725664822.

Mimi…… nakubali kwamba nitashiriki katika utafiti kuhusu mifumo ya usimamizi wa dawa ya warfarin na matokeo katika hospitali kuu ya Kenyatta.

Appendix IV: Fomu Ya Idhini

Nimeelezwa asili ya utafiti huu na kuakikishiwa kwamba kushiriki kwangu ni kwa hiari na kwamba hakutakua na athari mbaya kwa afya yangu.

Sahihi/alama ya kidole: ……

Tarehe: ……

Kauli ya Mtafiti

Nimeeleza madhumuni na maana ya utafiti kwa mshiriki.

Sahihi: ……

Tarehe: ……...

Appendix V: Eligibility Criteria Assessment Form

Screening number …… Date of Screening……..

Criteria	**Yes=1 No=2**
18 years and above	
On warfarin therapy for atrial fibrillation, mechanical heart valve or DVT/PE	
On warfarin therapy >=1 month and has attended clinic at least 2 times	
Has at least two INR readings	
If female patient, is patient non-gravid	

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

Based on the criteria above, is the patient eligible for the study? YES…… NO……..

If not eligible, what is/are the reason(s) for exclusion ……

Appendix VI: Data Collection Form

Warfarin management practices and outcomes in ambulatory patients at Kenyatta National Hospital

1. **PATIENT SOCIO-DEMOGRAPHICS**

Study serial number…… Date ……

1.1) Age …….Years

1.2) Sex…… 1. Male [ ] 2. Female [ ]

1.3) Marital status ….1. Married [ ] 2. Single [ ] 3. Divorced [ ] 4. Widowed [ ]

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

1.5) Education level …0.= None 1. Informal [ ] 2. Primary [ ] 3. Secondary [ ]
4. College and above [ ]

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

2. Patient clinical Characteristics (tick as appropriate)

2.1) Date started on anticoagulation……

2.2) Indication for anticoagulation ….1. DVT [ ] 2. PE [ ] 3. Atrial fibrillation [ ]
4. Mechanical heart valve ( )

2.3) Duration of warfarin therapy 1. <=3months [ ] 2. 3-6months [ ]
3. 6-12months [ ] 4. > 12months [ ]

2.3**)** **Indicate in the table below if patient has comorbidities and medication they take for each**

Disease	Tick as appropriate	On which medication
[1] Diabetes Mellitus		
[2] Hypertension		
[3] Congestive Cardiac Failure		
[4] Renal dysfunction		
[5] Liver failure		
[6] HIV		
[7] Cancer		
[8] Others (specify) include over-the-counter drugs if any		

3. The Oral Anticoagulation Knowledge (OAK) Test

To determine whether patient has been educated on aspects of warfarin therapy and whether the patient understood.

For each question, tick the answer you think is correct or best completes the sentence correctly.

1. Warfarin may be used to:
    a) Treat people that are likely to clot
    b) Treat people that have a high blood sugar level
    c) Treat people with high blood pressure
    d) Treat people with severe wounds
2. The INR test is a blood test that:
    a) Is used to monitor your warfarin therapy
    b) Is rarely done while on warfarin
    c) Checks the amount of Vitamin K in your diet
    d) Determines if you need to be on warfarin
3. A patient with an INR value below their 'goal range':
    a) Is at increased risk of bleeding
    b) Is at increased risk of developing a clot
    c) Is more likely to have a skin rash from the warfarin
    d) Is more likely to experience side effects from warfarin
4. Once you have stabilized on the correct dose of warfarin, how many times should your INR be checked?
    a) Once a week
    b) Once a month
    c) Once every 2 months
    d) Once every 3 months
5. Drinking alcohol while taking warfarin
    a) Is safe as long as you separate your dose of warfarin and alcohol consumption
    b) May affect your INR
    c) Does not affect your INR
    d) Is safe as long as you are on a low dose of warfarin
6. Which of the following vitamins interacts with warfarin?
    a) Vitamin B12 b) Vitamin A c) Vitamin B6 d) Vitamin K
7.

8. Taking a medication containing aspirin or other non-steroidal anti-inflammatory medications such as ibuprofen while on warfarin will:
    a) reduce the effectiveness of warfarin
    b) increase your risk of bleeding from warfarin
    c) cause a blood clot to form
    d) require you to increase your dose of warfarin
9. Occasionally eating a large amount of leafy green vegetables while taking warfarin can:
    a) increase your risk of bleeding from warfarin
    b) reduce the effectiveness of warfarin
    c) cause upset stomach and vomiting
    d) reduce your risk of having a blood clot
10. When it comes to diet, people taking warfarin should:
    a) never eat foods that contain large amounts of vitamin K
    b) keep a diary of all of the foods they eat
    c) be consistent and eat a diet that includes all types of food
    d) increase the amount of vegetables they eat
11. When is it safe to take a medication that interacts with warfarin?
    a) if you take warfarin in the morning and the interacting medication at night
    b) if your healthcare provide is aware of the interaction and checks your PT/INR
    c) if you take your warfarin every other day
    d) it is never safe to take a medication that interacts with warfarin

12. A patient with an INR value above the "goal range":
    a) is at an increased risk of having a clot
    b) is more likely to have drowsiness and fatigue from warfarin
    c) is at an increased risk of bleeding
    d) is less likely to experience side effects from warfarin
13. It is important for a patient on warfarin to monitor for signs of bleeding:
    a) only when their INR is above the goal range
    b) at all times
    c) only when their INR is below the goal range
    d) only when you miss a dose
14. Missing one dose of warfarin:
    a) has no effect
    b) can alter the drug's effectiveness
    c) is permissible as long as you take a double dose the next time
    d) is permissible as long as you watch which foods you eat

15. The best thing to do if you miss a dose of warfarin is to?
    a) double up the next day
    b) take the next scheduled dose and tell your healthcare provider
    c) call your healthcare provider immediately
    d) discontinue warfarin altogether
16. A person on warfarin should seek immediate medical attention if they:
    a) skip more than two doses of warfarin in a row
    b) notice blood in their stool when going to the bathroom
    c) experience a minor nosebleed
    d) develop bruises on their arms or legs

4. Dosage Adjustments During the Study Period

a. Has the dose of warfarin been changed or omitted during the study period .?

1. Yes [ ] 2. No [ ]

b. What was the INR value at the time of dose adjustment or dose omission and the altered dosage?

Date	INR value	Dose omission or dose adjustment

5. 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 values during the study period- January 2019-December 2019

INR reading	Date	INR value
Reading 1		
Reading 2		
Reading 3		
Reading 4		
Reading 5		
Reading 6		
Reading 7		
Reading 8		

6.To Determine Frequency of Bleeding Complications

Has the patient had any of these bleeding episodes during the study period?

	Yes	No
Critical area or organ bleed e.g., intracranial, intraspinal, retroperitoneal, intraarticular, pericardial, intramuscular		
Bleeding that led to fall in Hb by 2g/dl		
Bleeding that led to transfusion		
Hospital admission for bleeding excluding the above types of bleed		
Physician guided medical or surgical treatment for bleeding		
Interruption of warfarin therapy due to bleeding		

7. TO DETERMINE THE FREQUENCY OF THROMBOTIC COMPLICATIONS

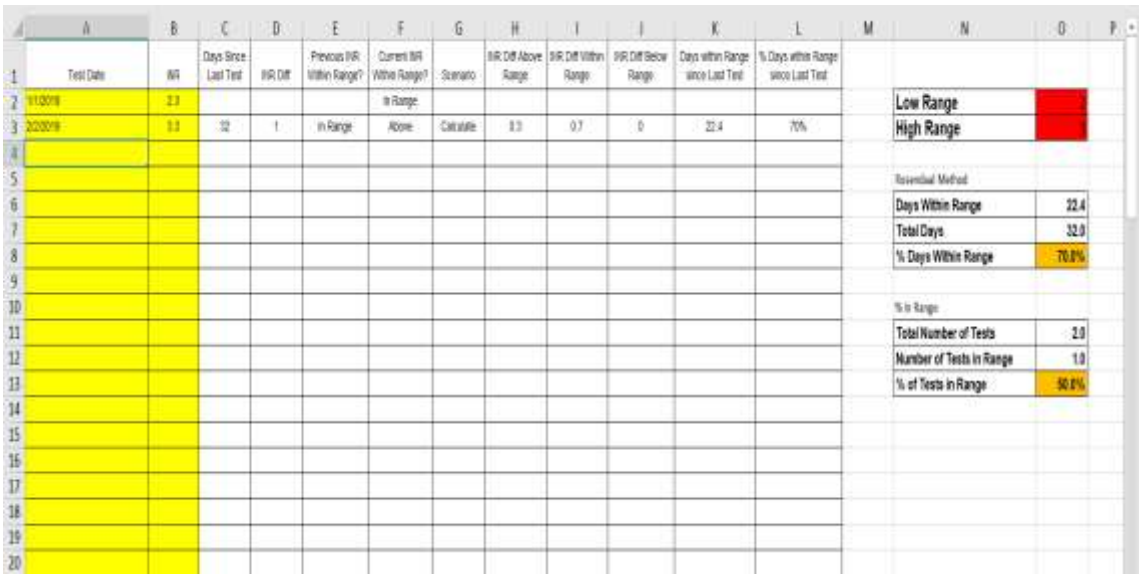
Has the patient been diagnosed with any of these during the study period?

c. Stroke ……1. Yes [ ] 2. No [ ]

d. DVT ……..1. Yes [ ] 2. No [ ]

e. Pulmonary embolism …1. Yes [ ] 2. No [ ]

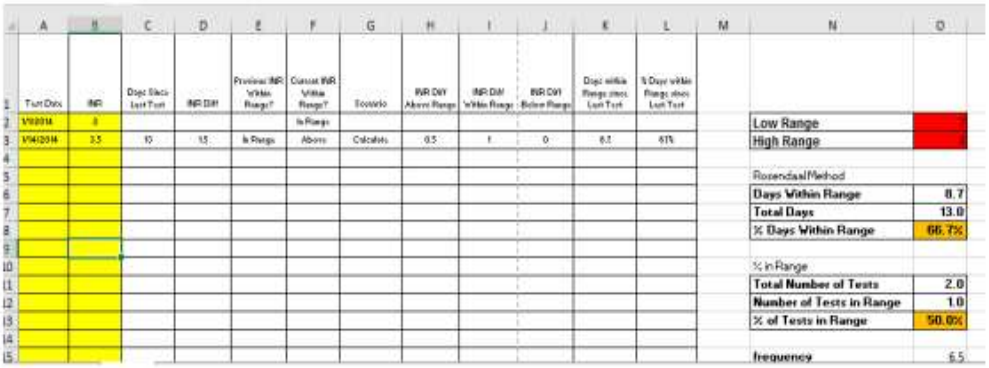
Appendix VII: Rosendaal Method for TTR Computation- Excel Template



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
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	1/1/2019	2.3				In Range								Low Range	2	
3	2/2/2019	3.3	32	1	In Range	Above	Calculate	0.3	0.7	0	22.4	70%		High Range	3	
4																
5														Rosendaal Method		
6														Days Within Range	22.4	
7														Total Days	32.0	
8														% Days Within Range	70.0%	
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																
16																
17																
18																
19																
20																

Steps

1. **Enter the therapeutic INR target depending on the indication for anticoagulation in the red cells O2 and O3; both the low and the high range**
2. **Enter the INR test dates for each INR and the result in the yellow cells- column A and B**
3. **View % in range results in cells O8 and O13 (orange cells)**



	Low Range	
	High Range	
	Rosendaal Method	
	Days Within Range	8.7
	Total Days	13.0
	% Days Within Range	66.7%
	% in Range	
	Total Number of Tests	2.0
	Number of Tests in Range	1.0
	% of Tests in Range	50.0%
	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%

BUDGET

Category	Item description	Units	Cost per unit	Total cost
Proposal development	Printing drafts	500 copies	10	5000
	Printing copies	500	10	5000
	Ethics committee fee	3000	1	3000
Data collection	Patient transport cost	200	150	40,000
	Stationery	20	10	2000
	Research assistant	2	45,000	45,000
	Consent forms	300	10	3000
	Study pro-forma	300	10	3000
Data analysis	Statistician	1	40,000	40,000
Thesis write up	Printing drafts	500 copies	10	5000
	Printing thesis	500 copies	10	5000
Contingencies				20,000
Total				176,000

Appendix

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Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725372
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/288

9th August, 2021

APPROVED
09 AUG 2021
KNH-UON ERC

Dr. Catherine Njeri Kibathi
Reg. No.H58/11452/2018
Dept. of Clinical Medicine and Therapeutics
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Kibathi

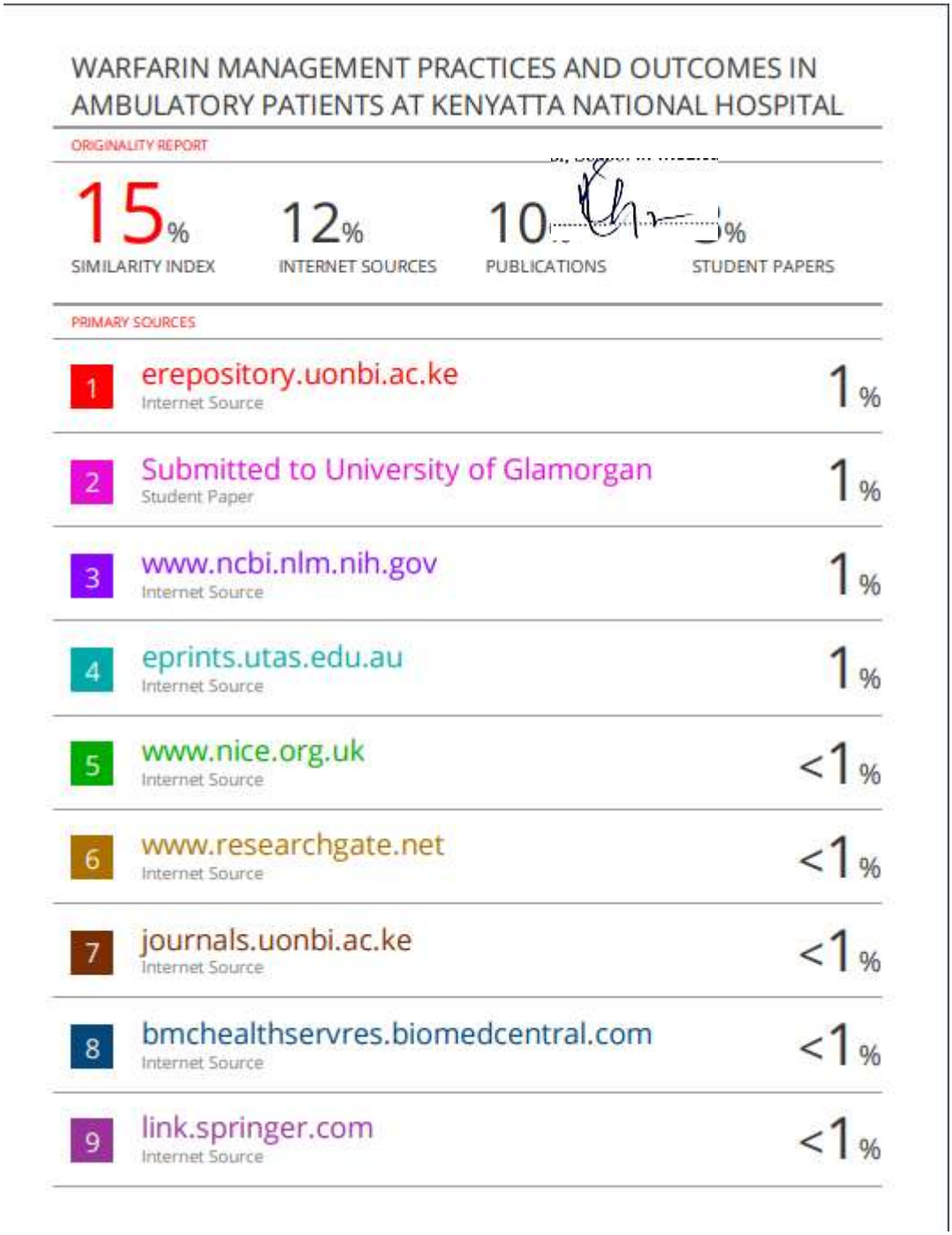
RESEARCH PROPOSAL: WARFARIN MANAGEMENT PRACTICES AND OUTCOMES IN AMBULATORY PATIENTS AT KENYATTA NATIONAL HOSPITAL (P232/04/2021)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and approved your above research proposal. The approval period is 9th August 2021 – 8th August 2022.

This approval is subject to compliance with the following requirements:

i. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
ii. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
iii. 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.
iv. 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.
v. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (Attach a comprehensive progress report to support the renewal)
vii. Submission of an executive summary report within 90 days upon completion of the study.

Appendix Plagiarism report



WARFARIN MANAGEMENT PRACTICES AND OUTCOMES IN AMBULATORY PATIENTS AT KENYATTA NATIONAL HOSPITAL

ORIGINALITY REPORT

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