College of Health Sciences
School of Pharmacy
Department of Social and Administrative Pharmacy

PHARMACIST-LED ANTICOAGULATION SERVICES AND PATIENT KNOWLEDGE, ADHERENCE, AND SATISFACTION WITH WARFARIN THERAPY: A MULTI-METHOD STUDY AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ETHIOPIA

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A PhD dissertation submitted to the Department of Social and Administrative Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Social and Administrative Pharmacy

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This is to certify that the dissertation prepared by Tamrat Assefa Tadesse, entitled **'Pharmacist-Led Anticoagulation Services and Patient Knowledge, Adherence, and Satisfaction with Warfarin Therapy: A Multi-Method Study at Tikur Anbessa Specialized Hospital, Ethiopia'** and submitted in partial fulfilment of requirements for the Degree of Doctor of Philosophy in Social and Administrative Pharmacy complies with the regulation of University and meets the accepted standard concerning originality and quality.

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List of Published Papers

This PhD dissertation is based on four original published papers. These papers are referred to as Papers I, II, III, and IV in this dissertation, and are listed below.

I. **Tadesse TA,** Tegegne GT, Yadeta D, Chelkaba L, Fenta TG. Anticoagulation control, outcomes, and associated factors in long-term care patients receiving warfarin in Africa: a systematic review. Thromb J. 2022 Oct 3;20 (1):58. doi: 10.1186/s12959-022-00416-9

II. **Tadesse TA**, Abiye AA, Endale S, Yadeta D, Chelkeba L, Fenta TG. Challenges of Anticoagulation Management Service and Need of Establishing Pharmacist-Led Anticoagulation Clinic in Tertiary Care Teaching Hospital, Ethiopia: A Qualitative Study. J Multidiscip Healthc. 2022 Apr 6; 15:743-754. doi: 10.2147/JMDH.S359558

III. **Tadesse TA**, Yadeta D, Chelkeba L, Gebremedhin A, Fenta TG. Knowledge, Adherence, and Satisfaction with Warfarin Therapy and Associated Factors Among Outpatients at University Teaching Hospital in Ethiopia. Clin Appl Thromb Hemost. 2024; 30:110760296241260736. Doi:10.1177/10760296241260736

IV. **Tadesse TA**, Gebremedhin A, Yadeta D, Chelkeba L, Fenta TG. Comparison of anticoagulation control and outcomes between usual medical care and pharmacist-led anticoagulation service in ambulatory patients taking warfarin at a tertiary hospital in Ethiopia: a quasi-experimental study. *J Pharm Health Care Sci*. 2024;10 (1):32. doi:10.1186/s40780-024-00355-9

Abstract

Pharmacist-Led Anticoagulation Services and Patient Knowledge, Adherence, and Satisfaction with Warfarin Therapy: A Multi-Method Study at Tikur Anbessa Specialized Hospital, Ethiopia

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Background: Warfarin remains the cornerstone for preventing thromboembolic events (TEEs), but a narrow therapeutic range, complex pharmacokinetics, and interactions with various substances complicate its use. Specialized anticoagulation management services (AMS) are known to improve warfarin control and outcomes; however, there is limited evidence of their effectiveness in Africa, particularly in Ethiopia.

Objective: This dissertation aimed to synthesize evidence on anticoagulation control and outcomes in Africa and explore experiences and challenges of the existing AMS and the need to establish pharmacist-led anticoagulation services (PLAS) at Tikur Anbessa Specialized Hospital (TASH), Ethiopia. It also assesses patients' knowledge, adherence, and satisfaction with warfarin therapy and compares anticoagulation control and outcomes between usual medical care (UMC) and PLAS in ambulatory patients receiving warfarin therapy at TASH.

Methods: This research employed four complementary study designs: systematic review, qualitative study, cross-sectional study, and quasi-experimental study. Anticoagulation Knowledge Assessment (AKA) questionnaire, Morisky Green Levine Scale (MGLS), and anticlot treatment scale (ACTS) were used to evaluate patients' knowledge, adherence and satisfaction with warfarin therapy, respectively. Data from quasi-experimental and cross-sectional studies were analyzed using the Statistical Package for the Social Sciences (SPSS) version 27.

Results: From 18 studies included in the systematic review, a mean TTR of 39.4%, 36.7%, and 46% using Rosendaal, direct, and cross-section-of-the-files methods were reported, respectively, ranging from 13.7% to 57.3%. Thromboembolic complications and bleeding events occurred in 1.6–7.5% and 0.006–59% of patients, respectively. The AMS at TASH lacked standard protocols, trained healthcare professionals and a separate AMS clinic. Inconsistent availability of international normalized ratio (INR) testing and anticoagulants, and long appointment times were the main challenges of the existing AMS. The mean AKA score was 59.35 ± 13.04 %, and only 23.4% of participants achieved a passing score. One hundred ninety-two (54.9%) study participants adhered

well to warfarin, and the mean level of satisfaction was 53.67 ± 8.56 and 52.6% of patients were satisfied with the warfarin therapy. Living with family improved adherence, while a lack of hyperthyroidism was associated with poor warfarin knowledge. The PLAC group had a significantly higher median TTR [60.89% vs. 53.65%, p<0.001] and more patients achieved optimal TTR [41.7% vs. 31.7%, p=0.002] than the UMC group. The odds of having a poor TTR were reduced by 43% (AOR = 0.57, 95% CI = 0.36–0.88, p = 0.01) in the PLAC group compared to the UMC group. The secondary outcomes showed no significant difference, except for fewer all-cause emergency visits (p = 0.003) in the PLAC group. Monitoring frequency was inversely related to poor TTR and bleeding risk. However, high CHA_2DS_2-VASc scores were strongly associated with TEEs. Additionally, fewer all-cause emergency visits were reported in the PLAS group.

Conclusions: Oral anticoagulation control among patients receiving warfarin in Africa was suboptimal. At TASH, AMS was also inadequate, hindered by both system-level and patient-related challenges. Following the implementation of PLAS, patients in the PLAS group had a significantly higher median TTR and a greater proportion achieved optimal TTR compared to the UMC group.

Keywords: anticoagulation management service; anticoagulation control and outcomes; warfarin; anticoagulation knowledge assessment; adherence; anticlot treatment scale; pharmacist-led anticoagulation clinic; usual medical care; Tikur Anbessa Specialized Hospital, Africa, Ethiopia

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Acronyms and Abbreviations

ACTS	Anticlot treatment scale
AKA	Anticoagulation knowledge assessment
AMS	Anticoagulation management service
AOR	Adjusted odds ratio
CAD	Coronary artery disease
CHA_2DS_2-VASc score	Congestive heart failure, Hypertension, Age >_75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female)
CHCs	Cardiac and hematology clinics
CI	Confidence interval
COR	Crude odds ratio
DVT	Deep vein thrombosis
ESC	European Cardiac Society
HAS-BLED score	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly
INR	International normalized ratio
IRR	Incidence rate ratio
IQR	Interquartile range
ISI	International Sensitivity index
MGLS	Morisky Green Levine Scale
OAT	Oral anticoagulant therapy
OR	Odds ratio
PE	Pulmonary embolism
PLAC	Pharmacist-led anticoagulation clinic
PLAS	Pharmacist-led anticoagulation services
PMAC	Pharmacist-managed anticoagulation clinic
PSM	Patient self-management
PST	Patient self-testing
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PT	Prothrombin time
QMUL	Queen Mary University of London
SPSS	Statistical Package for Social Sciences
TASH	Tikur Anbessa Specialized Hospital
TEEs	Thromboembolic events
TTR	Time in the therapeutic range
UMC	Usual medic care
US	United States
WDI	Warfarin drug interaction
VKA	Vitamin K antagonists
VTE	Venous thromboembolism

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Chapter One: Introduction

1.1 Background

Thrombosis is a pathological clot formation that occurs when hemostasis is inappropriately activated without bleeding (Litvinov & Weisel, 2023; Rumbaut RE, 2012). Thromboembolic disorders are major health problems that can lead to significant morbidity and mortality. Venous thromboembolism (VTE) is a common and lethal disorder that sssssss both hospitalized and non-hospitalized patients, (Anderson et al., 2019; Gregson et al., 2019). The incidence rate of VTE varies by country, with Western countries ranging from 1 to 2 per 1000 person-years, while Eastern countries have a lower incidence(Pastori et al., 2023). The diagnosis of VTE can be challenging because it often does not present with symptoms. Moreover, VTE, which is symptomatic but nonfatal, can lead to significant morbidity, long-term complications, and increased consumption of healthcare resources (Witt et al., 2018).

Identifying patients at risk of developing thromboembolic events (TEEs), the ongoing appropriateness of primary VTE prophylaxis according to the type, dose, and duration of prophylaxis and prevention of prolonged complications should be considered when managing patients who require anticoagulation therapy (Anderson et al., 2019). Anticoagulation therapy, including warfarin, is required to prevent the occurrence, recurrence, and complications of TEEs such as stroke, heart attack, pulmonary embolism, and deep vein thrombosis (Wigle et al., 2019) in patients with atrial fibrillation (AF) and mechanical heart valves or the treatment of venous thromboembolism (Kearon et al., 2016; Sonuga et al., 2016). The safety and efficacy of warfarin therapy depend mainly on careful monitoring and maintenance of the international normalized ratio (INR) within the optimal therapeutic range (Albabtain et al., 2020; Alghadeeer et al., 2020; L. Marcatto et al., 2021; Witt et al., 2018). Warfarin has unpredictable pharmacokinetics and dynamics, narrow therapeutic index, frequent medication interactions, and effects of concomitant diseases and requires individualized dosing to achieve optimal anticoagulation by monitoring INR (Ebrahim et al., 2018; L. R. Marcatto et al., 2018) (a standard test that helps to monitor the effectiveness of vitamin K antagonists like warfarin) (Siddiqui et al., 2018). The risk of bleeding and thromboembolic complications increases if the anticoagulation target ranges are not achieved (S. Karuri et al., 2019; Minno et al., 2017; Phelps et al., 2018).

Patient knowledge, adherence, and satisfaction with oral anticoagulation therapy (OAT) significantly affect optimal anticoagulation and decrease morbidity and mortality (X. Li et al.,

2018; L. Marcatto et al., 2021; Q. Wang et al., 2018). Knowledge of warfarin, its potential side effects, interacting medicines and foods, and the need for warfarin adherence play a role in attaining the desired therapeutic outcome while preventing adverse reactions(Shakya et al., 2023). A study conducted at Tripoli University Hospital in Libya revealed a positive correlation between oral anticoagulant knowledge, adherence to warfarin therapy, and time in the therapeutic range (TTR) (Mayet, 2015). Medication adherence is an integral part of patient care to achieve optimized anticoagulation control and outcomes. According to a Jordanian study, patients who adhered to their medication were more likely to have better anticoagulation control than non-adherent patients (Ababneh et al., 2016). Previous studies have shown that patients' adherence to warfarin therapy is suboptimal, that is, in the range of 27.5%–54.9% (Elbur et al., 2015; Mayet, 2016; Obamiro et al., 2018a). Several factors, including poor health literacy, lack of patient education, complex dosing regimens, clinical characteristics, knowledge of warfarin, low income, marital status, living arrangements, and drug regimens, play significant roles in warfarin non-adherence (Benzimra et al., 2018; Song et al., 2021).

A study conducted in Brazil documented that providing pharmaceutical care to improve adherence to warfarin therapy resulted in better anticoagulation quality compared with those who did not adhere to therapy(L. Marcatto et al., 2021). Furthermore, patient satisfaction is a critical factor that influences treatment adherence, clinical outcomes, and healthcare utilization (Shilbayeh & Ibrahim, 2020). Warfarin characteristics that include the need for regular blood testing, limitations of lifestyle, and the fear of bleeding may result in a reduction of both patient satisfaction and quality of life (Elbur et al., 2015). Few studies have documented a moderate level of patient satisfaction with oral anticoagulation therapy and its effect on anticoagulation control in patients taking warfarin (Fernández et al., 2018; Schwanda & Gruber, 2019; Shilbayeh & Ibrahim, 2020).

1.2 Statement of the Problem

Warfarin is a highly effective drug, but it's challenging to use in clinical practice (Albabtain et al., 2020; Björck et al., 2016). It is one of the top drugs associated with serious adverse events and emergency department admissions (Pengo & Denas, 2018). It also exhibits significant interindividual variations between and within patients in a dose-response manner (S. Li et al., 2015). In addition, it has many drug-food interactions (Minno et al., 2017). Miscommunication between patients and physicians regarding dosing, poor patient knowledge, adherence, and

satisfaction with anticoagulation treatment are also common problems associated with warfarin use (Ababneh et al., 2016; Mayet, 2016; Y. Wang et al., 2014).

Achieving a good TTR of at least 65% is the best indicator of good quality anticoagulation management in patients receiving warfarin therapy (Esteve-Pastor et al., 2018; Turen & Turen, 2023). However, managing warfarin therapy for adequate anticoagulation has been challenging due to its complexity, as studies conducted in both developing and developed countries have reported a lower percentage of TTR (<65%) (Albabtain et al., 2020; Botsile & Mwita, 2020b; Caldeira et al., 2014; Chan et al., 2015; de Castro et al., 2021; Farsad et al., 2016; Gateman et al., 2017; Krittayaphong et al., 2020; Mwita et al., 2018; Quinn et al., 2015; Ugur et al., 2015; Urbonas et al., 2019). Numerous studies have shown that a substantial proportion of warfarin-treated patients spend a significant amount of time outside their target INR range (Botsile & Mwita, 2020b; Carvalho et al., 2013; W. S. Karuri, 2016; Prinsloo et al., 2021; Urbonas et al., 2019), with higher risks of bleeding, thrombosis, and death owing to poor quality warfarin control during warfarin therapy (Ben Rejeb et al., 2019; Chan et al., 2015). Lower TTR in patients receiving warfarin has also been observed in studies conducted in different African countries (Jonkman et al., 2019; S. Karuri et al., 2019; Mariita et al., 2016; Ouali et al., 2021; Sadhabariss & Brown, 2021; Semakula et al., 2020). Poor anticoagulation control is associated with a higher risk of adverse clinical outcomes, including ischemic stroke, transient ischemic attack, major bleeding, intracranial hemorrhage, and death (Krittayaphong et al., 2020). A systematic review and meta-regression analysis revealed that an increased mean TTR is significantly associated with a lower rate of major bleeding and stroke/systemic embolism (Vestergaard et al., 2017).

Similarly, in Ethiopia, few studies have evaluated anticoagulation control in patients taking warfarin, with TTR reports in the range from 29-42.7% (Fenta et al., 2017; Getachew et al., 2023; Liyew et al., 2017; Masresha et al., 2021; Yimer et al., 2021), indicating Ethiopian settings are far behind the recommended TTR goal. Moreover, studies conducted in the same hospital showed inadequate counseling services provided by healthcare professionals regarding warfarin therapy (Dejene et al., 2017; Tadesse & Woldu, 2018). Another study from the Ayder Referral Hospital in Northern Ethiopia found that the prevalence of warfarin-drug interactions and hemorrhagic events was 99.2% and 16.5%, respectively (Teklay et al., 2014).

Poor knowledge of warfarin among patients and lack of education from healthcare providers may lead to worsened anticoagulation control. Only 13.9% of patients obtained a passing score on the anticoagulation knowledge assessment in Ethiopia (Assefa et al., 2014), while the mean score on oral anticoagulant treatment knowledge was 59.39% among Hungarian patients (Viola et al., 2017) and only 14.9% of Saudi Arabian patients had adequate knowledge(Elbur et al., 2015). In a study conducted in India, 50% of patients who had suffered a stroke or were at a high risk of thromboembolic events had inadequate knowledge of oral anticoagulant therapy (OAT)(Alphonsa et al., 2015).

Medication adherence is integral to patient care to achieve optimized anticoagulation control and outcomes(Pandya & Bajorek, 2017). The prevalence of adherence to warfarin varies from 27.5 to 54.9% (Mayet, 2016; Obamiro et al., 2018a). Patients taking warfarin who do not adhere to their medication regimen are more likely to have non-therapeutic INRs, which can contribute to unfavorable anticoagulation outcomes, including an increased risk of bleeding and thromboembolic events (L. Marcatto et al., 2021). Several factors, including poor health literacy, lack of patient education, complex dosing regimens, clinical characteristics, knowledge of warfarin, low income, marital status, living arrangements, and drug regimens, play significant roles in warfarin nonadherence (Benzimra et al., 2018; Song et al., 2021). The burden of anticoagulation treatment affects patient satisfaction with their anticoagulation treatment(Pandya & Bajorek, 2017). Patient satisfaction is an important factor in the success of anticoagulation therapy (Keita et al., 2017) as it can affect medication adherence and overall clinical outcomes. Studies have reported a moderate level of patient satisfaction with OAT and its effect on anticoagulation control in patients taking warfarin (Fernández et al., 2018; Schwanda & Gruber, 2019). Improving patient satisfaction with OAT can result in better clinical outcomes and reduce the risk of adverse events such as bleeding and thrombosis (G. D. Barnes & Kline-Rogers, 2015).

These persistent low TTR findings emphasize the necessity of alternative strategies to improve the quality of anticoagulant therapy. Specialized anticoagulation management services (AMS) have been successful in optimizing anticoagulation therapy by evaluating and monitoring patients, providing continuing patient education, and serving as a resource for both patients and physicians (G. D. Barnes et al., 2016; Clark, 2018; Elewa et al., 2016; Phelps et al., 2018). Pharmacist-led anticoagulation services (PLAS) represent the best practices for enhancing quality of care and improving outcomes in anticoagulation management, particularly in

developed countries (Aidit et al., 2017; Alghadeeer et al., 2020; Elewa et al., 2016; J. Harrison et al., 2015; Jiang et al., 2021; Thanimalai, 2013; Young et al., 2011). According to a study conducted in Canada, patients treated in pharmacist-managed anticoagulation clinics (PMAC) had a significantly higher TTR than those treated at usual medical care (UMC) (Young et al., 2011). Another systematic review and meta-analysis showed that pharmacist-led anticoagulation management resulted in reduced rates of total bleeding and thrombotic events (Hou et al., 2017). Additionally, a study conducted in Malaysia found significant improvements in TTR ($p < 0.01$) and expanded therapeutic INR range ($p<0.04$) and INR levels ($p<0.02$) in pharmacist-led warfarin medication therapy adherence clinics compared with the UMC group (Aidit et al., 2017). Increased TTR, decreased rates of admission and average clinic visits, lower risk of total hemorrhage and thrombosis events (Hou et al., 2017; Rudd & Dier, 2010; Shah et al., 2010), and improved adherence to treatment have been documented after pharmacist-led anticoagulation therapy (L. Marcatto et al., 2021; Mayet, 2015).

Therefore, expanding the role of pharmacists in anticoagulation care can significantly improve patient care in anticoagulation management (N. O. Ahmed, Osman, Abdelhai, & El-Hadiyah, 2017; Aidit et al., 2017; Alghadeeer et al., 2020; Hailemariam et al., 2019; Hou et al., 2017; Jones et al., 2020; Manzoor et al., 2017) by establishing pharmacist-led anticoagulation clinic (PLAC), which provides patients with consistent management, closer monitoring, education, and awareness of anticoagulation therapy (N. T. Tran et al., 2021). PLAC helps to achieve targeted anticoagulation control, maintains the desired INR range, reduces bleeding and thromboembolic complications, and detects interacting drugs and foods that can affect warfarin efficacy and safety, leading to improved AMS quality (Alghadeeer et al., 2020; Elewa et al., 2016; Jiang et al., 2021; Manzoor et al., 2017; Testa et al., 2012).

Considering the practical limitations and complex nature of effective anticoagulant delivery, adopting such practices may enhance treatment response and improve patient outcomes in resource-limited settings. Drawing evidence from previous studies on the significance of PLAS in improving anticoagulation quality in patients on warfarin (N. O. Ahmed, Osman, Abdelhai, & El-Hadiyah, 2017; Aidit et al., 2017; Hailemariam et al., 2019; Hou et al., 2017; Jones et al., 2020; Manzoor et al., 2017) and recommendations from need assessment study at the same hospital (Tadesse, Abiye, et al., 2022), the first PLAC in Ethiopia was established at the Tikur Anbessa Specialized Hospital (TASH). Although the differences in anticoagulation control and

outcomes between UMC and PLAC have been extensively explored in numerous studies, no similar study has been conducted in Ethiopia. This study is unique because of the specific healthcare context in Ethiopia, which requires tailored intervention strategies to address challenges such as resource constraints, diverse cultural settings, low health literacy levels, limited diagnostic tools, underdeveloped electronic health records, and a shortage of well-trained healthcare providers. Evidence from other regions cannot be directly applied to Ethiopia's healthcare system. Therefore, this study aimed to evaluate the feasibility and effectiveness of PLAC in resource-limited settings by comparing anticoagulation control and outcomes between PLAC and UMC groups, with the hypothesis that the PLAC group will achieve better anticoagulation control and improved clinical outcomes. Additionally, this study addressed the scarcity of research on patients' knowledge, adherence, and satisfaction with warfarin therapy in Ethiopia, despite its significance in optimizing anticoagulation control and outcomes, and identified the factors associated with these outcomes, specifically in those receiving AMS at the UMC of the hospital.

1.3 Significance of the Study

This study is crucial for understanding the differences between UMC and PLAC in anticoagulation management control and outcomes in patients taking warfarin by demonstrating potential improvements in patient outcomes, which can lead to the efficient use of healthcare resources. This would serve as the starting point for creating and designing a new anticoagulation management system in Ethiopia by developing strategies to address the possible poor outcomes. Moreover, this study is vital for identifying areas where healthcare professionals who manage patients require further information and education. The findings of this study can be extended to other hospitals in Ethiopia and similar healthcare settings, especially in low- and middle-income countries. Consequently, the intervention part of this study will allow future patients to benefit from new evidence-based recommendations for the management of oral anticoagulation therapy.

Furthermore, this study provides valuable evidence for policymakers to decide the type of AMS model for long-term oral anticoagulation. Characterizing and identifying the factors associated with anticoagulation control and outcomes as well as patient knowledge, adherence, and satisfaction are crucial for establishing a foundation for future studies. This study contributes to scientific advancement and provides a guide for future research on anticoagulation therapy and pharmacist-led care, with broad implications for various patient populations and healthcare systems.

1.4 Structure of Dissertation

This PhD dissertation is organized into seven chapters derived from four manuscripts. The First chapter, Introduction, covers background information on thrombosis, anticoagulation management, the role of pharmacists in anticoagulation control, a statement of the problems, and the significance of the study. Chapter Two reviews the literature related to the research topic and relates concepts and empirical issues to the research context. This chapter concludes by describing the conceptual framework of this study. Chapter Three outlines the research questions and objectives. Chapter Four presents the methods used to address the research questions, including the rationale for selecting these methods, study setting, design, population, sample size and selection, data collection methods, data processing and management, analysis, and ethical considerations. Chapter Five provides a summary of the research findings. Chapter Six presents a discussion of the four manuscripts included in this dissertation in the context of the existing literature. This chapter also describes the strengths and limitations of the research and highlights the implications of the findings for practice and policy. Chapter Seven presents the conclusions and recommendations of this dissertation, and suggests areas for further research on the long-term impact of PLAS and strategies to improve patient knowledge, satisfaction, and adherence to warfarin therapy.

Chapter Two: Literature Review

2.1 Overview of Thrombosis

Coagulation and fibrinolytic systems are composed of various activators and inhibitors that maintain a proper balance in the body. However, if any of these components are excessively activated or deactivated due to congenital or acquired abnormalities, it can lead to abnormal blood clotting (thrombosis) (Loftus, 2016). Thrombosis leads to the formation of a fibrin clot, which is a key event in the development of thrombotic diseases and the culmination of the coagulation cascade (Kattula et al., 2017; Litvinov & Weisel, 2023). An embolus is a small part of this clot that breaks off and travels through blood vessels to another part of the body. When the embolus is trapped in a small vessel, it causes obstruction, which results in reduced blood flow to the surrounding tissue, causing ischemia or infarction (Wendelboe & Raskob, 2016).

Thromboembolic conditions can be divided into arterial and venous types. Ischemic heart disease and ischemic stroke comprise the major arterial thromboses (Wendelboe & Raskob, 2016), whereas deep vein thrombosis and pulmonary embolism comprise VTE (Lutsey & Zakai, 2023). The cause of venous thrombosis is unclear, but it may be due to slow blood flow behind the venous valves and a hypoxic or inflammatory stimulus of endothelial cells, which triggers coagulation and causes them to release proteins that entrap platelets and leukocytes (Mackman, 2012). Individuals with cardiovascular diseases, such as valvular heart disease, atrial fibrillation, heart valve replacement, stroke, acute and chronic coronary syndrome, and cardiomyopathy, are at high risk of developing thromboembolism and its complications (Otto et al., 2021), which are major causes of cardiovascular death. There are approximately 10 million cases of VTE every year, and it is the third leading vascular disease after myocardial infarction and stroke (Gregson et al., 2019). It is estimated to affect one–two individuals per 1,000 person-years in Europe and the United States (US), with lower rates in other regions (Lutsey & Zakai, 2023).

2.2 Anticoagulation with Warfarin

Oral anticoagulants, including warfarin, are highly effective in preventing stroke in patients with atrial fibrillation or a mechanical valve and in preventing and treating VTE (G. D. Barnes & Kline-Rogers, 2015; Kearon et al., 2016). Anticoagulant selection should be guided by the risks, benefits, and specific pharmacological properties of each anticoagulant agent(Vinogradova et al., 2018). Warfarin is one of the anticoagulants used in long-term and extended-phase anticoagulation for VTE. It is a vitamin K antagonist that interferes with the

hepatic synthesis of procoagulant vitamin K-dependent clotting factors II, VII, IX, and X, as well as the synthesis of anticoagulant proteins C, S, and Z (Nutescu et al., 2016). Its narrow therapeutic index, hepatic metabolism, genotype, the influence of diet (foods high in vitamin K), drug-drug interactions, smoking, alcohol consumption, body weight, age, and health status of patients make it a drug that requires frequent dose adjustment (Tavares et al., 2018; Vianna et al., 2021). Therefore, warfarin dose must be determined by regular laboratory monitoring of prothrombin time (PT), which is reported as the international normalized ratio (INR). PT is sensitive to changes in the serum concentrations of vitamin K-dependent clotting factors. The extrinsic pathway of the coagulation cascade was accelerated by adding calcium and tissue thromboplastin to the plasma collected via venipuncture, and the time to clot formation was measured in seconds. However, the ability of thromboplastin reagents to detect warfarin-induced clotting defects varies considerably(Nutescu et al., 2016). To standardize the test results, the World Health Organization developed a system in which each commercial reagent batch produced by any manufacturer is assigned an International Sensitivity Index (ISI). This index is compared with the international reference thromboplastin, which has an ISI of 1.0. The ISI is used to convert prothrombin time in seconds to INR using a specific mathematical formula (Dorgalaleh et al., 2021; Nutescu et al., 2016):

$$INR = \frac{PT_{patient}{}^{ISI}}{PT_{mean\ normal}}$$

In general, using this method, the PT results obtained at different laboratories are consistent, as long as the instruments used for measurement are calibrated appropriately. For the prevention and treatment of VTE, the INR target is 2.5 with an acceptable range of 2–3(Nutescu et al., 2016) and 3 in the case of high-intensity anticoagulation in patients with mechanical valve replacement with a target range of 2.5 to 3.5(Ntlokotsi et al., 2018). Warfarin is highly susceptible to interactions with prescription and non-prescription drugs, as well as with herbal and other natural products. The concurrent use of agents that alter the absorption, distribution, metabolism, or excretion of warfarin can result in pharmacokinetic interactions that may elevate or reduce INR, thereby increasing the risk of hemorrhagic or thromboembolic complications (Nutescu et al., 2016). In addition, pharmacodynamic interactions can influence the response to warfarin without altering its pharmacokinetics or increasing the risk of bleeding or thromboembolism without influencing INR. Furthermore, many disease states and conditions can affect patient sensitivity to warfarin. Factors such as liver disease, heart failure,

thyroid disorders, and genetic variations should be considered when determining initial and ongoing doses of warfarin.

The efficacy and safety of warfarin therapy are closely associated with anticoagulation control (Esteve-Pastor et al., 2018). Several indices of anticoagulation quality have been proposed, with TTR being the most widely used (Nieto et al., 2019). Time in therapeutic range (TTR) is a useful indicator of anticoagulation control, which estimates the percentage of time a patient's INR levels remain within the desired treatment range over time (Farsad et al., 2016). The three common methods for calculating TTR are the Rosendaal linear interpolation method (the number of days in range divided by the total monitored days), the fraction of INRs in range, or the direct or traditional method (the number of INRs in ranges divided by the number of INRs tested), and the cross-section-of-the-files method, which takes each patient whose INR is within range at one point in time divided by the total number of INRs performed on all patients (Rosendaal et al., 1993; Siddiqui et al., 2018). The Rosendaal method assumes a linear progression of the change in INR between a patient's visits; in other words, it assumes that the INR changes by the same amount each day and computes the INR for any specific day(Rosendaal et al., 1993). Traditional and cross-sectional methods do not treat the INR as a dynamic value that changes over time. Instead, these methods consider each INR value as static or binary, either in or out of range. Owing to their design and inherent assumptions, each method can yield significantly different TTR values (Palareti et al., 2016; Siddiqui et al., 2018). In patients receiving vitamin K antagonists (VKAs), a TTR ≥65% results in optimal anticoagulation, which reduces the risk of stroke and bleeding (Farsad et al., 2016; Liyew et al., 2017; McAuliffe et al., 2018). However, the European Society of Cardiology (ESC) guidelines recommend a TTR ≥70% to ensure effective VKA treatment (Hindricks et al., 2021).

2.3 Patient Knowledge of Warfarin Therapy

Knowing how warfarin works, its potential side effects, the importance of regular INR monitoring, interacting drugs and food, and necessary precautions are crucial for enhancing anticoagulation outcomes and minimizing adverse reactions (H. Ahmed et al., 2021; Pourafkari et al., 2018; Shrestha et al., 2015). Good knowledge of anticoagulants is linked to improved attainment of the target INR, reduced side effects, and enhanced quality of oral anticoagulation (da Silva Praxedes et al., 2023; Obamiro et al., 2018b; Praxedes et al., 2016, 2020). However, despite its importance, patient knowledge regarding therapy is limited. A study from Nepal found that only 5.8 and 67.6 % of patients achieved passing scores and scored below 50% on

anticoagulation knowledge assessment (AKA) questionnaires, respectively (Shrestha et al., 2015).

Similarly, another study from the same country reported that only 15.8% of patients had good knowledge of warfarin therapy, and found a significant association between age, literacy level, education status, and knowledge of warfarin (Shakya et al., 2023). In Libya, many patients were unaware of drug interactions or vitamin K status and their effects, and only 40% were aware of the effect of green vegetables on warfarin, whereas others ignored this effect(H. Ahmed et al., 2021). Literature suggests that patient education is a key factor for optimizing anticoagulation and safety in patients taking warfarin (Cao et al., 2020; Joshua & Kakkar, 2015), which can be improved by developing structured educational programs, printed materials, and digital tools for oral anticoagulants, including warfarin therapy (H. Ahmed et al., 2021; Hawes, 2018).

2.4 Adherence to Warfarin Therapy

Long-term effective management requires good adherence to achieve target outcomes, but is often low (Gast & Mathes, 2019; Luger et al., 2015). Adherence to warfarin therapy is crucial for maintaining therapeutic effectiveness and minimizing the risk of adverse events (L. Marcatto et al., 2021). However, many patients do not take their medication as prescribed. Previous studies have identified a lower adherence rate among patients receiving warfarin (27.5 to 35.9% (Elbur et al., 2015; Kim et al., 2011; Shilbayeh et al., 2018; M. H. Tran et al., 2023). Factors associated with nonadherence to warfarin therapy were female sex, unemployment, younger age, absence of formal education (Mayet, 2016), male sex, and previous VTE history (M. H. Tran et al., 2023).

According to a systematic review and meta-analysis (Salmasi et al., 2020), non-adherent patients were more likely to experience stroke and death and incur higher medical costs than those with poor adherence. Understanding the magnitude and factors associated with nonadherence to warfarin therapy is crucial for developing effective interventions to improve medication adherence, prevent thromboembolic events, and optimize anticoagulation control (Ababneh et al., 2016). Despite the importance of adherence to warfarin therapy, no study has examined its magnitude and its associated factors in Ethiopia. Effective strategies, such as patient education, technological interventions, and pharmacist-led programs, have been proven

to enhance adherence to warfarin therapy(Ababneh et al., 2016; Kim et al., 2011; Murray, 2017).

2.5 Patient Satisfaction with Warfarin Therapy

The burden of anticoagulation treatment affects the patient satisfaction (Y. Wang et al., 2014). Treatment satisfaction has been identified as an important contributing factor to adherence to oral anticoagulant (OAC) therapy (Laba et al., 2015; Salmasi et al., 2021) and improved anticoagulation control (Keita et al., 2017; Y. Wang et al., 2014). In contrast, poor clinical outcomes and increased risks of blood clots or bleeding are apparent in dissatisfied patients(Balkhi et al., 2018). Patients with well-managed INR control tend to experience higher satisfaction with warfarin therapy, as this ensures that the treatment effectively manages their condition (34). Previous studies have reported different levels of patient satisfaction with warfarin therapy and their impact on anticoagulation control (Eltayeb et al., 2017; Fernández et al., 2018; Schwanda & Gruber, 2019; Shilbayeh & Ibrahim, 2020). However, 63.7% of patients in Saudi Arabia are satisfied with their anticoagulant treatment (Elbur et al., 2015). Improving patient satisfaction with OAT can result in better clinical outcomes and reduce the risk of adverse events such as bleeding and thrombosis (G. D. Barnes & Kline-Rogers, 2015).

2.6 Anticoagulation Management in Ethiopia

Few studies have been conducted on warfarin therapy in Ethiopia regarding the quality of anticoagulation, warfarin-drug interactions, and patients' and healthcare providers' knowledge of warfarin therapy. They have shown a lower mean TTR (29 to 47.24%) (Fenta et al., 2017; Getachew et al., 2023; Kebede & Ketsela, 2022; Liyew et al., 2017; Masresha et al., 2021; Yimer et al., 2021). Another study indicated that undertreatment with antithrombotic medications was high (64.78%) and associated with poorer outcomes in terms of ischemic stroke and/or all-cause (Gebreyohannes et al., 2018).

Low knowledge among patients receiving warfarin has been observed, which could be an important factor determining the degree of anticoagulation control and failure to achieve the treatment goal (Assefa et al., 2014). Furthermore, a prevalence of 99.2% (Teklay et al., 2014) and 21.1% (Tadesse & Woldu, 2018) of warfarin drug interactions were reported at Ethiopian university hospitals. Although warfarin is widely used as an anticoagulant in Ethiopia, no study has assessed three crucial components of anticoagulant management: knowledge, adherence, and satisfaction. Moreover, the effect of PLAS on anticoagulation control and outcomes has not yet been evaluated.

2.7 Anticoagulation Management Service Models

AMS encompasses four models of care: usual medical care (UMC), anticoagulation clinics (AC), patient self-management (PSM), and patient self-testing (PST). UMC is largely provided by physicians, whereas pharmacists primarily lead AC. In PST, patients use point-of-care devices to test their INR at home and report the results to a healthcare professional responsible for interpretation and warfarin-dosing decisions. In PSM, patients monitor their INR values directly, interpret the results, and adjust warfarin doses using a dosing algorithm. Patients must receive adequate training and motivation to successfully implement PMC and PSM (G. D. Barnes et al., 2016; Egunsola et al., 2021; Raphael, 2020; Witt et al., 2016).

The AMS has utilized anticoagulation clinics for over three decades as a key strategy to optimize anticoagulation management. This approach was first implemented in the United States to centralize, standardize, and improve the care of patients taking warfarin (G. D. Barnes et al., 2018). Since then, these clinics have evolved to provide care for patients with diverse conditions, clinical needs, and newly introduced medications (G. D. Barnes et al., 2016; Raphael, 2020). These services include comprehensive patient education, systematic INR monitoring, follow-up, and effective communication and decision-making on dosing between the medical staff and patients(Holbrook et al., 2012). A coordinated, efficient, and sustainable system-level initiative was designed to achieve optimal health outcomes related to anticoagulation and reduce avoidable adverse drug events (G. D. Barnes et al., 2020; Burnett & Barnes, 2022; Forum, n.d.). This is achieved through the implementation of evidence-based care; appropriate prescription, dispensing, and administration of anticoagulants; and the provision of appropriate patient monitoring and clinical responsiveness (Raphael, 2020). Anticoagulation clinics are widely considered the most effective models among various anticoagulation management strategies (G. D. Barnes et al., 2016, 2018; Raphael, 2020).

2.8 Impact of Pharmacists on Anticoagulation Control and Outcomes

The role of pharmacists in AMS has expanded to both developing and developed countries (N. O. Ahmed, Osman, Abdelhai, & El-hadiyah, 2017; Aidit et al., 2017; Alghadeeer et al., 2020; Cao et al., 2018; Tadesse, Abiye, et al., 2022). This results in improved therapeutic INR control and a reduced risk of complications associated with anticoagulation therapy compared with the usual management provided by physicians (Jiawen et al., 2020). Pharmacists are responsible for ensuring that patients receive the appropriate dosing and monitoring, providing education to patients on warfarin therapy, monitoring patient adherence, identifying potential warfarin-

drug/herb/food interactions, and conducting telephone follow-ups to support patient care (Elewa et al., 2016; Gupta et al., 2015; J. Harrison et al., 2015; L. R. Marcatto et al., 2020).

A study conducted in Saudi Arabia showed significantly higher TTR levels among patients attending pharmacist-led clinics than in physician-led clinic (87.27%± 3.82% and 52.48%± 5.49%, respectively; p< 0.001) (Alghadeeer et al., 2020). A study conducted in the United States found that the pharmacist-led group achieved a significantly higher percentage of INRs within the target range compared to the physician-led group (57.5% vs. 50.0%; p = 0.0004) (Gupta et al., 2015). A systematic review by Manzoor et al. proved that compared with routine care, pharmacist-managed outpatient-based anticoagulation services attained a better quality of anticoagulation control, lower bleeding and thromboembolic events, and resulted in lower healthcare utilization (Manzoor et al., 2017). Other studies conducted in Brazil among patients with atrial fibrillation with a low TTR (<50%) reported significantly improved TTR values after pharmaceutical care was provided(L. Marcatto et al., 2021; L. R. Marcatto et al., 2018). Furthermore, a systematic review and meta-analysis conducted by Hou et al. found that the incidence of total and minor hemorrhage and thrombosis events was significantly lower in the pharmacist-led anticoagulation management group than in other management models, without a significant difference in TTR and major hemorrhage events between the two groups. These findings suggest that pharmacist-led anticoagulation management effectively reduces the risk of adverse events in patients receiving anticoagulant therapy (Hou et al., 2017).

2.9 Conceptual Framework

The conceptual framework of this study was developed based on the factors identified as key barriers to the quality of AMS from previously published studies conducted in Ethiopia and other countries elsewhere in the world. Therefore, these factors were assessed in this study to determine whether they affected outcome variables. Differences between anticoagulation control and outcomes can be realized by addressing different healthcare system factors in patients receiving warfarin. Figure 1 presents the conceptual framework of this study.

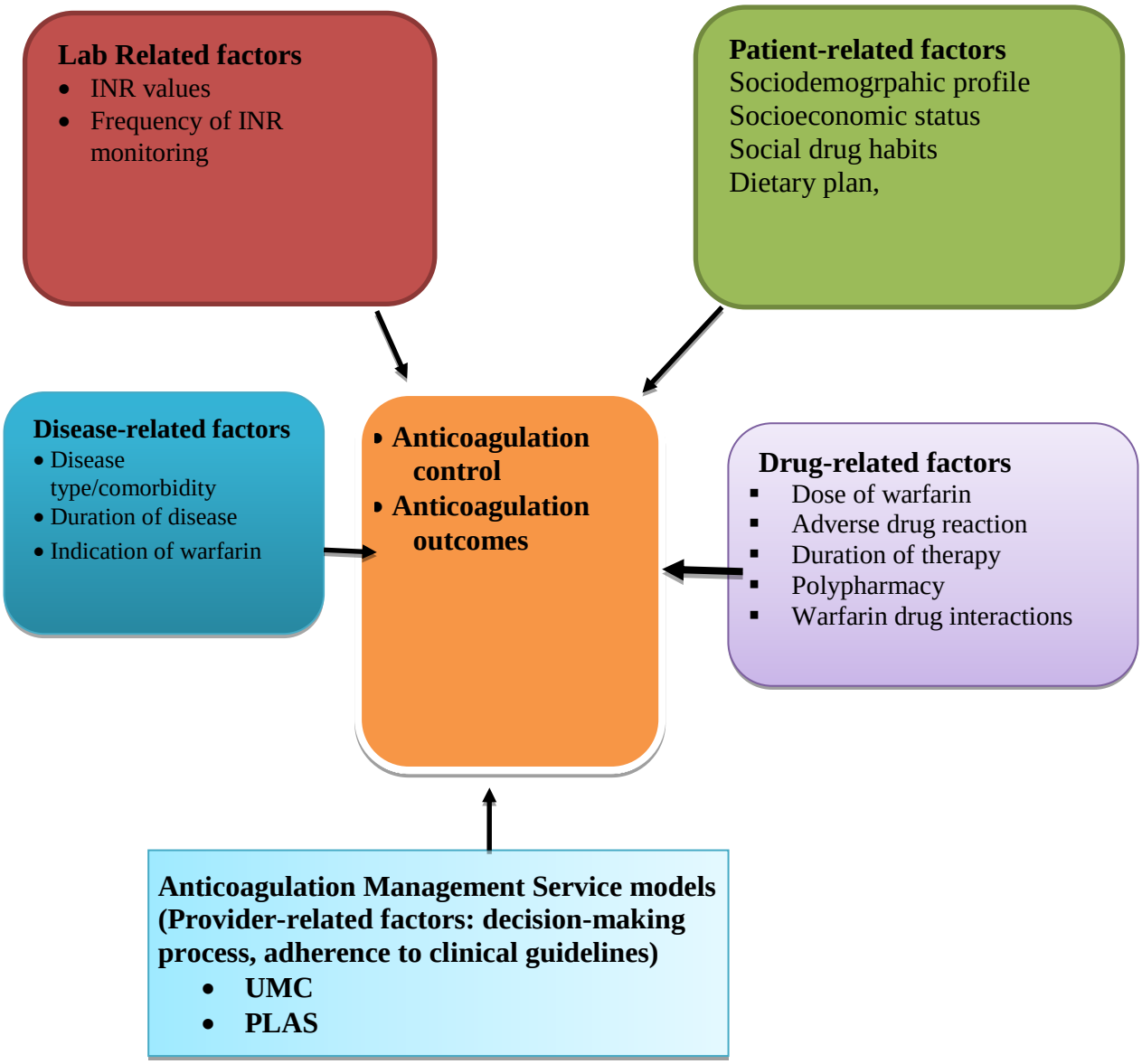

Figure 1: Conceptual framework showing factors involved in warfarin anticoagulation outcomes, knowledge, adherence, and satisfaction towards warfarin therapy

Chapter Three: Research Questions and Objectives

3.1 Research questions

The following research questions were addressed in this PhD dissertation.

- What are the average TTR percentages and associated clinical outcomes (e.g., thromboembolic and bleeding events) among African patients on long-term warfarin therapy, and what demographic, clinical, and behavioral factors influence these outcomes?
- What are the perceived challenges and benefits of the current AMS from the perspectives of healthcare providers and patients, and how does implementing PLAS address these challenges and enhance patient outcomes?
- What are the knowledge scores, adherence rates, and satisfaction levels among patients receiving warfarin therapy, and how do demographic, educational, and clinical factors influence these outcomes?
- How do TTR percentages, INR monitoring frequency, and the percentage of days outside therapeutic INR ranges differ between UMC and PLAS, and are these differences statistically significant?
- What are the differences in the incidence of thromboembolic events, bleeding complications, emergency department visits, and hospital admission rates between patients managed by UMC and those managed by PLAS, and are these differences statistically significant?
- What demographic, clinical, and behavioral factors contribute to differences in anticoagulation control (e.g., TTR) and clinical outcomes (e.g., thromboembolic and bleeding events) between UMC and PLAS?

3.2 Objectives

3.2.1 General Objective

- To assess effectiveness of pharmacist-led anticoagulation service on anticoagulation control and outcomes and patient knowledge, adherence, and satisfaction among ambulatory patients receiving warfarin at the Tikur Anbessa Specialized Hospital (TASH) in Ethiopia

3.2.2 Specific Objectives

- To systematically review anticoagulation control, treatment outcomes, and associated factors among warfarin patients in long-term care across Africa to identify patterns and gaps, and inform clinical practice
- To explore and identify the challenges faced in existing AMS at TASH and assess the perceived need for and benefits of implementing PLAS through qualitative interviews with healthcare providers and patients

- To evaluate patients' knowledge, adherence, and satisfaction with warfarin therapy using validated tools, and identify factors associated with these outcomes
- To compare anticoagulation control between UMC and PLAS in terms of difference in median TTR, the proportion of patients achieved optimal TTR, and the percentage of INR values within the therapeutic range.
- To compare anticoagulation outcomes between UMC and PLAS groups in terms of the incidence of thromboembolic events, bleeding complications, all-cause emergency visits, and all-cause hospitalizations
- To identify factors associated with anticoagulation control(low TTR) and the incidence of seceonday outcomes among patients receiving warfarin therapy

Chapter Four: Research Methods

4.1 Study Setting

This study was conducted at the CHCs and PLAC of the Tikur Anbessa Specialized Hospital (TASH) in Addis Ababa, Ethiopia. TASH is a university teaching hospital that provides specialized medical services to a large portion of the Ethiopian population. The CHCs operate four days a week, serving an average of 600 patients per week. Cardiologists, hematologists, cardiac and hematology fellows, residents, physicians, and nurses staffed clinics. PLAC was established at TASH in April 2018 as part of quality improvement initiative in anticoagulation management. It was designed to serve patients with frequent non-therapeutic INRs and a complex anticoagulation history, particularly referred from CHCs to the clinic. It is located in the multidisciplinary outpatient clinic of the hospital and staffed by four clinical pharmacists, provided services two days a week (Tuesday mornings and Friday afternoons), and offered phone consultations to patients with extreme non-therapeutic INRs who cannot wait for the next clinic day for warfarin dose adjustment. On average, 25 patients visited the PLAC daily, and each counseling session lasted approximately 10 minutes. Both CHCs and PLAC were the clinics that mostly prescribed anticoagulants, most notably warfarin for patients under follow-up in the hospital's outpatient department.

4.2 Study Design and Period

This research comprised four studies: a systematic review, qualitative study, cross-sectional study, and quasi-experimental study to address various aspects of anticoagulation control and outcomes of warfarin therapy. Each study was designed to address specific research questions and objectives and ultimately to achieve the research goal. This systematic review involved collecting and synthesizing the existing evidence on anticoagulation control and treatment outcomes in patients receiving warfarin for long-term care in African countries. A qualitative study was designed to explore the challenges of the existing AMS and the benefits of implementing PLAS in the TASH. A cross-sectional study was conducted to evaluate the magnitude of patient knowledge, adherence, and satisfaction with warfarin therapy. Based on the findings of three previous studies, a quasi-experimental intervention study was designed to assess the practical impact of PLAS on anticoagulation outcomes, comparing it with UMC and leveraging the insights gained from a systematic review, qualitative study, and cross-sectional study. The details of each study are summarized below.

4.2.1 Systematic Review

Protocol and reporting

The systematic review was registered in PROSPERO (CRD42021260772) and prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis PRISMA guidelines(Page et al., 2021).

Data source and search strategy

A literature search was conducted using PubMed, Ovid, Cochrane Library, African Journal of Online databases, Google Scholar, and Google, covering the period from inception to November 30 2021. The reference lists of all included studies were also reviewed. The search strategy used Medical Subject Heading (MeSH) terms and keywords, including anticoagulant agents, treatment outcome, bleeding, thromboembolism, time in therapeutic range, TTR, international normalized ratio, INR, Africa, and long-term care. Keywords were combined using "AND" and/ "OR" Boolean operators.

Inclusion and exclusion criteria

Eligible articles were assessed against the following inclusion criteria:

- Observational studies (cohort and cross-sectional studies) on warfarin use, anticoagulation control, and outcomes among adult patients in long-term care in African countries
- Studies reporting monitoring of INR and TTR
- Studies on warfarin therapy-related adverse outcomes (bleeding events, thromboembolic events, ischemic stroke, hospitalization, emergency room visits, and mortality).
- Studies published in English

However, following were excluded from the review

- Animal studies
- Studies on admitted and emergency patients.
- Pharmacogenomic studies and studies on other anticoagulation outcomes (e.g., knowledge, adherence, satisfaction, quality of life, economic outcomes, adverse drug events other than bleeding, and warfarin drug interactions)
- Qualitative studies, review articles, unpublished works (theses), case reports, case series, case-control studies, letters to the editor with incomplete information, author perspectives, abstract proceedings, and expert opinions

Article screening process

Articles from the electronic databases were exported to EndNote and imported into Covidence (H. Harrison et al., 2020) for screening, removing duplications, full-text analysis, and extraction. Title and abstract screening were done by two reviewers, with studies categorized as "yes," "no," or "maybe." Full texts of "yes" or "maybe" articles were evaluated against eligibility criteria by two authors. Discrepancies in data extraction were resolved through discussion between the two reviewers.

Data extraction

Data were extracted using a standardized Microsoft Excel format to capture the study characteristics (country, setting, author, publication year, design, population, and sample size) and results (TTR percentages and warfarin-related adverse effects).

Quality assessment

Methodological quality was assessed using the Joanna Briggs Institute (JBI) prevalence critical appraisal tool for cross-sectional studies(Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P,. Lisy K, 2017). This tool includes eight items that assess sampling, data collection, reliability, validity, case definition, and prevalence. Articles were rated for the risk of bias, with scores of 1 (yes) or 0 (no) summed to obtain an overall quality score. Studies scoring less than 50% were considered high risk. Disagreements were resolved by consensus, and the mean scores of the two authors were used for the final classification.

Outcome measurement

The primary outcome was the TTR. The secondary outcomes the included bleeding, thromboembolic events, hospitalization, and emergency department visits.

Data management and analysis

The mean and/or median percentages of TTR were extracted from all included studies. Secondary outcomes were reported as mean, percentage, or frequency, with factors contributing to the study outcomes, as described in previous studies.

4.2.2 Qualitative Study

Study participants

Fifteen physicians, heads of pharmacy and laboratory departments, and 20 patients were interviewed to explore their perceptions and experiences regarding the Anticoagulation Management System (AMS) and the need and benefit of implementing PLAS TASH. Physicians were selected using purposive sampling, while patients were selected using simple

random sampling. Severely ill patients and physicians with minimal experience in AMS did not participate in this study.

Data collection, management, and quality assurance

Semi-structured interviews were conducted using thematic content analysis. The interview covered information on the sufficiency of counseling services, availability of anticoagulants and INR tests, participants' experience with and status of existing AMS, suggestions for AMS improvement, and satisfaction with TASH AMS. Observations of AMS workflow and structure were also conducted. The interview guides were validated by clinical pharmacists and translated into English and Amharic to ensure consistency. Audio recordings were made for participants who consented, whereas notes were taken for those who did not. Two postgraduate students in Pharmacy Practice were engaged in collecting data from health professionals and another postgraduate student collected data from patients. The principal investigator supervised data collectors to ensure consistency and quality. The data collectors received one day of training on how to approach study participants and conduct the survey.

Data Analysis

A thematic analysis approach was used to analyze the data by identifying key themes, with transcriptions coded for anonymity.

Ethical considerations

Ethical approval was obtained from the Ethics Review Committee of the School of Pharmacy, College of Health Sciences, Addis Ababa University. Informed consent was obtained, confidentiality was ensured, and data were analyzed in aggregates without personal identifiers.

4.2.3 Cross-sectional Study

Study design and patient population

An interview-based cross-sectional study was conducted between March 1 and June 30, 2023, among patients with follow-up at the CHCs of TASH patients to evaluate their knowledge of, adherence to, and satisfaction with anticoagulation treatment.

Eligibility criteria

This study enrolled patients aged 18 years and older who had been on warfarin therapy for a minimum of six months. However, patients who were unwilling to participate, unable to complete the questionnaire in the Amharic language, critically ill (excluded to ensure consistency in data collection and interpretation), had mental health problems, and missing or incomplete medical and medication data were excluded from the study.

Sample size determination and sampling technique

Eligible 397 patients were interviewed, and 350 were included in the final analysis after excluding responses with incomplete or missing information. For better representativeness, the participants were enrolled weekly in proportion to the expected study population until the end of the data collection period.

Data collection instrument, procedures, and outcomes measurement

The data collection instrument was structured into four sections. Section I gathered the sociodemographic and socioeconomic characteristics of the study participants. Section II consists of anticoagulation knowledge assessment (AKA) questionnaires with 18 multiple-choice questions, developed from previous studies(Alphonsa et al., 2015; Cao et al., 2020; Obamiro et al., 2016; Viola et al., 2017). Correct answers were scored as 1, and incorrect and do not know answers were scored as 0. Adequate knowledge regarding AKA ranged from 70% to 75% (Alajami et al., 2021; Cao et al., 2020; Zahid et al., 2020), and accordingly, answering correctly at least 13 questions (72.22%) was considered passing scores in this study. Section III assessed adherence to warfarin using the Morisky Green Levine Scale (MGLS) with four yes/no questions, scoring 0-4. Adherence levels were high (0 points), medium (1-2 points), and low (3-4 points). The MGLS, validated for various diseases, has been widely used in research(Ugur et al., 2015). Section IV measured patient satisfaction with warfarin therapy using anticlot treatment scale (ACTS), a validated instrument with a validated instrument with 17 items across two subscales (Burdens and Benefits) (Cano et al., 2012). Thirteen items assessed the burden of anticoagulant treatment (12-item burden scale and one global question on treatment burden) and four items assessed the benefits of anticoagulant treatment (3-item benefits scale and one global question on treatment benefits). The study participants were asked to rate their experiences with anticoagulant treatment during the past four weeks on a 5-point scale of intensity (1=not at all, 2 = a little, 3 = moderately, 4 = quite a bit, and 5 = extremely). Reverse coding was used to calculate the Burden Scale, with higher scores indicating higher satisfaction. The total ACTS burden score ranged from 12 to 60, and the total score ranged from 3 to 15, with a total score ranging from 15 to 75. Patients were considered satisfied with the anticlot treatment if they scored above the mean score for all patients(Eltayeb et al., 2017).

Data collectors and quality assurance

Two pharmacists and two nurses fcollected the data. The questionnaires were prepared in English, translated into Amharic, and back-translated into English to maintain consistency and to facilitate better understanding. The Amharic version was used for patient the interviews. A

team of senior clinical pharmacists, cardiologists, and hematologists reviewed and approved the instruments for content, flow, completeness, and clarity. The AKA, MGLS, and ACTS have been validated and widely used to evaluate the knowledge, adherence, and satisfaction of patients on oral anticoagulants. The data collection tool was pretested for quality, clarity, and feasibility, with the necessary adjustments. The data collectors received a one-day training on using the instruments, explaining the study, obtaining verbal consent, sampling techniques, and maintaining confidentiality. The quality of the collected data was ensured by review and complete checks**.**

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 27. Descriptive data were summarized as percentages and frequencies, mean (±standard deviation), and median (interquartile range (IQR)). Logistic regression was used to identify the determinants of knowledge, adherence, and satisfaction among the patients taking warfarin. Variables with $p < 0.25$ from bivariable analysis were included in multivariable analysis to adjust for confounding effects. Associations between independent and dependent variables were determined using odds ratios (ORs) with 95% confidence intervals (CI). In multivariable analysis, a p-value of less than 0.05 indicated a significant association.

Ethical considerations

Ethical clearance was granted by the School of Pharmacy Ethical Review Committee (ERB/SOP/454/15/2022), and subsequently by the Institutional Review Board of the College of Health Sciences, Addis Ababa University (096/22/SoP). Written informed consent was obtained from all participants after they were informed of the study purpose, selection criteria, and expectations. Personal identifiers were not used to maintain confidentiality, and the data were analyzed in aggregates. The research team handled the data obtained from the study participants with utmost confidentiality.

4.2.4 Quasi-experimental Study

Study setting, design and period

This quasi-experimental study was conducted at the CHCs and PLAC of the TASH to compare the differences in anticoagulation control and outcomes between UMC and PLAS in adult patients receiving AMS with warfarin therapy at the TASH from July 2021 to June 2023.

Study groups, protocol, and intervention

Study participants who had been receiving AMS at CHCs and PLAC in the hospital were grouped into UMC (comparison) and PLAC (intervention) groups, respectively. The UMC

group received existing AMS from physicians without the involvement of clinical pharmacists, while the PLAC group followed the PLAS protocol, which incorporated clinical judgments and knowledge to develop a pharmaceutical care plan for dosage adjustments, follow-up INR testing, and patient counseling. Clinical pharmacists received standardized training to ensure consistency in dosage adjustment and patient counseling. The protocol provides detailed clinical guidance for managing long-term warfarin therapy including indications, target INR ranges, treatment duration, maintenance dosing algorithms, anticoagulation status and actions to follow, INR monitoring frequency, warfarin contraindications, potential drug interactions, and recommended measures. The following activities were performed in the PLAC to provide AMS:

- Accept and enroll eligible patients in PLAC
- Explain to patients the recruitment process and the services provided at the clinic.
- Review of patient's medical information from electronic software (iCare System) relevant to anticoagulation management
- Assess, develop goals, and individualize, and implement the pharmaceutical care plan
- Adjust warfarin dose based on INR values and other patient-related factors, including adherence status, consumption of foods high in vitamin K, alcohol intake, bleeding history, and warfarin drug interaction (WDI)
- Monitor and report adverse drug events/complications (e.g., hemorrhage, thromboembolism, stroke).
- Communicate with the treating physician, for changes in drug therapy if needed
- Conduct a medication review to identify drugs that interact with warfarin. If needed, the assigned physician was contacted to propose a change in drug, dose adjustment, or other measures to avoid or minimize interactions with warfarin.
- Refer patients who need warfarin/anticoagulation reversal to the emergency room or attending CHCs physicians.
- Provide education and deliver educational materials on anticoagulation therapy to the patient's PLAS
- Record all patient information and document all identified and intervened problems related to AMS in the PLAC using an Excel database prepared for this purpose and then linked to the hospital iCare system.

- Provide phone consultations for patients who miss their scheduled clinic visits or in cases of extreme non-therapeutic INRs (INR values <1.5 or >5), where waiting until the next clinic day for dose adjustment and further evaluation is not feasible.
- Identify patients who miss their appointments and call them to visit the clinic the nearest day.

All patients enrolled in the PLAC were educated using a follow-up booklet (a form with INR values, dosing scheme, next appointment date, and the most important messages) and brochure (prepared in Amharic), which lasted approximately 20 minutes. Education included all aspects of warfarin treatment, including indications for warfarin use, how warfarin works, meaning of the INR value and therapeutic range, effect and importance of adherence, diet, drug interactions, alcohol consumption, and changes in health status on the quality of anticoagulation and adverse drug reactions. Clinical pharmacists working in PLAC did not initiate warfarin for new patients and did not stop it; instead, they provided recommendations to the assigned physicians. The source population for this study consisted of all outpatients receiving follow-up care at the CHCs and PLAC of TASH. The study population included all patients who received AMS at these clinics and who fulfilled the inclusion criteria. To evaluate patients' knowledge, adherence, and satisfaction with warfarin therapy, the study population included all patients who received AMS at the CHCs of the TASH and met the eligibility requirements.

Eligibility criteria

In both groups, patients aged 18 years and older who received warfarin for at least six months and had at least three consecutive INR values (to obtain consistent INR data and for better determination of TTR) were included. Furthermore, to be included in the PLAC cohort, patients had to have initially started warfarin therapy at the CHCs. Patients with interrupted INR values or temporarily planned interruptions, those who missed more than one consecutive visit, those who received AMS at both the PLAC and CHCs during the follow-up period, and those with missing or incomplete medical and medication data were excluded. The exclusion criteria included patients with interrupted or temporarily planned interruptions in their INR values, those who missed more than one consecutive visit, those who received AMS at both the PLAC and CHCs during the follow-up period, and those with missing or incomplete medical or medication data.

Sample size, sampling technique, and participant recruitment

The sample size was calculated based on a mean TTR of 42% from a recent study conducted in

an Ethiopian public hospital(Yimer et al., 2021). The standard deviation of the TTR was assumed to be 0.25, considering that anticoagulation control before PLAS implementation was better than that reported in a previous study (0.42). The calculation also accounted for a Type I error (α-level) of 0.05, a power of 80%, and a UMC: PLAS ratio of 2:1. To achieve a minimum clinically important difference of 0.08 (i.e., an improvement from 42% to 50% in TTR), a sample of at least 304 patients in the UMC group and 152 in the PLAS group was required, including a 10% contingency for loss to follow-up. Following this determination and adherence to eligibility criteria, 350 and 175 patients in the UMC and PLAS groups, respectively were included in the final analysis. Eligible participants were recruited through a systematic random sampling method using the formula ($k = N/n$), where every k^{th} patient was reviewed until the target sample size was reached. The sampling fraction (k) varied across different days and between the UMC and PLAS groups due to fluctuations in patient attendance. The first participant was selected through simple random sampling, and thereafter, every fourth or fifth patient from the UMC group and every second patient from the PLAS group was enrolled. For better representativeness, we attempted to enroll a proportional number of participants per week, based on the expected study population. Clinical and anticoagulation-related data were collected retrospectively from the same participants to form the control group. Similarly, clinical and anticoagulant data were collected from patients who underwent PLAS (the intervention group).

Study variables

Independent variables

- Patient sociodemographic characteristics (age, sex, educational level, marital status, etc.)
- Social habits (chat chewing, smoking, and alcohol drinking)
- INR values
- Comorbidities
- Study group (UMC vs. PLAC)
- Target INR range
- Warfarin dose per day
- Duration of warfarin therapy
- Indication of warfarin
- Warfarin interacting drugs

Dependent variables

- Difference in percentage of time in therapeutic range
- Difference in proportion of patients with optimal TTR
- Differences in warfarin clinical outcomes (thromboembolic and bleeding events) and other warfarin-related events (emergency department visits and hospitalization)
- Level of warfarin dose adjustment

Data collection instrument

A structured data collection tool was developed to gather participants' sociodemographic characteristics and clinical information. It captured details on comorbidities or underlying disease conditions, warfarin indications, daily warfarin dose, target INR ranges, and INR values at each visit. The tool also recorded the frequency of INR monitoring and anticoagulation status (subtherapeutic, in-target, or supratherapeutic). Moreover, it documented interventions by physicians and pharmacists, potential warfarin-interacting drugs, adverse drug events, thromboembolism and bleeding events, as well as emergency room visits and hospitalizations occurring between clinic visits. The electronic database (iCare) of the TASH was used to collect patient data and anticoagulation management-related information. A comprehensive Excel database was created to systematically document and capture relevant information on anticoagulation management during each visit in the PLAC group.

Study outcomes

The primary outcome was the percentage of median TTR differences between the two groups. TTR was calculated using the Rosendaal method, which accounts for both the frequency and values of INR measurements, assuming linear progression between consecutive readings (Rosendaal et al., 1993). In this study, a TTR $\geq$ 65% was considered as the cutoff for good/optimal anticoagulation control with warfarin therapy (Esteve-Pastor et al., 2018; Turen & Turen, 2023). The secondary outcomes were differences in bleeding (major bleeding, clinically relevant non-major bleeding, or minor bleeding), thromboembolic events (ischemic stroke, transient ischemic attack, and peripheral arterial embolism), emergency department visits, and hospitalization for any cause during anticoagulation management follow-up between groups. Major bleeding is defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, or intraocular, resulting in vision changes; retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells. All non-major bleeding events

were considered minor bleeding events(Franco et al., 2020). These include bruising, nose bleeding, gum bleeding, hematuria, and menstrual bleeding, none of which require further action. Stroke and bleeding risks were evaluated at baseline in patients with atrial fibrillation using the CHA_2DS_2-Vasc and HAS-BLED scoring systems (Hindricks et al., 2021). The CHA_2DS_2-VASc score assesses risk factors including congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, and sex category (0 for men and for women). The HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly >65 years, and drug/alcohol use) was used to identify patients at high risk of bleeding, with a score of ≥3 indicating increased risk. Differences in the prevalence of warfarin-drug interactions were also an outcome of the present study and only absolute contraindications and major and moderate warfarin-drug interactions were considered as significant interactions. The Micromedex Health Care Series software drug-drug interaction checker(*Micromedex Healthcare Series [Intranet Database]. Version 5.1. Greenwood Village, Colo: Thomson Micromedex.*, n.d.) was used to identify warfarin-drug interactions. Another important outcome of this study was the difference in the appropriateness of warfarin dose adjustment by clinical pharmacists and physicians for non-therapeutic INR.

Data collectors and recruitment

Data for the comparative study were collected by four clinical pharmacists chosen based on their educational qualifications, clinical and research experience, and familiarity with managing patients on warfarin therapy in one way or another.

Data quality assurance

The content, flow, completeness, and clarity of data collection tool was reviewed and validated by a team of senior clinical pharmacists, cardiologists, and hematologists. A pre-test was conducted on 5% of the study population from both groups, leading to necessary amendments. Data collectors received one day of training on using the instruments, study criteria, sampling techniques, data confidentiality, and collecting patient data from the hospital's electronic database (I-care system). During data management, storage, and analysis, the collected data were assessed for completeness and consistency.

Data analysis

Data were analyzed using SPSS version 27 with descriptive statistics employed to summarize patients' demographic and clinical characteristics. Normally distributed variables are presented as mean and standard deviation (SD), and non-normally distributed variables are presented as

medians and interquartile ranges (IQR). A two-sample Wilcoxon rank-sum (Mann–Whitney U) test was used to compare continuous variables between groups. Categorical variables were reported as counts and percentages and compared between groups using Pearson's chi-square test or Fisher's exact test. Binary logistic regression analysis was performed to identify factors associated with TTR, while negative binomial regression analysis was used to determine predictors of secondary outcomes. Variables with a p-value <0.25 in the bivariate analysis and binary negative binomial regression were included in the multivariable regression model and multivariable negative binomial regression analysis. Odds ratios (OR) and incidence rate ratios (IRRs) at 95% confidence intervals (CI) were used to determine the associations with $p < 0.05$, indicating the significance of the association. The goodness-of-fit of the negative binomial regression model was evaluated using a likelihood ratio test by comparing fitted and null models.

Ethical considerations

Ethical clearance was obtained from the School of Pharmacy Ethical Review Committee (ERB/SOP/454/15/2022), and subsequently from the Institutional Review Board of the College of Health Sciences, Addis Ababa University (096/22/SoP). Approval to access the clinical data of the study participants was granted by the hospital's outpatient department, and only the research team handled information obtained from the data collection. Personal identifiers were not used in the analysis, and the data were analyzed in aggregates. During enrollment in the PLAC, patients in the PLAS group were informed of how they were selected to receive AMS at the PLAC and were provided with details about the services available to them. As the PLAS at TASH has been delivered under the supervision of cardiologists and hematologists, any anticipated/potential risks have been communicated to patients and linked to consultant cardiologists and hematologists.

Operational definitions

Anticoagulation management service (AMS) is a specialized healthcare service that focuses on the management and monitoring of patients receiving anticoagulants to ensure the safe and effective use of these medications, reduce the risk of adverse events such as bleeding or clotting, and optimize therapeutic outcomes.

Anticoagulation outcomes in warfarin therapy refer to the clinical and therapeutic results associated with using warfarin to prevent and treat thromboembolic disorders. These outcomes include the incidence of thromboembolic events, bleeding complications, and overall patient safety. The effectiveness of anticoagulation with warfarin is largely influenced by the quality

of anticoagulation control, which is typically measured by the time in therapeutic range (TTR) or similar indicators.

Major bleeding: fatal bleeding, symptomatic bleeding in a critical area or organ, and/or bleeding causing a hemoglobin level of 2 g/dL (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red blood cells. All non-major bleeds were considered minor bleeding.

Medication adherence refers to the degree to which patients correctly follow medical advice and instructions regarding the timing, dosage, and frequency of their medication regimens.

Pharmacist-led anticoagulation clinic represents an anticoagulation care model that pharmacists provide to patients with more consistent management, closer monitoring, and more education and awareness on anticoagulation therapy, especially regarding interacting drugs and food that can alter warfarin efficacy and safety.

Pharmacist-Led Anticoagulation Service (PLAS) refers to a specialized healthcare service in which clinical pharmacists take a central role in the management of patients receiving anticoagulant therapy, particularly warfarin and other oral anticoagulants.

Time in therapeutic range (TTR): estimates the percentage of time a patient's INR is within the desired therapeutic range or goal.

Usual medical care: An anticoagulation management service provided by physicians without the involvement of clinical pharmacists.

Warfarin drug interaction: Presence of drugs(s) that interact with warfarin and only moderate- or clinically significant warfarin-drug interaction regimens using Micromedex® health care series software drug interaction checker

Chapter Five: Results

5.1 Findings from Systematic Review

A total of 298 articles were retrieved from various electronic databases. Of these, 59 were excluded due to duplication. Title and abstract screening was performed on the remaining 239 articles, and 188 articles were deemed irrelevant. Full-text screening was conducted on 47 articles, of which 29 were excluded due to ineligibility (e.g., absence of the outcome of interest). Ultimately, 18 articles were eligible for inclusion in this systematic review (Figure 2).

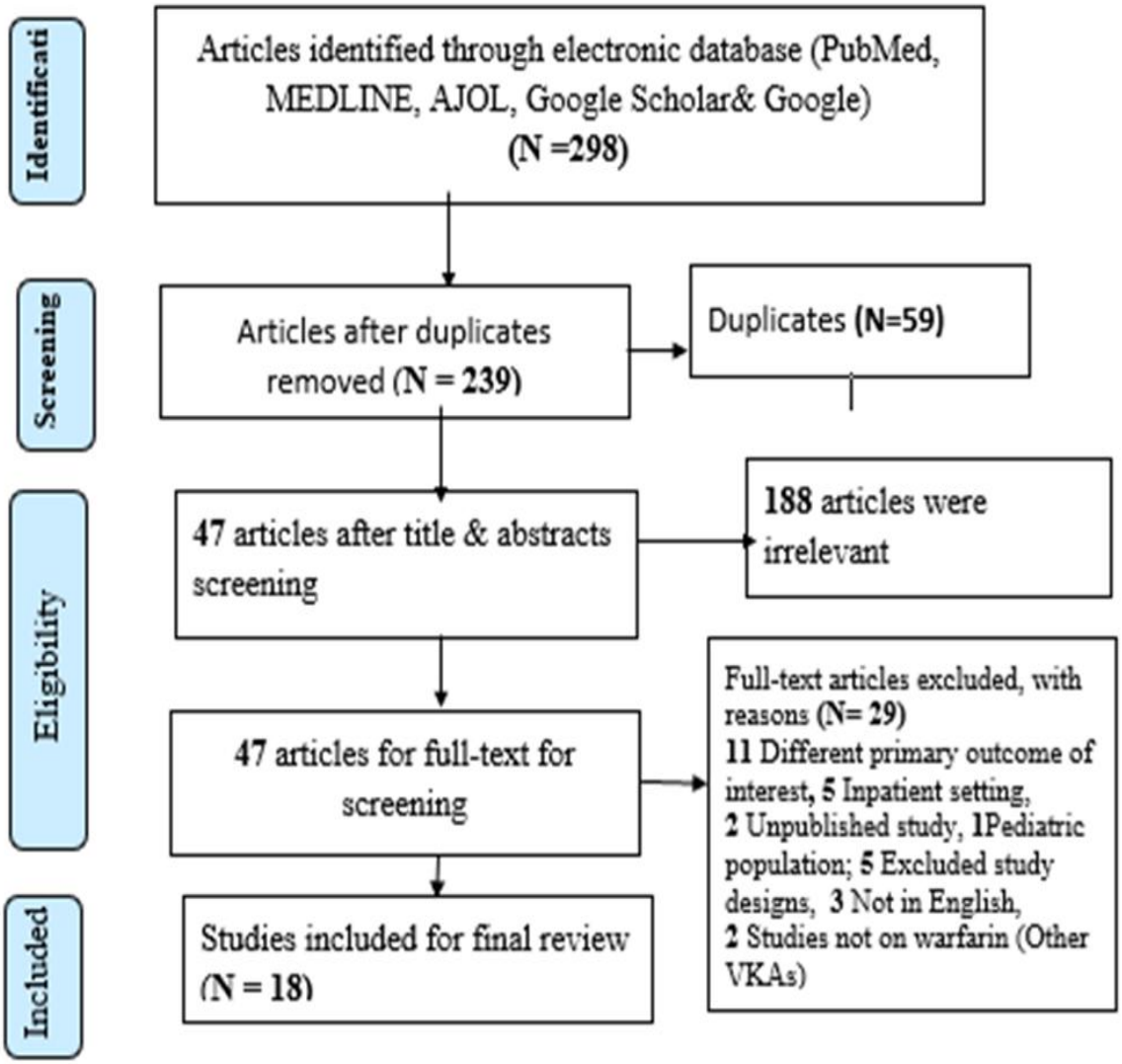

Figure 2: PRISMA flow diagram for study selection

The included studies were published between 2006 and 2021 and predominantly used a retrospective design (15 of 18 studies) (Abusin, 2019; Ben Rejeb et al., 2019; Botsile & Mwita, 2020b; Ebrahim et al., 2018; Fenta et al., 2017; Jonkman et al., 2019; S. Karuri et al., 2019; Masresha et al., 2021; Mwita et al., 2018; Ntlokotsi et al., 2018; Prinsloo et al., 2021; Sadhabariss & Brown, 2021; Semakula et al., 2021; Sonuga et al., 2016; Yimer et al., 2021). One study used a pre-post intervention design (N. O. Ahmed, Osman, Abdelhai, & El-Hadiyah, 2017) and two studies were prospective (Mariita et al., 2016; Ouali et al., 2021). Five studies were conducted in South Africa (Ebrahim et al., 2018; Ntlokotsi et al., 2018; Prinsloo et al., 2021; Sadhabariss & Brown, 2021; Sonuga et al., 2016), three in Ethiopia (Fenta et al., 2017; Masresha et al., 2021; Yimer et al., 2021), two each in Sudan (Abusin, 2019; N. O. Ahmed, Osman, Abdelhai, & El-Hadiyah, 2017), Kenya (S. Karuri et al., 2019; Mariita et al., 2016), Tunisia (Ben Rejeb et al., 2019; Ouali et al., 2021), Botswana (Botsile & Mwita, 2020b; Mwita

et al., 2018), one in Namibia (Jonkman et al., 2019) and one jointly in South Africa and Uganda. Overall, 4,730 participants were included, with the smallest and largest studies having 21 (Abusin, 2019) and 915 participants (Ouali et al., 2016), respectively. The follow-up period varied from four months (Schapkaitz et al., 2006) to 19 years (Ntlokotsi et al., 2018). All studies were conducted in outpatient settings, primarily in government health facilities (Paper I, Table 1).

Quality assessment of included studies

Except for two, all included studies in the systematic review had low-risk methodological quality according to the modified Joanna Briggs Institute (JBI) critical appraisal tool as indicated in Appendix 1.

Primary Outcome: Time in the therapeutic range

Various methods were used to determine the TTR in the included studies: Roosendaal's method (11 studies), the direct method (three studies), the cross-section-of-the-files method (two studies), a combination of direct and Roosendaal's methods (two studies). TTR was reported as the mean and/or median percentage or percentage. The lowest mean TTR (13.7%) was observed in a South African study of adult patients with prosthetic heart valves, while the highest (57.3%) was reported in a Tunisian study. A post-interventional study in Sudan reported a mean TTR of 68.3%. The mean TTR of 39.4±8.4%, 36.7±11.5%, and 46% were reported by Roosendaal, the direct, and the cross-section-of-the-files methods, respectively. Thirteen studies documented the percentage of patients with a TTR ≥ 65%, with the highest (32.25%) in Tunisia, and the lowest (10%) (TTR ≥ 65%) in Nambia and 10.4% (TTR ≥ 70%) in Kenya, respectively. The details are presented in Paper I-Table 2).

Secondary outcomes

Three studies reported both major and minor bleeding events (Ben Rejeb et al., 2019; Botsile & Mwita, 2020b; Ouali et al., 2021), whereas others documented either event. The highest bleeding incidence (59%) was observed in Tunisia (Ben Rejeb et al., 2019), with 9.5% major and 49.5% minor bleeding. The lowest bleeding incidence (0.006% per patient-year) was documented in a South African study (Ntlokotsi et al., 2018). Six studies reported thromboembolic events ranging from 0.002% per patient year to 22.5% (Botsile & Mwita, 2020a; Masresha et al., 2021; Ntlokotsi et al., 2018; Ouali et al., 2021; Sonuga et al., 2016). Four studies reported thromboembolic complications in the range of 1.64% to 7.5% (Ben Rejeb et al., 2019; Masresha et al., 2021; Ouali et al., 2021; Sonuga et al., 2016). Emergency

department visits and mortality rates were 1.5% and 5.6%, respectively, in studies from Ethiopia and Tunisia(Masresha et al., 2021; Ouali et al., 2021) (Paper I-Table 3).

Factors associated with optimal anticoagulation and secondary outcomes in patients receiving warfarin

Various sociodemographic and clinical characteristics have been identified as factors contributing to poor TTR, bleeding, and thromboembolic events. Heart failure (S. Karuri et al., 2019; Masresha et al., 2021; Ouali et al., 2021; Yimer et al., 2021), renal dysfunction (S. Karuri et al., 2019), and pulmonary hypertension (Ebrahim et al., 2018) were significant contributors. Taking more than two drugs alongside warfarin (Yimer et al., 2021) and the presence of medications that could potentially interact with warfarin (39) have been frequently reported. Younger age (less than 50 years) (Prinsloo et al., 2021), female sex, lower educational level (47), and smoking (Botsile & Mwita, 2020b) were also significant factors. In addition, hospitalization (Prinsloo et al., 2021) and frequent INR monitoring (Ebrahim et al., 2018) have been identified as predictors of poor anticoagulation, resulting in a lower TTR. Only studies that reported significant associations were included (Papers I-Table 4).

5.2 Qualitative Study Key Findings

Socio-demographic characteristics of key informants

Seventeen health professionals were interviewed, including 15 physicians, one pharmacist (head of the pharmacy), and one medical laboratory technician (head of the laboratory). The interview also included 20 patients. Findings are organized into six core themes: adequacy of the current institution to provide adequate AMS, availability of resources (functional protocols, coagulation tests, and anticoagulants), challenges of AMS and proposed solutions, quality of AMS, benefits of establishing PLAC, and the role of clinical pharmacists in PLAC were the main themes identified.

Suitability of current setup to provide adequate AMS

Most participants (86.67%) believed that the facility was inadequate for optimal AMS, primarily because of the absence of a dedicated clinic, as highlighted by 60% of the respondents. Overcrowding and high workload have also been cited, leading to insufficient attention being paid to patients needing AMS.

[…] The delay in getting a coagulation test (MD1) and the lack of a separate determination corner in the hospital make the facility poor for providing the necessary AMS to patients. (MD12)

In contrast, two other respondents indicated that the facility was adequate to provide AMS. (MD12)

The setup is suitable for providing an appropriate AMS because there are multiple specialties (MD 4) and well-trained staff (MD5) inthe hospital.

Availability of resources

Lack of resources was identified as a significant barrier. Functional protocols and coagulation tests were insufficient. Only a few departments have the necessary protocols, and the irregular availability of coagulation tests and anticoagulants remains a persistent issue. The waiting time for INR test results varied widely, and some participants questioned the reliability of these results. The details are provided in Paper 2-Table 2.

Challenges of anticoagulation management service

The irregular availability of tests and medications was the main challenge cited, and supply problems were the main reason for this. In addition, most study participants explained the consequences of the unavailability of tests and medications.

This exposes patients to the high costs of INR determination and obtaining drugs from privatepharmacies outside the hospital. (MD6)

One respondent explained his organization's challenges as follows:

[….] We have limited knowledge about the interaction between anticoagulants and other drugs and the duration of anticoagulation, which affects the quality of anticoagulation therapy. (MD 1)

The lack of clear SOPs and dedicated AMS clinic compounded these issues. One participant also mentioned inadequate patient education, difficulties with timely consultations, the absence of specific hospital/national INR target ranges, and unreliable INR results as significant challenges.

Quality of anticoagulation management service

Two-thirds of participants rated the quality of AMS as poor, whereas one-third described it as satisfactory. The establishment of a PLAC was unanimously seen as beneficial for improving the quality of AMS emphasizing the need for qualified staff and consistent services.

Proposed solutions to address AMS challenges

The respondents suggested several solutions, including regularly availing coagulation tests and anticoagulants, central management of anticoagulation by a multidisciplinary team, and ensuring the involvement of well-trained healthcare professionals.

Another respondent suggested as a solution to the AMS challenges:

[…] The use of antithrombotics that do not require laboratory monitoring (INR) is a method to improve AMS, as we have not been able to optimize anticoagulation with a drug such as warfarin that requires frequent INR monitoring. (MD14)

Timely consultations, the development of SOPs, and performing coagulation testing in dedicated hemostatic laboratories (each mentioned by one respondent) were also suggested as solutions for addressing existing problems with AMS in their hospital.

Advantages of establishing a PLAC

All respondents agreed that establishing a functional PLAC in the hospital would significantly enhance the quality of care for patients requiring anticoagulation therapy.

More focused and efficient patient care will be provided if PLAC is opened and functional in our hospital. (MD1)

However, it was stressed that the mere establishment of a clinic would not suffice; the assignment of well-trained healthcare professionals and sustainability of the service are crucial. Without these factors, the problems associated with AMS would persist. Several respondents who noted that a functional PLAC would be essential for achieving these goals reiterated the importance of regular follow-up and optimized therapy. Another participant emphasized the issue of ownership and specific training for the staff assigned to the clinic, underlining that these factors must be considered before setting up the clinic. Finally, 40% of the participating physicians underlined the need to ensure the sustainability of the clinic. When discussing the importance of a multidisciplinary team (MDT), including the pharmacy team, most respondents described collaboration as "very important," "very encouraging and necessary," and "highly recommended and very good." This teamwork is viewed as crucial for the successful operation of PLAC and the improvement of patient care.

The role of clinical pharmacists in PLAC

Clinical pharmacist involvement is expected to significantly benefit patient follow-up and anticoagulation therapy. They are considered crucial for improving AMS by managing drug interactions and enhancing medication adherence.

This was reinforced by one respondent as follows.

Clinical pharmacists in PLAC help address the problem of drug interactions/complications and medication adherence. (MD8)

Laboratory and pharmacy heads' perspectives

The laboratory head noted insufficient INR testing equipment and reagents, whereas the pharmacy head highlighted the irregular supply of anticoagulants and inadequate patient

education. Both recommended the establishment of a PLAC with proper SOPs, trained staff, and a sustainable supply of medication.

Patients' experiences and opinions on the current AMS

Availability of warfarin and INR testing

Patients frequently complained about the unavailability of INR tests and warfarin both within the hospital and externally, which imposed additional costs. They stressed the importance of regular INR testing for effective warfarin therapy.

One respondent said:

We want the test to be done in the hospital. Without this, the drug warfarin is worthless to us. (P7)

Anticoagulation Management Service Challenges

Patients identified several challenges, including inadequate waiting areas, high patient load, difficulty in obtaining patient cards, and poor hospitality from the staff.

Because of the large number of patients using the service, I did not have enough time to ask for consultation and inform the doctor about my situation properly. (P11)

They suggested dedicated rooms for AMS, hiring more health professionals, and ensuring the availability of INR testing within the hospital to improve AMS.

Patient Satisfaction

Nearly half of the patients expressed dissatisfaction with the AMS they received, underscoring the need for significant improvements in service delivery and patient care.

5.3 Findings of Cross-sectional Study

Sociodemographic characteristics of study participants

The study included 350 patients receiving warfarin, of whom 245 (70%) were female and the mean (SD) was 44.05 (±14.72, range =18–82) years. Most were married (55.7%), lived in Addis Ababa (70%), and were Orthodox Christians (70%). Half of the participants had low monthly incomes (0-300 birr) and 33.7% were unemployed. The majority of participants lived with their families (89.7%) and used community-based health insurance (75%). The mean duration of warfarin therapy was 5.95 (±5.20 (range = 0.5–29.5) years and participants received an average of 4.16 drugs (±1.76) (range =1–13). Moreover, 29.7% of the participants reported polypharmacy (Table 1).

Table 1: Socio-demographic characteristics of patients receiving warfarin therapy

Items of description	**N**	**%**	**Mean/SD**
Sex			
Female	245	70	
Male	105	30	
Age in years			
18-30	76	21.7	
31-45	135	38.6	44.05±14.72
46-64	101	28.9	
≥65	38	10.9	
Residence			
Addis Ababa	247	70.6	
Out of Addis Ababa	103	29.4	
Marital Status			
Single	106	30.3	
Married	195	55.7	
Widowed/Divorced/Separated	49	14	
Religion			
Orthodox	246	70.3	
Muslim	64	18.3	
Protestant	40	11.4	
Educational Status			
Unable to read and write	51	14.6	
Primary school (Grades 1-8)	101	28.9	
Secondary school (Grades 9-12)	110	31.4	
Degree and above	45	12.9	
Certificate/Diploma	43	12.3	
Family monthly income in Birr			
0-300	177	50.6	
301-2,500	49	19.7	2367.61±3399.57
2,501- 5,000	69	14.0	
>5,001	55	15.7	
Employment Status			
Unemployed/not working	128	36.6	
Employed (paid work)	82	23.4	
Housewife	67	19.1	
Self-employed/Private work	44	12.6	
Retired	29	8.3	
With whom do you live?			
With Family	314	89.7	
Alone	36	10.3	

Alcohol Intake Status			
No	333	95.1	
Yes	17	4.9	
Smoking in the last two years			
No	349	99.7	
Yes	1	0.3	
Chat Chewing status			
No	347	99.1	
Yes	3	0.9	
Medical service coverage			
Community-based health insurance	260	74.3	
Out-of-pocket/Paying	74	21.1	
Free	16	4.6	
Duration of warfarin in years			
0.5-1	72	20.6	
>1-5	126	36.0	5.95±5.20
6-10	102	29.1	
>10	50	14.3	
Number of medications received per patient			
<5	246	70.3	4.16±1.76
≥5	104	29.7	

Clinical characteristics of patients receiving warfarin

Most of the participants (76.4%) had at least one comorbidity that did not require warfarin, most of whom had heart failure (45.4%), valvular heart disease (41.4%), and hypertension (24%), a history of stroke, including thromboembolism and vascular disease, was recorded in 18.9 and 11.1% of patients, respectively. The most common indication for warfarin was atrial fibrillation (60%), followed by valvular heart disease with a left atrial/venous thrombus (13.1%), post-mechanical heart valves (mitral and/or aortic valves) (12.6%), and recurrent and/or unprovoked deep vein thrombosis (10.6%). During follow-up, 89 bleeding episodes and 64 all-cause emergency visits were recorded. Details are presented in Table 2.

Table 2: Clinical characteristics of patients taking warfarin

Characteristics	**N=350) n (%)**
Presence of comorbidity	
No	62 (17.7)
Yes	288 (82.3)
Comorbidities that do not need warfarin indication	
Polycythemia vera	8 (2.3)
Hypertensive heart disease	11 (3.1)
Heart failure	158 (45.4)

Gastric illnesses	9 (2.6)
Renal Diseases	8 (2.3)
Liver diseases	8 (2.3)
Hypertension	84 (24.0)
Diabetes Mellitus	28 (8.0)
Seizure disorders	17 (4.9)
HIV/AIDS	12 (3.4)
Valvular heart disease	145 (41.4)
Hyperthyroidism	10 (2.9)
Hypothyroidism	4 (1.1)
Neurologic disorders [a]	19 (5.4)
History of Stroke [b] and thromboembolism	66 (18.9)
Chronic Pulmonary diseases [c]	10 (2.9)
Cancer	12 (3.4)
Rheumatologic diseases	9 (2.6)
Dyslipidemia	10 (2.9)
Pulmonary Hypertension	43 (12.3)
Psychiatric disorders	3 (0.9)
Amiodarone use	6 (1.7)
Aspirin, clopidogrel, NSAIDs use	26 (7.4)
Vascular disease history (prior MI, PAD, or aortic plaque)	39 (11.1)
CAD/IHD without thrombus	18 (5.1)
Portal hypertension	7 (2.0)
Cardiomyopathy	17 (4.9)
Iron deficiency anemia	6 (1.7)
Others [d]	18 (5.1)
Indication of warfarin	
Chronic rheumatic valvular heart disease with left atrial/venous thrombus	46 (13.1)
Atrial fibrillation with or without cardiac lesion	210 (60.0)
Cardioembolism [e]	33 (9.4)
Post-heart valves (mechanical)*	44 (12.6)
Cardiac Thrombus [f]	10 (2.9)
(Bio) prosthetic valve replacement/repair*	8 (2.3)
Post-percutaneous mitral balloon valvotomy*	12 (3.4)
Cardiomyopathy	4 (1.1)
IHD with thrombus	4 (1.1)
Deep vein thrombosis	37 (10.6)
Pulmonary embolism	7 (2.0)
Portal vein thrombosis	11 (3.1)
Incidence of clinical events	
Bleeding episodes	89 (25.43)

Thromboembolism events	15 (4.29)
Emergency department visits	64 (18.29)
All-cause hospitalization	62 (17.71)

[a]hemiplegia, peripheral neuropathy, Parkinson's disease, chronic lower back pain; [b] including transient ischemic attack (TIA), subarachnoid hemorrhage (SAH), arteriovenous malformations (AVM), and intracranial hemorrhage (ICH); [c] includes COPD, Asthma, etc.; NSAIDS, non-steroidal anti-inflammatory drugs; MI, myocardial infarction; PAD, peripheral artery disease; CAD/IHD, coronary artery disease/ischemic heart disease; gynecological disorders, benign prosthetic hyperplasia, pituitary microadenoma, erectile dysfunction, tuberculosis, infective endocarditis, myoma, visual impairment; [e] includes cardioembolic stroke, peripheral artery embolism), other site embolism), or non-embolic stroke (ischemic stroke); [f] includes left ventricular/apical/arterial thrombus. * By themselves are not indications for warfarin; patients should have atrial fibrillation, high CHA_2DS_2-VASc, cardioembolism, cavity thrombus, or ventricular thrombus.

Knowledge of warfarin therapy

Of the 350 patients who participated in the study, 82 (23.4%) achieved a passing score, and that is, they answered at least 13 questions correctly (Figure 3).

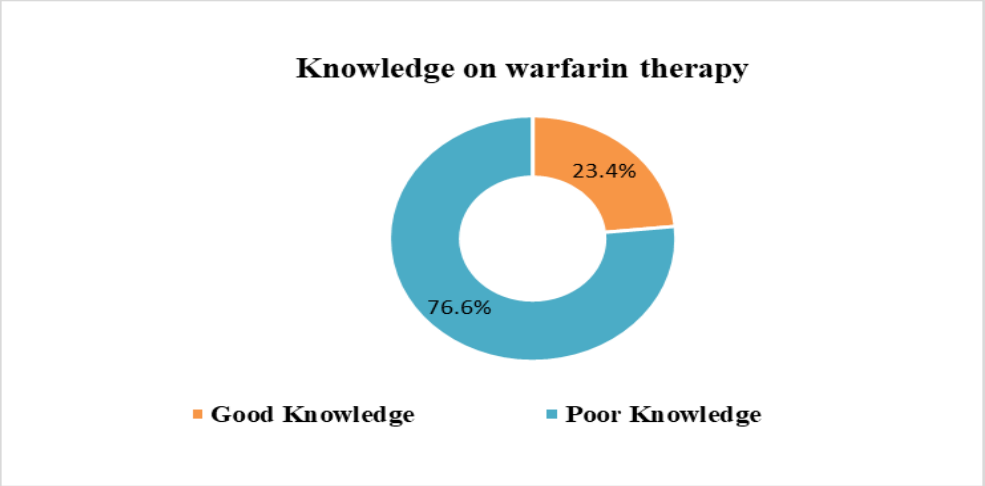

Figure 3: Study participants' knowledge of warfarin based on the AKA questionnaire

Adherence to warfarin

Based on the MGLS, approximately one-third (34.3%) of the participants indicated that they had forgotten to take warfarin during the past four weeks (Paper III-Table 3). In this study, 54.9% of participants showed good adherence to warfarin therapy (Figure 4).

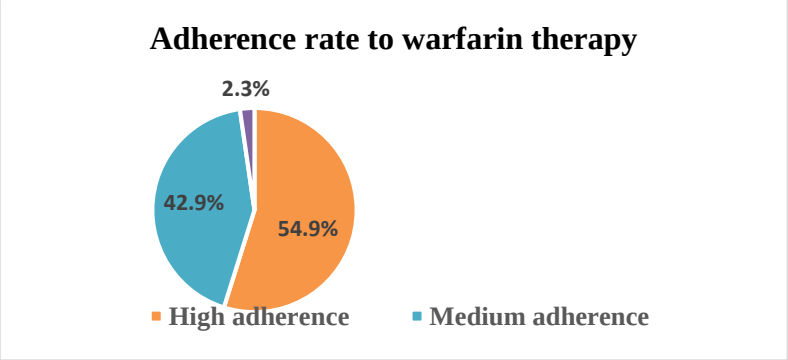

Figure 4: Patients adherence to warfarin.

Reasons for nonadherence to warfarin

Among participants with less than 100% adherence in the past four weeks, the most common reason for nonadherence was forgetfulness (67.7%), followed by fear of warfarin side effects and being busy with work; both were reported by 15.2% of participants (Figure 5).

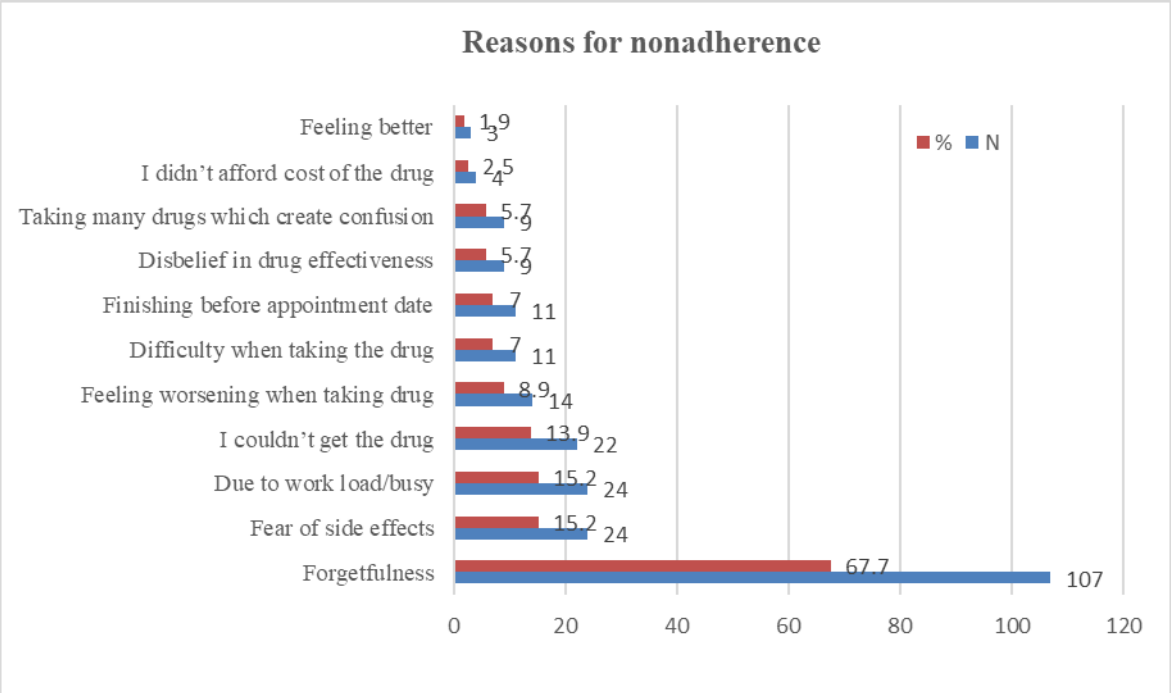

Figure 5: Reasons for nonadherence to warfarin

Satisfaction with warfarin treatment

The mean satisfaction scores on the participants' responses on the anticlot-treatment scale, was 53.67 ± 8.56 with mean scores of 41.93 ± 7.80 and 11.74 ±2.43 in the ACTS burden and benefit sub-scales, respectively. Among the participants, 184 (52.6) were satisfied with warfarin therapy, and the remaining 47.4% were not satisfied. The highest mean satisfaction

scores were related to ‘effect of possible anticlot treatment-related bleeding on doing physical activity’ (4.17 ±1.27) and ‘confidence level with anticlot treatment in its benefit’ (4.15±1.00). The lowest satisfaction scores were for ‘the impact of warfarin on food and drink limitations’ and overall satisfaction with the treatment (Table 3).

Table 3: Mean satisfaction scores of participants on the anticlot treatment scale

Item description		**Mean± SD**
Burden Subscale		
1	How much does the possibility of bleeding as a result of your anticlot treatment limit you from doing physical activity?	4.17 ±1.27
2	How much does the possibility of bleeding as a result of your anticlot treatment limit you from taking part in your usual activities?	4.02 ±1.16
3	How bothered are you by the possibility of bruising as a result of your anticlot treatment?	3.92 ±1.45
4	How bothered are you by having to avoid other medicines as a result of your anticlot treatment?	3.84 ±1.39
5	How much does your anticlot treatment limit what you eat and drink?	2.79 ±1.46
6	How much of a hassle(inconvenience) are the daily aspects of your anticlot treatment? (e.g., remembering to take your medicine at a certain time, taking the correct dose of your medicine, following a diet, limiting alcohol, etc.)	3.98±1.22
7	How much of a hassle (inconvenience) are the occasional aspects of your anticlot treatment? (e.g., the need for blood tests, going to or contacting the clinic/doctor, making arrangements for treatment while traveling, etc.).	2.87±1.55
8	How difficult is it to follow your anticlot treatment?	3.07±1.49
9	How time-consuming is your anticlot treatment?	2.65±1.44
10	How much do you worry about your anticlot treatment?	3.25±1.56
11	How frustrating is your anticlot treatment?	4.04±1.22
12	How much of a burden is your anticlot treatment?	3.33±1.48
13	Overall, how much of a negative impact has your anticlot treatment had on your life?	3.39±1.49
Benefit subscale		
14	How confident are you that your anticlot treatment will protect your health?	4.15±1.00
15	How reassured do you feel because of your anticlot treatment?	3.95±1.06
16	How satisfied are you with your anticlot treatment?	3.65±1.15
17	Overall, how much of a positive impact has your anticlot treatment had on your life?	3.78±1.14

Factors associated with warfarin therapy knowledge

In univariate binary logistic regression analysis, HIV/AIDS and hyperthyroidism were significantly associated with poor knowledge of warfarin therapy. Notably, patients without hyperthyroidism were 4.28 times (AOR = 4.28, 95% CI: 1.01–18.22, p = .049) more likely to have poor knowledge of warfarin than those with hyperthyroidism (Table 4).

Table 4: Factors associated with knowledge of warfarin therapy

	Knowledge on warfarin				
Variable	**Yes n(%)**	**No n (%)**	**COR (95% CI)**	**AOR (95%CI)**	**p-value**
Age in years					
18-30	16(4.6)	60 (17.1)	1	1	
31-45	36(10.3)	99(28.3)	1.73(0.72-4.17)	1.33(0.45-3.90)	0.606
46-64	18(5.1)	83(23.7)	1.27(0.58-2.78)	1.05(0.41-2.68)	0.919
≥ 65	12(3.4)	26(7.4)	2.13(0.91-4.99)	1.88(0.73-4.83)	0.189
Marital status					
Single	28(8.8)	78(22.3)	1	1	
Married	40(11.4)	55(44.3)	1.11(0.52-2.37)	0.76(0.31-1.88)	0.558
Divorced/Widowed /Separated	14(4.0)	35(10.0)	1.55(0.76-3.15)	1.11(0.49-2.52)	0.805
Presence of comorbidity					
No	9(2.6)	53(15.1)	1	1	
Yes	73(20.9)	15(61.4)	2.00(0.94-4.25)	2.27(0.91-5.64)	0.077
Heart failure					
No	40(11.5)	50(53.1)	1	1	
Yes	42(12.1)	116(33.3)	1.36(0.83-2.23)	1.02(0.57-1.84)	0.938
Hypertension					
No	57(16.3)	09(59.7)	1	1	
Yes	25(7.1)	59(16.9)	1.55(0.89-2.70)	1.38(0.72-2.65)	0.330
HIVAIDS					
No	76(21.7)	62(74.9)	1	1	
Yes	6(1.7)	6(1.7)	3.45(1.08-10.99)	3.29(0.89-12.15)	0.074
Vascular disease history					
No	68 (19.4)	43(69.4)	1	1	
Yes	14(4.0)	25(7.1)	2.00(0.99-4.06)	2.04(0.90-4.64)	0.089
Valvular heart diseases that don't need warfarin					
No	46(13.1)	59(45.4)	1	1	
Yes	36(10.3)	109(31.1)	1.71(0.87-3.36)	1.83(0.84-3.98)	0.130
Hyperthyroidism					
Yes	6(1.7)	4(1.1)	1	1	
No	76(21.7)	64(75.4)	5.21(1.43-18.94)	4.28(1.01-18.22)	0.049

Presence of warfarin interacting drugs					
No	44(12.6)	23(35.1)			
Yes	38(10.9)	45(41.4)	0.73(0.45-1.20)	0.58(0.33-1.01)	0.054
Number of CHC visits during follow-up					
3-6	23(6.6)	47(13.4)	1	1	
7-10	25(7.1)	99(28.3)	0.49(0.21-1.12)	0.61(0.24-1.53)	0.291
11-14	23(6.6)	76(21.7)	0.95(0.43-2.09)	1.11(0.46-2.66)	0.819
≥15	11(3.1)	46(13.1)	0.79(0.35-1.77)	0.94(0.39-2.29)	0.901
Cardioembolism or non-embolic stroke warfarin indication					
No	77(22.0)	40(68.6)	1	1	
Yes	5(1.4)	28(8.0)	0.56(0.21-1.49)	0.57(0.20-1.63)	0.298

Associated factors with adherence to warfarin

In the multivariate logistic regression analysis, living alone and visiting CHCs 15 or more times were significantly associated with adherence to warfarin therapy. Patients living with their families had 56% lower odds of poor adherence than those living alone (AOR: 0.44; 95% CI: 0.21–0.93; p = .032) (Table 5).

Table 5: Factors associated with adherence to warfarin therapy

Variables	Adherence to warfarin		**COR (95% CI)**	**AOR (95% CI)**	**P-value**
	Good Yes, n (%)	Poor Yes, n (%)			
Family monthly income in Birr					
0-300	86(24.6)	91(26.0)	1	1	
301-2,500	31(8.9)	18(5.1)	1.18(0.64-2.16)	1.25(0.66-2.35)	0.494
2,501- 5,000	46(13.1)	23(6.6)	0.65(0.29-1.42)	0.70(0.307-1.61)	0.404
>5,001	29(8.3)	26(7.4)	0.56(0.27-1.16)	0.54(0.25-1.17)	0.117
With whom do you live?					
Alone	15(4.3)	21(6.0)	1	1	
With family	177(50.6)	137(39.1)	0.55(0.27-1.11)	0.44(0.21-0.93)	0.032
Duration of warfarin in years					
0.5-1	34(9.7)	38(10.9)	1	1	
>1-5	74(21.1)	52 (14.9)	1.68(0.81-3.48)	1.38(0.63-3.01)	0.417
6-10	54(15.4)	48(13.7)	1.05(0.54-2.05)	0.72(0.36-1.47)	0.373
>10	30(8.6)	20 (5.7)	1.33(0.67-2.65)	1.07(0.523-2.20)	0.847
Hypertension					
No	151(43.1)	15(32.9)			
Yes	41(11.7)	43(12.3)	0.73(0.44-1.19)	0.71(0.42-1.12)	0.199
HIVAIDS					
No	188(53.7)	150(42.9)	1	1	

Yes	4(1.1)	8(2.3)	0.40(0.12-1.35)	0.42(0.12-1.52)	0.185
Knowledge of warfarin therapy					
Good	49 (14.0)	33(9.4)	1	1	
Poor	143(40.9)	125(35.7)	0.77(0.47-1.27)	0.73(0.43-1.24)	0.245
Number of CHCs visit during follow-up					
3-6	39(11.1)	31(8.9)	1	1	
7-10	69(19.7)	55(15.7)	0.62(0.31-1.26)	0.59(0.2771.28)	0.183
11-14	59(16.9)	40(11.4)	0.62(0.33-1.17)	0.56(0.28-1.09)	0.089
≥15	25(7.1)	32(9.1)	0.53(0.27-1.02)	0.50(0.25-1.01)	0.052
Post-percutaneous mitral balloon valvotomy					
No	183(52.3)	55(44.3)	1	1	
Yes	9(2.6)	3(0.9)	2.54(0.68-9.55)	2.26(0.57-9.02)	0.247

Factors associated with satisfaction with anticoagulation treatment

Eleven variables were assessed for their association with patient satisfaction with anticoagulation treatment using a univariate binary logistic regression analysis. Multivariate logistic regression analysis revealed that living alone, older age, better educational status, living outside Addis Ababa, portal vein thrombosis, warfarin indication, and history of bleeding were associated with a higher likelihood of dissatisfaction with warfarin therapy. However, none of these factors was significantly associated with satisfaction with anticoagulant treatment in this study (Table 6).

Table 6: Factors associated with satisfaction with anticoagulation treatment in patients receiving warfarin

Variables	Satisfaction with warfarin		COR (95% CI)	AOR (95% CI)	P-value
	Good Yes, n (%)	Poor No, n (%)			
Age in years					
18-30	36(10.3)	40 (11.4)	1	1	
31-45	77(22.0)	58(16.6)	0.90 (0.57-1.41)	1.20(0.50-2.86)	0.685
46-64	54(15.4)	47(13.4)	1.23(0.94-1.87)	1.63(0.73-3.66)	0.232
≥65	17(4.9)	21(6.0)	1.15(0.78-1.70)	1.53(0.67-3.48)	0.311
Residence					
Addis Ababa	134(38.3)	13(32.3)			
Out of Addis Ababa	50(14.3)	53(15.1)	1.19(0.92-1.52)	1.30(0.79-2.15)	0.297
Education Status					
Unable to read and write	27(7.7)	24(6.9)	1	1	

Primary school (Grade 1-8)	2(14.9)	49(14.4)	1.12(0.65-1.95)	1.31(0.54-3.17)	0.548
Secondary school (Grade 9-12)	6(16.0)	54(15.4)	1.06(0.72-1.57)	1.07(0.50-2.28)	0.869
Degree and above	27(7.7)	16(4.6)	1.04(0.71-1.51)	1.09(0.52-2.28)	0.819
Certificate/Diploma	22(6.3)	23(6.6)	1.69(0.91-3.13)	1.87(0.75-4.64)	0.176
With whom do you live?					
With family	168(48.0)	46(41.7)			
Alone	16(4.6)	20(5.7)	1.15(0.92-1.44)	1.43(0.69-2.98)	0.332
Medical service coverage					
CBHI	136(38.9)	24(35.4)	1	1	
Out-of-pocket/Paying	42(12.0)	32(9.1)	1.10(0.86-1.40)	1.24(0.39-3.88)	0.715
Free	6(1.7)	10(2.9)	1.31(0.83-2.08)	1.38(0.41-4.59)	0.602
Vascular disease history					
No	166(47.4)	145(41.4)			
Yes	18(5.1)	21(6.0)	1.14(0.92-1.43)	1.17(0.57-2.39)	0.674
Post-mitral and/or aortic valve replacement (mechanical)					
No	163(46.6)	143(40.9)			
Yes	21(6.0)	23(6.6)	1.14(0.91-1.43)	1.52(0.75-3.05)	0.242
Portal vein thrombosis					
No	181(51.7)	58(45.1)			
Yes	3(0.9)	8(2.3)	1.15(0.92-1.42)	2.56(0.56-11.67)	0.224
Number of CHC visits during follow-up					
3-6	39(11.1)	31(8.9)	1	1	0.454
7-10	65(18.6)	59(16.9)	1.26(0.78-2.012)	1.73(0.77-3.87)	0.182
11-14	57(16.3)	42(12)	1.10(0.77-1.57)	1.34(0.63-2.88)	0.449
≥15	23(6.6)	34(9.7)	1.36(0.91-2.02)	1.68(0.81-3.48)	0.162
INR monitoring frequency in days (mean)					
≤ 30	17(4.9)	19(5.4)	1	1	0.499
31-60	91(26.0)	89(25.4)	0.89(0.46-1.72)	1.62(0.51-5.14)	0.408
61-90	65(18.6)	43(12.3)	1.02(0.76-1.37)	1.49(0.60-3.67)	0.386
>91	11(3.1)	15(4.3)	1.51(1.03-2.22)	1.98(0.78-5.03)	0.148
Bleeding episodes					
No	158(45.1)	131(37.4)			
Yes	26(7.4)	35(10.0)	1.21(0.96-1.52)	1.32(0.72-2.44)	0.371

5.4. Key Finding from Quasi-experimental Study

Study population

During the follow-up period, 1,185 patients received warfarin therapy at the PLAC and CHCs. Of them, 720 and 189 patients in the UMC and PLAC groups, respectively, met the inclusion criteria. Using the study sampling techniques, all patients from the PLAC group and every other patients in the UMC group were included in the study. This resulted in a final analysis of

525 patients, with 350 (66.7%) in the UMC group and 175 (33.3%) in the PLAC group.

Socio-demographic characteristics of study participants

Of the 525 study participants, 375 (71.4%) were female, with a median age of 40 years (range, 32–53 years). The majority of patients in both groups were female, with no significant sex differences between the groups (p = 0.31). The median age in the UMC group was 41.00 years (IQR: 32-55, range: 18-82), while the PLAC group had a median age of 39 years (IQR: 32-49, range: 20-85) with no a significant age difference between the groups (p = 0.15). A significant difference was observed in the patient's place of residence, with the majority of residents living in Addis Ababa in both the UMC (247, 70.6%) and PLAC (148, 84.6%) (p <0.001) (Table 7).

Table 7: Socio-demographic characteristics of patients receiving warfarin compared between UMC and PLAC at TASH

Variables	Total (N=525) n (%)	UMC Group (N=350) n (%)	PLAC Group (N=175)n (%)	P-value
Sex				
Female	375(71.4)	245(70.0)	130(74.3)	0.31
Male	150(28.6)	105(30.0)	45(25.7)	
Age in years				
18-30	107(20.4)	72(20.6)	35(20.0)	0.46
31-45	231(44.0)	148(42.3)	83(47.4)	
46-64	135(25.7)	97(27.7)	38(21.7)	
≥65	52(9.9)	33(9.4)	19(10.9)	
Median (IQR) age	40.00(32-53)	41(32-55)	39(32-49)	0.15
Residence				
Addis Ababa	395(75.2)	247(70.6)	148(84.6)	<0.001
Out of Addis Ababa	130(24.8)	103(29.4)	27(15.4)	

Clinical characteristics of patients

Most patients in both groups had at least one comorbidity, with a significantly higher proportion in the UMC group (82.3% vs. 64.6%, p <0.001). The most common comorbidity in the UMC group was heart failure (45.4%), followed by chronic rheumatic valvular heart disease (CRVHD) (41.4%). In contrast, the majority of the patients in the PLAC group had CRVHD (32.6%), followed by heart failure (29.1%). Additionally, significant differences (p<0.05) in the distribution of comorbidities were recorded between the groups with heart failure, hypertension, aspirin and/or clopidogrel use, history of vascular disease, coronary artery disease/ischemic heart disease, and polycythemia vera, which were more prevalent in the UMC group (Table 8).

Table 8: Clinical characteristics of patients receiving warfarin compared between UMC and PLAC at TASH

Characteristics	Total (N=525) n (%)	UMC Group (N=350)n (%)	PLAC Group (N=175)n (%)	P-value
Presence of comorbidity				
Yes	401(76.4)	288(82.3)	113(64.6)	<0.001
Underlying heart problems, comorbidities, or medication use				
Heart failure	209(39.8)	158(45.4)	51(29.1)	<0.001
Valvular heart disease	202(38.5)	145(41.4)	57(32.6)	0.06
Hypertension	109(20.8)	84(24.0)	25(14.3)	0.01
Stroke and thromboembolism history[a]	88(16.8)	66(18.9)	22(12.6)	0.08
Amiodarone use	6 (1.1)	6 (1.7)	0 (0)	0.19
Aspirin, clopidogrel, NSAIDs use	31 (5.9)	26 (7.4)	5 (2.9)	0.04
Pulmonary Hypertension	63(12.0)	43(12.3)	20(11.4)	0.78
Vascular heart disease history [b]	43(8.2)	39(11.1)	4(2.3)	<0.001
Diabetes Mellitus	35(6.7)	28(8.0)	7(4.0)	0.08
CAD/IHD without thrombus	20(3.8)	18(5.1)	2(1.1)	0.02
Seizure disorders	20(3.8)	17(4.9)	3(1.7)	0.09
Other neurologic disorders [c]	22(4.2)	19(5.4)	3(1.7)	0.06
Cardiomyopathy	23(4.4)	17(4.9)	6(3.4)	0.51
HIV/AIDS	14(2.7)	12(3.4)	2(1.1)	0.16
Cancer	13(2.5)	12(3.4)	1(0.6)	0.07
Hypertensive heart disease	20(3.8)	11(3.1)	9(5.1)	0.33
Hyperthyroidism	14(2.7)	10(2.9)	4(2.3)	0.78
Chronic Pulmonary diseases [d]	14(2.7)	10(2.9)	4(2.3)	0.78
Dyslipidemia	11(2.1)	10(2.9)	1(0.6)	0.11
Rheumatologic diseases	13(2.5)	9(2.6)	4(2.3)	0.55
Gastric illness/peptic ulcer diseases	10(1.9)	9(2.6)	1(0.6)	0.18
Portal hypertension	7(1.3)	7(2.0)	0(0.0)	0.10
Renal Diseases	12(2.3)	8(2.3)	4(2.3)	0.63
Liver diseases	11(2.1)	8(2.3)	3(1.7)	0.76
Polycythemia vera	8(1.5)	8(2.3)	0(0)	<0.001
Iron deficiency anemia	7(1.3)	6(1.7)	1(0.6)	0.43
Hypothyroidism	6(1.1)	4(1.1)	2(1.1)	0.68
Psychiatric disorders	5(0.9)	3(0.9)	2(1.1)	0.54
Others [e]	27(5.1)	18(5.1)	9(5.1)	0.59

[a]includes transient ischemic attack(TIA), subarachnoid hemorrhage (SAH), arteriovenous malformations (AVM), and intracranial hemorrhage (ICH); [b]incudes prior, myocardial infarction, peripheral artery disease, or aortic plaque; [c]includes hemiplegia, peripheral neuropathy, Parkinson's disease, chronic lower back pain; [d] includes COPD, asthma, etc.;

NSAIDS, non-steroidal anti-inflammatory drugs; CAD/IHD, coronary artery disease/ischemic heart disease; egynecological disorders, benign prosthetic hyperplasia, pituitary microadema, erectile dysfunction, tuberculosis, infective endocarditis, myoma, and visual impairment.

Among 210 and 125 patients diagnosed in the UMC and PLAC groups with atrial fibrillation, respectively, 39.5% in the UMC group had a high CHA_2DS_2-VASc score, while 45.6% in the PLAC group had a low CHA_2DS_2-VASc score ($p<0.001$). In contrast, the majority of patients in both groups had a moderate bleeding risk, with 71.4% in the UMC group and 54.4% in the PLAC group, showing statistically significant differences between groups ($p <0.001$) (Table 9).

Table 9: Baseline stroke and bleeding risk scores among atrial fibrillation patients receiving warfarin compared between UMC and PLAC at TASH

Risk score	Total (N=335) n (%)	UMC Group (N=210) n (%)	PLAC Group (N=125) n(%)	P-value
CHA_2DS_2-VASc Risk				
Low	110(32.8)	53(25.2)	57(45.6)	<0.001
Moderate	120(35.8)	74(35.3)	46(36.8)	
High	105(31.4)	83(39.5)	22(17.6)	
HAS-BLED Risk				
Low	80(23.8)	34(16.2)	46(36.8)	<0.001
Moderate	218(65.1)	150(71.4)	68(54.4)	
High	37(11.1)	26(12.4)	11(8.8)	

Warfarin indication

The most common warfarin indication was for atrial fibrillation, with 210 (60.0%) and 125 (71.4%) patients in the UMC and PLAC groups, respectively. This was followed by CRVHD 46 (13.1%) patients in the UMC group and mechanical valve in 40 (22.9%) patients in the PLAC group. A statistically significant difference in distribution among the groups was observed for atrial fibrillation ($p=0.01$), mechanical heart valve ($p= 0.002$), bioprosthetic valve replacement/repair ($p=0.002$), and post-percutaneous mitral balloon valvotomy ($p=0.01$), which was most commonly observed in the PLAC group. Patients with deep vein thrombosis ($p<0.001$) and portal vein thrombosis ($p=0.019$) were managed only at the UMC (Table 10).

Table 10: Warfarin indications among outpatients compared between UMC and PLAC

Indication of warfarin	**Total (N=525) n (%)**	**UMC Group (N=350)n (%)**	**PLAC Group (N=175) n (%)**	**P-value**
Atrial fibrillation	335 63.8)	210 (60.0)	125 (71.4)	0.01
Valvular heart disease	59 (11.2)	46 (13.1)	13 (7.4)	0.05
Cardioembolism [a]	49 (9.3)	33 (9.4)	16 (9.1)	0.92
Post-mechanical heart valves [c]	84 (16.0)	44 (12.6)	40 (22.9)	0.002
Cardiac Thrombus [b]	18 (3.4)	10 (2.9)	8 (4.6)	0.31
(Bio) prosthetic valve replacement/ repair [c]	22 (4.2)	8 (2.3)	14 (8.0)	0.002
Post-percutaneous mitral balloon valvotomy [c]	27 (5.1)	12 (3.4)	15 (8.6)	0.012
Cardiomyopathy [c]	10 (1.9)	4 (1.1)	6 (3.4)	0.091
IHD with thrombus	10 (1.9)	4 (1.1)	6 (3.4)	0.091
Deep vein thrombosis	37 (7.0)	37 (10.6)	0 (0)	<0.001
Pulmonary embolism	7 (2.0)	7 (2.0)	0 (0)	0.102
Portal vein thrombosis	11 (2.1)	11 (3.1)	0 (0)	0.019

[a] includes cardioembolic stroke, peripheral artery embolism, embolism at other sites), or non-embolic stroke (ischemic stroke).

[b] includes left ventricular/apical/arterial thrombus

[c] by themselves are not indications for warfarin; patients should have atrial fibrillation, high CHA_2DS_2-VASc, cardioembolism, cavity thrombus, or ventricular thrombus

INR target range, monitoring frequency, and dose of warfarin

The majority of patients in both groups had an INR target range of 2.0–3.0, with a statistically significant difference between groups ($p = 0.002$). In the UMC group, INR was monitored every 51.54 days (IQR: 37.18–69.14), compared to every 40.08 days (IQR: 33.17–48.83) in the PLAC group, showing a statistically significant difference ($p < 0.001$) with more frequent monitoring in the PLAC group. The median weekly dose of warfarin was 35 mg (IQR: 27-42.5) in the PLAC group and 32.26 mg (IQR: 25.21-40.56) in the UMC group, with no statistically significant difference between the groups ($p = 0.239$). Similarly, the median prescribed warfarin dose did not differ significantly between groups (Table 11).

Table 11: INR target range, monitoring frequency, and dose of warfarin compared between UMC and PLAC at TASH

Item description	**Total (N=525) n (%)**	**UMC Group (N=350) n %)**	**PLAC Group (N=175) n (%)**	**P-**value
Target INR range				
2.0-3.0	441(84.0)	306 (87.4)	135 (77.1)	0.002
2.5-3.5	84 (16.0)	44 (12.6)	40 (29.9)	
INR monitoring frequency in days				
Median (IQR)	46.45 (36.15-61.6)	51.54 (37.18-69.14)	40.08(33.17-48.83)	<0.001
Number of Visits				
Median (IQR)	9 (7-9)	10 (7-13)	9 (7-11)	0.044
Average Weekly Dose				
Median (IQR)	33.22 (25.9-41.33)	32.36 (25.21-40.56)	35 (27-42.5)	0.239
Average daily Dose				
Median (IQR)	4.75(3.7-5.9)	4.62 (3.6-5.80)	3.86(3.86-6.07)	0.239

The average weekly-prescribed warfarin dose for the UMC and PLAC group patients varied from 7.35 to 129.4 mg and 12.81 to 91.76 mg, respectively without significant difference between the groups.

INR distributions within different ranges

Overall, 3,181 and 1,419 INR values were recorded for the therapeutic range of 2.0–3.0 in the UMC and PLAC groups, respectively. Additionally, 458 and 356 INR values were documented for the 2.5–3.5 range in the UMC and PLAC groups, respectively. A higher percentage of patients in the PLAC group (55.3%) achieved the target INR range of 2-3 compared to those in the UMC group (45.7%). The PLAC group also had fewer patients with an INR <1.50 and > 5.00. For the target INR range of 2.5-3.5, the PLAC group had a higher percentage of patients (43.5%) within the target range than the UMC group (24.7%), with fewer patients having INR below 1.50. The distribution of INR values showed significant differences between the two groups ($p<0.001$), indicating that the PLAC group had better INR control within the specified target ranges (Table 12).

Table 12: INR distributions within different ranges compared between UMC and PLAC groups at TASH

Item description	UMC Group n (%)	PLAC Group N (%)	Chi-square value	p-value
INR distribution category in Target INR 2-3				
< 1.50	358 (11.3)	120 (8.5)	150.74	001
1.5-1.99	698 (21.9)	244 (17.2)		
2.00-3.00	1453 (45.7)	785 55.3)		
3.01-4.00	426 (13.4)	179 (12.6)		
4.01-5.00	136 (4.3)	60 (4.2)		
>5.00	110 (93.5)	31 (2.2)		
INR distribution category in Target INR 2.5-3.5				
<1.50	55 (12.0)	27 (7.6)	39.18	<0.001
1.50-2.49	246 (53.6)	133 (37.4)		
2.50-3.50	113 (24.7)	155 (43.5)		
3.51-4.50	26 (5.7)	28 (2.8)		
4.51-5.00	7 (1.5)	4 (1.1)		
>5.00	11 (2.4)	9 (2.5)		

Differences in the time spent in different INR ranges

Compared with the UMC group, patients in the PLAC group demonstrated a significantly higher median (IQR) TTR [60.89% (43.5–74.69%) vs. 53.65% (33.92–69.14%)] p< 0.001. Additionally, the percentage of time spent below the target range (TBR) was significantly lower in the PLAC group (21%) compared to the UMC group (27.34%) (p = 0.01). However, there was no difference in the percentage of median time above the range between the UMC and PLAC groups (p= 0.47). Further analysis using the Rank-Biserial correlation coefficient (r-value) revealed that the effect size associated with the difference between UMC and PLAC groups was 0.02. This value reflects a small effect size of 2%, favoring PLAC (Figure 6).

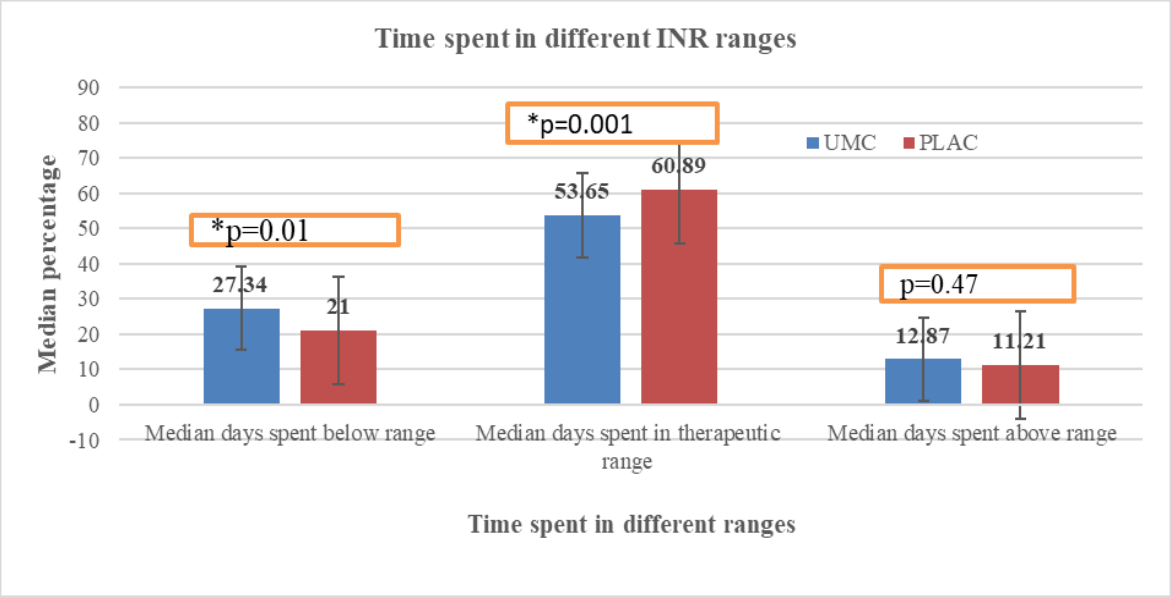

Figure 6: Time Spent in Different INR Ranges between UMC and PLAC

Optimal anticoagulation control difference between the groups

Optimal TTR (≥ 65%) was achieved in a higher percentage of patients in the PLAC group (41.7%) compared to the UMC group (31.7%), with a statistically significant difference (p= 0.002) (Table 13).

Table 13: Comparison of optimal TTR differences between UMC and PLAC

Group	TTR <65%		TTR ≥65%		P value
	N (%)	95%CI	n (%)	95% CI	
UMC	239(68.3)	(63.1,73.1)	111(31.7)	(26.9,36.9)	0.02
PLAC	102(58.3)	(50.6,65.7)	73 (41.7)	(34.3,49.4)	

Anticoagulation status and measures taken on warfarin dosing

In this study, INR values of 3561 and 1643 were recorded in the UMC and PLAC groups, respectively. Compared with physicians (UMC), pharmacists (PLAC) took significantly more correct actions on warfarin dosing (p<0.001) for INRs in the subtherapeutic, therapeutic, and supratherapeutic ranges. Therefore, fewer incorrect actions were performed in the PLAC group (Table 14).

Table 14: Anticoagulation status and measures taken in warfarin dosing among patients attending UMC and PLAC of TASH

Anticoagulation status	Group (Number of INRs	Number of correct actions (%)	Number of incorrect actions (%)	Chi-square value	p-value
Subtherapeutic range	UMC (Total=1314)	612 (46.57)	702 (53.42)	47.79	<0.001
	PLAC (Total=470)	300 (63.83)	170 (36.17)		
In therapeutic range	UMC (Total=1546)	1182 (76.46)	364 (23.54)	326.18	<0.001
	PLAC (Total=865)	771 (89.13)	94 (10.87)		
Supratherapeutic range	UMC (Total=701)	464 (66.19)	237 (33.81)	14.51	<0.001
	PLAC (Total=308)	226 (73.28)	82 (26.62)		

Warfarin drug interaction

In this study, approximately one-third of the patients in the UMC group 31.1% (95% CI=26.3-36.3), and 14.3% in the PLAC group (95% CI=9.5-20.4) took at least one drug that interacted with warfarin, respectively, with a significant difference between the groups (p<0.001) (Table 15).

Table 15: Drug interactions among patients receiving warfarin therapy at UMC VS PLAC

Variable	Total		UMC		PLAC		P-value
	N (%)	95%CI	N (%)	95%CI	N (%)	95%CI	
No	391(75.5)	(70.5,78.2)	241(68.9)	(63.7,73.7)	150(85.7)	(79.6,90.5)	<0.001
Yes	134(25.5)	(21.8,29.5)	109(31.1)	(26.3,36.3)	25(14.3)	(9.5,20.4)	

Aspirin 28 (8.0%), amitriptyline 16 (4.6%), and clopidogrel 11(3.1%) were the most identified warfarin-interacting drugs in the UMC groups, followed by erythromycin 8 (2.3%), and glibenclamide 7 (2.0%). In the PLAC group, the most commonly prescribed interacting drugs were aspirin 11 (6.3%), phenytoin 3 (1.7%), and azithromycin 3 (1.7%). Detailed interactions are presented in Table 16.

Table 16: Warfarin drug interactions among patients attending UMC and PLAC of TASH

UMC Group		PLAC Group	
Interacting drugs	N (%)	Interacting drugs	N (%)
Aspirin	28 (8.0)	Aspirin	11 (6.3)
Amitriptyline	16 (4.6)	Azithromycin	3 (1.7)
Clopidogrel	11 (3.1)	Phenytoin	3(1.7)

Erythromycin	8 (2.3)	Propylthiouracil	2 (1.1)
Glibenclamide	7 (2.0)	Amitriptyline	1 (0.6)
Pantoprazole	6 (1.7)	Valproic acid	1(0.6)
Amiodarone	6 (1.7)	Simvastatin	1 (0.6)
Propylthiouracil	6 (1.7)	Phenobarbitone	1(0.6)
Azithromycin	5 (1.4)	Omeprazole	1(0.6)
Valproic acid	5 (1.4)	Carbimazole	1 (0.6)
Carbamazepine	5 (1.4)	Rifampicin/isoniazid	1(0.6)
Amoxicillin with clavulanic acid	4 (1.1)	Budesonide/formoterol turbohaler	1(0.6)
Simvastatin	4 (1.1)		
Phenytoin	4(1.1)		
Combined oral contraceptive	3 (0.9)		
Phenobarbitone	2(0.6)		
Indomethacin	2 (0.6)		
Cephalexin	2 (0.6)		
Cotrimoxazole	2(0.6)		
Prednisolone	2 (0.6)		
Levothyroxine	2 (0.6)		
Ciprofloxacin	1 (0.3)		
Fluoxetine	1 (0.3)		
Ceftriaxone	1 (1.3)		
Allopurinol	1 (0.3)		
Tamoxifen	1 (0.3)		
Paracetamol	1 (0.6)		

Predictors of poor the time in therapeutic range

The odds of having a poor TTR were reduced by 43% among patients in the PLAC group compared to those in the UMC group (AOR = 0.57, 95% CI = 0.36–0.88, p = 0.01). Patients with low HAS-BLED scores were 49% less likely to have poor TTR compared to those with no risk (AOR=0.51, 95%CI=0.29, 0.91, p=0.02). In contrast, patients with moderate and high HAS-BLED scores were 1.68 and 3.08 times more likely to have a poor TTR (AOR = 1.68, 95% CI = 1.07, 2.64, p = 0.03) and (AOR=3.08, 95% CI = 1.17, 8.09, p = 0.02), respectively, than those with no risk. Additionally, patients with post-MVR/AVR mechanical valves were twice more likely to have poor TTR than those without mechanical valves (AOR = 2.11, 95% CI = 1.17, p=0.01). On the other hand, the odds of poor TTR were decreased by 2% for every increase in the frequency of INR monitoring (AOR=0.98, 95%CI=0.97, 0.99, p=0.002) (Table 17).

Table 17: Factors associated with poor TTR in patients receiving warfarin therapy

Variable	TTR ≥65%	TTR<65%	COR (95%CI)	AOR (95%CI)	P-value
Treatment group					
UMC	111(21.1)	239(45.5)	1.00	1.00	**0.01***
PLAC	73(13.9)	102(19.4)	0.65(0.45,0.95)	0.57(0.36,0.88)	
Sex					
Female	132(25.1)	243(46.3)	1.00	1.00	0.79
Male	52(9.9)	98(18.7)	1.02(0.69,1.52)	0.95(0.62,1.44)	
Age in years					
18-30	32(6.1)	75(14.3)	1.00	1.00	
31-45	81(15.4)	150(28.6)	0.79(0.48,1.29)	0.79(0.47,1.32)	0.36
46-64	53(10.1)	82(15.6)	0.66(0.39,1.13)	0.57(0.32,1.02)	0.06
≥65	18(3.4)	34(6.5)	0.81(0.39,1.63)	0.45(0.19,1.03)	0.06
HAS-BLED risk scores					
No risk	65(12.4)	125(23.8)	1.00	1.00	
Low risk	46(8.8)	34(6.5)	0.38(0.23, 0.66)	0.51(0.29,0.91)	**0.02***
Moderate risk	65(12.4)	153(29.1)	1.22(0.81,1.86)	1.68(1.07,2.64)	**0.03***
High risk	8(1.5)	29(5.5)	1.89(0.82,4.36)	3.08(1.17,8.09)	**0.02***
Post MVR/AVR mechanical					
No	163(31.0)	278(53.0)	1.00	1.00	**0.01***
Yes	21(4.0)	63(12.0)	1.76(1.04,2.99)	2.11(1.17,3.81)	
Post PMTC valvotomy					
No	169(32.2)	329(62.7)	1.00	1.00	
Yes	15(2.9)	12(2.3)	0.41(0.19,0.89)	0.49(0.22,1.13)	0.09
INR monitoring interval			0.99(0.98,1.01)	0.98(0.97,0.99)	**0.002***

Secondary outcomes findings

A total of 89 (25.4%) bleeding events were reported in the UMC group, with the highest number of eight bleeding episodes occurring in a single patient. Forty-nine of these bleeding episodes were recorded in different patients, while the remaining episodes were reported multiple times during various patient visits. In the PLAC group, 29 (16.6%) bleeding episodes occurred, with four episodes recorded in two patients and one episode in three patients. The remaining 18 bleeding episodes were reported in different patients. There were no significant differences in bleeding events between the groups (p = 0.715). All bleeding events were minor, including nosebleeds, gum and tooth bleeding, bruising, and menstruation. Fifteen (4.3%) thromboembolic events were recorded in the UMC group, while eight (4.6%) were reported in the PLAC group, with no significant difference between the groups (p = 0.435). All-cause emergency department visits were documented in 64 (18.3%) patients in the UMC group and

five (2.9%) patients in the PLAC group, with a statistically significant difference between the groups (p = 0.003) (Table 18).

Table 18: Secondary outcomes among patients receiving warfarin compared between UMC and PLAC

Secondary outcomes	**Total n (%)**	**UMC n %)**	**PLAC n (%)**	**p-value**
Bleeding episodes	118(22.5)	89(25.4)	29(16.6)	0.715
Thromboembolic episodes	23(4.4)	15(4.3)	8(4.6)	0.435
All cause-emergency department visit	69(13.1)	64(18.3)	5(2.9)	0.003
Hospitalization	76(14.5)	62(17.7)	14(8.0)	0.469

Predictors of secondary outcomes

Negative binomial regression revealed that the incidence of bleeding events decreased by 3% (IRR = 0.97, 95% CI =0.96–0.99, p<0.001) for each increase in the INR monitoring frequency. The incidence of thromboembolic events was 15.13 times higher (IRR = 15.13, 95% CI = 1.47–155.52, p=0.02) among patients with a high-risk CHA_2DS_2-VASc score compared to those with a moderate score. The incidence of all-cause emergency department visits was 7.59 times higher (IRR=7.59, 95% CI=2.68, 21.50, p<0.001) in the UMC group compared to the PLAC group. The incidence of all-cause emergency department visits was reduced by 69% (IRR=0.31, 95%CI=0.13, 0.73, p=0.007) in patients with a TTR<65% compared to those with a TTR≥ 65%. For every increase in the INR INR monitoring frequency, the incidence of emergency department visits was decreased by 3% (IRR=0.97, 95%CI=0.95, 0.99, p<0.001). The incidence of hospitalization was 73% lower (IRR=0.27, 95%CI=0.10, 0.70, p=0.007) in patients with TTR<65% compared to those with a TTR≥ 65% (Table 19).

Table 19: Poisson regression analysis of secondary outcomes among patients receiving warfarin therapy

	Bleeding episodes		**Thromboembolic events**		**Emergency department visit**		**Hospitalization**	
Variable	**IRR (95%CI)**	**p-value**	**IRR (95%CI)**	**p-value**	**IRR (95%CI)**	**p-value**	**IRR (95%CI)**	**p-value**
Patient group								
UMC	1.45(0.79,2.65)	0.22	0.84(0.26,2.68)	0.77	7.59(2.68,21.50)	**<0.001**	1.75(0.79,3.87)	0.17
PLAC	1.00		1.00		1.00		1.00	
Sex								
Female	0.90(0.53,1.53)	0.69	0.55(0.21,1.45)	0.23	1.50(0.79,2.84)	0.21	0.82(0.43,1.57)	0.55
Male	1.00		1.00		1.00		1.00	
Age								
18-30	**0.74(0.26,2.16)**	**0.58**	**0.85(0.13,5.53)**	**0.86**	**2.02(0.72,5.69)**	**0.19**	**1.31(0.39,4.39)**	**0.67**
31-45	1.12(0.43,2.91)	0.82	1.07(0.21,5.46)	0.94	0.84(0.31,2.28)	0.73	1.00(0.33,3.02)	1.00
46-64	0.78(0.31,1.95)	0.59	0.69(0.13,3.66)	0.66	0.61(0.22,1.67)	0.34	0.51(0.17,1.56)	0.24
≥65	1.00		1.00		1.00		1.00	
Residence								
Addis Ababa	1.04(0.59,1.84)	0.89	1.25(0.41,3.84)	0.69	1.16(0.65,2.07)	0.62	1.57(0.77,3.17)	0.21
Out of Addis Ababa	1.00		1.00		1.00		1.00	
Presence of comorbidities								
No	1.65(0.56,4.87)	0.37	1.73(0.26,11.31)	0.57	0.69(0.22,2.25)	0.55	0.75(0.18,3.04)	0.68
Yes	1.00		1.00		1.00		1.00	
CHA_2DS_2-VASc Risk								
High risk	1.87(0.78,4.52)	0.16	15.13(1.47,155.52)	**0.02**	1.79(0.80,4.03)	0.15	2.22(0.80,6.14)	0.13
Low risk	1.59(0.67,3.77)	0.29	4.09(0.44,38.07)	0.22	0.38(0.14,1.08)	0.06	1.11(0.37,3.32)	0.85
Moderate risk	1.00		1.00		**1.00**		**1.00**	
HAS-BLED risk								
High risk	0.81(0.27,2.39)	0.70	0.14(0.01,1.93)	0.14	0.44(0.14,1.44)	0.18	0.63(0.17,2.24)	0.47

Low risk	0.69(0.27,1.77)	0.44	1.56(0.29,8.08)	0.59	2.27(0.79,6.53)	0.13	1.09(0.35,3.41)	0.88
Moderate risk	1.00		1.00		1.0		1.00	
Target INR range								
2-3	0.87(0.42,1.78)	0.69	0.86(0.25,3.01)	0.81	1.06(0.41,2.79)	0.90	0.87(0.35,2.17)	0.76
2.5-3.5	1.00		1.00		1.00		1.00	
Presence of warfarin drug interaction								
No	0.99(0.57,1.72)	0.97	0.69(0.24,2.04)	0.51	0.90(0.49,1.62)	0.73	0.92(0.45,1.86)	0.81
Yes	1.00		1.00		1.00		1.00	
Time in the therapeutic range								
<65%	0.86(0.39,1.88)	0.71	0.35(0.08,1.53)	0.16	0.31(0.13,0.73)	**0.007**	0.27(0.10,0.70)	**0.007**
≥65	1.00		1.00		1.0		1.00	
Comorbidity score								
No	0.22(0.05,0.97)	0.05	0.38(0.02,6.33)	0.49	0.54(0.12,2.38)	0.41	0.33(0.05,2.11)	0.24
Mild	0.43(0.16,1.17)	0.09	0.81(0.12,5.58)	0.83	0.99(0.37,2.71)	0.99	0.70(0.21,2.38)	0.57
Moderate	0.63(0.24,1.63)	0.34	0.31(0.04,2.53)	0.28	0.93(0.35,2.45)	0.88	1.18(0.36,3.85)	0.78
Severe	1.00		1.00					0.06
INR monitoring interval	0.97(0.96,0.99)	**<0.001**	0.98(0.96,1.01)	0.17	0.97(0.95,0.99)	**<0.001**	0.98(0.97,1.00)	
Percentage of days in different INR ranges								
Time below range	1.02(0.99,1.04)	0.07	0.99(0.93,1.07)	0.99	0.99(0.90,1.01)	0.83	0.99(0.95,1.03)	0.55
Time therapeutic range	1.01(0.99,1.04)	0.33	0.98(0.91,1.05)	0.53	0.97(0.88,1.06)	0.48	0.97(0.93,1.02)	0.19
Time above range	1.01(0.99,1.02)	0.38	0.99(0.92,1.06)	0.75	0.99(0.90,1.09)	0.83	1.00(0.97,1.04)	0.88
Average weekly warfarin dose	0.99(0.98,1.01)	0.93	0.99(0.96,1.02)	0.54	0.99(0.98,1.01)	0.71	0.99(0.98,1.02)	0.82

IRR: incidenc rate ratio; CI: confidence interval

Chapter Six: Discussion

This PhD dissertation comprises a series of interrelated studies that collectively address the overarching research questions using a combination of theoretical and methodological approaches. A conceptual framework (Figure1), developed based the literature review, guided the research by identifying key determinants of anticoagulation control and outcomes among patients receiving warfarin. It integrated system-level, drug-related, and patient-centered factors, which were explored through different study designs to offer a holistic understanding of anticogalation management with warfarin therapy.

The research employed multiple methodologies to examine anticoagulation management from various angles. A systematic review synthesized existing evidence from African countries, revealing widespread suboptimal control and highlighting context-specific challenges. A qualitative study provided deeper insight into system-level barriers at the study site, such as limited infrastructure, inconsistent INR monitoring, and staffing shortages. Complementing this, a cross-sectional study assessed patient-level factors that include knowledge, adherence, and satisfaction by emphasizing the need for targeted strategies. These findings informed the design of a quasi-experimental study, which evaluated a PLAS against UMC, demonstrating significantly better outcomes in anticoagulation control and reduced adverse events with PLAC. Together, these studies form a clear body of evidence that highlights the complex challenges facing anticoagulation management in Ethiopia. They also emphasise the value of PLAS in bridging gaps at both the system and patient levels, offering practical solutions for optimizing warfarin therapy in resource-limited settings. Furthermore, the study identified, factors associated with these outcomes, and provided implications for clinical practice and recommendations based on finding. This section presents key findings from each study, followed by a discussion of these results in relation to relevant literature

All studies included in the systematic review reported TTR values below the recommended thresholds (Esteve-Pastor et al., 2018) and the ESC 2020 guideline recommendation (≥70 %) (Hindricks et al., 2021). Similar low TTRs have been reported in countries such as China (38.2%)(Chan et al., 2015), Lithuania (Urbonas et al., 2019) (40%), and Turkey (42.3%) (Ugur et al., 2015), whereas higher TTRs were reported in the FANTASIA and ORBIT-AF registries

(Pokorney et al., 2015; Rivera-caravaca et al., 2018). However, the TTRs reported in this systematic review were lower compared to those reported in Canada (58.76%), the USA (mean TTR of 65 ± 20% and median TTR of 68% [IQR 53–79%), and South Africa (58.1% ± 16%) (Gateman et al., 2017; Parbhoo & Jacobson, 2019; Pokorney et al., 2019) thereby highlighting the need for improved anticoagulation control in low-income countries. Our review noted significant TTR variations across African countries. Similarly, TTR variation was observed among different studies conducted in Canada (TTR of 44.2 to 61%) (Defoe et al., 2021; Gateman et al., 2017; Quinn et al., 2015), Saudi Arabia, Iran, Kuwait, and Brazil, with a mean TTR of 52.6 to 59% (Alyousif & Alsaileek, 2016; Carvalho et al., 2013; Farsad et al., 2016; Zubaid et al., 2013), indicating disparities in anticoagulation control and quality of care, including differences in the methods used to determine TTR (Pharmd et al., 2003; Siddiqui et al., 2018). Furthermore, in this review, a low percentage of patients achieved optimal anticoagulation (TTR ≥ 65%), with only 10–32.25% of patients reaching this target.

A higher TTR is the best indicator of good AMS (Pastori et al., 2018). The lower TTR reported in Africa raises questions regarding the quality of anticoagulation services. Factors contributing to low TTR in Africa include lack of standardized protocols, insufficient resources, absence of specialized anticoagulation services, inappropriateness of the current setup for providing expected AMS, and lack of a multidisciplinary team in managing anticoagulation services in health facilities (Anakwue, 2020). Effective anticoagulation management is hindered by these gaps, emphasizing the need for evidence-based strategies like ‘warfarin care bundles’(Mouton et al., 2020) improved INR control measures (N. O. Ahmed, Osman, Abdelhai, & El-hadiyah, 2017; Nyamu et al., 2017), decentralization of anticogualtion services, implementing locally validated dose initiation and dose adjustment algorithms and better access to warfarin and laboratory testing. Task-shifting to mid-level healthcare workers and staff training has also been recommended(Fenta et al., 2017).

Our review also explored factors associated with poor anticoagulation in patients receiving warfarin therapy in African countries. These included comorbidities (heart failure, renal dysfunction, and pulmonary hypertension), polypharmacy, warfarin interactions, sociodemographic factors, hospitalization history, and frequent INR monitoring. One study from South Africa included in this review (Prinsloo et al., 2021) showed that patients aged < 50 years had worse INR

control. However, a plethora of studies have shown controversial results regarding the association between age and TTR; some studies indicated that younger patients had worse control, whereas others found improved TTR with older age(Ugur et al., 2015; Wieloch et al., 2011).

Findings from the qualitative study revealed that the current AMS are inadequate. Key challenges include insufficient infrastructure, irregular INR testing, high patient load, and a shortage of adequately trained professionals. Patients face long waiting times for INR testing and limited access to anticoagulant medications. Overall, anticoagulation service structures in Africa remain poorly developed (Mouton et al., 2020; Rc et al., 2014). The study highlighted the benefits of specialized anticoagulation clinic in TASH as they use standardized procedures to achieve better anticoagulation control than UMC, citing evidence from other countries (Aidit et al., 2017; Falamić et al., 2018, 2019, 2021; Hou et al., 2017) where such clinics improved therapeutic outcomes, reduced hospital admissions, and decreased bleeding incidences. Furthermore, studies have shown that facility-specific protocols and the involvement of a multidisciplinary team are essential for high-quality AMS (Chen & Rose, 2015; Kearon et al., 2016) which are lacking in our study.

Participants reported that INR testing in the TASH was often unavailable or delayed, leading patients to seek unreliable and expensive external tests. This may affect timely anticoagulation management decisions and resuling in inconsistent anticoagulation control, poor adherence, and suboptimal anticoagulation outcomes, which may lead to adverse events such as thromboembolism (Kimmel et al., 2007). Test calibration varies from laboratory to laboratory, and standards of practice differ; therefore, the results may be biased (Medical Advisory Secretariat, 2009). Longer periods of frequent INR monitoring were cited as barriers to AMS in the qualitative study. Many international guidelines suggest a patient-specific INR monitoring frequency by considering factors such as the duration since warfarin initiation, non-therapeutic INR levels, presence of medications that interact with warfarin, presence of disease, and comorbidities that affect INR levels (Aidit et al., 2017; G. Barnes et al., 2020; January et al., 2014; Kearon et al., 2016; Witt et al., 2016, 2018).

Based on key informants recommendations and literature consultations (N. O. Ahmed, Osman, Abdelhai, & El-Hadiyah, 2017; Aidit et al., 2017; Elewa et al., 2016; Jiawen et al., 2020) regarding the benefits of PLAC in optimizing anticoagulation control and outcomes, PLAC was established in

the TASH to provide AMS for patients requiring warfarin therapy. This clinic aims to offer targeted patient care, education, and a multidisciplinary approach to enhance the AMS quality and patient satisfaction. The anticoagulation protocol (Appendix) provides guidance on anticoagulation management and supports clinical practice.

The mean knowledge score on warfarin therapy in the present study ($59.35 \pm 13.04\%$) was comparable to findings from a Hungarian study ($59.39 \pm 17.62\%$) (Viola et al., 2017) and and a systematic review and meta-analysis reporting a pooled estimate of 60.4% (da Silva Praxedes et al., 2023), and slightly lower than that of China ($62.3 \pm 8.8\%$) (Cao et al., 2020), but higher than that of Nader et al. (2020), with an overall mean score of 29.3% (Pourafkari et al., 2018). In addition, only 23.4% of patients had good knowledge of warfarin therapy. The lower knowledge level among our study participants might be due to a lack of proper understanding or inadequate counseling provided by the treating physicians. These findings highlight that long-term warfarin users require continuing education by designing educational programs and sustained communication between healthcare providers for successful anticoagulation management, and ultimately, to improve clinical outcomes (Collins et al., 2014; Shilbayeh et al., 2018).

Adherence to warfarin therapy is beneficial in clinical practice for identifying patients who require close monitoring and educational interventions (Vianna et al., 2021). In the present study, approximately 55% of the patients reported adherence to warfarin, higher than the adherence rates of 5.4% and 37.6% in Sudan and Vietnam, respectively (Eltayeb et al., 2017; M. H. Tran et al., 2023), but much lower than the Turkish study report (79.8%) (Tülek et al., 2019). This finding suggests that there is room for improvement in patients' adherence to warfarin to shape positive attitudes toward warfarin therapy. In the current study, forgetfulness, fear of side effects and workload/being busy were the most common self-reported reasons among the non-adherent cohorts. Hence, strategies that include memory refreshment to avoid forgetfulness, tailored education and provision of written format recommendations and reminders, pharmacist consultation between clinic visits focused on explaining misconceptions and encouraging adherence, telephone counseling, and open discussions with the patient to minimize doubts or fears have the potential to significantly improve warfarin adherence (Ababneh et al., 2016; Murray, 2017). Structured education focused on warfarin can have a favorable impact on patients' attitudes towards

medication, leading to an improvement in their quality of life. Patients are more inclined to adhere to the warfarin regimen by acknowledging the negative experiences associated with the drug as manageable(Park & Jang, 2021).

The overall mean level of satisfaction with warfarin therapy (53.67 ± 8.56) in the present study was lower than that reported in a previous study (Elbur et al., 2015). Our study found that 52.6% of patients were satisfied with the anticlot treatment, which is similar to the satisfaction level reported in Sudanese patients (50.5%) (Eltayeb et al., 2017) but lower than the Saudi Arabian study's report (63.7%) (Elbur et al., 2015). Regarding the ACTS subscale scores, the mean ACTS burden score was lower than that reported in studies conducted in Canada, Japan, and Saudi Arabia (Okumura et al., 2018; Salmasi et al., 2021; Shilbayeh & Ibrahim, 2020) among patients receiving warfarin therapy. Conversely, a higher ACTS benefit score was reported in our study when compared with the same studies but was consistent with the Saudi study (11.74 ±2.43 vs 11.92± 2.4) (Shilbayeh & Ibrahim, 2020). The differences in the degree, mean level of satisfaction, and ACTS subscale scores in the present study may be explained by differences in the patient's demographic characteristics (sex, age, and educational level), quality of anticoagulation management service, sample size, and indications for warfarin. We did not find a significant association between the independent variables and the ACTS scores in the multiple regression analysis. However, participants who lived outside Addis Ababa lived alone, had post-mechanical heart valves and portal vein thrombosis, warfarin indications, and bleeding history, and had a long INR monitoring frequency were more likely to be unsatisfied with anticlot treatment when compared with their counterparts, without a significant difference in satisfaction level. However, significant associations with ACTS have been identified in previous studies (Elbur et al., 2015; Eltayeb et al., 2017; Salmasi et al., 2021; Y. Wang et al., 2014).

In quasi-experimental study, the PLAC group showed a significantly higher median TTR compared to the UMC group ($p< 0.001$). This finding is consistent with prior studies that demonstrated the effectiveness of PLAC in achieving better TTR outcomes compared to UMC, highlighting its superiority in managing anticoagulation control (Alghadeeer et al., 2020; Falamić et al., 2018; Jiang et al., 2021; X. Li et al., 2018; L. R. Marcatto et al., 2018). Furthermore, a systematic review by Manzoor et al. (2017) found that the majority of studies included in the review (83.0%) reported a

statistically significant improvement in TTR in the pharmacist-managed group compared to routine medical care (Manzoor et al., 2017). Other studies also confirmed the superiority of PLAS over UMC in managing warfarin therapy, showing a significantly higher TTR in the pharmacist-managed group (Entezari-maleki et al., 2016; Hou et al., 2017). Furthermore, in this study, a significantly higher percentage of patients in the PLAC group achieved optimal anticoagulation control (TTR $\geq$ 65%) compared to those in the UMC group (41.7% vs. 31.7%, $p<0.002$). This finding aligns with other studies that have shown a higher proportion of patients in the pharmacist-led group achieving target anticoagulation levels compared to those in the physician-led clinic (Alghadeeer et al., 2020; Falamić et al., 2018). These findings emphasize the potential advantages of incorporating pharmacist-led services into AMS, demonstrating a novel approach to improving anticoagulation control and outcomes in patients receiving warfarin therapy (G. D. Barnes & Kline-Rogers, 2015). This contributes significantly to the ongoing discussion on enhancing chronic disease management in resource-limited settings, such as Ethiopia.

The effectiveness of PLAS emphasizes the potential of specialized anticoagulation services within the African healthcare context (N. O. Ahmed, Osman, Abdelhai, & El-Hadiyah, 2017) aligns with global trends that advocate improved management of warfarin therapy (Hou et al., 2017). Despite facing various challenges, including resource limitations, the successful implementation of PLAS in Ethiopia highlights the significance of delivering quality AMS to enhance anticoagulation control and outcomes. Our findings align with the broader global trend of incorporating pharmacist-led interventions into the management of chronic diseases (Eldooma et al., 2023). This approach is increasingly valued for its capacity to deliver personalized patient education, ensure regular monitoring, and facilitate precise dosage adjustments, particularly in managing complex therapies like warfarin (Malham et al., 2021). The difference between the outcomes of this study and typically lower TTRs reported in African countries (Tadesse, Tegegne, et al., 2022) further emphasizes the unique impact of PLAS in resource-constrained settings. This suggests that PLAS could expand beyond high-income countries, and offer a viable solution for enhancing anticoagulation management in diverse healthcare contexts.

This study observed more frequent INR monitoring in the PLAC group (40.08 median days), than in the UMC group (51.54 median days) ($p<0.001$), which is a crucial factor for achieving better

anticoagulation control. Previous studies have emphasize the importance of frequent monitoring and timely dose adjustments to maintain patients within the therapeutic INR ranges (Kebede & Ketsela, 2022; Remer et al., 2022; Witt et al., 2016). This increased monitoring frequency in the PLAC group may have contributed to the observed improvement in TTR in the present study.

The warfarin dosing decisions in response to changes in the INR may affect TTR and the composite clinical outcome of stroke, systemic embolism, and major bleeding and it requires the clinical skills of the healthcare practitioners (Urbonas et al., 2019). In this study, pharmacists (PLAC) performed significantly more correct actions regarding warfarin dosing than physicians (UMC) did ($p<0.001$). This finding emphasizes the clinical expertise of pharmacists in managing complex anticoagulation therapy, which leads to fewer incorrect actions and improved patient outcomes. Studies have also indicated that the implementation of warfarin-dosing algorithms is crucial for effective anticoagulation management and contributes to improved anticoagulation outcomes (Cai et al., 2023; Samuel et al., 2021). The difference between the groups may be due to the use of the warfarin-dosing algorithm in the PLAC group and wide inconsistencies in warfarin dosing strategies among UMC physicians in this study. However, the reported measures taken by pharmacists and physicians for warfarin dose adjustment in this study might not accurately reflect actual practice. This is because healthcare practitioners might have taken other alternatives, such as more frequent INR monitoring, managing warfaring-intercating drugs, action on warfarin dosing during active bleeding in case of the subthereaptic or intherapeutic INR ranges, counseling on how to consume foods high in vitamin K and alcohol, and ensuring adherence. The interventions of treating healthcare providers on these strategies during their warfarin dose adjustment practice were not evaluated in this study, as complete information on patient history was not recorded, particularly in the UMC group.

Prescription of at least one drug that interacted with warfarin was significantly higher in the UMC group. This difference may indicate that pharmacists are better at recognizing and managing potential drug interactions, optimizing therapy, and minimizing adverse effects. The lower prevalence of WDI in the PLAC group might be attributed to the interventions made by pharmacists, including identifying drug(s) that interact with warfarin and contacting the treating physicians with a proposal for drug change, dose modification, or another measure to avoid or

minimize interactions with warfarin. Another possible explanation could be that there were more multimorbidities in the UMC group (Table 8) than in the PLAC group, which might have required these drugs. Most of the prescribed drugs interact with warfarin increase its effect by different mechanisms, primarily by inhibiting liver enzymes. However, carbamazepine, phenobarbitone, and rifampicin decrease the effect of warfarin even though phenytoin has a biphasic effect on warfarin action (Mar et al., 2022). Aspirin was the most commonly identified warfarin-interacting drug in both groups (Table 1). The concomitant use of warfarin should be used cautiously to minimize bleeding. A meta-analysis reported that the risk of bleeding events was significantly lower in patients receiving warfarin alone than in those receiving aspirin plus warfarin(Bandaru et al., 2024). Another study also showed that the odds of a bleeding event were higher in the warfarin and aspirin groups ($p = 0.0131$) than in the warfarin-alone group (Yi et al., 2024). Additionally, the aspirin group had a higher rate of bleeding events ($p < 0.001$) and bleed-related emergency department visits ($p = 0.001$) than the warfarin group (Metrics, 2024). The concurrent use of antiplatelet drugs and warfarin should be determined based on the patient's specific needs, with benefits surpassing potential risks (Floyd & Ferro, 2017).

Amitryptine was also the most common warfarin-interacting drug in the UMC group, and a few macrolide-antibiotic interactions were observed in both groups. Antiepileptic drugs (AEDs) were prescribed more frequently in the UMC group than in the PLAC group. Warfarin interacts with carbamazepine (CYP2C9 inducer) and valproic acid (CYP2C9 inhibitor) and reduces and increases warfarin anticoagulation effect(Mar et al., 2022; Zhou et al., 2018). Therefore, when healthcare providers decide to prescribe warfarin with AEDs, they should consider measures such as close INR and therapeutic drug monitoring to optimize treatment outcomes. Due to the long-term concurrent use of warfarin and AEDs, it is recommended to avoid prescribing warfarin with AEDs by opting for direct-acting oral anticoagulants if available or by exploring other therapeutic options to manage seizures. Concurrently, six patients in the UMC group were prescribed amiodarone with warfarin. Amiodarone is a strong inhibitor of CYP4502C9 and CYP4503A4, which results in the inhibition of warfarin hydroxylation, thereby potentiating its anticoagulant effect (Mar et al., 2022). Hence, when using these drugs together, it is recommended to decrease warfarin dose by 25% and accompany closer INR monitoring to prevent unnecessary severe bleeding (Holm et al., 2017).

The present study identified multiple factors associated with poor TTR in patients receiving warfarin therapy. Multivariate regression analysis revealed that receiving the intervention (PLAC) (AOR = 0.57, 95% CI = 0.36–0.88, p = 0.01) was an independent protective factor against suboptimal anticoagulation quality (TTR< 65%). This result is consistent with findings of previous studies (Cope et al., 2021; L. R. Marcatto et al., 2018; Qiu et al., 2021) which reported PLAS as a key intervention to reducing poor TTR among patients receiving anticoagulation therapy. The analysis also highlighted the relationship between an increased HAS-BLED score and poor TTR, emphasizing the vital need for careful evaluation of the bleeding risk in anticoagulation management planning. These findings further support the necessity of integrating comprehensive risk assessments into clinical decision-making to optimize patient outcomes in anticoagulation therapy (Hindricks et al., 2021).

In the current study, it was also found that the odds of poor TTR decreased with every increase in the INR monitoring frequency. This finding aligns with that of study conducted in China, that identified prolonged INR monitoring intervals as an independent risk factor for poor anticoagulation quality (Qiu et al., 2021). However, another study showed that increasing the INR testing interval did not significantly decrease the overall mean TTR (Papala et al., 2022). Frequent INR monitoring with appropriate dose adjustments may have contributed to better-optimized anticoagulation control in PLAC group in this study. Moreover, patients with mechanical heart valves were more likely to have poor TTR (AOR, 1.76; p =0.01). This signifies the importance of implementing individualized care plans tailored to the unique needs of this high-risk population, ensuring optimal anticoagulation control and reducing the likelihood of thromboembolic complications(Kuramatsu et al., 2018).

In this study, the incidence of all the secondary outcomes was higher in the UMC group. However, a statistically significant difference was observed only in all-cause emergency visits (p=0.003) between the two groups. Entezari-Maleki et al.(2016) also reported fewer emergency department visits among patients managed in a pharmacist-led group (p <0 .001), further supporting pharmacist-managed warfarin therapy (Entezari-maleki et al., 2016). Two studies conducted in China also reported the absence of significant differences in the incidence of bleeding and thromboembolic events between pharmacist-led interventions and other anticoagulation management models (Jiang et al., 2021; Qiu et al., 2021). However, other observational studies and

systematic reviews have reported significantly lower incidences of bleeding and thromboembolic events in patients managed with pharmacist-led warfarin therapy (Entezari-maleki et al., 2016; Manzoor et al., 2017). The observed lower incidence of emergency department visits among patients in the PLAC group in our study may highlight the proactive nature of PLAS in mitigating complications that would typically necessitate emergency intervention.

A key finding of the present study was the association between frequent INR monitoring and a notable reduction in both bleeding events and emergency department visits. This observation highlights the crucial role of close monitoring in optimizing anticoagulation outcomes and minimizing warfarin-associated complications. To improve patient safety and therapeutic efficacy, frequent INR monitoring should be prioritized (Witt et al., 2016). Additionally, patients with higher CHA2DS2-VASc scores exhibited an increased risk of thromboembolic events, aligning with previous research that identified the CHA2DS2-VASc score as a predictor of thromboembolism (D'Souza et al., 2018).

6.6 Strengths and Limitations of the Study

6.6.1 Strengths of the Study

This PhD study had several strengths. We triangulated various methodological designs to synthesize evidence on anticoagulation control and outcomes, identify gaps in AMS, and develop and implement interventions (PLAS). This intervention was implemented in a clinical setting as planned, which allowed us to identify what worked on the ground. This is the first study to demonstrate anticoagulation control and outcomes in different African countries by characterizing TTR and other secondary outcomes. Identifying the existing AMS challenges and the need for and benefits of establishing PLAC based on qualitative study findings was used as the basis for establishing PLAC in TASH. Furthermore, findings from the three important aspects of oral anticoagulation with warfarin therapy, namely knowledge, adherence, and satisfaction, can inform the development of targeted interventions to improve warfarin therapy. This is the first study in Ethiopia to evaluate the effect of PLAS on anticoagulation control and outcomes by directly comparing PLAS with UMC in patients receiving warfarin therapy. A notable strength of this study is the implementation of a structured anticoagulation management protocol that encompasses a comprehensive set of interventions. These include a standardized warfarin-dosing algorithm, continuous adherence support, and extensive patient education covering multiple aspects of warfarin therapy. Furthermore, the use of a quasi-experimental study design allowed for a more rigorous

evaluation of PLAS effectiveness in real-world clinical practice, reinforcing its potential applicability in resource-limited healthcare settings.

6.6.2 Limitations of the study

The limitations of the systematic review included the inclusion of only English-language articles, which might lead to potentially missing important studies and underestimating findings; the variation in AMS practices across studies which necessitates further assessment of TTR pooled estimates; most studies lacked relevant data, such as the incidence of thrombotic and bleeding events; and the results may not represent all African countries due to excluded studies and the limited scope of care in some regions. Moreover, the exclusion of key healthcare professionals, such as pharmacists in discussions about PLAC and nurses in the context of AMS and patient care, may have constrained the comprehensiveness and depth of stakeholder perspectives. In the qualitative study, the absence of a clearly defined theoretical framework, the lack of a specified research approach, the omission of detailed data analysis procedures, and the failure to address the researcher's positionality, potential biases, or reflexivity may have affected the research process, compromised the study's rigor, and limited the replicability of findings. Limitations of the cross-sectional design include difficulty in establishing a relationship between cause and effect based on the nature of the design; this is a single-center study where results cannot be generalized to a large patient population receiving warfarin. This study relied on self-reported data collected from the patients, which may be prone to response and recall bias. The quasi-experimental study was conducted in a hospital setting in Addis Ababa, Ethiopia; hence, the feasibility and effectiveness of PLAS may differ in other healthcare environments with varying resources, patient populations, and organizational structures, which limits the generalizability of the findings. Furthermore, the quasi-experimental design lacked baseline measurements (e.g., TTR, adherence, and anticoagulation history), and there were notable differences in patient characteristics such as a higher prevalence of heart conditions, comorbidities, and medication use in the UMC group. These factors make it difficult to attribute observed differences solely to the PLAC intervention, as pre-existing group differences may have influenced the outcomes. Additionally, this study did not evaluate differences in patient knowledge, satisfaction, and adherence to warfarin therapy. Furthermore, the study did not evaluate the financial or economic implications of implementing PLAS compared with UMC. Without a cost-effectiveness analysis, potential savings from reduced complications, emergency visits, and hospitalizations remain uncertain, limiting their value for policy decisions and adaptation

in resource-limited settings. A final limitation of this study was the exclusion of pharmacogenetic testing (e.g., VKORC1 and CYP2C9 genotyping), which plays a critical role in personalizing warfarin therapy by predicting dose requirements and improving anticoagulation outcomes. As a result, the impact of genetic variation on warfarin metabolism and sensitivity could not be evaluated, limiting the assessment of individualized treatment approaches.

6.7 Implications of the Study

The implications of current study on warfarin therapy management in Ethiopia are profound and multifaceted. The potential implications of the findings of this PhD study for policymakers, clinical practice, and future research are summarized below.

6.7.1 Practice implications

It is important to provide training to healthcare providers on anticoagulation management, especially for those who provide AMS at UMC. Collaboration among pharmacists, physicians, and other healthcare providers can improve the management of anticoagulation therapy, ensure comprehensive care, and minimize the risk of complications. This study supports the crucial role of pharmacists as key contributors in managing complex medication therapies such as warfarin. The success of PLAS in enhancing TTR through more consistent follow-up and reducing complications associated with warfarin therapy highlights the importance of including pharmacists in multidisciplinary care teams. Their expertise in medication management and patient education could lead to improved self-management and fewer adverse outcomes. Furthermore, understanding patients' knowledge, adherence, and satisfaction with warfarin therapy can inform the development of targeted interventions that include comprehensive educational programs and family support to improve warfarin therapy in Ethiopia.

6.7.2 Policy Implications

This study highlights the need for health policymakers to support the expansion and facilitate the integration of PLAS into Ethiopian tertiary care hospitals, where warfarin remains the drug of choice for the prevention and treatment of thrombosis in many patients. This support can include funding this initiative, training, equipping pharmacists with anticoagulation services, and availing necessary infrastructure. Moreover, the implementation of these specialized clinics serves not only as a model for optimizing anticoagulation therapy but also as a benchmark for healthcare quality improvement, providing actionable data that can guide resource allocation and healthcare planning. Our study's insights extend beyond the Ethiopian context, contributing to the global discourse on

chronic disease management and the implementation of patient-centered care models to improve treatment outcomes. Developing regulatory frameworks that recognize and formalize the role of pharmacists in anticoagulation management is crucial and may include defining and expanding the scope of practice. However, to strengthen the evidence base before recommending policy changes for anticoagulation management in Ethiopia, the existing anticoagulation protocol developed through this PhD study can be systematically evaluated, refined, and piloted across diverse healthcare settings. Engaging stakeholders and aligning the refined protocol with national guidelines will demonstrate its feasibility, effectiveness, and scalability, laying a solid foundation for advocating pharmacist-led anticoagulation services as a national care model.

Chapter Seven: Conclusions and Recommendations

7.1 Conclusions

Anticoagulation control was suboptimal in African patients taking warfarin, as demonstrated by the low TTR observed in the systematic review. A qualitative study concluded that the hospital's AMS was not optimal for providing adequate services during the study period. Based on the findings of this study and recommendations from key informants and literature consultations, PLAC was established at TASH to provide anticoagulation services to patients who need warfarin therapy. Only about a quarter of the patients had good knowledge of warfarin therapy. More than half of the study participants adhered well to warfarin, and forgetting, fear of side effects, and workload/being busy were the most frequent reasons for non-adherence. Approximately half of the patients were satisfied with warfarin therapy. This study provides opportunities to improve patients' knowledge, adherence, and satisfaction with warfarin therapy by designing targeted interventions in Ethiopia. Future research should explore the impact of patient education and counseling on improving the knowledge, adherence, and satisfaction with anticoagulation treatment among patients receiving warfarin. A quasi-experimental study concluded that patients in the PLAC group had a significantly higher median TTR compared to those in the UMC group. A higher proportion of patients in the PLAC group achieved optimal TTR than those in the UMC group. The likelihood of poor TTR was lower in the PLAC group than in the UMC group. No statistically significant differences were observed between the groups in terms of secondary outcomes, except for all-cause emergency department visits. This study contributes substantially to the argument that PLAS is a vital advancement in managing patients on warfarin to enhance both clinical outcomes and healthcare efficiency.

7.2 Recommendations

- The success of PLAS in TASH may serve as a model for expanding PLAC to other tertiary care hospitals in Ethiopia and developing countries with similar health systems.
- TASH should sustain, expand, and integrate PLAS across hospital departments to reach a broader patient population. Additionally, hospital should enhance the anticoagulation management protocol, strengthen patient education, and invest in infrastructure and resources to optimize care and improve patient outcomes.

- Developing and implementing comprehensive educational programs and providing intervention support are essential for patients to enhance their understanding of, adherence to, and satisfaction with warfarin therapy.
- While the focus of this dissertation was evaluating the effectiveness of PLAS in managing warfarin therapy, it also recommends the importance of assessing the availability, accessibility, and cost-effectiveness of novel oral anticoagulants and low-molecular-weight heparin (LMWH) in the Ethiopian context. By incorporating analyses of access barriers, cost comparisons, and policy recommendations, the study aims to offer a more comprehensive and practical framework for improving anticoagulation management in Ethiopia.
- Future studies should comprehensively document and categorize the full range of clinical interventions provided by pharmacists beyond dose adjustments and drug interaction management to include areas such as bleeding risk reduction, adjunctive therapy, and individualized treatment adjustments based on patient-specific factors. This would offer a more complete understanding of a pharmacist's clinical role and its impact on patient outcomes.

7.3 Directions for further research

Recognizing the contributions and limitations of this study, we suggest the following future research directions to build upon evidence in this area..

- Future systematic reviews on anticoagulation control and outcomes in Africa should include meta-analyses to estimate pooled TTR and secondary outcomes
- Future studies in Ethiopia should conduct longitudinal evaluations comparing the two anticoagulation models in terms of patients' knowledge, satisfaction, and adherence to warfarin therapy. This will help to assess the impact of education and counseling interventions and provide valuable insights for optimizing anticoagulation management and improving patient outcomes.
- Intervention studies that include multiple centers with larger sample sizes would provide a more robust framework for evaluating the impact of PLAS.
- Further research using mixed-method approaches is needed comprehensively evaluate the effectiveness, acceptability, and appropriateness of the PLAS at TASH and other hospital settings, insights into patients' and providers' experiences, implementation challenges, and contextual factors influencing the success of PLAS

- Incorporating direct measures of patient adherence to warfarin could offer deeper insights into the nuances of patient behavior.
- A cost-effectiveness analysis is essential to gauge the economic feasibility of incorporating PLAS into the Ethiopian healthcare system. Such an analysis could provide additional justification for investing in this model, thereby ensuring that healthcare resources are allocated efficiently and effectively.
- Randomized controlled trials should be designed to minimize the risk of bias that might occur in in such type of study design.

In summary, this PhD study lays the foundation for understanding anticoagulation control and outcomes in patients receiving warfarin in Africa, highlighting the challenges of the existing AMS in TASH, benefits associated with PLAS implementation, and the magnitude of patients' knowledge, adherence, and satisfaction with warfarin therapy. Future research should address the limitations of this study and explore potential improvements.

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PAPER I

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REVIEW Open Access

Anticoagulation control, outcomes, and associated factors in long-term-care patients receiving warfarin in Africa: a systematic review

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Abstract

Background: Oral anticoagulation therapy with warfarin requires frequent monitoring level of anticoagulation by the international normalized ratio (INR). In Africa, studies that explore anticoagulation control, treatment outcomes, and associated factors are reported in various ways in long-term patients receiving warfarin therapy to generate concrete scientific evidence.

Methods: The literature search was conducted in PubMed, Cochrane Library, African Journal of Online databases, Google Scholar, and Google. An advanced search strategy was computed to retrieve relevant studies related to anticoagulation control and outcomes. Duplication, title and abstract screening, and full-text assessment were conducted in Covidence software. Study quality was assessed using the Joanna Briggs Institute Critical appraisal quality assessment tool. The systematic review is registered in PROSPERO (CRD42021260772) and performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline.

Results: Out of 298 identified articles, 18 articles were eligible for the final review and analysis. The mean of 39.4 ± 8.4% time in therapeutic range (TTR) (29.4 to 57.3%), 36.7 ± 11.5% TTR (range 25.2–49.7%) and 46% TTR (43.5–48.5%) was computed from studies that determined TTR by Rosendaal, direct and cross-section-of-the-files methods, respectively. In this review, the lowest percentage of TTR was 13.7%, while the highest was 57.3%. The highest percentage of patients (32.25%) who had TTR ≥ 65% was reported in Tunisia, but the lowest percentages were in Namibia (10%, TTR ≥ 65%) and Kenya (10.4%, TTR ≥ 70%). Most of the included studies (11 out of 18) used Rosendaal's method while the direct method was employed by three studies. Generally, 10.4–32.3% of study participants achieved desired optimal anticoagulation level. Regarding secondary outcomes, 1.6–7.5% and 0.006–59% of patients experienced thromboembolic complications and bleeding events, respectively. Having chronic comorbidities, taking more than two drugs, and presence of medications that potentially interact with warfarin, and patient-related factors (patients aged < 50 years old, female gender, lower education level, smoking history) were the frequently reported predictors of poor anticoagulation therapy.

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Conclusions: Oral anticoagulation control was suboptimal in patients taking warfarin as evidenced by low TTR in Africa. Therefore, there is an urgent need for further improving oral anticoagulation management services.

Keywords: Anticoagulation control, Anticoagulation outcomes, Warfarin, Long-term care, Africa

Background

Vitamin K-dependent anticoagulants (VKAs) continue to be the principal anticoagulants for the treatment and prevention of thromboembolism [1] despite the introduction of direct-acting oral anticoagulants (DOACs) [2, 3]. It is used for the prevention and treatment of thromboembolic events (TEEs) and their complications in patients with atrial fibrillation, pulmonary embolism, deep venous thromboembolism, and valvular heart diseases [4, 5]. However, oral anticoagulation therapy with warfarin requires frequent international normalized ratio (INR) monitoring [6]. In addition, warfarin therapy is complicated by its unpredictable pharmacokinetics and dynamics features, multiple drugs and food interactions, narrow therapeutic index, and life-threatening complications due to subtherapeutic or excessively elevated INRs [7–10].

The quality of anticoagulation control with warfarin is majorly reflected by the mean individual patients spend in the therapeutic range [11, 12]. Time in therapeutic range (TTR) estimates the percentage of time a patient's INR is within the desired treatment range or goal and is used as an indicator of anticoagulation control [13]. The fraction of INRs in range or the direct method, the Rosendaal linear interpolation method, and the cross section-of-the-files method were the three common methods of TTR determination [14].

To achieve the optimal clinical outcome, the TTR should be $\geq$ 65% [15] and, the recent European Cardiac Society (ESC) guidelines suggested TTR of $\geq$ 70% [16] whereby the rates of thromboembolic events/complications and major bleeding-related due to VKA are low [17]. However, various studies conducted globally reported suboptimal anticoagulation with warfarin therapy by documenting low TTRs (< 65% [13, 18–22]. The extent of anticoagulation control and outcome in patients receiving warfarin in long-term care vary in Africa as TTR ranges from 29 to 49.7% [7, 23]. Moreover, these studies reported anticoagulation control, and treatment outcomes, and associated factors inconsistently. In addition, there has been no aggregate data in patients receiving warfarin therapy to generate concrete scientific evidence in Africa. Therefore, this systematic review was conducted to summarize anticoagulation control, treatment outcomes, and associated factors in patients taking warfarin for its various indications in Africa in long-term care by synthesizing and providing robust evidence.

Methods

Protocol and reporting

This systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42021260772. In addition, the review was prepared based on PRISMA guidelines [24].

Data source and search strategy

The literature search was conducted in PubMed/Ovid, Cochrane Library, African Journal of Online databases (AJOL), Google Scholar, and Google from database inception to November 2021. The reference lists of all included studies were also reviewed. The search strategy used Medical Subject Heading (MeSH) and keywords; anticoagulant agents, treatment outcome, bleeding, thromboembolism, TTR, time in therapeutic range, international normalized ratio, INR, Africa, and long-term care. These keywords were combined using "AND" and/ "OR" Boolean operators. They were combined as follows: [Anticoagulant OR (anticoagulant agents) OR (agents anticoagulation) OR (anticoagulation agents) OR (anticoagulant drugs) OR (warfarin) OR (Coumadin) OR (warfarin therapy) OR (warfarin potassium) OR (warfarin sodium) OR (vitamin K antagonist) OR (oral anticoagulant)] AND [treatment outcome OR (outcome treatment) OR (patient-related outcome) OR (clinical effectiveness) OR (treatment effectiveness) OR (treatment efficacy) OR (clinical) OR (efficacy) OR (bleeding) OR (bleeding events) OR (hemorrhage) OR (hemorrhagic events) OR (stroke) OR (ischemic stroke) OR (thromboembolism) OR (thromboembolic events) OR (hospitalization) OR (emergency department visit) OR (mortality) OR (intracranial hemorrhage) OR (intracranial bleeding)] AND [international normalized ratio OR (INR)) OR (monitoring) OR (time in therapeutic range) OR (TTR)] AND [long term care OR (long-term care) OR (outpatient) OR (outpatient department) OR (cardiac clinic) OR (hematology clinic) OR (anticoagulation clinic) OR (anticoagulation management service) OR (anticoagulation management quality)] AND [Africa OR (sub-Saharan Africa) OR (Africa central) OR (Africa eastern) OR (Africa southern) OR (Africa western) OR (Africa northern) OR (low-income country) OR (developing country)] OR (middle-income country)].

Inclusion and exclusion criteria

Observational studies that reported on warfarin use, anticoagulation control, and outcomes among adult patients in long term care in African countries (monitoring of international normalized ratio and time in therapeutic range); or warfarin therapy-related adverse outcomes among these patient groups (bleeding events, thromboembolic events, stroke (ischemic stroke), hospitalization, emergency room visit and mortality) were included. In addition, only studies published in English were considered. Animal studies, studies conducted on admitted and emergency patients, and pharmacogenomics studies were also excluded. Furthermore, studies that reported merely other anticoagulation outcomes (patients' knowledge, adherence, satisfaction, quality of life, economic outcomes, adverse drug events other than bleeding, warfarin drug interactions) were excluded. Further, qualitative studies, review articles, unpublished works (thesis), case reports, case series, case–control studies, letters to the editor with incomplete information, author perspective, abstract proceedings, and expert opinions were excluded from the review.

Article screening process

Articles identified from various electronic databases were exported to ENDNOTE reference software version 9 (Thomson Reuters, Stamford, CT, USA) with compatible formats. Then, they were imported to Covidence software [25] for screening, full-text analysis, and extraction. Duplicate records were identified, recorded, and removed with Covidence. Title and abstract screening were performed by the two reviewers (TAT and GTT). Three categories (yes, no, maybe) were used during the selection process. The full text of studies reported as "yes" or "maybe" during the initial screening process were evaluated based on the eligibility criteria by two authors (TAT and GTT). Any discrepancy in the screening processes was resolved by discussion.

Data extraction

Data were extracted by TA using a standardized data abstraction format prepared in Microsoft Excel. This tool contains data related to study characteristics (country and study setting, first author, publication year, study design, population characteristics, and sample size) and the result of studies (percentage of time in therapeutic range and warfarin-related adverse effects).

Quality assessment

Studies' methodological quality was assessed using Joanna Briggs Institute Prevalence Critical Appraisal Tool (JBI) for cross-sectional study [26]. It is an 8-item rating scale developed for prevalence studies. Sampling, data collection, reliability, and validity of study tools, case definition, and prevalence periods were included in the tool. The rating scale was categorized as having a low risk of bias ("yes" answers to domain questions) or a high risk of bias ("no" answers to domain questions) for each article. Each study was assigned a score of 1 (Yes) or 0 (No) for each domain, and these scores were summed to provide an overall study quality score. Studies with less than 50% scores were considered as high studies. For the final risk of bias classification, disagreements between the reviewers were resolved via consensus. Two independent authors (TAT and GTT) assessed the quality of included studies. Discrepancies between the two reviewers were resolved through discussion. The mean score of 2 authors was taken for scaling studies.

Outcome measurement

The primary outcome of the review was a time in the therapeutic range while bleeding, thromboembolic events/complications, hospitalization, emergency department visit, and mortality were the secondary outcomes. According to the criteria of International Society on Thrombosis and Haemostasis (ISTH), major bleeding is defined as fatal bleeding and/ or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular resulting in vision changes, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome; and/ or bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells. All non-major bleeds will be considered minor bleeds. Minor bleeds will be further divided into those that are clinically relevant and those that are not [27].

Data management and analysis

The mean and/or median percentages of TTR or percentages of TTR were extracted in all included studies. Secondary outcomes were reported by mean, percentage, or frequency. Factors contributing to primary and secondary outcomes were reported as described by studies.

Results

Literature identification and search findings

A total of 298 articles were obtained from different electronic databases. 59 articles were removed due to duplication. Title and abstract screening were performed on 239 articles and, 188 articles were irrelevant. The full-text screening was then conducted on 47 articles, and 29 articles were excluded due to their ineligibility (e.g., absence of the outcome of interest). Finally, 18-articles were eligible and included in the systematic review (Fig. 1).

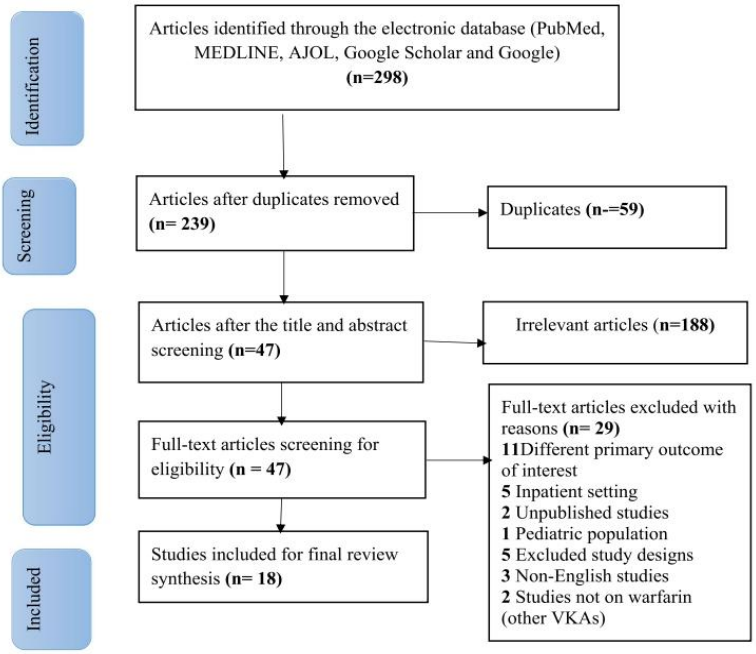

Fig. 1 PRISMA Flow diagram for study selection for systematic review

The included studies were published between 2006 to 2021. The majority of them (15 out of 18) were conducted using retrospective study designs [7, 23, 28–40]. Pre-post intervention [41] and prospective study designs [42, 43] were employed by one and two studies, respectively. Five studies were conducted in South Africa [7, 28, 33, 37, 38], 3 in Ethiopia [23, 31, 40], 2 in Sudan [32, 41], 2 in Kenya [36, 42], 2 in Tunisia [29, 43] and 2 in Botswana [39, 44]. One study was included from Namibia [35] and the remaining one study was conducted both in South Africa and Uganda. A total of 4,730 study participants were included in 18 studies. The smallest and the largest sample size was 21 [32] and 915 [45], respectively. In addition, the minimum cohort follow-up period was 4 months [46], and the maximum was 19 years [28]. All studies were conducted in outpatient settings (cardiology clinic anticoagulation clinic, INR testing clinic, warfarin clinic, cardiac, hemato-oncology, and cardiothoracic clinics, etc.). Except for one study [32], all studies were conducted in government health facilities. Various indications of warfarin were reported in the included studies (Table 1).

Quality assessment of included studies

With the exception of two studies, the majority of the included studies have a low-risk methodological quality according to the modified the Joanna Briggs Institute (JBI) critical appraisal tool as is indicated in a supplementary table.

Primary outcome: time in therapeutic range

Direct, Roosendaal's, cross-section of-the-files methods, or a mixture of direct and Roosendaal's methods were used to determine TTR in the included studies. Eleven studies used Rosendaal's method, while the direct method was employed by three studies. The direct method (the fraction of INRs in range) and the cross-section-of- the-files method were utilized by two studies [37, 47]. In the remaining two studies [32, 33, 35], TTR was calculated both by direct and Roosendaal's methods [32, 35]. The included studies reported TTR as mean and /or median TTR percentages or only percentages.

The lowest percentage of TTR was 13.7% (mean) which was reported by a study conducted in adult patients with prosthetic heart valves at the medical outpatient

Table 1 Characteristics of included studies in the systematic review

Author ID	Country	Study design	Study population	Sample size	Follow up time	Mean or Median age in years	Service setting	Indication of warfarin
Salaheldin A, 2019 [32]	Sudan	Retrospective	Private cardiology clinic attendants	21	14 months	Mean: 64, Median: 62	Cardiology Clinic	AF, VHD, DVT, PE, LVT
Karuri et al., 2019 [36]	Kenya	Retrospective	Adult outpatients	406	2 years and 6 months	Mean: 42.7 (SD: 16.9)	Cardiac, hemato-oncology, and clinic	DVT, PE, Prosthetic valves, AF, VHD
Sana et al., 2020 [43]	Tunisia	Prospective	AF patients ≥ 20 years	915	12 months	Mean: 64.27	In- and outpatients setting	AF
Lauren et al., 2019 [35]	Namibia	Retrospective	Adult outpatients	215	12 months	Median: 46	Warfarin Clinic	DVT, PE, AF, CVA, AVR, LVT, DCM, MVR, DVR, Others
Sonuga et al., 2016 [37]	South Africa	Retrospective	Adult patients	136	6 months	Mean: 62 (for male), Median: 66 (for female)	INR Clinic	VHD, mechanical heart valve replacement
Fenta et al., 2017 [23]	Ethiopia	Retrospective	Adults outpatients	360	12 months	Mean: 35.3	Cardiac and hematology clinics	AF, DVT, PE, VHD, MI, HVR, PVR
Semakula et al., 2020 [5]	South Africa and Uganda	Retrospective	Outpatients	229	6 months	Median: 56	Anti-coagulation clinic	VTE, AF, VHD
Prinsloo et al., 2021 [38]	South Africa	Retrospective	Adult patients	191	12 months	Median: 56	INR Clinic	AF, VTE, MPHV, APS, and LVT
Ahmed et al., 2017 [41]	Sudan	Pre-and post- Intervention	Adult patients	135	12 months	Mean: 41.8	Anticoagulation clinic	MVR, DVR, total valve replacement
Botsile et al., 2020 [39]	Botswana	Retrospective	Patients aged ≥ 18 years	142	5 months	Mean: 42	INR Clinic	MHV replacement
Masresha et al., 2021 [31]	Ethiopia	Retrospective	Adult outpatients	202	2 years	Mean: 44.33	Outpatient department	AF, VHD, DVT, and PE
Kizito et al., 2016 [47]	Kenya	Prospective	Adult outpatients	147	NA	Mean: 41	Hemato-oncology and cardiothoracic clinics	Heart disease, VTE, HVR
Yimer et al., 2021[40]	Ethiopia	Retrospective	Adult outpatients	300	2 years	Mean: 56.4	Anticoagulation Clinic	AF
Sadhabiriss and Brown, 2021 [33]	South Africa	Retrospective	Adult outpatients	263	1 year	Mean age for AF patients: 64.68, mean age for PHV patients:41.83	Outpatient adult medical department	non-valvular AF, PHV, venous thrombosis or embolism, arterial or left ventricle thrombus, valvular AF, HF
Ntlokotsi et al., 2018 [28]	South Africa	Retrospective	Adult patients	95	19 years	Mean 39.7 (SD:18)	Academic hospital	HVR
Rejeb et al., 2019 [29]	Tunisia	Retrospective	Adult patients	200	3 years	Mean: 58.8 ± 12	Cardiac clinic	AF
Mwita et al., 2017 [30]	Botswana	Retrospective	Adult patients	410	2 years	Median: 46(35–58 IQR)	Outpatient medical clinic	Mechanical valves, DVT, AF, Intracardiac thrombosis, pulmonary hypertension

Table 1 (continued)

Author ID	Country	Study design	Study population	Sample size	Follow up time	Mean or Median age in years	Service setting	Indication of warfarin
Ebrahim et al., 2018 [7]	South Africa	Retrospective	Adult out patients	363	6 years	Median: 55(IQR 44—64)	Warfarin anticoagulation Clinic	AF, VHD, PE VTE, SLE, hypercoagulable states

AF Atrial fibrillation, *VHD* Valvular heart disease, *DVT* Deep vein thrombosis deep, *PE* Pulmonary embolism, *CVA* Cerebrovascular accident, *AVR* Atrial valve replacement, *LVT* Left ventricular thrombus, *DCM* Dilated cardiomyopathy, *DVR* Double valve replacement, *MVR* Mitral valve replacement, *MI* Myocardial infarction, *SLE* Systemic lupus erythematosus, *HF* Heart failure, *APS* Antiphospholipid syndrome, *MHV* Mechanical heart valve, *HVR* Heart valve replacement, *MPHV* Mechanical prosthetic heart valve, *IQR* Interquartile range, *SD* Standard deviation, *INR* International normalized ratio

department in KwaZulu-Natal, South Africa [33]. However, a mean TTR of 44.5% was reported in this South African study among AF patients. The highest (57.3%) was observed in a study conducted in Tunisia [29]. In another way, a higher mean TTR of 68.3% was also documented in the post-interventional study from Sudan [41]. The mean of 39.4 ± 8.4% TTR (29.4 to 57.3%), 36.7 ± 11.5% TTR (range 25.2–49.7%) and 46% TTR (43.5–48.5%) was computed from studies that determined TTR by Rosendaal, direct and cross-section-of-the-files methods, respectively.

The percentage of patients with optimal anticoagulation (TTR ≥ 65%) or above as indicated by studies was documented by 13 studies. Accordingly, the highest percentage of patients (32.25%) who had TTR ≥ 65% was reported in studies conducted in Tunisia [43] and lowest percentages i.e. 10% (TTR ≥ 65%) [35] and 10.4% (TTR ≥ 70%) [36] were obtained in studies conducted in warfarin anticoagulation clinic at Windhoek Central Hospital in Namibia and Kenyatta National Hospital (KNH), Kenya, respectively (Table 2).

Secondary outcomes

Bleeding/hemorrhagic events were reported in three studies as both major and minor bleeding events [29, 39, 43], and the remaining studies that documented these events reported either of them. The highest percentage of bleeding incidence [(59%, (9.5% major bleeding, 49.5% minor bleeding)] was reported by studies carried out in Tunisia [29] and the lowers incidence (0.006% per patient-year) was reported from Dr. George Mukhari Academic Hospital [28] study in South Africa. During follow-up period, six studies [28, 31, 37, 43, 48, 49] reported that 0.002% per-patient year) [43] to 22.5% [39] of the patients developed thromboembolic events. Thromboembolic complications/events in range of 1.64 to 7.5% were occurred in four remaining studies [29, 31, 43, 50]. All-cause hospital admission during the study period was reported only by two studies with the incidence of 32.5% [38] and (10.4%) before intervention vs 3.7% after intervention) [41], respectively. Emergency department visits and mortality during the study period were reported by studies conducted in Ethiopia and Tunisia in 1.5% [31, 51] and 5.6% [43] of patients, respectively (Table 2).

Factors associated with optimal anticoagulation in patients receiving warfarin

There were various patients' sociodemographic and clinical characteristics (age, sex, hospitalization, mortality, disease, and medication-related factors) that contributed to poor TTR, and occurrences of bleeding and thromboembolic events. The most frequently reported factors were the presence of comorbidities (heart failure comorbidity [31, 36, 40, 43], renal dysfunction [36], pulmonary hypertension [7]), taking more than two drugs with warfarin [40], presence of potentially interacting medication with warfarin [31], patients' socio-demographic profile (age less than 50 years [38], female gender and lower education level [47] and smoking [39]). In addition, hospitalization [38] and frequent INR monitoring [7] were also reported as predictors of poor anticoagulation (lower TTR) in included studies. The detail on these associations and other associations with secondary outcomes is provided in Table 3. Only studies that reported significant association were included in the table.

Discussion

This systematic review was conducted to assess the level of anticoagulation control, treatment outcome, and associated factors among patients receiving warfarin in long-term care in Africa. Suboptimal anticoagulation was reported in this review with TTR ranging from 13.7% to 57.3% as compared to the recommended TTR level (≥ 65%) [52] or ESC 2020TTR recommendation (≥ 70%) [16].

The lowest TTR level was observed in studies conducted in China (38.2%) [21], Lithuania (40%) [53], and Turkey (42.3%) [54]. On the other hand, a higher TTR values of 61.5% [52] and 65% [55] were reported by the FANTASIIA and ORBIT-A registries, respectively. Moreover, a huge variation in the percentage of TTRs was observed in patients receiving warfarin in different African countries. Similarly, TTR variation was seen among different studies conducted in Canada (TTR of 44.2 to 61%) [20, 56, 57], Saudi Arabia, Iran, Kuwait, and Brazil with the mean TTR of 52.6 to 59% [13, 58–60]. However, TTRs reported in this systematic review were lower as compared with reports from Canada (58.76%) [20], the USA (overall mean and median TTR of 65 ± 20% and 68% [IQR 53–79%) and South Africa (58.1% ± 16%) [20, 61, 62]. The discrepancies might be due to the difference in method used to determine TTR, and sample size [14].

Higher TTR is the best indicator of good anticoagulation management service [63]. The lower TTR reported in Africa questioned the quality of anticoagulation service [2, 34]. Despite the presence of several risk factors, this might be partly explained by the limited and ineffective implementation of evidence-based AMS recommended by international guidelines. This includes the inappropriateness of the current setup for providing expected AMS (poorly developed structure in Africa), unavailability of working manuals e.g., functional protocols; resources (coagulation tests and anticoagulants); prescribing anticoagulation prescription with little or no monitoring. absence of specialty anticoagulation clinics/

Table 2 Anticoagulation control, primary and secondary outcomes of included studies in the systematic review

Author ID	Primary outcomes				Secondary Outcomes		
	Method to determine TTR	Percentage of TTR	% of patients within the therapeutic range	% of patients with TTR ≥ 65% or indicated by a study	Bleeding during warfarin therapy (%)	Major bleeding (%)	Thromboembolic events (%)
Salaheldin A, 2019 [32]	Rosendaal and Direct Method	Median 37% by Rosendaal method, and median TTR 42.9% by Direct Method	NA	23% of patients with TTR> 72%	9.50	NA	NA
Karuri et al., 2019 [36]	Rosendaal method	Mean 31.1% (± 26.7)	82% of MVR (mech), 54% of patients with MVR (prosthetic)	10.4% of pts (TTR ≥ 70%)	NA	NA	NA
Sana et al., 2020 [43]	Rosendaal method	Mean 48.87 ± 28.69% in 341 patients	NA	32.50	5.80	5.80	1.64
Lauren et al., 2019 [35]	Rosendaal and Direct Method	Mean 29.4% by Rosendaal method and 25.2% by direct method	NA	10	NA	NA	NA
Sonuga et al., 2016 [37]	Cross-section-of-the-files method	48.50%	48	NA	14.00	NA	2.20
Fenta et al., 2017 [23]	Direct Method	Mean 29%	NA	NA	NA	NA	NA
Semakula et al., 2020 [5]	Rosendaal method	Median 41%	NA	NA	NA	NA	NA
Prinsloo et al., 2021 [38]	Rosendaal method	Median 37.2%	NA	17.80%	NA	NA	NA
Ahmed et al., 2017 [41]	Direct Method	BI mean 51.5% and AI 68.3%	BI mean 51.5% and AI 68.3%	NA	BI 37% of patients, AI 53 of patients	0.00	NA
Botsile et al., 2020 [39]	Rosendaal method	Median 29.8%	NA	14.80	14.10	14.10	22.50
Masresha et al., 2021 [31]	Rosendaal method	Mean 41%	NA	29.20	4.50	NA	7.40
Kizito et al., 2016 [47]	Cross-section-of-the-files method	Mean 43.5%	43.50	NA	NA	NA	NA
Yimer et al., 2021[40]	Rosendaal method	Mean 42.03%	NA	12.67	20.67	NA	NA
Sadhabiriss and Brown, 2021 [33]	Rosendaal method	Mean TTR for the AF group was 44.5% and for PHV was 13.7%	NA	10.4% for the AF group had a range of more than 70% but none in the PHV group achieved this	24.00	NA	NA
Ntlokotsi et al., 2018 [28]	Direct method	49.70%	NA	Cut-off TTR was ≥ 70%	0.006% per patient-year	NA	0.002% per patient-year
Rejeb et al., 2019 [29]	Rosendaal method	Mean 57.3%	NA	24.5%; Cut-off TTR was ≥ 70%	0.59	9.50	15 patients
Mwita et al.,2017 [30]	Rosendaal method	Median 30.8%	NA	14.90	NA	NA	NA
Ebrahim et al., 2018 [7]	Rosendaal method	Mean 47%	NA	25.10	NA	NA	NA

MVR Mitral valve replacement, *PHV* Prosthetic heart valve, *BI* Before the intervention, *AI* After the intervention, *TTR* Time in therapeutic range, *NA* Not applicable

Table 3 Factors associated with poor anticoagulation and other secondary outcomes in long term care in Africa

Authors' name	Factors associated with poor anticoagulation outcomes (low TTR%)	Factors associated with bleeding events	Factors associated with Thromboembolism events	Factors associated with hospitalization events	Factors associated with mortality during warfarin therapy
Karuri et al., 2019 [36]	CHF, renal dysfunction	NA	NA	NA	NA
Sana et al., 2020 [43]	CHF, and nonvalvular AF type	Hypertension and antiplatelet use	obstructive sleep apnea and higher CHA2DS2VASc score	NA	CHF, and hypertension
Prinsloo et al., 2021 [38]	Patents aged < 50, hospitalization	NA	NA	NA	NA
Ahmed et al., 2017 [41]	Absence of pharmacists' intervention	NA	NA	clinical pharmacy intervention (-)	NA
Botsile et al., 2020 [39]	NA	Duration of warfarin use, Increased level of education	NA	NA	NA
Masresha et al., 2021 [31]	potential medication interaction, presence of co-morbid conditions	NA	NA	NA	NA
Kizito et al., 2016 [47]	female gender, lower education level	NA	NA	NA	NA
Yimer et al., 2021 [40]	Receiving > 2 drugs with warfarin, heart failure comorbidity	NA	NA	NA	NA
Rejeb et al., 2019 [29]	NA	Poor TTR (< 50%)	NA	NA	NA
Mwita et al.,2017 [30]	Smoking and pulmonary hypertension	NA	NA	NA	NA
Ebrahim et al., 2018 [7]	Frequent INR monitoring	NA	NA	NA	NA

CHF heart failure, *NA* Not applicable, *TTR* Time in therapeutic range, *AF* Atrial fibrillation, *INR* International normalized ratio

services; lack of a multidisciplinary team in managing anticoagulation service in health facilities [2]. Application of evidence-based strategies should be settled, like implementing 'warfarin care bundles' that include process- and patient-centered activities [64], employing interventions that improve INR control [41, 65], decentralization of anticoagulation services, setting up of anticoagulation clinics, improving access to warfarin, improving access to laboratory testing and/or scaling up point-of-care INR testing, task-shifting of anticoagulation care to mid-level health care workers, staff training, and implementing locally validated dose initiation and dose adjustment algorithms [23].

Regarding patients with optimal anticoagulation (i.e., TTR ≥ 65%), a lower percentage of patients (10 to 32.25%) achieved this target. The maximum percentage (32.25%) was reported by Tunisia prospective study [43]. In the same way, the Lithuanian (20%) [53] and Brazilian studies (31%) [60] studies reported a similar range of patients who achieved TTR above 65%. However, a study that evaluated the TTRs in four European countries in AF patients found that 44.2 to 47.8% of patients achieved TTR above 70% and with a higher percentage (65.4%) in United Kingdom patients [66]. A higher percentage of patients with optimal anticoagulation was also reported in Canada [19]. A lower percentage of patients in achieving recommended TTR may indicate a higher likelihood of suboptimal anticoagulation with warfarin in Africa countries which mandate a significant room for improvement of anticoagulation control in countries across low-income countries including Africa. Decentralization of anticoagulation care, together with expanded access to anticoagulants and monitoring, and enhanced support to practitioners and patients, developing and using initiation and maintenance/adjustment dosing protocols that developed by taking consideration of locally relevant factors into account is crucial to achieve better anticoagulation control in resource-limited settings [64].

Our review also explored factors associated with poor anticoagulation in patients receiving warfarin therapy. Having heart failure, renal dysfunction, and pulmonary hypertension comorbidities, taking more than two drugs along with warfarin, presence of interacting medication with warfarin, different socio-demographic characteristics, history of hospitalization, and frequent INR monitoring were identified as predictors of poor anticoagulation. A plethora of literature showed controversial results on the association of age with poor TTR.

This review study conducted by Prinsloo et al., in South Africa, showed patients less than 50 years had worsened INR control [38]. A Swedish study reported this correlation the other way round that is the presence of correlation between improved TTR and older age [67]. However, the quality of anticoagulation was minimal in the aged population, and there was a negative association between age and TTR levels in a study conducted in Turkey [54].

Having congestive heart failure as a comorbidity was reported as an independent predictor of poor control of anticoagulation in three studies included in this review [36, 40, 43]. This effect was also documented in patients with non-valvular atrial fibrillation in a private setting in Brazil among patients with atrial fibrillation, and in, Israel [68] among patients with non-valvular atrial fibrillation in primary care (Fantas-TIC Study) [69]. This might be due to abnormal blood flow in patients with left ventricular dysfunction (including regional areas of dyskinesis or aneurysm) resulted in the development of LV thrombus. While all the components of Virchow's triad may apply to HF patients, blood flow abnormalities are presumed to play the biggest role in imparting stroke risk [70]. This implies that having heart failure may be considered a double burden in managing/ controlling anticoagulation in these patient populations. Furthermore, patients with comorbidities require more drugs/polypharmacy for their management, which makes them more vulnerable to warfarin drug interactions which in turn, affect optimal anticoagulation [31, 40].

Strength and limitation of study

This systematic review is the first to show anticoagulation control and outcome in different African countries by characterizing time in therapeutic range and other secondary outcomes. The review has some limitations. First, we included only articles reporting in the English language, which may result in the loss of some important studies and thereby underestimation of the findings. Second, the practice of AMS varies across the studies, which require further assessment of TTR pooled estimates. Third, some relevant data (e.g., the incidence of thrombotic and bleeding events) were not reported in most of the studies. Finally, the results of this systematic review may not be representative of all Africa countries as there might be studies that were not included and also due to a limited aspect of care provided in these regions.

Conclusion and recommendations

Oral anticoagulation control was suboptimal in patients taking warfarin in Africa as evidenced by low TTR when compared with the recommended target by different international guidelines to achieve optimal anticoagulation. Special emphasis should be given to improving AMS in Africa region by working towards optimizing anticoagulation and decreasing harms (thromboembolic and bleeding events) in patients taking anticoagulation. Moreover, establishing dedicated anticoagulation clinics led by pharmacists or multidisciplinary teams using standardized approaches in Africa health care settings may achieve better anticoagulation control than routine models of care, where anticoagulation patients are seen as part of the general patient mix.

Abbreviations

AF: Atrial fibrillation; AJOL: African Journal of Online; ESC: European Society of Cardiology; INR: International normalized ratio; MESH: Medical Subject Heading; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; PROSPERO: Prospective Register of Systematic Reviews; TTR: Time in therapeutic range; VKAs: Vitamin K antagonists.

Supplementary Information

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Publisher's Note

PAPER II

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ORIGINAL RESEARCH

Challenges of Anticoagulation Management Service and Need of Establishing Pharmacist-Led Anticoagulation Clinic in Tertiary Care Teaching Hospital, Ethiopia: A Qualitative Study

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Pupose: To explore the challenges of anticoagulation management (AMS) and assess the need for establishing a pharmacist-led anticoagulation clinic (PLAC) at Tikur Anbessa Specialized Hospital (TASH) in Addis Ababa, Ethiopia.

Methods: We conducted a qualitative study at TASH. Using a semistructured interview guide, we interviewed 15 physicians from different specialties, heads of pharmacy and laboratory departments. We also included 20 patients to explore their general perceptions, and experiences with and challenges of AMS; and the need to implement PLAC in the hospital.

Results: Only three physicians responded that they had protocols for initiating and maintaining warfarin dosing. Having protocols for venous thromboembolism (VTE) risk assessment, VTE prophylaxis and treatment, bleeding risk assessment, and contraindication to anticoagulant therapy were reported by seven, six, four, and three participants, respectively. Lack of trained healthcare professionals and a separate AMS clinic, inconsistency in INR testing and anticoagulant availability, and longer appointment times were the biggest challenges of the existing AMS, according to 80% of respondents. Fourteen patient respondents indicated that their satisfaction with the AMS was affected by long wait times and inconsistent availability of anticoagulants and INR testing. The head of the laboratory stated that the facilities for INR testing are inadequate and affect the quality of AMS and customer satisfaction, and supplemented by the head of the pharmacy by adding irregularities of supplies and inadequate counseling on anticoagulants. Respondents suggested that there is a need to establish a PLAC with well-adopted standard operating procedures, qualified manpower, adequate training of assigned staff, and sustained supply of anticoagulants and INR testing.

Conclusion: The hospital's AMS is not optimal to provide adequate services during the study period. Based on these findings and recommendations, the supporting literature, and the experiences of other facilities, the PLAC was established in TASH.

Keywords: anticoagulation, need assessment, anticoagulation management service, pharmacist-led anticoagulation clinic, Ethiopia

Introduction

Thrombosis is pathological clot formation caused by inappropriately activated hemostasis without a bleeding event. The adequacy of primary prophylaxis for venous thromboembolism (VTE) in terms of type, dose, duration, and prevention of prolonged complications must be considered in the treatment of VTE.[1] Warfarin is the standard therapy for patients with VTE. Its efficacy in preventing and treating thromboembolism is well established. The percentage of time the international normalized ratio (INR) is within the therapeutic range is used to predict the efficacy and safety of warfarin therapy.[2,3] It is risky to use warfarin in clinical practice without considering factors such as the narrow therapeutic window, variability in dose-response, numerous drug and food interactions, miscommunication between patient and physician about dosing, and lack of patient compliance.[4–7]

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The complexity of anticoagulation management has led to the development of different models of care in many countries, including patient self-management, anticoagulation clinics, and pharmacist-led services. Mechanisms such as consistent monitoring, warfarin dosage adjustment algorithms, early identification of patient risk factors, standardized and continuous patient education, and pharmacist-managed anticoagulation clinics (PMACs) achieve better patient outcomes than traditional models of care.[8–11] Young et al reported that patients in a pharmacist-led anticoagulation service spent significantly more TTR (73% vs 65%, $p < 0.0001$) than the usual medical care (UMC) group. Another study documented a significant increase in the percentage of INR within the target range in PMAC (65.1%, $p < 0.005$) compared to UMC (48.3%). In addition, the rate of hospitalizations was 6.5 and 28.2 events per 100 person-years in the PMAC and UMC groups, respectively.[12]

In a retrospective cohort study by Aidit et al, pharmacist involvement had a positive effect on PMAC, as reflected by pharmacist acceptance of recommendations ($p = 0.01$).[13] A recent systematic review and meta-analysis showed a lower risk of overall, minor bleeding, and thrombosis with pharmacist led anticoagulation management.[5]

In a study conducted in Mekelle in the Tigray region of Ethiopia, almost all patients were taking medications that interact with warfarin. At least one abnormal drug interaction was present in 50% of the study participants. Twenty-two (16.5%) patients developed bleeding complications.[14] Several studies conducted at TASH pointed to the poor quality of AMS, as evidenced by low TTR (29%),[15] inadequate knowledge of patients and medical staff about warfarin therapy,[16,17] and poor practice in VTE risk assessment and inadequate use of thromboprophylaxis.[18,19] In Ethiopia, oral anticoagulants with more predictable pharmacological properties than warfarin are occasionally available. Therefore, warfarin is still the main treatment and prophylactic option for thrombosis and related events because of the high cost of these drugs. In Ethiopia, patients taking warfarin are managed by physicians in UMC, as is the case for general patients. Therefore, the aim of this qualitative study was to identify the challenges of AMS and the gaps that exist in the current AMS; and to assess the need for establishing a PLAC in Tikur Anbessa Specialized Hospital (TASH) in Addis Ababa, Ethiopia.

Methods

Study Area

The study setting was Tikur Anbessa Specialized Hospital (TASH). TASH is the largest tertiary teaching hospital in Ethiopia and has more than 700 beds. In TASH, ten thousand patients require anticoagulants and antithrombotics for VTE management.

Study Design and Period

The design was a qualitative study. We interviewed physicians (various specialties), heads of pharmacy and laboratory departments, and patients using a semi-structured questions guide. The interview explored perceptions and experiences towards the AMS at TASH and PLAC establishment needs in TASH.

Eligibility Criteria and Sampling Technique

Study participants' (key informants) selection was by using a purposive sampling technique based on their rich experience in the area of AMS. Accordingly, 15 physicians from different specialties, heads of pharmacy, and laboratory departments were included in this study. We also included 20 patients from those who had follow-up at the cardiac clinic of TASH, and taking warfarin using a simple random sampling technique. Seriously ill patients and physicians with minimal role and experience in AMS did not partake in the current study.

Data Collection and Management

The collection of data was by using thematic content analysis. A semi-structured interview guide was used by interviewing 15 physicians from different specialties, heads of pharmacy, and laboratory departments. We also included 20 patients to explore their overall ideas, perception, experience about AMS and the challenges of AMS, and the need to establish PLAC in the hospital. The prepared questionnaire for interview purposes includes questions that explore the knowledge of participants on the anticoagulant regimen they were taking, the sufficiency of counseling service, the availability of anticoagulants, and INR test, participants' suggestions on the UMC AMS, and their overall satisfaction with TASH AMS. Moreover, the questionnaire included questions that addressed possible ways to improve the AMS of

TASH. Then, observation was made to have a clear picture of the current workflow of AMS and its structure. The interview guide questions were developed from different works of literature.

Data Quality Assurance

Two experienced clinical pharmacists validated the instrument for clarity, simplicity, and comprehensibility and modified it before the interview began. The English version of the interview guide for interviewing patients was translated into Amharic and then translated back into English to maintain consistency or to compare the translations with the original text for quality and accuracy and to assess equivalence of meaning between the source and target texts. In case of discrepancies during transcription, translation, back-translation, and coding, consensus was reached through discussions with the investigator. The Amharic and English versions were used to interview patients and medical staff, respectively, in the study. An interview lasted an average of 15 to 40 minutes. An audio recording was made for those who were willing, and a note was made for those who refused to record their voice.

Data Collectors

Two postgraduate students in Pharmacy Practice from the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, Addis Ababa University were engaged in collecting data from health professionals and another post-graduate student from the same program collected data from patients. Data collection was supervised by the principal investigator of this study to ensure consistency and quality of data. The data collectors received one day of training on how to approach study participants and conduct the survey.

Data Analysis

A thematic analysis approach was used to analyze the data. Data analysis was based on the identification of key themes by two authors (TAT and AAA). Both the unrecorded (noted) and recorded interviews were transcribed verbatim, and the raw data were assigned to different themes. Participating patients were assigned code numbers from P1 to P20, and physicians were coded MD1 to MD15 at MD. We used these codes to describe each participant's individual outcomes when necessary.

Ethical Considerations

Ethical approval was obtained from the Ethics Review Committee of the School of Pharmacy, College of Health Sciences Addis Ababa University (ERB/SOP/27/10/2018). All participants were provided informed consent before participating in the study. Study participants were informed that the information they provided was kept strictly confidential. Personal identifiers were not used in the analysis and data were analyzed in aggregates.

Results

Socio-Demographic Characteristics of Healthcare Professionals

A total of 17 health professionals were interviewed. Fifteen of them were physicians, 1 pharmacist (head of the pharmacy), and 1 medical laboratory technician (MLT) (head of the laboratory). With the exception of 1 participant, they were all male and aged between 30 and 59 years (Table 1).

Experiences and Opinions of Health Professionals on AMS

For the analysis and interpretation of the results, a thematic content analysis was conducted in six core thematic categories. The adequacy of the current institution to provide adequate AMS, availability of resources (functional protocols, coagulation tests, and anticoagulants), challenges of AMS and proposed solutions, quality of AMS, benefits of establishing PLAC, and the role of clinical pharmacists in PLAC were the main themes identified.

Suitability of Current Setup to Provide Adequate AMS

The majority of study participants (13, 86.67%) indicated that the facility was not suitable for providing optimal AMS in the hospital. The lack of a dedicated clinic was repeatedly cited by 60% of respondents as the main reason for the

Table 1 Socio-Demographic Characteristics of Healthcare Professionals (N=17)

Variables		N	(%)
Sex	Male	16	94.12
	Female	1	5.88
Age (in years)	30–39	7	41.18
	40–49	6	35.29
	50–59	4	23.53
Maximum qualification	Cardiologist (Adult and Pediatric)	6	35.30
	Surgeon (Cardiothoracic and Orthopedic)	3	17.65
	Hematologist/Oncologist	3	17.65
	Pharmacist and MLT (Pharmacy and Lab Heads)	2	11.76
	Gynecologist and Obstetrician	1	5.88
	Emergency Medicine Specialist	1	5.88
	Internist	1	5.88
Year of experience in managing anticoagulation (in years)	2–5	7	41.18
	6–10	4	23.53
	>10	6	35.29

inconvenience of setting up AMS. In addition, four respondents stated that the workload and overcrowding of the facility result in patients who need AMS receiving less attention because they are treated the same as others. This was reinforced by a statement from two respondents.

> [… …] The delay in getting coagulation test (MD1) and the lack of a separate determination corner in the hospital make the facility poor for providing necessary AMS to patients. (MD12)

In contrast to this statement, two other respondents indicated that the facility is adequate for providing AMS.

> The setup is good for providing appropriate AMS because there are multiple specialties (MD 4) and well-trained staff (MD5) in the hospital.

Availability of Resources

Respondents indicated that lack of resources to provide anticoagulation services was one of the barriers to clinic operations. In terms of resources, functional protocols, coagulation tests, and anticoagulants were most commonly mentioned.

Functional Protocols

Regarding the availability of functional protocols/manuals, respondents indicated that there is no single department/clinic that has all the necessary protocols/manuals that assist delivering optimized AMS. However, the most responses were to the questions about risk stratification for VTE development assessment, and VTE prophylaxis and treatment protocols, which were answered by 7 (46.67%) and 6 (40%) respondents, respectively. It was mentioned that most clinical units did not have the other protocols/manuals, as their existence was reported only by 6.67% to 20% of the study participants (Table 2). The lack of an organized team to develop the protocols/manuals was cited by 5 respondents as the main reason for not having the protocols. Two physicians suggested that the development of these protocols/manuals was the

Table 2 Physicians' Response to the Availability of Functional Protocols for Providing AMS (N=15)

SN	Functional Protocols	No. of Response	
		Yes	No
1	Warfarin initiation dosing protocol	3	12
2	Warfarin maintenance dosing protocol	3	12
3	Indication, target INR and duration of anticoagulation	3	12
4	Frequency of INR monitoring	1	14
5	Risk stratification for VTE development assessment	7	8
6	Protocol on VTE prophylaxis and treatment	6	7
7	Risk stratification for bleeding assessment	4	11
8	Contraindication to warfarin and other anticoagulant therapy	4	11
9	List of drugs that interact with warfarin and their management	1	14
10	Warfarin reversal protocol with elevated INR	1	14
11	Patient education on anticoagulation protocol	1	14
12	Anticoagulation management during pre and post-operative	2	13

responsibility of other clinical departments, such as cardiology and hematology, which have the greatest burden of patients requiring anticoagulation therapy.

Availability of Coagulation Tests and Anticoagulant Drugs

Regular availability of coagulation tests (prothrombin time (PT), activated thromboplastin time (aPTT), INR) was reported as poor by 5 (33.34%) of the participants. A similar number of respondents answered that the availability of these important tests is rare/not constant. However, one physician responded that they are quite readily available in the hospital. Regarding the availability of anticoagulants (oral and parenteral), 40% of respondents indicated that they are "fairly well" or "well" available. Conversely, the same number of physicians stated that the availability of these vital anticoagulants was "not consistent or not constant or not regular or not sustained." In contrast, the remaining 20% of study participants said the availability of these agents was poor at the hospital.

Regarding the waiting time for INR test values from the laboratory, study participants had different experiences/views. Thus, long waiting time (>3 days), 2–3 days and 1 day were described by 40, 33.34 and and 5.34% of the respondents respectively. However, two study participants stated that they had no information about the waiting time for INR value. The reliability of INR values was described as good, moderate and less reliable/bad/doubtful by 5.34, 33.34% and 20% of the study participants respectively. The remaining (40%) participants were unaware of the reliability of the INR values they received from the laboratories.

Challenges of Anticoagulation Management Service

Irregular availability of coagulation profile tests and anticoagulants was cited as the main challenge to providing the required AMS in the hospital studied, and a supply problem was quoted as the reason for the irregularity. In addition, most study participants explained the consequences of the unavailability of the tests and medications.

> This exposes patients to high costs for INR determination and obtaining medications drug outside the hospital from private pharmacies. (MD6)

One respondent explained his organization's challenges as follows:

> [….] we have limited knowledge about the interaction of anticoagulants with other drugs and the duration of anticoagulation, which affects the quality of anticoagulation therapy. (MD 1)

Another study participant explained the AMS challenge in the hospital as;

> There are problems with compliance in continuing thromboprophylaxis in many patients for the specified period after surgery once they are discharged from the hospital, resulting in our patients being readmitted to the hospital for recurrent thromboembolic events (TEs). (MD4)

Inadequate patient education strategies, difficulty with timely consultations, a lack of beds to admit patients who developed TE, a longer wait time for patients requiring frequent follow-up and monitoring, unreliable INR results, and the lack of hospital/national INR target ranges (rather than relying solely on international recommendations) were cited mentioned by one participant as the greatest challenges of AMS in the hospital studied. In addition, 4 (26.67%) respondents indicated that the lack of clear standard operating procedures (SOPs) is one of the key challenges of the current AMS. The same number of study participants cited workload at the current facility as another key challenge, as patients seeking AMS do not receive the attention they need in such a busy clinical environment. Another key challenge cited by almost all respondents was the lack of a separately responsible clinic staffed with qualified professionals to manage AMS-related activities.

Proposed Solutions to Address Anticoagulation Management Service Challenges

Respondents to the study proposed various solutions to overcome the existing AMS problems. Nime (60%) and 8 (53.34%) study participants suggested the provision of coagulation profile testing (aPTT, PT, INR) and anticoagulant as a key way to improve AMS, respectively. Two-thirds of respondents indicated that anticoagulation should be managed centrally, ie, in one unit by creating a responsible multidisciplinary team (MDT) to address current gaps in AMS in the hospital. In addition, two physicians reminded that qualified healthcare professionals (HCPs) with adequate training are essential for providing optimal AMS.

Another respondent suggested as a solution to the AMS challenges:

> […] the use of antithrombotics that do not require laboratory monitoring (INR) as a method to improve AMS, as we have not been able to optimize anticoagulation with a drug such as warfarin that requires frequent INR monitoring. (MD14)

Timely consultations, development of SOPs, and performing coagulation testing in dedicated hemostatic laboratories (each mentioned by one respondent) were also suggested solutions for addressing existing problems with AMS in their hospital.

Quality of Anticoagulation Management Service

Two-thirds of the participants described the quality of AMS in the hospital as poor, declaring it as"not adequate/not good/below standard/suboptimal." On the other hand, 5 (33.34%) of the physicians described the quality as satisfactory, using words such as "average", "reasonably good," and "fairly to good."

Advantages of Establishing a PLAC

All respondents indicated that the establishment of a functional PLAC in the hospital has great benefits in improving the quality of care for patients requiring anticoagulation therapy.

> More focused and efficient patient care will be provided if PLAC is opened and functional in our hospital. (MD1)

However, a few respondents emphasized the importance of the assignment of HCPs to the service and the consistency of the service. This was reinforced by the following statements from respondents.

> Opening the clinic alone will not solve the problems associated with AMS if well-trained HCPs are not assigned and if the consistency/sustainability of the service is not ensured. (MD9, MD10, MD12)

> PLAC improves regular follow-up of patients and optimizes anticoagulation therapy. (MD 11, MD 13)

> […] better patient follow-up and education and optimized anticoagulation management will be achieved if this new clinic is opened in the hospital. Finally, he stated that the establishment of a functional clinic is essential. (MD15)

Another participant adds a statement that supports this:

> […] a PLAC is very important in our hospital, but the issue of ownership and the specific training of the staff assigned to the clinic are very important issues to consider before setting up the clinic. (MD14)

Finally, 6 (40%) of the participating physicians emphasized the need to ensure the sustainability of the clinic without interruption.

When asked about the importance of working as MDT, ie, with the pharmacy team in PLAC, most respondents indicated that it was "very important", "very encouraging and necessary," and "highly recommended and very good" to work in a team.

The Role of Clinical Pharmacists in PLAC

Regarding respondents' perceptions of clinical pharmacists' involvement in PLAC, 5 (33.34%) indicated that they will contribute tremendously to improving patients' follow-up of their anticoagulation therapy. Two respondents described that clinical pharmacists will have a tremendous impact by providing a list of medications that interact with anticoagulants.

This was reinforced by one respondent as follows.

> Clinical pharmacists in the PLAC are helpful in addressing the problem of drug interactions/complications, and medication adherence. (MD8)

Laboratory and Pharmacy Heads Perspectives

When questioned by the laboratory head about issues related to INR testing in the hospital, the respondent stated that:

> […] there is no enough INR testing equipment and reagents needed for INR testing in the hospital.

In addition, the respondent recommended that a regular supply of these commodities is essential to ensure good quality of service and increase patient satisfaction with AMS.

> […] a separate INR machine is required in the proposed clinic and also the laboratory department will assign one or two laboratory staff to work in the clinic.

The head of the hospital's pharmacy department responded that

> […] there is an irregular supply of anticoagulants, especially warfarin, and inadequate education and counseling on the use of anticoagulants due to the workload and lack of a dedicated room.

In addition, this respondent said that

> […] there is no standard protocol for warfarin dosing and counseling. Also, nothing has been done with other departments regarding AMS and the establishment of PLAC.

However, an interviewee pointed out there is a need to establish a PLAC with a well-adopted SOP, qualified staff, sufficient training for assigned staff, and a sustainable supply of anticoagulation medications.

Patients' Experiences and Opinions on the Current AMS

An interview was conducted on 20 patients (P) (8 males and females). The median age was 51 years (range 19–72).

Availability of Warfarin and INR Testing

Regarding the availability of INR tests and warfarin, almost all clients complained about the unavailability of INR tests and the drug warfarin. This was confirmed by the statement of one patient.

> Most of the time, I could not find the drug warfarin at the hospital. The same is true for the INR tests. (P2)

Another respondent confirmed this thought,

> The problem is not only getting the drug and the test in the hospital, but also finding them outside easily. We are looking for it all over Addis Ababa. (P4)

Considering the problem of unavailability, patients are forced to get them from outside the hospital, which involves additional costs.

This was further strengthened by a quote from a 48 years old male patient

> There is a big price difference between the hospital and other sources. It's expensive in the other sources and we can not afford it permanently if we keep getting it from an outside source. (P14)

Warfarin being the most used anticoagulant, INR testing is a must regularly for patients.

One respondent said:

> We really want the test to be done in the hospital. Without it, the drug warfarin is worthless to us. (P7)

Anticoagulation Management Service Challenges

Patients discussed several factors about AMS challenges in the hospital. Most patients agreed on the general problems, with slight differences in problem depth and perspective. The commonly mentioned challenges were inadequate patient waiting area, high patient load, unavailability of the card, and poor hospitality.

One 64-year-old patient described the situation as follows:

> There are not enough patient waiting areas for patients like us. Moreover, the space/waiting area is not comfortable for patients. (P12)

In addition, most patients also complained about the patient load.

One patient said:

The problem with patient card management is another limitation in the delivery of UMC services. Some of the patients reported how difficult it is for them to get their cards for treatment from the card room.

> Because of the large number of patients using the service, I did not have enough time to ask for a consultation and inform the doctor properly about my situation. (P11)

A 72-year-old patient said:

> For an old man like me, looking for a lost card is a burden. I look for it by myself from one building to another (P18)

Regarding card administration, more than 10 patients complained about the poor hospitality they receive from card administration staff and nurses.

One patient said:

> When I look for my card, the officers do not respect me. Even with my card, they insult me. (P12)

Another patient corroborated:

> The nurses are always angry with us. They are enraged, irritable, apoplectic, ignore and despise us for no reason. (P7)

In addition to the challenges, most patients also offered suggestions on how to solve the problems. The solutions can be summarized in three main points. A separate room should be available for service, additional health professionals should be hired, and INR testing should be available in the hospital.

In this context, one patient said:

> How can I ask for a consultation? How can I maintain my queue for service in such a crowd? If we do not have a separate room for service, we will not get good service. (P9)

Patient load is mentioned as a major challenge. They suggested that more professionals are needed to reduce the workload.

When asked about patients' satisfaction with AMS, almost half of the patients were poorly satisfied with the services they received.

Discussion

In this qualitative study, we explored the challenges of AMS and assessed the need for establishing a PLAC at TASH from the perspective of healthcare professionals and patients receiving long-term oral anticoagulants (warfarin). Most study participants indicated that the current AMS is not adequate to provide appropriate services, citing lack of prerequisites (basic infrastructure) such as a separate clinic/room, hospital/country-specific INR target ranges and functional work protocols, longer office hours, unreliable coagulation testing, and high workload. In addition, poor availability of coagulation tests and anticoagulants, longer waiting times for INR testing and AMS service utilisation, and lack of trained professionals to provide AMS were among the most frequently cited drawbacks affecting AMS quality in the hospital studied.

The inadequate facilities identified in this study (lack of a dedicated anticoagulation clinic and a separate corner for coagulation testing), workload and overcrowding, long waiting and appointment times) may affect the quality of AMS. A study conducted by Anakwue showed that the structure of anticoagulation in Africa is poorly developed.[20]

Specialized anticoagulation clinics (AC) that use standardized procedures achieve better control of anticoagulation than UMC, where patients requiring anticoagulation are seen as part of the general patient population, which is not common in sub-Saharan Africa, including Ethiopia.[21] A study conducted at a Malaysian tertiary hospital by Thanimalai et al showed that patients in the warfarin medication therapy adherence clinic (WMTAC) had significantly higher actual TTR (65.1 vs 48.3%; $p < 0.05$), lower admission rate (6.5 vs 28.2 events per 100 person-years), and lower bleeding incidence compared with the UMC group.[13] Another systemic review and meta-analysis showed that the risk of hemorrhagic events and thrombotic events decreased significantly in pharmacist-led anticoagulation management groups compared with other management models.[5] Furthermore, a series of randomized clinical studies from elderly rural patients receiving warfarin in Croatia showed that pharmacist interventions improved median TTR significantly (93 vs 31.2% for intervention and control, respectively; $P < 0.001$),[22] report of lower cumulative incidence of adverse drug reactions in the intervention group (6-months rate 29% vs 85% for intervention and control, respectively;[23] and also improved health-related quality of life significantly in the intervention group by scoring lower to all domain of satisfaction questionnaire (median being 86.5 and 66.0 in the control and intervention groups, respectively; $p < 0.001$), indicating the higher health-related quality of life.[24]

Facility-specific protocols are critical to the delivery of optimal, high-quality AMS care by minimizing decision variability among working healthcare providers.[25,26] However, the current study found that essential work protocols for AMS care were rarely found in the hospital (Table 2). The lack of validated guidelines/protocols for the local population has been shown to lead to inconsistent practice among hospital prescribers, with a wide range of warfarin initiation doses being used and adjusted for non-therapeutic INRs.[27] This requires the collaborative work of experts from different disciplines who organize purposefully to develop and modify hospital guidelines and protocols.

Regarding the availability of INR testing in the study, issues were raised by physicians and patients. Both participants confirmed that the test is often unavailable on the hospital campus when they need it. Even when it is available, there is the problem of inconsistency and delayed reporting of INR results (long wait time), which discourages patients from taking the test and forces them to get tested from an outside source. When the test is from an external source, laboratories in Addis Ababa are not easily accessible due to lack of awareness, transportation, and other factors, INR testing is much more expensive in private laboratories than in government hospitals, and test results from external sources are not always reliable. Test calibration varies from laboratory to laboratory and standards of practice differ, so results may be biased.[28] These performance limitations impact prescribing physicians' timely and outcome-based anticoagulant dosing decisions.

To address the above service-related issues, INR testing should be performed from the point of care, a central laboratory should be established within the hospital, the waiting time for the INR test report should be shortened, and work should be done on the continuous provision of the testing service when available.[21] As commonly described by physicians and patients, the inadequate availability of anticoagulants such as warfarin in the study hospital forces patients

to obtain the drugs from private sources at high cost. Furthermore, this contributes to poor adherence and suboptimal anticoagulation outcomes, which may lead to thromboembolic events.[29]

Inadequate knowledge about anticoagulation, particularly about the interaction between warfarin and other drugs, was another challenge most frequently cited by physicians in providing the expected AMS. A study conducted by Dejene et al at the same hospital confirmed this finding, with only 9.8% of healthcare providers correctly answering the question about medications that may interact with warfarin.[17] Longer waiting times for patients requiring frequent follow-up and monitoring have been cited as a barrier to existing AMS services. However, many international guidelines and validated institutional manuals suggest a patient-specific INR monitoring frequency that takes into account factors such as duration since warfarin initiation, nontherapeutic INR levels, presence of medications that interact with warfarin, presence of disease, and comorbidities that affect INR levels.[6,13,26,30–36]

Provision of facilities for coagulation testing and anticoagulants, management of anticoagulation in a dedicated central facility, assignment of trained HCPs, SOPs, and timely counseling were the main solutions recommended by most HCPs involved in the study. Providing blood thinners and coagulation tests, increasing the number of trained healthcare professionals, and establishing dedicated (separate) rooms for AMS were also suggested as solutions by patients. This was reinforced by statements from the Anticoagulation Forum in its guidance on the core elements of anticoagulation stewardship programs.[37]

Regarding the overall assessment of the quality of AMS in the hospital, it was described as suboptimal by the majority of physicians. Similar quality concerns were frequently expressed by patients, citing poor anticoagulation counseling, prolonged unavailability of INR testing in the hospital, which affects anticoagulation monitoring and satisfaction with AMS, and poor control of anticoagulation, which puts patients at risk of developing warfarin-related complications such as thromboembolism and bleeding.[38]

The establishment of a PLAC in the hospital has been proposed by all HCPs to improve the quality of care for patients requiring anticoagulation therapy through targeted and efficient patient care, improved patient education and care, optimization of AMS, and incorporation of a multidisciplinary team approach. Studies from Saudi Arabia,[39] Malaysia,[13] Sudan,[40] China,[41] and Thailand[42] reported that the quality of AMS improved in patients in PLAC with a higher percentage of TTR compared with patients in UMC.

PLAC pharmacists provide patient education and pharmaceutical counseling to those who had been taking warfarin for a long period of time, but in whom the prothrombin time-i value was unstable and sometimes outside the target range. Accordingly, management, education, and counseling on anticoagulation therapy in ambulatory patients are critical for better treatment outcomes. A study conducted in Japan confirmed the pharmacist's pivotal role in providing information to facilitate patient education, positively influence appropriate anticoagulation therapy for AF, and improve patient satisfaction.[43] Improving AMS through the establishment and functioning of PLAC will be more effective if approached as a multidisciplinary team (consisting of pharmacists and physicians) working in the clinic and putting patients at the center of the process.[21] This has been supported by studies done elsewhere on anticoagulation management.[5,8]

Based on the findings from this study and recommendations from the literature on the importance of improving AMS, the PLAC was established in April 2018 at TASH. The Anticoagulation Protocol, which provides guidance on anticoagulation management, is used to support the work of the clinic. It is located in a multidisciplinary outpatient clinic of the hospital. Since then, she has been providing AMS two days a week (Tuesday morning and Friday afternoon) and counselling by phone to patients with non-therapeutic INRs who cannot wait for the next clinic day for warfarin dose adjustment. On average, 25 patients visit the PLAC daily, and each counselling session lasts about 10 minutes.

Strength and Limitation of the Study

Our study has some important strengths. It is the first study in Ethiopia to address the challenges of AMS and the need to establish PLAC, which can serve as a basis for establishing and expanding PLAC service to other hospitals in the country. This study identified gaps and opportunities for the establishment of PLAC in the hospital, which in turn helped us to start pharmacist-led anticoagulation patient care. In addition, the study attempted to include the views of HCPs and patients. On the other hand, the study also has some limitations. Although the researchers made every effort to interview key informants to obtain in-depth information about the topic under study, some of them were unwilling to participate (move or act with great haste) in the study.

Conclusions

This study identified the general challenges of AMS and the need to establish PLAC. In summary, the hospital's AMS is not optimal to provide adequate services during the study period. Based on the results of the current study and the experiences in other hospitals, the PLAC was established at TASH and provides anticoagulation care.

Abbreviations

AC, anticoagulation clinic; ACCP, American College of Chest Physicians; AVK, antivitamin K; DOAC, direct oral anticoagulant; INR, international normalization ratio; LMWH, low molecular weight heparin; NOAC, novel oral anticoagulants; PLAC, pharmacist-led anticoagulation clinic; PMAC, pharmacist-led anticoagulation clinic; TASH, Tikur Anbessa Specialized Hospital; TTR, total therapeutic range; UFH, unfractionated heparin; UMC, usual medical care; VTE, venous thromboembolism; WMTAC, warfarin medication therapy adherence clinic.

Ethical Approval

Ethical approval was obtained from the Ethics Review Committee of the School of Pharmacy, College of Health Sciences Addis Ababa University (approval number: ERB/SOP/27/10/2018). Informed consent was obtained from all participants prior to participation in the study. The participants informed consent included publication of anonymized responses.

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Disclosure

The authors report no potential conflicts of interest related to the research, authorship, and/or publication of this article.

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PAPER III

Original Research Article

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Knowledge, Adherence, and Satisfaction With Warfarin Therapy and Associated Factors Among Outpatients at University Teaching Hospital in Ethiopia

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Abstract

Anticoagulation management using warfarin is challenging in clinical practice. This study aimed to evaluate the knowledge, adherence, and satisfaction with warfarin therapy and associated factors among outpatients at the Tikur Anbessa Specialized Hospital (TASH) in Addis Ababa, Ethiopia. An interview-based cross-sectional study was conducted among 350 patients receiving warfarin therapy at cardiac and hematology clinics of TASH. Anticoagulation knowledge assessment (AKA) questionnaires assessed the patients' warfarin knowledge. Adherence to warfarin was evaluated using the Morisky Green Levine Scale (MGLS), and patient satisfaction with warfarin therapy was assessed using the 17-item anticlot treatment scale (ACTS). Binary logistic regression was used to determine factors associated with the outcome variables, and $p < .05$ was used as the cut-off point to declare a significant association. The mean AKA score was 59.35 ± 13.04% (10.68 ± 2.34 correct answers), and 82 (23.4%) of participants achieved a passing score. Based on the MGLS, 192 (54.9%) study participants adhered well to warfarin. The mean level of satisfaction was 53.67 ± 8.56, with mean scores of 41.93 ± 7.80 and 11.74 ± 2.43 in the ACTS burden and benefit subscales, respectively. One hundred eighty-four (52.6%) patients were satisfied with warfarin therapy. The absence of hyperthyroidism was significantly associated with poor knowledge of warfarin therapy (adjusted odds ratio [AOR] = 4.28, 95% confidence interval [CI]: 1.01–18.22). Those living with family had a 56% lower chance of poor warfarin adherence (AOR: 0.44; 95% CI: 0.21–0.93) than those living alone. This study shows room for improvement in patient knowledge, adherence, and satisfaction with warfarin therapy.

Keywords

warfarin, anticoagulation knowledge assessment, adherence, anticlot treatment scale

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Introduction

Warfarin is the most commonly prescribed anticoagulant for preventing and treating thrombosis.[1] However, anticoagulation management is notoriously challenging in clinical practice because of the vast number of factors that influence international normalized ratio (INR) control, including its narrow therapeutic window,[2,3] many drug and food interactions,[4] miscommunication about dosing between the patient and physician, poor patient knowledge,[5,6] adherence,[7] and satisfaction[8] regarding anticoagulation treatment. Knowledge of warfarin, its potential side effects, interacting medicines and foods, and

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the need for warfarin adherence play a role in attaining the desired therapeutic outcome while preventing adverse reactions.[9] However, minimal patient knowledge about warfarin therapy was seen elsewhere, including only 13.9% of patients receiving a passing score in Ethiopia,[10] a mean score of 59.39% in Hungarian patients,[11] only 14.9% of Saudi Arabian patients with adequate knowledge[12] and 50% of the patients with a poor knowledge score on oral anticoagulation therapy in Indian study.[12]

Medication adherence is integral to patient care to achieve optimized anticoagulation control and outcomes. Poor adherence to warfarin therapy has a significant effect on anticoagulation control and is one of the most common barriers to obtaining favorable anticoagulation outcomes.[13] Previous studies have shown that patients' adherence to warfarin therapy is suboptimal, that is, in the range of 27.5%–54.9%.[5,12,14] Several factors, including poor health literacy, lack of patient education, complex dosing regimens, clinical characteristics, knowledge of warfarin, low income, marital status, living arrangements, and drug regimens, play significant roles in warfarin nonadherence.[15,16]

The burden of anticoagulation treatment affects patient satisfaction.[8] Patient satisfaction is critical for treatment adherence, clinical outcomes, and healthcare utilization.[17] The characteristics of warfarin, including regular blood testing, lifestyle limitations, and fear of bleeding, may result in reduced patient satisfaction.[12] Few studies have documented a moderate level of patient satisfaction with oral anticoagulation therapy and its impact on anticoagulation control in patients taking warfarin.[17–19] Improving patient satisfaction with opioid agonist therapy can result in better clinical outcomes and reduce the risk of adverse events such as bleeding and thrombosis.[20] Despite the importance of warfarin therapy and the known factors influencing patients' knowledge, adherence, and satisfaction, studies in the Ethiopian context are lacking. This study addressed this gap by evaluating patients' knowledge, adherence, and satisfaction with warfarin therapy, and identifying the determinants of these outcomes in Ethiopia.

Methods

Study Setting

This study was conducted at the Tikur Anbessa Specialized Hospital (TASH) and included patients receiving warfarin therapy at cardiac and hematology clinics (CHCs). The clinics are staffed with cardiologists, hematologists, cardiac and hematology fellows, resident physicians, nurses, and support members, and each clinic functions 4.5 days per week.

Study Design and Period

An interview-based cross-sectional study was conducted between March 1 and June 30, 2023, among patients on warfarin to evaluate their knowledge of, adherence to, and satisfaction with anticoagulation treatment. We also collected the clinical data of the study participants from the electronic medical records (iCare system).

Source and Study Population

The source population was outpatients with follow-up at the CHCs of the TASH, whereas the study population included all patients who received anticoagulation management services (AMS) in the same hospital, had been receiving warfarin therapy, and fulfilled the inclusion criteria.

Eligibility Criteria

We enrolled patients aged ≥18 years who had been taking warfarin for at least 6 months. However, we excluded patients who were unwilling to participate, unable to complete the questionnaire in Amharic, critically ill, or had mental health issues, and those with missing or incomplete medical and medication data.

Sample Size Determination and Sampling Technique

This study included all eligible patients who visited and received AMS during the data-collection period. Accordingly, we interviewed 397 study participants, and 350 were included in the final analysis after excluding responses with incomplete or missing information. For better representativeness, we attempted to enroll a proportional number of participants per week, based on the expected study population in that week, until the end of the data-collection period.

Data Collection Instrument, Procedures, and Outcomes Measurement

The data collection instrument was structured into 4 sections. Section I gathered the study participants' sociodemographic and socioeconomic characteristics, while Section II consisted of anticoagulation knowledge assessment (AKA) questionnaires. The AKA questionnaire was developed based on validated questionnaires from previous studies to assess patients' knowledge of warfarin.[11,12,21,22] Eighteen multiple-choice questions were administered, and the patients were asked to choose 1 answer from the available choices for all questions. Scoring was conducted using a dichotomous scale, with correct responses as 1 and "incorrect" and "do not know" responses as 0. The cumulative scores were presented as a percentage of correct answers, and adequate knowledge regarding AKA ranged from 70% to 75%.[22–24] In our study, at least 13 questions answered correctly (72.22%) were considered passing scores. Section III evaluates patient adherence to warfarin using the Morisky Green Levine Scale (MGLS).[25] It included 4 questions with yes/no response options, with total scores ranging from 0 to 4—3 levels of medication adherence. The MGLS resulted in 3 levels of medication adherence based on these scores: high, medium, and low adherence, with 0, 1–2, and 3–4 points, respectively. The measurement was scored

bivariate (0 = no, 1 = yes) to assess adherence to anticoagulation treatment. A dichotomous definition of adherence based on the MGLS is also commonly used, with 0 point indicating perfect adherence and 1+ points indicating some level of nonadherence. Potential reasons for nonadherence were also assessed in a cohort of participants who reported <100% adherence in the past 4 weeks. As the MGLS has been validated for the broadest range of diseases, including patients with low literacy, it is the most widely used scale in research. The last section addressed patient satisfaction with warfarin therapy using an anticlot treatment scale (ACTS). It is a robustly validated, patient-reported instrument for measuring treatment satisfaction with anticoagulants. It comprises 17 items across 2 subscales (burdens and benefits). Thirteen items assessed the burden of anticoagulant treatment (12-item burden scale and 1 global question on treatment burden), and 4 items assessed the benefits of anticoagulant treatment (3-item benefits scale and 1 global question on treatment benefits). Study participants were asked to rate their experiences of anticoagulant treatment during the past 4 weeks on a 5-point scale of intensity (1=not at all, 2 = a little, 3 = moderately, 4 = quite a bit, and 5 = extremely). Reverse coding was used to calculate the burden scale, with higher scores indicating higher satisfaction. The ACTS burdens total score ranges from 12 to 60, and the ACTS benefits total score ranges from 3 to 15, with a total score ranging from 15 to 75 scores.[26] Patients were considered satisfied with the anticlot treatment if they scored above the mean score for all patients and dissatisfied if their score was below this cut-off point.[27] Data related to the patients' clinical and medication records were collected from the patients' electronic records (iCare system).

Data Collectors and Quality Assurance

Two pharmacists and 2 nurses collected the data. They were selected based on their educational level, clinical and research experience, and possible familiarity with serving patients who have received warfarin therapy in one way or another. The questionnaires for the exit interviews were prepared in English, translated into Amharic, and translated again into English to maintain consistency and facilitate better understanding. The Amharic version was used to interview patients. The instruments were reviewed and approved by a team of senior clinical pharmacists, cardiologists, and hematologists for their content, flow, completeness, and clarity to be used by data collectors and their suitability for extracting the required information before using them for data collection. The AKA, MGLS, and ACTS have been validated and widely used to evaluate the knowledge, adherence, and satisfaction of patients on oral anticoagulants. We pretested the data collection tool before data collection to ensure its quality, clarity, and feasibility of use, after which amendments were made to its structure. A 1-day training session was given to the data collectors on how to use data collection instruments, explaining the study purpose to participants, approaching and obtaining verbal consent, implementing sampling techniques, and conducting interviews to collect and maintain data confidentiality. The quality of collected data was ensured by reviewing and checking for completeness.

Data Analysis

Data were analyzed using the Statistical Package for Social Science version 27. Percentages and frequencies, mean (±standard deviation), and median (interquartile range) were used to summarize the descriptive data. Logistic regression was used to identify the determinants of knowledge, adherence, and satisfaction among the patients taking warfarin. Variables with $p <$ .25 from the bivariable analysis were candidates for multivariable analysis to adjust for confounding effects. Odds ratios () (ORs) at 95% confidence intervals (CIs) were used to determine the association between the independent and dependent variables. In multivariable analysis, $p < .05$ was used to declare the significance of the association.

Ethical Considerations

Ethical clearance was granted by the School of Pharmacy Ethical Review Committee (ERB/SOP/454/15/2022), and subsequently by the Institutional Review Board of the College of Health Sciences, Addis Ababa University (096/22/SoP). Written informed consent was obtained from all participants after they were provided with information about the purpose of the study, why and how they were selected to be involved in the study, and what was expected from them. To maintain confidentiality, the research team avoided using personal identifiers and analyzed the data in the aggregate. The research team handled the data obtained from the study participants with the utmost confidentiality.

Results

Sociodemographic Characteristics of Study Participants

Three hundred fifty patients receiving warfarin participated in the present study, among whom 245 (70%) were female, and the mean age was 44.05 (±14.72, range = 18–82) years. Most participants (55.7%) were married, and 70% resided in Addis Ababa. Most participants (70.0%) were Orthodox Christians, half (50.6%) had low monthly incomes (0–300 birr), and one-third (33.7%) of participants were unemployed. Most participants (89.7%) lived with their families, and 75% used community-based health insurance. The mean duration of warfarin therapy was 5.95 years (±5.20 years) (range = 0.5–29.5 years), and participants received an average of 4.16 drugs (±51.76) (range = 1–40). Moreover, 29.7% of participants reported polypharmacy (Table 1).

Clinical Characteristics of Patients Receiving Warfarin

Most of the participants (76.4%) had at least 1 comorbidity that did not require warfarin, most of whom had heart failure

Table 1. Sociodemographic Profile of Patients Receiving Warfarin Therapy.

Items of Description	*N*	%	Mean ± SD
Sex			
Female	245	70	
Male	105	30	
Age in years			
18–30	76	21.7	
31–45	135	38.6	44.05 ± 14.72
46–64	101	28.9	
≥65	38	10.9	
Residence			
Addis Ababa	247	70.6	
Out of Addis Ababa	103	29.4	
Marital status			
Single	106	30.3	
Married	195	55.7	
Widowed/divorced/separated	49	14	
Religion			
Orthodox	246	70.3	
Muslim	64	18.3	
Protestant	40	11.4	
Educational status			
Unable to read and write	51	14.6	
Primary school (Grades 1–8)	101	28.9	
Secondary school (Grades 9–12)	110	31.4	
Degree and above	45	12.9	
Certificate/diploma	43	12.3	
Family monthly income in Birr			
0–300	177	50.6	
301–2500	49	19.7	2367.61 ± 3399.57)
2501–5000	69	14.0	
>5001	55	15.7	
Employment status			
Unemployed/not working	128	36.6	
Employed (paid work)	82	23.4	
Housewife	67	19.1	
Self-employed/private work	44	12.6	
Retired	29	8.3	
With whom do you live?			
With family	314	89.7	
Alone	36	10.3	
Alcohol intake status			
No	333	95.1	
Yes	17	4.9	
Smoking in the last 2 years			
No	349	99.7	
Yes	1	0.3	
Chat chewing status			
No	347	99.1	
Yes	3	0.9	
Medical service coverage			
Community-based health insurance	260	74.3	
Out-of-pocket/paying	74	21.1	
Free	16	4.6	
Duration of warfarin in years			
0.5–1	72	20.6	
>1–5	126	36.0	5.95 ± 5.20
6–10	102	29.1	
>10	50	14.3	
Number of medications received per patient			
<5	246	70.3	4.16 ± 51.76
≥5	104	29.7	

(45.4%), valvular heart disease (41.4%), and hypertension (24%). History of stroke and vascular diseases were recorded in 18.9% and 11.1% of patients, respectively. The most common indication for warfarin was atrial fibrillation (60%), followed by valvular heart disease with left atrial/venous thrombus (13.1%), post mechanical heart valves (mitral and/or aortic valves) (12.6%), and recurrent and/or unprovoked deep vein thrombosis (10.6%). During the follow-up, 89 bleeding episodes and 64 all-cause emergency visits were recorded. The details are presented in Supplemental File 1.

Knowledge of Warfarin Therapy

The mean AKA questionnaire score was 59.35 ± 13.04% (10.68 ± 2.34 correct answers). None of the patients scored 0 or 100%, and 16.7% scored below 50%. The minimum and maximum scores were 11.1% and 83.3%, respectively. All patients correctly answered questions regarding risky activities while taking warfarin. Seven of the questions were answered correctly by at least 70% of the patients (71.7%–100%) (Table 2). Questions "on the effect of high intake alcohol in a single evening" and "how to eat green leafy vegetables while on warfarin" were answered correctly only by 6.9% and 9.4% of respondents, respectively. Similarly, frequently incorrect questions covered knowledge of the INR target range, decisions on advice regarding the consumption of herbal supplements, conditions/actions that may have a significant effect on warfarin work, INR value above the target range, and warfarin drug interaction, as 42.3%–76.3% of patients did not select correct responses.

Of the 350 patients who participated in the study, 82 (23.4%) achieved a passing score and they answered at least 13 questions correctly (Figure 1).

Adherence to Warfarin

Based on the MGLS, approximately one-third (34.3%) of the participants indicated that they had forgotten to take warfarin during the past 4 weeks (Table 3).

In this study, 54.9% of the participants adhered well to their warfarin (Figure 2).

Reasons for Nonadherence to Warfarin

Among the cohort participants who reported <100% adherence in the past 4 weeks, self-reported reasons for medication nonadherence were asked, and 11 potential reasons for nonadherence were identified. Forgetfulness (67.7%) was the most self-reported reason, followed by fear of warfarin side effects and workload/being busy, as both were reported by 15.2% of nonadherent study participants (Figure 3).

Satisfaction With Warfarin Treatment

The mean level of satisfaction was 53.67 ± 8.56, with mean scores of 41.93 ± 7.80 and 11.74 ± 2.43 in the ACTS burden and benefit subscales, respectively. In this study, 184

Table 2. Study Participants' Knowledge of Warfarin Therapy Based on AKA Questionnaire.

SN	Items Description (questions)	Answered Correctly *n* (%)	Answered Incorrectly *n* (%)
1	What is the indication of warfarin?	319 (91.1)	31 (9.1)
2	For how long do you need to take warfarin once it is started?	231 (66)	119 (34)
3	Which of the following food items most likely would interfere with your warfarin?	315 (90)	35 (10)
4	The best time of day for you to take your warfarin is	286 (81.7)	64 (18.3)
5	While out with friends for dinner, you have just finished your third glass of wine. This amount of alcohol consumed in a single evening will	24 (6.9)	326 (93.1)
6	Eating green leafy vegetables while on warfarin you	33 (9.4)	317 (90.6)
7	You just remembered that you forgot to take your last evening warfarin dose. You would	218 (62.8)	132 (37.7)
8	Which of the following activities are riskier while taking warfarin?	350 (100)	0 (0)
9	While on warfarin, for which of the following would you go directly to the emergency room?	279 (79.7)	71 (20.3)
10	If you ran out of your prescription for your warfarin, you would—	251 (71.7)	99 (28.3)
11	The results of your INR test tell the physicians /pharmacists	309 (88.3)	41 (11.7)
12	What do you need to remember when making a dental appointment while taking warfarin?	278 (79.8)	72 (20.6)
13	What is your target INR range?	162 (46.3)	188 (53.7)
14	Your neighbor brings over this great "all-natural" herbal supplement that she bought from a traditional healer. She says this helps all her aches and pains and recommends taking it when you ache. Do you decide to?	83 (23.7)	267 (76.3)
15	Which of the following may significantly affect how your warfarin works?	188 (53.7)	162 (46.7)
16	Occasionally eating a large amount of leafy green vegetables while taking warfarin can:	211 (60.3)	139 (39.7)
17	If your INR value is above the "goal range":	202 (57.7)	148 (42.3)
18	When is it safe to take a medication that interacts with warfarin?	190 (54.3)	160 (54.3)

Abbreviations: AKA, anticoagulation knowledge assessment; SN, serial number; INR: international normalized ratio.

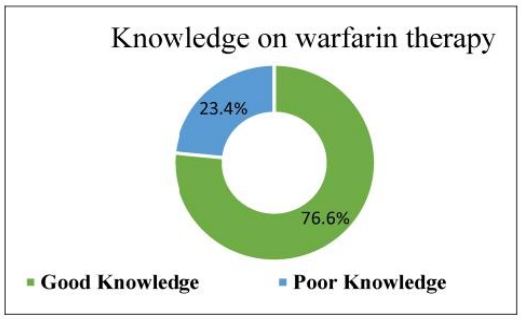

Figure 1. Study participants' knowledge of warfarin based on the anticoagulation knowledge assessment (AKA) questionnaire.

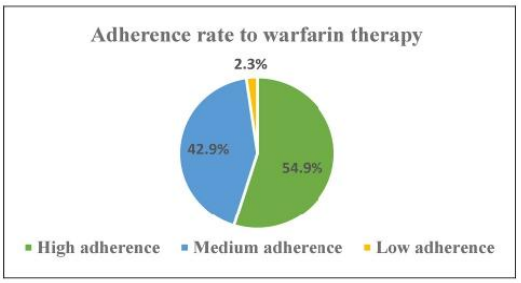

Figure 2. Adherence to warfarin using the Morisky Green Levine Scale (MGLS) among patients receiving warfarin.

Table 3. Adherence to Warfarin among Patients Attending CHCs of TASH ($N = 350$).

SN	MGLS Questions	Yes *N* (%)	No *N* (%)
1	Do you ever forget need to remember to take your warfarin?	120 (34.3)	230 (65.7)
2	Do you ever have problems remembering to take your warfarin?	30 (8.6)	320 (91.4)
3	When you feel better, do you sometimes stop taking your warfarin?	13 (3.7)	337 (96.3)
4	Sometimes, when you feel worse when you take warfarin, do you stop taking it?	32 (9.1)	318 (9.1)

Abbreviations: TASH, Tikur Anbessa Specialized Hospital; SN, serial number; MGLS, Morisky Green Levine Scale.

(52.6) patients were satisfied with warfarin therapy and the remaining 47.4% were unsatisfied. The highest mean satisfaction scores 4.17 ± 1.27 and 4.15 ± 1.00 were reported on the "effect of possible anticlot treatment-related bleeding on doing physical activity" and "confidence level with anticlot treatment in its benefit" in burden and benefit subscales, respectively. In another way, the "impact of warfarin therapy on food and drinking limitations" and "satisfaction with anticlot treatment" were subscales with the lowest mean satisfaction scores (Table 4).

Factors Associated With Warfarin Therapy Knowledge

Twelve variables (Table 5) were evaluated to identify their association with study participants' knowledge of warfarin therapy. In the univariate binary logistic regression analysis, HIV/AIDS and hyperthyroidism were significantly associated with poor knowledge of warfarin therapy. However, patients without hyperthyroidism were 4.28 times (adjusted OR [AOR] = 4.28, 95% CI: 1.01–18.22, $p = .049$) more likely to have poor knowledge of warfarin than those with hyperthyroidism (Table 5).

Associated Factors With Adherence to Warfarin

In the multivariate logistic regression analysis, living alone and visiting CHCs 15 or more times demonstrated a statistically significant association with adherence to warfarin therapy. The odds of poor adherence to warfarin were reduced by 56% among patients living with family (AOR: 0.44; 95% CI: 0.21–0.93; $p = .032$) compared to those living alone (Table 6).

Factors Associated With Satisfaction With Anticoagulation Treatment

Eleven variables were assessed to identify their association with patient satisfaction with anticoagulation treatment, using univariate binary logistic regression analysis. Multivariate logistic regression revealed that living alone, older age, better educational status, living outside Addis Ababa, portal vein thrombosis, warfarin indication, and bleeding history were all associated with being more likely to be dissatisfied with warfarin therapy. However, none of these factors was significantly associated with the current study's satisfaction with anticoagulant treatment (Table 7).

Discussion

This is the first study in Ethiopia to evaluate patients' knowledge, adherence, and satisfaction regarding warfarin therapy. The participants in this study comprised a diverse group of patients with various comorbidities and different warfarin indications for long-term care to prevent thrombosis. The patient population was relatively younger, with a mean age of 44.05 ± 7.9 years, which may have resulted from a higher prevalence of rheumatic heart disease in our study and Ethiopia.[28]

The mean knowledge of warfarin therapy (59.35 ± 13.04%) obtained in the present study was comparable with the Hungarian study 59.39 (±17.62)[11] and a systematic review and meta-analysis report of 60.4% average level of knowledge

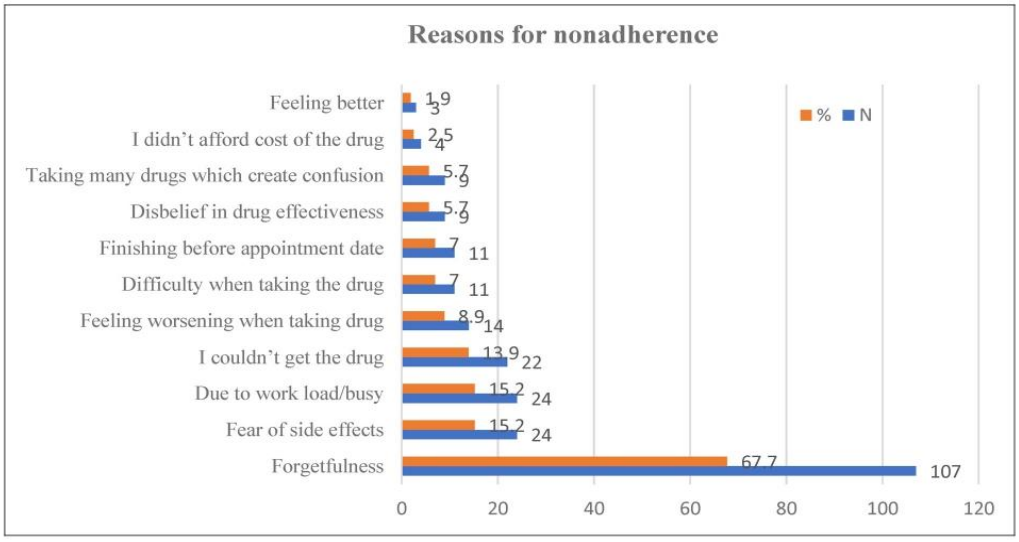

Figure 3. Reasons for nonadherence to warfarin.

Table 4. Mean Score of Participants to Anticlot Treatment Scale (ACTS).

Item	Description	Mean ± SD
Burden subscale		
1	How much does the possibility of bleeding as a result of your anticlot treatment limit you from doing physical activity?	4.17 ± 1.27
2	How much does the possibility of bleeding as a result of your anticlot treatment limit you from taking part in your usual activities?	4.02 ± 1.16
3	How bothered are you by the possibility of bruising as a result of your anticlot treatment?	3.92 ± 1.45
4	How bothered are you by having to avoid other medicines as a result of your anticlot treatment?	3.84 ± 1.39
5	How much does your anticlot treatment limit what you eat and drink?	2.79 ± 1.46
6	How much of a hassle (inconvenience) are the daily aspects of your anticlot treatment? (eg, remembering to take your medicine at a certain time, taking the correct dose of your medicine, following a diet, limiting alcohol, etc)	3.98 ± 1.22
7	How much of a hassle (inconvenience) are the occasional aspects of your anticlot treatment? (eg, the need for blood tests, going to or contacting the clinic/doctor, making arrangements for treatment while traveling, etc).	2.87 ± 1.55
8	How difficult is it to follow your anticlot treatment?	3.07 ± 1.49
9	How time-consuming is your anticlot treatment?	2.65 ± 1.44
10	How much do you worry about your anticlot treatment?	3.25 ± 1.56
11	How frustrating is your anticlot treatment?	4.04 ± 1.22
12	How much of a burden is your anticlot treatment?	3.33 ± 1.48
13	Overall, how much of a negative impact has your anticlot treatment had on your life?	3.39 ± 1.49
Benefit subscale		
14	How confident are you that your anticlot treatment will protect your health?	4.15 ± 1.00
15	How reassured do you feel because of your anticlot treatment?	3.95 ± 1.06
16	How satisfied are you with your anticlot treatment?	3.65 ± 1.15
17	Overall, how much of a positive impact has your anticlot treatment had on your life?	3.78 ± 1.14

on warfarin therapy[29] and slightly lower than that found by Hua et al[30] in China (62.3 ± 8.8%). However, the mean score in our study was much higher than that reported by Nader and co-workers,[31] with an overall mean score of 29.3%. In the present study, 23.4% of patients achieved an AKA passing score (good knowledge of warfarin therapy), higher than previous studies that reported passing scores between 5.8% and 15.8%.[6,9,32] Nevertheless, 75.2% of patients had good knowledge of warfarin (scoring ≥ 75%) in a study carried out at the King Khalid University Hospital outpatient anticoagulant

Table 5. Factors Associated With Knowledge of Warfarin Therapy.

Variable	Knowledge on Warfarin		COR (95% CI)	AOR (95% CI)	*P*-value
	Yes, *n* (%)	No, *n* (%)			
Age in years					
18–30	16 (4.6)	60 (17.1)	1	1	
31–45	36 (10.3)	99 (28.3)	1.73 (0.72–4.17)	1.33 (0.45–3.90)	.606
46–64	18 (5.1)	83 (23.7)	1.27 (0.58–2.78)	1.05 (0.41–2.68)	.919
≥65	12 (3.4)	26 (7.4)	2.13 (0.91–4.99)	1.88 (0.73–4.83)	.189
Marital status					
Single	28 (8.8)	78 (22.3)	1	1	
Married	40 (11.4)	155 (44.3)	1.11 (0.52–2.37)	0.76 (0.31–1.88)	.558
Divorced/widowed/separated	14 (4.0)	35 (10.0)	1.55 (0.76–3.15)	1.11 (0.49–2.52)	.805
Presence of comorbidity					
No	9 (2.6)	53 (15.1)	1	1	
Yes	73 (20.9)	215 (61.4)	2.00 (0.94–4.25)	2.27 (0.91–5.64)	.077
Heart failure					
No	40 (11.5)	150 (53.1)	1	1	
Yes	42 (12.1)	116 (33.3)	1.36 (0.83–2.23)	1.02 (0.57–1.84)	.938
Hypertension					
No	57 (16.3)	209 (59.7)	1	1	
Yes	25 (7.1)	59 (16.9)	1.55 (0.89–2.70)	1.38 (0.72–2.65)	.330
HIV/AIDS					
No	76 (21.7)	262 (74.9)	1	1	
Yes	6 (1.7)	6 (1.7)	3.45 (1.08–10.99)	3.29 (0.89–12.15)	.074
Vascular disease history					
No	68 (19.4)	243 (69.4)	1	1	
Yes	14 (4.0)	25 (7.1)	2.00 (0.99–4.06)	2.04 (0.90–4.64)	.089
Valvular heart diseases that do not need warfarin					
No	46 (13.1)	159 (45.4)	1	1	
Yes	36 (10.3)	109 (31.1)	1.71 (0.87–3.36)	1.83 (0.84–3.98)	.130
Hyperthyroidism					
Yes	6 (1.7)	4 (1.1)	1	1	
No	76 (21.7)	264 (75.4)	5.21 (1.43–18.94)	4.28 (1.01–18.22)	.049
Presence of warfarin interacting drugs					
No	44 (12.6)	123 (35.1)			
Yes	38 (10.9)	145 (41.4)	0.73 (0.45–1.20)	0.58 (0.33–1.01)	.054
Number of CHCs visits during follow-up					
3–6	23 (6.6)	47 (13.4)	1	1	
7–10	25 (7.1)	99 (28.3)	0.49 (0.21–1.12)	0.61 (0.24–1.53)	.291
11–14	23 (6.6)	76 (21.7)	0.95 (0.43–2.09)	1.11 (0.46–2.66)	.819
≥15	11 (3.1)	46 (13.1)	0.79 (0.35–1.77)	0.94 (0.39–2.29)	.901
Cardioembolism or non-embolic stroke					
No	77 (22.0)	240 (68.6)	1	1	
Yes	5 (1.4)	28 (8.0)	0.56 (0.21–1.49)	0.57 (0.20–1.63)	.298

Abbreviations: COR, crude odds ratio; 95% CI: 95% confidence interval; AOR, adjusted odds ratio, CHCs: cardiac and hematology clinics

clinic in Riyadh, Saudi Arabia.[33] The lower knowledge level among our study participants might be due to a lack of proper understanding among the patients or inadequate counseling provided by the treating physicians.

In this study, 7 frequently incorrect answers (Table 2) were potential areas for improvement in patient education on warfarin therapy, and more broadly show that long-term warfarin users require continuing education and sustained beneficial communication between healthcare providers for successful anticoagulation management. To address this, healthcare providers, including pharmacists, should strengthen their role in providing patient education and counseling by designing educational programs to improve the clinical outcomes of those on warfarin therapy. We did not find a significant association between any sociodemographic characteristic and knowledge of warfarin therapy. However, in studies conducted elsewhere, age, educational status, living alone or with family, and duration of warfarin therapy were significantly associated with knowledge of warfarin therapy.[24,31,34,35]

Adherence to warfarin therapy is beneficial in clinical practice, as it can help identify patients who require closer monitoring and educational interventions to improve treatment outcomes.[36] In the present study, ~55% of patients reported adherence to warfarin, which was higher than in prior studies,

Table 6. Factors Associated With Adherence to Warfarin Therapy.

Variables	Adherence to Warfarin: Good Yes, *n* (%)	Adherence to Warfarin: Poor Yes, *n* (%)	COR (95% CI)	AOR (95% CI)	*P*-value
Family monthly income in Birr					
0–300	86 (24.6)	91 (26.0)	1	1	
301–2500	31 (8.9)	18 (5.1)	1.18 (0.64–2.16)	1.25 (0.66–2.35)	.494
2501–5000	46 (13.1)	23 (6.6)	0.65 (0.29–1.42)	0.70 (0.307–1.61)	.404
>5001	29 (8.3)	26 (7.4)	0.56 (0.27–1.16)	0.54 (0.25–1.17)	.117
With whom do you live?					
Alone	15 (4.3)	21 (6.0)	1	1	
With family	177 (50.6)	137 (39.1)	0.55 (0.27–1.11)	0.44 (0.21–0.93)	.032
Duration of warfarin in years					
0.5–1	34 (9.7)	38 (10.9)	1	1	
>1–5	74 (21.1)	52 (14.9)	1.68 (0.81–3.48)	1.38 (0.63–3.01)	.417
6–10	54 (15.4)	48 (13.7)	1.05 (0.54–2.05)	0.724 (0.36–1.47)	.373
>10	30 (8.6)	20 (5.7)	1.33 (0.67–2.65)	1.07 (0.523–2.20)	.847
Hypertension					
No	151 (43.1)	115 (32.9)			
Yes	41 (11.7)	43 (12.3)	0.73 (0.44–1.19)	0.71 (0.42–1.12)	.199
HIV/AIDS					
No	188 (53.7)	150 (42.9)	1	1	
Yes	4 (1.1)	8 (2.3)	0.40 (0.12–1.35)	0.42 (0.12–1.52)	.185
Knowledge of warfarin therapy					
Good	49 (14.0)	33 (9.4)	1	1	
Poor	143 (40.9)	125 (35.7)	0.77 (0.47–1.27)	0.73 (0.43–1.24)	.245
Number of CHCs visits during follow-up					
3–6	39 (11.1)	31 (8.9)	1	1	
7–10	69 (19.7)	55 (15.7)	0.62 (0.31–1.26)	0.59 (0.277–1.28)	.183
11–14	59 (16.9)	40 (11.4)	0.62 (0.33–1.17)	0.56 (0.28–1.09)	.089
≥15	25 (7.1)	32 (9.1)	0.53 (0.27–1.02)	0.50 (0.25–1.01)	.052
Post-percutaneous mitral balloon valvotomy					
No	183 (52.3)	155 (44.3)	1	1	
Yes	9 (2.6)	3 (0.9)	2.54 (0.68–9.55)	2.26 (0.57–9.02)	.247

Abbreviations: COR, crude odds ratio; 95% CI. 95% confidence interval; AOR, adjusted odds ratio; CHCs, cardiac and hematology clinics.

with 5.4% and 37.6% adherence rates in Sudan and Vietnam, respectively.[27,32] However, our findings contradict a Turkish study that found a higher adherence rate (79.8%).[37] This suggests that there is room for improvement in patient adherence to warfarin to shape positive attitudes among pharmacists. A significant association was only observed between living with family (AOR = 0.44, 95% CI: 0.21–0.93, $p = .03$) and poor warfarin adherence (negative association) in the multivariate regression analysis, which contradicts with other previous studies,[38] while other sociodemographic and clinical characteristics did not show a significant association.

Similarly, our study did not find a significant association between knowledge of warfarin (AOR = 0.73, 95% CI: 0.43–123, $p = .245$) and adherence, contrary to previous reports.[32,38] In the current study, forgetting, fear of side effects, workload, and not receiving warfarin on time were the most common self-reported reasons among nonadherent cohorts. Improving warfarin adherence is crucial for effective anticoagulation therapy and for reducing the risk of thromboembolic events.[7] Hence, strategies that include memory refreshment to avoid forgetfulness, tailored education and provision of written format recommendations and reminders, pharmacist consultation between clinic visits focused on explaining misconceptions and encouraging adherence, telephone counseling, and open discussions with the patient to minimize doubts or fears have the potential to significantly improve warfarin adherence[7,39] . Structured education focused on warfarin can have a favorable impact on patients' attitudes toward medication, leading to an improvement in their quality of life. Patients are more inclined to adhere to the warfarin regimen by acknowledging the negative experiences associated with the drug as manageable.[38]

The overall mean level of satisfaction with warfarin therapy (53.67 ± 8.56) in the present study was lower than that reported in a previous study.[12] Our study found that 52.6% of patients were satisfied with the anticlot treatment, which is similar to the satisfaction level reported in Sudanese patients (50.5%),[27] but lower than the Saudi Arabian study's report (63.7%).[12] Regarding ACTS subscale scores, the mean ACTS burden score was lower than that reported in studies conducted in

Table 7. Factors Associated With Satisfaction With Anticoagulation Treatment in Patients Receiving Warfarin.

Variables	Satisfaction with Warfarin: Good Yes, *n* (%)	Satisfaction with Warfarin: Poor No, *n* (%)	COR (95% CI)	AOR (95% CI)	*P*- value
Age in years					
18–30	36 (10.3)	40 (11.4)	1	1	
31–45	77 (22.0)	58 (16.6)	0.90 (0.57–1.41)	1.20 (0.50–2.86)	.685
46–64	54 (15.4)	47 (13.4)	1.23 (0.94–1.87)	1.63 (0.73–3.66)	.232
≥65	17 (4.9)	21 (6.0)	1.15 (0.78–1.70)	1.53 (0.67–3.48)	.311
Residence					
Addis Ababa	134 (38.3)	113 (32.3)			
Out of Addis Ababa	50 (14.3)	53 (15.1)	1.19 (0.92–1.52)	1.30 (0.79–2.15)	.297
Education Status					
Unable to read and write	27 (7.7)	24 (6.9)	1	1	
Primary school (Grades 1–8)	52 (14.9)	49 (14.4)	1.12 (0.65–1.95)	1.31 (0.54–3.17)	.548
Secondary school (Grades 9–12)	56 (16.0)	54 (15.4)	1.06 (0.72–1.57)	1.07 (0.50–2.28)	.869
Degree and above	27 (7.7)	16 (4.6)	1.04 (0.71–1.51)	1.09 (0.52–2.28)	.819
Certificate/Diploma	22 (6.3)	23 (6.6)	1.69 (0.91–3.13)	1.87 (0.75–4.64)	.176
With whom do you live?					
With family	168 (48.0)	146 (41.7)			
Alone	16 (4.6)	20 (5.7)	1.15 (0.92–1.44)	1.43 (0.69–2.98)	.332
Medical service coverage					
CBHI	136 (38.9)	124 (35.4)	1	1	
Out-of-pocket/Paying	42 (12.0)	32 (9.1)	1.10 (0.86–1.40)	1.24 (0.39–3.88)	.715
Free	6 (1.7)	10 (2.9)	1.31 (0.83–2.08)	1.38 (0.41–4.59)	.602
Vascular disease history					
No	166 (47.4)	145 (41.4)			
Yes	18 (5.1)	21 (6.0)	1.14 (0.92–1.43)	1.17 (0.57–2.39)	.674
Post-mitral and/or aortic valve replacement (mechanical)					
No	163 (46.6)	143 (40.9)			
Yes	21 (6.0)	23 (6.6)	1.14 (0.91–1.43)	1.52 (0.75–3.05)	.242
Portal vein thrombosis					
No	181 (51.7)	58 (45.1)			
Yes	3 (0.9)	8 (2.3)	1.15 (0.92–1.42)	2.56 (0.56–11.67)	.224
Number of CHCs visits during follow-up					
3–6	39 (11.1)	31 (8.9)	1	1	.454
7–10	65 (18.6)	59 (16.9)	1.26 (0.78–2.012)	1.73 (0.77–3.87)	.182
11–14	57 (16.3)	42 (12)	1.10 (0.77–1.57)	1.34 (0.63–2.88)	.449
≥15	23 (6.6)	34 (9.7)	1.36 (0.91–2.02)	1.68 (0.81–3.48)	.162
INR monitoring frequency in days (mean)					
≤30	17 (4.9)	19 (5.4)	1	1	.499
31–60	91 (26.0)	89 (25.4)	0.89 (0.46–1.72)	1.62 (0.51–5.14)	.408
61–90	65 (18.6)	43 (12.3)	1.02 (0.76–1.37)	1.49 (0.60–3.67)	.386
>91	11 (3.1)	15 (4.3)	1.51 (1.03–2.22)	1.98 (0.78–5.03)	.148
Bleeding episodes					
No	158 (45.1)	131 (37.4)			
Yes	26 (7.4)	35 (10.0)	1.21 (0.96–1.52)	1.32 (0.72–2.44)	.371

Abbreviations: COR, crude odds ratio; 95% CI. 95% confidence interval; AOR, adjusted odds ratio; CBHI, community-based health insurance; CHCs, cardiac and hematology clinics; INR, international normalized ratio.

Canada, Japan, and Saudi Arabia[17,40,41] among patients receiving warfarin therapy. Conversely, a higher ACTS benefit score was reported in our study when compared with the same studies, but was consistent with the Saudi study (11.74 ± 2.43 vs 11.92 ± 2.4). The differences in the degree, mean level of satisfaction, and ACTS subscale scores in the present study may be explained by the differences in the patients' demographic characteristics (sex, age, and education level), quality of anticoagulation management service, sample size, and indications for warfarin. Multiple regression analysis revealed no significant association between independent variables and ACTS scores. Participants who lived outside Addis Ababa, lived alone, had postmitral and/or aortic valve replacement (mechanical) and portal vein thrombosis warfarin indication and bleeding history, and had an extended INR monitoring frequency were more likely to be unsatisfied with anticlot

treatment when compared with their counterparts, without significant difference in satisfaction level (Table 7). However, significant associations with anticlot treatment satisfaction have been identified in previous studies.[8,12,27,40]

Strengths and Limitations of the Study

The present study had a relatively large sample size. This is also the first study in Ethiopia to assess the 3 essential aspects of oral anticoagulation. Hence, this study provides unique insights into patient knowledge, adherence, and satisfaction with anticlot treatment in our study population, which have not been previously reported, and our findings can inform the development of targeted interventions to improve warfarin therapy. Despite these strengths, this study has several limitations. The first is its cross-sectional design, which made it difficult to establish a relationship between cause and effect. Second, this single-center study recruited participants from outpatient CHCs; therefore, the results cannot be generalized to a large patient population receiving warfarin. Third, this study relied on self-reported data collected from patients, who may be prone to response and recall bias. Participants may have provided socially desirable answers or inaccurately represented their behavior in the medication adherence and satisfaction questionnaires.

Conclusions

This study highlights the importance of understanding the knowledge, adherence, and satisfaction with anticoagulation treatment of patients receiving warfarin at TASH, Ethiopia. About a quarter of the patients passed the AKA questionnaire. More than half of the study participants adhered well to warfarin, and forgetting, fear of side effects, and workload/being busy were the most frequent reasons for nonadherence. Approximately half of the patients were satisfied with the warfarin therapy. This study shows room for improvement in the knowledge, adherence, and satisfaction of patients taking warfarin. Future research should explore the impact of patient education and counseling on improving knowledge, adherence, and satisfaction with anticoagulation treatment among patients receiving warfarin.

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Supplemental Material

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PAPER IV

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RESEARCH ARTICLE Open Access

Comparison of anticoagulation control and outcomes between usual medical care and pharmacist-led anticoagulation service in ambulatory patients taking warfarin at tertiary hospital in Ethiopia: a quasi-experimental study

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Abstract

Background We aimed to compare anticoagulation control and outcomes between usual medical care (UMC) and pharmacist-led anticoagulation services (PLAS) in patients receiving warfarin at the Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia.

Methods A quasi-experimental study was conducted, including 350 (66.7%) and 175 (33.3%) patients from the UMC and PLAS groups, respectively, from 525 patients. The time in therapeutic range (TTR) was determined using the Rosendaal method, with a TTR ≥ 65% set as the cut-off for optimal anticoagulation. The two-sample Wilcoxon rank-sum (Mann–Whitney U) test was used to compare continuous variables between groups. Categorical variables were compared between groups using Pearson's chi-square test or Fisher's exact test. Logistic regression and negative binomial regression analyses were conducted to identify the factors associated with suboptimal TTR and secondary outcomes, respectively, at the p values < 0.05, and 95% confidence interval (CI).

Results Compared with the UMC group, the patients in the PLAC group showed a significantly higher median (IQR) TTR [60.89% (43.5–74.69%) vs. 53.65% (33.92–69.14%), $p < 0.001$]. A significantly higher optimal TTR (≥ 65%) was achieved in the PLAC group (41.7% vs. 31.7%) than in the UMC group ($p = 0.002$). The odds of having a poor TTR were reduced by 43% (AOR = 0.57, 95% CI = 0.36–0.88, $p = 0.01$) among patients in the PLAC group compared to those in the UMC group. There were no statistically significant differences in the secondary outcomes between the groups, except for all-cause emergency visits ($p = 0.003$). The incidence of bleeding events decreased by 3% (IRR = 0.97, 95% CI = 0.96–0.99, $p < 0.001$) for every increase in INR monitoring frequency. The incidence of thromboembolic events increased by a factor of 15.13 (IRR = 15.13, 95% CI = 1.47–155.52, $p = 0.02$) among patients with a high-risk CHA_2DS_2-VASc score compared with those with a moderate score.

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Conclusion Patients in the PLAC group had a significantly higher median TTR than those in the UMC group did. There were no statistically significant differences in the secondary outcomes between the groups, except for fewer all-cause emergency department visits in the PLAC group.

Keywords Oral anticoagulation, Pharmacist-led anticoagulation clinic, Usual medical care, Quasi-experimental study, Warfarin, Ethiopia

Introduction

Warfarin is a widely used anticoagulant to prevent and treat thrombosis in various conditions, including venous thromboembolism (VTE), atrial fibrillation, post-myocardial infarction, and heart valve replacement [1–3]. Its narrow therapeutic range; frequent drug, herbal, and food interactions; and the effect of comorbidities place patients at risk of bleeding and thromboembolic complications if the recommended anticoagulation target ranges are not achieved [4–8]. Studies have shown that the effectiveness of warfarin therapy depends on the percentage of time that the international normalized ratio(INR) is within the therapeutic range or the time in the therapeutic range (TTR) [5, 9–12]. A minimum TTR of 65% is required for warfarin to be considered effective in the prevention and treatment of thromboembolic diseases [13, 14]. The risk of thromboembolism and bleeding has also been shown to depend on TTR [15], as evidenced by increased adverse clinical outcomes (ischemic stroke/transient ischemic attack, major bleeding, intracranial hemorrhage, and death) in patients with non-valvular atrial fibrillation in Thailand [16]. In addition, a systematic review and meta-regression analysis showed the importance of higher mean TTR, as it was significantly associated with a decreased rate of major bleeding and stroke/systemic embolism [17]. However, in clinical practice, maintaining adequate anticoagulation with warfarin has proven challenging, as demonstrated by studies conducted globally documenting a low TTR (< 65%) [18–28]. This problem appears to be the worst in Africa because the lowest TTRs have been reported in studies conducted in various regions of the continent [1, 8, 24, 29–32]. Lower TTRs (29–42.7%) were recorded in patients receiving warfarin in Ethiopia [33–37] Furthermore, a prevalence of 99.2% [38] and 21.1% ([39] of warfarin-drug interactions were documented in two Ethiopian hospitals.

These findings highlight the need for alternative strategies to improve anticoagulant therapy [40, 41]. Specialized anticoagulation management services (AMS) have successfully optimized anticoagulation therapy to evaluate and monitor patients, provide ongoing patient education, and serve as a resource for both patients and physicians. Pharmacist-led anticoagulation service (PLAS) is becoming the best practice to achieve a better quality of care in patients receiving anticoagulants compared to other models. Increased TTR, decreased rates of admission and average clinic visits, lower risk of total bleeding and thrombosis events [42–44], and improved adherence to treatment have been documented in the pharmacist-led anticoagulation clinic (PLAC) group compared to the physician-led group [45, 46]. Furthermore, systematic reviews and meta-analyses have shown that pharmacist-led anticoagulation management results in lower rates of total bleeding and thrombotic events [42, 47], better quality of anticoagulation control, and lower healthcare utilization [47]. A retrospective cohort study in Malaysia revealed a significant association between the usual medical care (UMC) group and pharmacist-led warfarin medication therapy adherence clinics (WMTAC) in terms of TTR ($p = 0.01$), expanded therapeutic INR range ($p < 0.04$), and INR levels ($p = 0.02$) [48]. Another study conducted in Brazil reported significantly improved TTR values after pharmaceutical care in patients with AF with a low TTR (< 50%) [45, 49].

Given the practical limitations and complex nature of effective anticoagulant delivery, the adoption of such practices might improve the treatment response and patient outcomes in resource-constrained settings. Based on evidence reported elsewhere regarding the importance of PLAS in improving the quality of anticoagulation in patients receiving warfarin [42, 47, 48, 50–52] and needs assessment study recommendations in the same hospital [53], the first pharmacist-led anticoagulation clinic (PLAC) in Ethiopia was established at the Tikur Anbessa Specialized Hospital (TASH) in April 2018 under the cardiac clinic. The novelty of our study lies in the distinctive healthcare context of Ethiopia, which requires specific intervention strategies tailored to resource-constrained environments, culturally diverse settings, lower health literacy levels, limited diagnostic tools, underdeveloped electronic health records, and a shortage of well-trained healthcare providers. By focusing on these distinctive intervention strategies, our study was designed to evaluate the feasibility and effectiveness of PLAC in resource-limited settings by comparing anticoagulation control and outcomes between PLAC and UMC, hypothesizing improved anticoagulation control and outcomes in the PLAC group.

Methods

Study setting

This study was conducted at the cardiac and hematology clinics (CHCs) and PLAC of the Tikur Anbessa Specialized Hospital (TASH), a central referral hospital in Addis Ababa, Ethiopia. The CHCs operate four days per week, with an average of 600 patients per week. Cardiologists, hematologists, cardiac and hematology fellows, residents, physicians, and nurses staffed the clinics. PLAC was established at TASH in April 2018 as part of the anticoagulation management quality improvement process, and it is the only clinic in Ethiopia. The PLAC was staffed with four clinical pharmacists who provided AMS two days per week (Tuesday morning and Friday afternoon). It was established to serve patients with frequent nontherapeutic INRs, complicated anticoagulation history, and poor adherence to warfarin at the CHCs of the hospital. CHCs and PLAC were the clinics that mostly prescribed anticoagulants (mainly warfarin) for patients who had been followed up at the outpatient department of the hospital.

Study design and period

A quasi-experimental study was conducted to evaluate the differences in anticoagulation control and outcomes between UMC and PLAS in adult patients receiving anticoagulation management services (AMS) with warfarin therapy at TASH from July 2021 to June 2023. The electronic database (iCare) of TASH was used to collect patient data related to clinical profiles and anticoagulation management-related information. A comprehensive Excel database was developed to systematically document and capture pertinent information regarding anticoagulation management during each visit for the PLAC group.

Study protocol and intervention

Study participants who had been receiving AMS at the PLAC and CHCs in the hospital were grouped into an intervention group (PLAC) and a comparison group (UMC). Anticoagulation management services focus on optimizing anticoagulation control by managing patients receiving anticoagulants that require proper management to minimize serious adverse events, including excessive bleeding. The UMC group received existing AMS from physicians without the involvement of clinical pharmacists. The PLAC protocol, clinical judgment, and knowledge were used to develop a care plan for warfarin dose adjustment, follow-up INR testing, and patient counselling. Based on the hospital PLAC protocol recommendations, patients with at least two consecutive nontherapeutic INRs, complicated anticoagulation history, and recent warfarin non-adherence history at the UMC were assigned to the PLAC group and explained how they were enrolled and the services provided at the clinic. The protocol included detailed clinical information on the management of long-term warfarin therapy (indication, INR target ranges, duration of treatment, maintenance dosing algorithm (dosing adjustment recommendation), status of anticoagulation and action to be followed, frequency of INR monitoring, any warfarin-interacting drugs, and measures to be taken). The PLAC protocol was reviewed and approved by the anticoagulation team to provide adequate and appropriate AMS. Education (prepared in the Amharic language) that included all aspects of warfarin treatment was provided for approximately 20 min to all patients after enrolment in PLAC. The participants were provided with a follow-up booklet (a form with INR values, dosing scheme, next appointment date, and the most important messages provided during education). Furthermore, a medication review was performed to minimize drug interactions with warfarin. If necessary, the treating physicians communicated with a proposal for a drug change, dose adjustment, or another measure. For patients who did not visit the clinic per schedule or in cases of extreme non-therapeutic INRs (INR values < 1.5, or > 5) in which it was difficult to wait until the next clinic day to adjust the dose, phone consultation was used for appropriate actions and further evaluation. However, clinical pharmacists working in PLAC did not initiate warfarin for new patients and did not stop it; instead, they provided recommendations to the assigned physicians.

Source and study population

The source population for this study included all outpatients who had follow-up at CHCs and PLAC of the TASH, whereas the study population consisted of patients who received AMS from these clinics, had been receiving warfarin therapy, and met the predefined study inclusion criteria.

Eligibility criteria

In both groups, we enrolled patients aged ≥ 18 years who had received warfarin for at least six months and had a documented history of at least three consecutive INR measurements. This criterion was implemented to ensure the consistency and reliability of INR data, excluding individuals who were newly initiated on warfarin therapy, and to facilitate accurate calculation of TTR. Additionally, to qualify for inclusion in the PLAC cohort, patients were required to have initially received warfarin therapy at CHCs. Patients with interrupted INR monitoring or planned temporary interruptions, those who missed more than one consecutive clinic visit, those who received AMS from both PLAC and CHCs during the follow-up period, and those with incomplete or

missing medical and medication records were excluded. These exclusion criteria were implemented to maintain the integrity of the study cohort and ensure the reliability of data analysis.

Sample size determination, sampling technique, and participants' recruitment

The sample size was calculated using the mean TTR of 42% from a recent study report at the Ethiopian public hospital [33], and the standard deviation of TTR was 0.25, based on the fact that anticoagulation control before implementing PLAS was better than that found in a previous study (0.42). It also assumed a Type I error (α-level) rate of 0.05, power of 80%, and UMC: PLAS ratio of 2:1. To achieve a minimum clinically important difference of 0.08 (i.e., an improvement from 42 to 50% in TTR), at least 304 patients in the control group (UMC) and 152 PLAS participants (including a 10% contingency for loss to follow-up) were required. Based on the determination and maintenance of the indicated eligibility criteria, we included 350 and 175 patients in the UMC and PLAS groups, respectively, in the final analysis. All patients who received AMS at CHCs, PLAC, and warfarin for at least six months prior to data collection were initially screened from clinical records. Eligible patients were recruited by a systematic random sampling technique using the formula ($k = N/n$), and every kth (actual sampling fraction) patient data were reviewed among patients who visited the clinics up to the sample size achieved. The actual sampling fraction (k) varied on different days as well as between the UMC and PLAC owing to variations in the total number of patients attending the clinics. The first study participant was selected by simple random sampling and every four–five and two patients were enrolled from the UMC and PLAC, respectively.

Data collection instrument

A structured data collection tool was designed to collect all the required sociodemographic characteristics and clinical data. It included information on comorbidities, warfarin therapy, warfarin indications, daily warfarin dose, target INR ranges, INR values at each visit, interval days between INR monitoring, anticoagulation status at each visit (subtherapeutic, in target, and supratherapeutic ranges), measures taken by physicians and pharmacists, potential warfarin-interacting drugs, adverse drug events, any thromboembolism and bleeding events (both minor and major bleeding), emergency room visits, and hospitalizations between clinic visits. Stroke and bleeding risks were assessed at baseline in patients with atrial fibrillation using the CHA2DS2-Vasc score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female) = 0 in men, or 1 in women) and by the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (> 65 years), Drugs/alcohol) score to identify patients at high risk of bleeding (HAS-BLED score ≥ 3) [54].

Study outcomes

The primary outcome was the percentage of median TTR differences between the two groups. TTR was determined using the Roosendaal Method, which determines TTR by incorporating INR measurement frequency and values, assuming that changes between consecutive INR measurements are linear [55]. In this study, a TTR ≥ 65% was used as the cutoff range for good/optimal anticoagulation control with warfarin therapy [13, 14]. Bleeding episodes, thromboembolic events, all-cause hospitalization, and emergency department visits differences between groups were the secondary outcomes of this study.

Data collectors' recruitment

Four clinical pharmacists who were selected based on their educational qualifications, clinical and research experience and familiarity with serving patients who required warfarin therapy collected data.

Data quality assurance

The data collection instrument was reviewed and validated by a team of senior clinical pharmacists, cardiologists, and hematologists for its content, flow, completeness, and clarity to be used by data collectors and its suitability to the local context. A pre-test was conducted on 5% of the study population in both groups, and all necessary amendments and modifications were made to the structure before actual data collection. One-day training was provided to the data collectors on how to use the data collection instruments, study criteria/protocol, implementation of sampling techniques, maintenance of data confidentiality, and collection of patient data from the hospital's electronic database (I-care system). Collected data were evaluated for completeness and consistency during data management, storage, and analysis.

Data analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 27. Descriptive statistics were used to summarize the demographic and clinical characteristics, CHA2DS-2VASc score, HAS-BLED score, percentage of days with different therapeutic ranges, and the incidence of secondary outcomes. The two-sample Wilcoxon

rank-sum (Mann–Whitney U) test was used to compare continuous variables between groups. Categorical variables were compared between groups using Pearson's chi-square test or Fisher's exact test. Binary logistic regression analysis was conducted to identify factors associated with poor TTR. Negative binomial regression analysis was performed to identify predictors of secondary outcomes, including bleeding episodes, thromboembolic events, all-cause emergency department visits, and hospitalization. Variables with a p-value < 0.25 in the bivariate analysis and binary negative binomial regression were included in the multivariable regression model and multivariable negative binomial regression. The significance of the association was determined at a 95% confidence level and a p-value < 0.05 both in the multivariable model and negative binomial regression analysis. The goodness-of-fit of the negative binomial regression model was evaluated using a likelihood ratio test by comparing fitted and null models.

Ethical approval

Ethical approval was obtained from the Ethical Review Committee of the School of Pharmacy (ERB/SOP/454/2022) and Institutional Review Board (096/22/SoP) of the College of Health Sciences, Addis Ababa University, Ethiopia. Written permission to access the clinical data of the study participants was obtained from the outpatient department of the hospital. Since the PLAS at the TASH has been provided under the supervision of cardiologists and hematologists, any anticipated risk to patients has been communicated and linked to consultant cardiologists and hematologists.

Results

Socio-demographic characteristics of study participants

Of the 525 patients who participated in the study, 350 (66.7%) and 175 (33.3%) were included in the UMC and PLAC groups, respectively, and 375 (71.4%) were female. Most patients in both groups were female, with no significant differences ($p = 0.31$) between the groups in each sex category. The median (IQR) age in the UMC was 41.00 [32–55] years, with a range of 18–82 years, while in the PLAC group, the median ± IQR of age was 39.00 [32–49] years, with a range of 20–85 years without any significant difference between the groups ($p = 0.15$). A significant difference was observed based on the residence of the patients, and the majority of patients were residents of Addis Ababa (study area) in both the UMC and PLAC: 247 (70.6) and 148 (84.6), respectively ($p < 0.001$) (Table 1).

Clinical characteristics of patients

The clinical characteristics of the patients revealed a notable prevalence of underlying heart problems and comorbidities in both study groups, with a significantly higher incidence in the UMC group than in the PLAC group (82.3% vs. 64.6%, $p < 0.001$). The most prevalent clinical conditions in the UMC cohort were heart failure (45.4%) and chronic rheumatic valvular heart disease (CRVHD) (41.4%). Conversely, in the PLAC group, CRVHD (32.6%) was the predominant comorbidity, followed by heart failure (29.1%). Furthermore, notable differences ($p < 0.05$) in the presence of heart failure, hypertension, history of vascular disease, coronary artery disease/ischemic heart disease, and polycythemia vera and aspirin and/or clopidogrel use were observed between the two groups and were more frequently encountered in the UMC group than in the PLAC group, as shown in Table 2.

Table 1 Socio-demographic characteristics of patients receiving warfarin compared between UMC and PLAC at TASH

Variables	Total ($N = 525$) n (%)	UMC Group ($N = 350$) n (%)	PLAC Group ($N = 175$) n (%)	P-value
Sex				
Female	375(71.4)	245(70.0)	130(74.3)	0.31
Male	150(28.6)	105(30.0)	45(25.7)	
Age in years				
18–30	107(20.4)	72(20.6)	35(20.0)	0.46
31–45	231(44.0)	148(42.3)	83(47.4)	
46–64	135(25.7)	97(27.7)	38(21.7)	
≥ 65	52(9.9)	33(9.4)	19(10.9)	
Median (IQR) age	40.00 (32–53)	41(32–55)	39(32–49)	0.15
Residence				
Addis Ababa	395(75.2)	247(70.6)	148(84.6)	< 0.001
Out of Addis Ababa	130(24.8)	103(29.4)	27(15.4)	

Table 2 Clinical characteristics of patients receiving warfarin compared between UMC and PLAC at TASH

Characteristics	Total ($N=525$) *n* (%)	UMC Group ($N=350$) *n* (%)	PLAC Group ($N=175$) *n* (%)	*P*-value
Presence of heart problems or comorbidities				
Yes	401(76.4)	288(82.3)	113(64.6)	< 0.001
Underlying heart problems, comorbidities, or medication use				
Heart failure	209(39.8)	158(45.4)	51(29.1)	< 0.001
Valvular heart disease	202(38.5)	145(41.4)	57(32.6)	0.06
Hypertension	109(20.8)	84(24.0)	25(14.3)	0.01
Stroke and thromboembolism history	88(16.8)	66(18.9)	22(12.6)	0.08
Amiodarone use	6 (1.1)	6 (1.7)	0 (0)	0.19
Aspirin, clopidogrel, NSAIDs use	31 (5.9)	26 (7.4)	5 (2.9)	0.04
Pulmonary Hypertension	63(12.0)	43(12.3)	20(11.4)	0.78
Vascular heart disease history[b]	43(8.2)	39(11.1)	4(2.3)	< 0.001
Diabetes Mellitus	35(6.7)	28(8.0)	7(4.0)	0.08
Neurologic disorders[c]	22(4.2)	19(5.4)	3(1.7)	0.06
CAD/IHD without thrombus	20(3.8)	18(5.1)	2(1.1)	0.02
Seizure disorders	20(3.8)	17(4.9)	3(1.7)	0.09
Cardiomyopathy	23(4.4)	17(4.9)	6(3.4)	0.51
HIV/AIDS	14(2.7)	12(3.4)	2(1.1)	0.16
Cancer	13(2.5)	12(3.4)	1(0.6)	0.07
Hypertensive heart disease	20(3.8)	11(3.1)	9(5.1)	0.33
Hyperthyroidism	14(2.7)	10(2.9)	4(2.3)	0.78
Chronic Pulmonary diseases[d]	14(2.7)	10(2.9)	4(2.3)	0.78
Dyslipidemia	11(2.1)	10(2.9)	1(0.6)	0.11
Rheumatologic diseases	13(2.5)	9(2.6)	4(2.3)	0.55
Gastric illness/peptic ulcer diseases	10(1.9)	9(2.6)	1(0.6)	0.18
Portal hypertension	7(1.3)	7(2.0)	0(0.0)	0.10
Renal Diseases	12(2.3)	8(2.3)	4(2.3)	0.63
Liver diseases	11(2.1)	8(2.3)	3(1.7)	0.76
Polycythemia vera	8(1.5)	8(2.3)	0(0)	< 0.001
Iron deficiency anemia	7(1.3)	6(1.7)	1(0.6)	0.43
Hypothyroidism	6(1.1)	4(1.1)	2(1.1)	0.68
Psychiatric disorders	5(0.9)	3(0.9)	2(1.1)	0.54
Others[e]	27(5.1)	18(5.1)	9(5.1)	0.59

[a] includes transient ischemic attack (TIA), subarachnoid hemorrhage (SAH), arteriovenous malformations (AVM), and intracranial hemorrhage (ICH)

[b] incudes prior, myocardial infarction, peripheral artery disease, or aortic plaque

[c] includes hemiplegia, peripheral neuropathy, Parkinson's disease, and chronic lower back pain

[d] includes COPD, Asthma, etc.; HIV/AIDS, nonsteroidal anti-inflammatory drugs; CAD/IHD, coronary artery disease/ischemic heart disease; and ecological disorders, benign prosthetic hyperplasia, pituitary microadema, erectile dysfunction, tuberculosis, Infective Endocarditis, myoma, and visual impairment

Among the 210 patients in the UMC group and 125 patients in the PLAC group diagnosed with atrial fibrillation, 39.5% of those in the UMC group had a high CHA2DS2-VASc score, while 45.6% of patients in the PLAC group had a low CHA2DS2-VASc score. This discrepancy was statistically significant ($P<0.001$). In contrast, the majority of patients in both cohorts presented with a moderate bleeding risk, constituting 71.4% of the UMC group and 54.4% of the PLAC group, with statistically significant differences between the groups ($p<0.001$) (Table 3).

A statistically significant difference in warfarin indication distribution among the groups was observed for atrial fibrillation ($p=0.01$), mechanical heart valves ($p=0.002$), bioprosthetic valve replacement/repair ($p=0.002$), and post-percutaneous mitral balloon valvotomy ($p=0.01$), as was most commonly indicated for the PLAC group. Patients with deep vein thrombosis ($p<0.001$) and portal vein thrombosis ($p=0.019$) were managed only at the UMC (Table 4).

Table 3 Baseline stroke and bleeding risk score among atrial fibrillation patients receiving warfarin compared between UMC and PLAC at TASH

Risk score	Total (*N* = 335) *n* (%)	UMC Group (*i* = 210) *n* (%)	PLAC Group (*N* = 125) *n* (%)	*P*-value
CHA_2DS_2-VASc Risk				
Low	110(32.8)	53(25.2)	57(45.6)	
Moderate	120(35.8)	74(35.3)	46(36.8)	< 0.001
High	105(31.4)	83(39.5)	22(17.6)	
HAS-BLED Risk				
Low	80(23.8)	34(16.2)	46(36.8)	
Moderate	218(65.1)	150(71.4)	68(54.4)	< 0.001
High	37(11.1)	26(12.4)	11(8.8)	

INR target range, monitoring frequency, and dose of warfarin

The majority of the patients in both groups had an INR target range of 2.0–3.0, with a statistically significant difference between the groups ($p = 0.002$). The INR was monitored at median intervals of 51.54 (IQR 37.18–69.14) days for the UMC group and 40.08 (IQR 33.17–48.83) days in the PLAC group, with a notable difference between the two cohorts ($p < 0.001$). The median weekly warfarin dose used in the PLAC group was 35 (27–42.5) mg, while in the UMC group, it was 32.26 (25.21- 40.56) mg without a statistically significant difference between the groups ($p = 0.239$). Similarly, there were no significant differences in the median prescribed warfarin dose between the two groups, as depicted in Table 5).

Differences in the time spent in different INR ranges

Compared with the UMC group, patients in the PLAC group showed a significantly higher percentage of median (IQR) TTR 60.89% (43.5–74.69%) vs. 53.65% (33.92–69.14%), $p < 0.001$]. The percentage of time below range (TBR) was significantly lower in the PLAC group (21%, (8.5–37.78%) than in the UMC group ($p = 0.01$). Further analysis using the *R*-value (rank-biserial correlation coefficient) revealed that the effect size associated with the difference between UMC and PLAC, as measured by r, was 0.02. This indicated a 2% effect size, favoring PLAC (Fig. 1).

A significantly higher optimal TTR (≥ 65%) was achieved in the PLAC group (41.7% vs. 31.7%) than in the UMC group ($P = 0.02$) (Table 6).

Table 4 Warfarin indication among outpatients compared between UMC and PLAC

Indication of warfarin	Total (*N* = 525) *n*(%)	UMC Group (*N* = 350) *n* %)	PLAC Group (*N* = 175) *n* (%)	*P*-value
Atrial fibrillation	335 (63.8)	210 (60.0)	125 (71.4)	0.01
Valvular heart disease	59 (11.2)	46 (13.1)	13 (7.4)	0.05
Cardioembolism[a]	49 (9.3)	33 (9.4)	16 (9.1)	0.92
Post heart valves (mechanical)[c]	84 (16.0)	44 (12.6)	40 (22.9)	0.002
Cardiac Thrombus[b]	18 (3.4)	10 (2.9)	8 (4.6)	0.31
(Bio) prosthetic valve replacement/ repair[c]	22 (4.2)	8 (2.3)	14 (8.0)	0.002
Post-percutaneous mitral balloon valvotomy[c]	27 (5.1)	12 (3.4)	15 (8.6)	0.012
Cardiomyopathy[c]	10 (1.9)	4 (1.1)	6 (3.4)	0.091
IHD with thrombus	10 (1.9)	4 (1.1)	6 (3.4)	0.091
Deep vein thrombosis	37 (7.0)	37 (10.6)	0 (0)	< 0.001
Pulmonary embolism	7 (2.0)	7 (2.0)	0 (0)	0.102
Portal vein thrombosis	11 (2.1)	11 (3.1)	0 (0)	0.019

[a] includes cardioembolic stroke, peripheral artery embolism), other site embolism), or non-embolic stroke (ischemic stroke)

[b] includes left ventricular/apical/arterial thrombus

[c] By themselves are not indications for warfarin; patients should have atrial fibrillation, high CHA2DS2-VASc, cardioembolism, cavity thrombus, or ventricular thrombus

Table 5 INR target range, monitoring frequency, and dose of warfarin compared between UMC and PLAC at TASH

Item description	Total (*N* = 525) *n* (%)	UMC Group (*N* = 350) *n* %)	PLAC Group (*N* = 175) *n* (%)	*P*-value
Target INR range				
2.0–3.0	441(84.0)	306 (87.4)	135 (77.1)	0.002
2.5–3.5	84 (16.0)	44 (12.6)	40 (29.9)	
INR monitoring frequency in days				
Median (IQR)	46.45 (36.15–61.6)	51.54 (37.18–69.14)	40.08(33.17–48.83)	< 0.001
Number of Visits				
Median (IQR)	9 (7–9)	10 (7–13)	9 (7–11)	0.044
Average Weekly Dose				
Median (IQR)	33.22 (25.9–41.33)	32.36 (25.21–40.56)	35 (27–42.5)	0.239
Average daily Dose				
Median (IQR)	4.75(3.7–5.9)	4.62 (3.6–5.80)	5.00 (3.86–6.07)	0.239

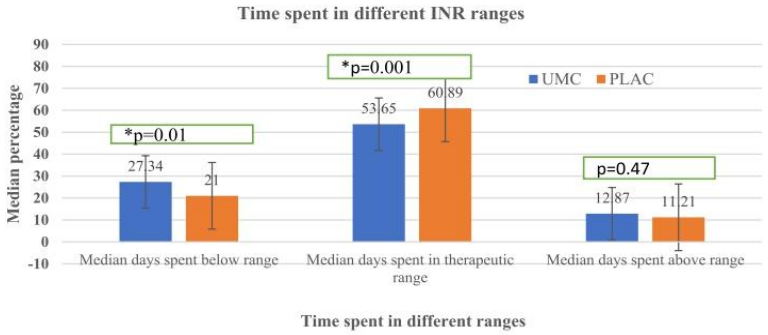

Fig. 1 Difference in the time spent in different INR ranges between UMC and PLAC at TASH

Table 6 Comparison of optimal TTR difference between UMC and PLAC

Group	TTR < 65%		TTR ≥ 65%		*P* value
	N (%)	95%CI	*n* (%)	95% CI	
UMC	239(68.3)	(63.1,73.1)	111(31.7)	(26.9,36.9)	0.02
PLAC	102(58.3)	(50.6,65.7)	73 (41.7)	(34.3,49.4)	

Predictors of poor the time in therapeutic range

The results of the multivariate logistic regression analysis showed that the odds of having a poor TTR were reduced by 43% (AOR = 0.57, 95% CI = 0.36–0.88, $p = 0.01$) among patients in the PLAC group compared to those in the UMC group. Patients with low HAS-BLED scores were 49% (AOR = 0.51, 95% CI = 0.29- 0.91, $p = 0.02$) less likely to have a poor TTR than those with no risk. Patients with moderate and high HAS-BLED scores were two and three times more likely to have a poor TTR (AOR = 1.68, 95% CI = 1.07–2.64, $p = 0.03$) and (AOR = 3.08, 95% CI = 1.17–8.09, $p = 0.02$), respectively, than patients with no risk. Additionally, patients with mechanical heart valves were twice as likely to have poor TTR (AOR = 2.11, 95% CI = 1.17–3.81 $p = 0.01$). The odds of poor TTR were reduced by 2% for every increase in the frequency of INR monitoring (AOR = 0.98, 95% CI = 0.97–0.99, $p = 0.002$) (Table 7).

Secondary outcomes

Eighty-nine (25.4%) bleeding events were reported in the UMC group, with the highest record of eight bleeding episodes in a single patient. Forty-nine bleeding episodes occurred in the different patients. The remaining bleeding episodes were reported more than once during the different patient visits. In the PLAC group, 29 (16.6%) bleeding episodes occurred; four and one episodes were recorded in two and three patients, respectively, and the remaining 18 were recorded in different patients. There were no differences in bleeding events between the groups ($p = 0.715$). All bleeding events were minor, including bleeding from the nose, gums, and

Table 7 Factors associated with poor TTR among patients receiving warfarin therapy

Variable	TTR ≥ 65%	TTR < 65%	COR (95%CI)	AOR (95%CI)	*P*-value
Treatment group					
UMC	111(21.1)	239(45.5)	1.00	1.00	**0.01***
PLAC	73(13.9)	102(19.4)	0.65(0.45,0.95)	0.57(0.36,0.88)	
Sex					
Female	132(25.1)	243(46.3)	1.00	1.00	0.79
Male	52(9.9)	98(18.7)	1.02(0.69,1.52)	0.95(0.62,1.44)	
Age in years					
18–30	32(6.1)	75(14.3)	1.00	1.00	
31–45	81(15.4)	150(28.6)	0.79(0.48,1.29)	0.79(0.47,1.32)	0.36
46–64	53(10.1)	82(15.6)	0.66(0.39,1.13)	0.57(0.32,1.02)	0.06
≥ 65	18(3.4)	34(6.5)	0.81(0.39,1.63)	0.45(0.19,1.03)	0.06
HAS-BLED risk scores					
No risk	65(12.4)	125(23.8)	1.00	1.00	
Low risk	46(8.8)	34(6.5)	0.38(0.23, 0.66)	0.51(0.29,0.91)	**0.02***
Moderate risk	65(12.4)	153(29.1)	1.22(0.81,1.86)	1.68(1.07,2.64)	**0.03***
High risk	8(1.5)	29(5.5)	1.89(0.82,4.36)	3.08(1.17,8.09)	**0.02***
Post-mechanical heart valves					
No	163(31.0)	278(53.0)	1.00	1.00	**0.01***
Yes	21(4.0)	63(12.0)	1.76(1.04,2.99)	2.11(1.17,3.81)	
Post PMTC valvotomy					
No	169(32.2)	329(62.7)	1.00	1.00	0.09
Yes	15(2.9)	12(2.3)	0.41(0.19,0.89)	0.49(0.22,1.13)	
INR monitoring interval			0.99(0.98,1.01)	0.98(0.97,0.99)	**0.002***

Table 8 Secondary outcomes among patients receiving warfarin compared between UMC and PLAC

Secondary outcomes	Total *n* (%)	UMC *n* (%)	PLAC *n* (%)	*p*-value
Bleeding episodes	118(22.5)	89(25.4)	29(16.6)	0.715
Thromboembolic episodes	23(4.4)	15(4.3)	8(4.6)	0.435
Emergency department visits	69(13.1)	64(18.3)	5(2.9)	0.003
Hospitalization	76(14.5)	62(17.7)	14(8.0)	0.469

teeth, bruising, and menstruation. Fifteen (4.3%) and eight (4.6%) thromboembolic events were recorded in the UMC and PLAC groups, respectively, with no significant difference between the groups ($p = 0.435$). All-cause emergency department visits were documented in 64 (18.3%) and five (2.9%) patients in the UMC and PLAC groups, respectively, with a statistically significant difference between the groups ($p = 0.003$) (Table 8).

Predictors of secondary outcomes

Negative binomial regression showed that the incidence of bleeding events decreased by 3% (IRR = 0.97, 95% CI = 0.96–0.99, $p < 0.001$) for every increase in INR monitoring frequency. The incidence of thromboembolic events increased by a factor of 15.13 (IRR = 15.13, 95% CI = 1.47–155.52, $p = 0.02$) among patients who had a high-risk CHA_2DS_2-VASc score compared to those with a moderate score. The incidence of all-emergency department visits was increased by a factor of 7.59 (IRR = 7.59, 95% CI = 2.68- 21.50, $p < 0.001$) in the UMC group compared to that in the PLAC group. All-emergency department visits were reduced by 69% (IRR = 0.31, 95% CI = 0.13–0.73, $p = 0.007$) in patients with a TTR < 65% compared to those with a TTR ≥ 65%. For every increase in the frequency of INR monitoring, the incidence of all-emergency department visits was reduced by 3% (IRR = 0.97, 95% CI = 0.95–0.99, $p < 0.001$). The incidence of hospitalization was reduced by 73% (IRR = 0.27, 95% CI = 0.10- 0.70, $p = 0.007$) in patients with a TTR < 65% compared with those with a TTR ≥ 65% (Table 9).

Discussion

This study aimed to compare the effectiveness of UMC and PLAC in terms of anticoagulation control and outcome in patients receiving warfarin. It also provides crucial insights into optimizing warfarin therapy in resource-limited healthcare settings by highlighting the significant role pharmacists can play in enhancing anticoagulation management. Moreover, we identified factors

Table 9 Poisson regression analysis of secondary outcomes among patients receiving warfarin therapy

	Bleeding episodes		Thromboembolic events		Emergency department visit		Hospitalization	
Variable	**IRR (95%CI)**	***p*-value**	**IRR (95%CI)**	***p*-value**	**IRR (95%CI)**	***p*-value**	**IRR (95%CI)**	***p*-value**
Patient group								
UMC	1.45(0.79,2.65)	0.22	0.84(0.26,2.68)	0.77	7.59(2.68,21.50)	**< 0.001***	1.75(0.79,3.87)	0.17
PLAC	1.00		1.00		1.00		1.00	
Sex								
Female	0.90(0.53,1.53)	0.69	0.55(0.21,1.45)	0.23	1.50(0.79,2.84)	0.21	0.82(0.43,1.57)	0.55
Male	1.00		1.00		1.00		1.00	
Age								
18–30	0.74(0.26,2.16)	0.58	0.85(0.13,5.53)	0.86	2.02(0.72,5.69)	0.19	1.31(0.39,4.39)	0.67
31–45	1.12(0.43,2.91)	0.82	1.07(0.21,5.46)	0.94	0.84(0.31,2.28)	0.73	1.00(0.33,3.02)	1.00
46–64	0.78(0.31,1.95)	0.59	0.69(0.13,3.66)	0.66	0.61(0.22,1.67)	0.34	0.51(0.17,1.56)	0.24
≥ 65	1.00		1.00		1.00		1.00	
Residence								
Addis Ababa	1.04(0.59,1.84)	0.89	1.25(0.41,3.84)	0.69	1.16(0.65,2.07)	0.62	1.57(0.77,3.17)	0.21
Out of Addis Ababa	1.00		1.00		1.00		1.00	
Presence of comorbidities								
No	1.65(0.56,4.87)	0.37	1.73(0.26,11.31)	0.57	0.69(0.22,2.25)	0.55	0.75(0.18,3.04)	0.68
Yes	1.00		1.00		1.00		1.00	
CHA_2DS_2-VASc Risk								
High risk	1.87(0.78,4.52)	0.16	15.13(1.47,155.52)	**0.02***	1.79(0.80,4.03)	0.15	2.22(0.80,6.14)	0.13
Low risk	1.59(0.67,3.77)	0.29	4.09(0.44,38.07)	0.22	0.38(0.14,1.08)	0.06	1.11(0.37,3.32)	0.85
Moderate risk	1.00		1.00		1.00		1.00	
HAS-BLED risk								
High risk	0.81(0.27,2.39)	0.70	0.14(0.01,1.93)	0.14	0.44(0.14,1.44)	0.18	0.63(0.17,2.24)	0.47
Low risk	0.69(0.27,1.77)	0.44	1.56(0.29,8.08)	0.59	2.27(0.79,6.53)	0.13	1.09(0.35,3.41)	0.88
Moderate risk	1.00		1.00		1.0		1.00	
Target INR range								
2–3	0.87(0.42,1.78)	0.69	0.86(0.25,3.01)	0.81	1.06(0.41,2.79)	0.90	0.87(0.35,2.17)	0.76
2.5–3.5	1.00		1.00		1.00		1.00	
Presence of warfarin drug interaction								
No	0.99(0.57,1.72)	0.97	0.69(0.24,2.04)	0.51	0.90(0.49,1.62)	0.73	0.92(0.45,1.86)	0.81
Yes	1.00		1.00		1.00		1.00	
Time in the therapeutic range								
< 65%	0.86(0.39,1.88)	0.71	0.35(0.08,1.53)	0.16	0.31(0.13,0.73)	**0.007***	0.27(0.10,0.70)	**0.007***
≥ 65	1.00		1.00		1.0		1.00	
Comorbidity score								
No	0.22(0.05,0.97)	0.05	0.38(0.02,6.33)	0.49	0.54(0.12,2.38)	0.41	0.33(0.05,2.11)	0.24
Mild	0.43(0.16,1.17)	0.09	0.81(0.12,5.58)	0.83	0.99(0.37,2.71)	0.99	0.70(0.21,2.38)	0.57
Moderate	0.63(0.24,1.63)	0.34	0.31(0.04,2.53)	0.28	0.93(0.35,2.45)	0.88	1.18(0.36,3.85)	0.78
Severe	1.00		1.00					
\ INR monitoring interval	0.97(0.96,0.99)	**< 0.001***	0.98(0.96,1.01)	0.17	0.97(0.95,0.99)	**< 0.001***	0.98(0.97,1.00)	0.06
Percentage of days in different INR ranges								
Time below range	1.02(0.99,1.04)	0.07	0.99(0.93,1.07)	0.99	0.99(0.90,1.01)	0.83	0.99(0.95,1.03)	0.55
Time therapeutic range	1.01(0.99,1.04)	0.33	0.98(0.91,1.05)	0.53	0.97(0.88,1.06)	0.48	0.97(0.93,1.02)	0.19
Time above range	1.01(0.99,1.02)	0.38	0.99(0.92,1.06)	0.75	0.99(0.90,1.09)	0.83	1.00(0.97,1.04)	0.88
Average weekly warfarin dose	0.99(0.98,1.01)	0.93	0.99(0.96,1.02)	0.54	0.99(0.98,1.01)	0.71	0.99(0.98,1.02)	0.82

associated with these outcomes (time in the therapeutic range and secondary outcomes, including bleeding, thromboembolic events, all-cause emergency department visits, and hospitalization). Although most patients in both groups were female and the UMC group experienced noticeably higher disease burdens, significant associations of sex and patient background differences with study outcomes were not found in our study.

In the present study, a significantly higher percentage of the median TTR was found in the PLAC group than in the UMC group ($p < 0.001$). This outcome aligns with previous studies demonstrating the superiority of PLAC over UMC in achieving a good TTR [9, 49, 56–58]. Moreover, a systematic review by Manzoor et al. [47] indicated that the majority of the included studies (83.0%) reported a statistically significant TTR in the pharmacist-managed group compared to routine medical care [47]. Another systematic review and meta-analysis also documented the superiority of PLAS over UMC in managing warfarin therapy based on observational studies, with a significantly higher TTR in the pharmacist-managed group [42, 59]. Furthermore, in this study, the proportion of patients who achieved optimal anticoagulation control (TTR ≥ 65%) was significantly higher in the PLAC group than in the UMC group (41.7% vs. 31.7%, $p < 0.002$), which is consistent with other reports that a higher proportion of patients in the pharmacist-led group reached the target anticoagulation physician-led clinic [9, 58]. These findings emphasize the potential of integrating pharmacist-led services into AMS, indicating a novel approach to improve anticoagulation control and outcomes in patients receiving warfarin therapy [60]. By comparing UMC with PLAS, the current study provides convincing evidence of the tangible benefits of pharmacist involvement in managing patients taking warfarin, offering a significant contribution to the evolving discourse on enhancing chronic disease management in limited-resource settings such as Ethiopia.

The effectiveness of PLAS not only emphasizes the potential of specialized anticoagulation services within the African healthcare landscape [50], but also aligns with global trends of advocating for enhanced warfarin therapy management [42]. Despite facing multifaceted challenges, including resource constraints, the successful implementation of PLAS in Ethiopia reflects the importance of providing quality AMS to optimize anticoagulation control and outcomes that resonate with a broader global shift towards the incorporation of pharmacist-led interventions in chronic disease management. This approach has been increasingly recognized for its capacity to provide personalized patient education, ensure consistent monitoring, and facilitate precise dosage adjustments, including the management of complex therapies, such as warfarin [61]. The difference between the outcomes of this study and the typical lower TTRs reported in African countries [32] further emphasizes the unique impact of PLAS in resource-limited settings. This finding suggests that PLAS may expand beyond high-income countries and offer a viable solution for improving anticoagulation management. This study noted more frequent INR monitoring in the PLAC group (40.08 median days) than in the UMC group (51.54 median days) ($p < 0.001$), which is an integral component for achieving better anticoagulation control in patients receiving warfarin therapy. Existing studies have shown the necessity for regular monitoring and timely dosage adjustments to maintain patients within their therapeutic range [62–64], which might have contributed to the observed improvement in TTR within the PLAC group in our study.

In the present study, the incidence of all the secondary outcomes was higher in the UMC group. However, a statistically significant difference was observed only in all-cause emergency visits ($p = 0.003$) between the two groups, and Entezari-Maleki et al. (2016) also reported fewer emergency department visits in the pharmacist-led group ($p < 0\,0.0001$) [59]. The absence of significant differences between pharmacist-led interventions and other anticoagulation models in the incidence of bleeding and thromboembolic events has also been reported in two Chinese studies [56, 65]. However, other observational studies and systematic reviews have reported a significantly lower incidence of bleeding and thromboembolic events in pharmacist-warfarin therapy management [47, 59]. The observed lower incidence of emergency department visits among patients in the PLAC group in this study may highlight the proactive nature of PLAS in mitigating complications that would typically necessitate emergency intervention.

We identified several factors associated with poor TTR and incidence of secondary outcomes among patients receiving warfarin therapy. Multivariate regression analysis showed that intervention (PLAC) (AOR = 0.57, 95% CI = 0.36–0.88, $p = 0.01$) was an independent protective factor for poor anticoagulation quality (TTR < 65%). This finding aligns with previous studies conducted in China [65] and elsewhere [49, 66], which reported PLAS as an important intervention to reduce poor TTR in patients receiving anticoagulation therapy. The analysis also highlighted the relationship between an increased HAS-BLED score and poor TTR, emphasizing the vital need to evaluate the bleeding risk in anticoagulation management planning. This principle is widely acknowledged in international anticoagulation management guidelines, which advocate a balanced approach that considers both the therapeutic

benefits and potential bleeding risks associated with warfarin therapy [54].

In the current study, we also found that the odds of poor TTR decreased with every increase in the INR monitoring frequency. Qiu et al. [65] reported this effect in other ways, that is, increasing the average interval of INR monitoring as an independent risk factor for poor anticoagulation quality [65]. However, Papala et al. (2021) showed that an increase in the INR testing interval length did not significantly decrease the overall mean clinical TTR [67]. Frequent INR monitoring with appropriate dose adjustments may contribute to better optimized anticoagulation control of PLAC. Moreover, patients with mechanical heart valves were more likely to have a poor TTR (AOR, 1.76; $p = 0.01$). This signifies the need for intensified monitoring with potentially more aggressive anticoagulation measures in these patient groups by implementing individualized care strategies and addressing the specific needs and higher risk of thromboembolic complications in patients with mechanical heart valves [68].

One of the findings of our study was the association between frequent INR monitoring and a notable reduction in the incidence of bleeding events and emergency department visits. This observation highlights the indispensable role of close monitoring in optimizing anticoagulation outcomes and reducing the incidence of warfarin-related complications. More frequent INR monitoring should be performed to improve patient safety and therapeutic efficacy, more-frequent INR monitoring should be performed [64]. Patients with higher CHA2DS2-VASc scores were at increased risk of thromboembolic events. This is consistent with a previous study that demonstrated that the CHA_2DS_2-VASc score is associated with thromboembolism [69].

The implications of this study on the management of warfarin therapy using PLAS in Ethiopia are profound and multifaceted. This supports the pivotal integration of pharmacists as essential contributors to the management of complex medication therapies, including warfarin, and highlights the necessity for health policymakers to advocate for the expansion of PLAS-type models in Ethiopian health systems. This approach is instrumental in enhancing the clinical outcomes of patients taking warfarin, particularly in resource-constrained settings such as Ethiopia, where warfarin is the drug of choice for the prevention and treatment of thrombosis in many patients. The success of PLAS in improving TTR and reducing complications related to warfarin therapy highlights the importance of incorporating pharmacists into multidisciplinary care teams, emphasizing their expertise in medication management and patient education. The potential benefits of such services within the Ethiopian healthcare system emphasize the universal applicability and efficacy of pharmacist-led care models in enhancing the management of warfarin therapy, and by extension, chronic disease management.

Strengths and limitations of the study

This is the first study to evaluate the effects of PLAS on anticoagulation control and outcomes by comparing PLAS with UMC in Ethiopian patients undergoing warfarin therapy. The present study was unique in that it used an anticoagulation management protocol that consisted of a package of measures, including a warfarin-dosing algorithm, adherence support, and patient education regarding many aspects of warfarin therapy. This finding may serve as input for expanding PLAS to other Ethiopian health facilities and developing countries with similar health systems. However, it is essential to acknowledge the limitations of the present study. First, the execution of the study in a single healthcare center may limit its generalizability. This study was implemented in a hospital setting in Addis Ababa, Ethiopia; hence, the feasibility and effectiveness of PLAS may vary in other healthcare settings with different resources, patient populations, and organizational structures, thereby limiting the generalizability of the study findings. There could be inconsistencies among clinical pharmacists and physicians in their practices based on their educational backgrounds, which could affect the consistency and effectiveness of the intervention and require further consideration. This study did not compare the differences between the two anticoagulation models in terms of patients' knowledge, satisfaction, and adherence to warfarin therapy, and we did not evaluate the economic implications of PLAS compared to UMC.

Conclusion

This study concluded that patients in the PLAC group had a significantly higher median TTR than those in the UMC group did. A higher proportion of patients in the PLAC group achieved optimal TTR than those in the UMC group. The likelihood of poor TTR was lower in the PLAC group than in the UMC group. There were no statistically significant differences in the secondary outcomes between the groups, except for all-cause emergency department visits. This study substantially contributes to the argument that PLAS represents a crucial development in the management of patients taking warfarin to improve clinical outcomes and healthcare efficiency. A cost-effectiveness analysis is essential for evaluating the economic feasibility of incorporating PLAS into the Ethiopian healthcare system.

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Authors' contributions
TAT conceptualized and designed the study, conducted the study, performed statistical analyses, interpreted the data, and drafted the initial version of the manuscript. AG, DY, LC, and TGF contributed to the methodological design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, and the final approval of the submitted version. All the authors critically reviewed the article and approved the final version of the manuscript for publication.

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Availability of data and materials
Data is available upon request to the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by Ethical Review Committee of the School of Pharmacy (ERB/SOP/454/2022) and Institutional Review Board (096/22/SoP) of the College of Health Sciences, Addis Ababa University, Ethiopia. Written permission to access the clinical data of the study participants was obtained from the outpatient department of the hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

Appendices

Appendix 1: Quality assessment of the included studies based on modified JBI's critical appraisal for cross-sectional studies

Author ID	**Joanna Briggs Institute's critical appraisal checklist**									
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Total**	**%**
Salaheldin 2019	No	No	No	No	No	No	Yes	No	1	12.5
Karuri 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	100
Sana 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	100
Lauren 2019	Yes	Yes	Yes	Yes	No	No	Yes	Yes	6	75
Sonuga 2016	Yes	Yes	Yes	Yes	No	No	Yes	Yes	6	75
Fenta 2017	Yes	No	Yes	Yes	No	No	Yes	Yes	5	62.5
Semakula2020	No	No	No	No	No	No	Yes	No	1	12.5
Prinsloo 2021	Yes	No	No	Yes	Yes	Yes	Yes	Yes	6	75
Ahmed 2017	Yes	No	Yes	Yes	No	No	No	No	5	62.5
Botsile 2020	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7	87.5
Masresha 2021	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7	87.5
Kizito 2016	Yes	Yes	No	No	Yes	Yes	No	Yes	5	62.5
Yimer 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	100
Sadhabiriss 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	100
Ntlokotsi 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	100
Rejeb 2019	Yes	Yes	No	Yes	No	No	Yes	Yes	6	75

Mwita 2017	No	Yes	Yes	No	Yes	Yes	Yes	Yes	7	87.5
Ebrahim 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	100

[Q1-8, JBI's Critical Appraisal Checklist for Analytical Cross-Sectional studies [Q1: Were the criteria for inclusion in the sample clearly defined? Q2: Were the study subjects and the setting described in detail? Q3: Was the exposure measured in a valid and reliable way? Q4: Were objective, standard criteria used for measurement of the condition? Q5: Were confounding factors identified? Q6: Were strategies to deal with confounding factors stated? Q7: Were the outcomes measured in a valid and reliable way? Q8: Was an appropriate statistical analysis used?]

Addis Ababa University

College of Health Sciences School of Pharmacy

Appendix 2: Study Information Sheet for Qualitative Study (Key Informants Interview with Patients) ([English Version]

Need of establishing pharmacist-led anticoagulation clinic (PLAC) at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia

Introduction

You are invited to participate in a postgraduate research project conducted by Addis Ababa University, Ethiopia, as part of a PhD requirement in Social and Administrative Pharmacy. Participation is entirely voluntary and will not affect your current treatment. It is essential to understand the research purpose and participation details before making a decision. Please read the information carefully and feel free to discuss it with others or ask for clarification.

Aims of the research: This study aims to explore patients' experiences and perceptions regarding anticoagulation management services at Tikur Anbessa Specialized Hospital and their views on the need to establish a pharmacist-led anticoagulation clinic (PLAC).

What participation is involved?

If you agree to participate, you will be interviewed one-on-one about your experiences and perceptions regarding anticoagulation management service at Tikur Anbessa Specialized Hospital and your view on the need to establish a pharmacist-led anticoagulation clinic (PLAC) in the hospital. The interview will last approximately 40 minutes.

Risks and discomforts: There are no expected risks associated with participating in this study. You can decline to answer any question or stop the interview if you feel uncomfortable at any time.

Possible benefits: This study aims to improve anticoagulation management services at the Tikur Anbessa Specialized Hospital. Upon completion, the findings will be shared with participants either through a meeting or through a leaflet.

Confidentiality: Your participation will remain confidential. Personal data will not include your name or identifying information and will be stored securely. Only the principal researcher will know the source of the information, and all data will be discarded after the analysis.

Voluntary participation and withdrawal: Participation in this study is voluntary. You can withdraw from the study at any time, without the need to provide a reason.

Contacts information:

- Principal Investigator: Tamrat Assefa: +251912023382
- Supervisos: Prof. Teferi Gedif, Dr. Legese Chelkeba Dr. Dejuma Yadeta and Dr. Amha Gebremedhin.
- Institutional Review Board, College of Health Sciences, Addis, Addis Ababa University Mobile number: +251947339272; email: chs.irb@aau.edu.et

Appendix 3: Written consent form for qualitative study (English Version)

Written consent form for the data collection on 'Need of establishing pharmacist-led anticoagulation clinic (PLAC) at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia'

Greetings,

My name is _____. I am working as a data collector with a team carrying out a study on the topic "**Need of establishing pharmacist-led anticoagulation clinic (PLAC) at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia**" at the School of Pharmacy, College of Health Sciences, Addis Ababa University. In this study, participants will be asked about their patients' experiences and perceptions regarding anticoagulation management services at Tikur Anbessa Specialized Hospital and their views on the need to establish a pharmacist-led anticoagulation clinic (PLAC). Your participation in this study is voluntary, and you can refuse to participate or you are free to withdraw yourself from the study at any time. Participation in this study will not affect the services that you receive from the hospital. The information you provide will be handled with strict confidentiality and at no time will you be required to identify yourself by name. The information you provide is important to improve anticoagulation management services in hospitals. You may skip any questions you do not want to answer. The entire process of this questionnaire took a maximum of 40 minutes.

Would you be volunteer to participate in the study? □ Yes □ No

If yes, the study participant signature _____ Date _____

Signature _____ Date _____

Investigator Name _____

Signature _____ Date _____

If you have any enquey regarding this study, please do not hesitate to contact:

Principal Investigator: Tamrat Assefa Department Social and Administrative Pharmacy, Addis Ababa University Mobile No: 0912023382 Email: tamrat.assefa@aaau.edu.et	Advisors: Prof. Teferi Gedif Dr. Legese Chelkeba Dr. Dejuma Yadeta Dr. Amha Gebremedhin

Appendix 4: Guide for patient interview on the ‘need and benefit of establishing pharmacist-led anticoagulation clinic at TASH (English version)

1. Patient's age: _____ Patient's sex: _____
2. Do you feel that the advice you receive about your anticlot medication (warfarin) is sufficient?
   - If your answer is no, what do you think is the reason?
3. Do you always get the prescribed warfarin from the hospital?
   - If not, where do you get it? Is there a price difference compared with what you get at this hospital?
4. Do you always get ordered laboratory tests (INR) at the hospital?
   - If not, where do you go for it? Is there a price difference compared with this hospital?
5. Please share your overall opinion regarding the laboratory testing services related to anticlot treatment.
6. Describe any issues you face when you come to receive anticoagulation management service for your appointment (e.g., delays, lost cards,).
7. Is there any area where the current anticoagulation management service needs to be improved
8. Overall, how satisfied are you with the anticoagulation management services provided to you?
   a) Very satisfied
   b) Satisfied
   c) Somewhat satisfied
   d) Not satisfied at all
9. If you have, any other comments to add to our point of discussion you can raise them.

አዲስ አበባ ዩኒቨርሲቲ፣ ጤና ሳይንስ ኮሌጅ

ፋርማሲ ትምህርት ቤት

Appendix 5: Amharic version of the Written Consent Form for interviewing patients (Qualitative study)

አባሪ፡ ተሳታፊዎች በጥናቱ ላይ ለመሳተፍ ፍቃደኝነታቸዉን ይሚገፁበት ቅፅ

Research Title: on 'Need of establishing pharmacist–led anticoagulation clinic (PLAC) at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia'

ጤና ይስጥልኝ _____ እባላለሁ። በአዲስ አበባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅ ፋርማሲ ትምህርት ቤት የፒኤችዲ ጥናት: በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል በፋርማሲስት የሚመራ የደም ማቅጠኛ ክሊኒክ እንደቋቋም ለማድረግ አስፈላጊነት ላይ በመረጃ ሰብሳቢነት እየሰራሁ ነው። በዚህ ጥናት ተሳታፊዎች በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል የደም መቅጠኛ አገልግሎትን በተመለከተ ስላላቸው ልምድ እና ግንዛቤ እና በፋርማሲስት የሚመራ የደም መቅጠኛ ክሊኒክ መመስረት አስፈላጊነት ላይ ያላቸውን አስተያየት ይጠይቃሉ። በዚህ ጥናት ውስጥ ያለዎት ተሳትፎ ሙሉ በሙሉ በፈቃደኝነት ላይ የተመሰረተ ሲሆን፤ በዚህ ጥናት መሳተፍም ሆነ አለመሳተፍ በሆስፒታሉ ዉስጥ በሚየገኙት አገልግሎት ላይ ምንም አይነት ተፅእኖ የማይኖረዉ ሲሆን ቃለመጠይቁን ማቁረጥ ወይም ጥያቄዎችን አለመመለስ ይችላሉ:: በጥናቱ ዉስጥ የሚሰጡአቸዉ መልሶች ሙሉ በሙሉ በሚስጥር የሚጠበቁ ሲሆን የእርሰዎ ስም በማንኛዉም መልኩ በጥናቱ ዉስጥ አይገለፅም:: የሚሰጡት መረጃ በሆስፒታሉ የደም ማቅጠኛ አገልግሎትን ለማሻሻል ይጠቅማል:: የዚህ መጠይቅ አጠቃላይ ሂደት ቢበዛ 40 ደቂቃዎችን ይወስዳል።

በጥናቱ ለመሳተፍ ፈቃደኛ ነዎት ☐ አዎ ☐ አይደለሁም

አዎ ከሆነ፣ የጥናት ተሳታፊ ፊርማ _____ ቀን _____

ዋና ተመራማሪ፡ ታምራት አሰፋ

ስልክ ቁጥር፡ 0912023382

E-mail: tamrat.assefa@aau.edu.et

አማካሪዎች፡ ፕ/ር ተፈሪ ገድፍ

ዶ/ር ለገስ ጨልቀባ

ዶ/ር ደጁማ ያደታ

ዶ/ር አመሃ ገብረመድን

Appendix 6: Guide for patient interview on the ‘need of establishing pharmacist–led anticoagulation clinic at TASH (Amharic version)

1. የታካሚው ዕድሜ----------የታካሚው ፆታ-------

2. ስለ ሚወስዱት ደም መቅጠኛ መድሀኒት(ዋርፋሪን) የሚያገኙት ምክር በቂ ነው ብለው ያስባሉ?

- መልስዎ አዎ ካልሆነ፣ ምክንያቱ ምን ይመስልዎታል?

3. የሚታዘዝልዎትን መድሃኒት((ዋርፋሪን) ሁልጊዜ ከሆስፒታሉ ያገኛሉ ወይ?

- ካላገኙ ከየትነው የሚወስዱት፤ እዚህ ሆስፒታል ከሚገዙበት ዋጋ ጋር ልዩነት አለዉ?

4. በየጊዜው የሚታዘዝልዎትን የላቦራቶሪ ምርመራ(INR) ብሆስፒታሉ ውስጥ ያገኛሉ?

ካላገኙ የት ነው የሚያሰሩት፤ እዚህ ሆስፒታል ከሚያሰሩበት ዋጋ ጋር ልዩነት አለዉ?

5. በአጠቃላይ የደም መቅጠኛ ላቦራቶሪ ምርመራ ጋር ተያይዞ ያለዎት አስተያየት ቢነግሩ፡፡

6. የደም መቅጠኛ አገልግሎት ለማግኘት በቀጠሮ ቀን ሲመጡ ያሉትን ችግሮች(ወረፋ፣ ካርድ መጥፋት ወዘተ.) እንዴት ይገልፁታል?

7. የደም መቅጠኛ አገልግሎት ለመሻሻል ያለበት ነገር ካለ ይግለጹልን

8. በአጠቃላይ በሚሰጠዎ የደም መቅጠኛ አገልግሎት ምን ያህል እረክተዋል?

ሀ)በደንብ እረክቼያለሁ

ለ) እረክቼያለሁ

ሐ) በተወሰነ መልኩ እረክቼያለሁ

መ) ምንም አልረካሁም

9. በምንወያይበት ርእስ ላይ ማንኛውም ነገር ለመጨመር ከፈለጉ ማንሳት ይችላሉ፡፡

Appendix 7: Written consent form for interviewing healthcare professionals (Qualitative study)

Written consent form for healthcare professinals on 'Need of establishing pharmacist–led anticoagulation clinic (PLAC) at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia'

The main aim of this key informant interview is to support the project 'Need of assessment of Establishment of pharmacist-led anticoagulation Anticoagulation Clinic in Tikur Anbessa Specialized Hospital (TASH), which is being undertaken by Tamrat Assefa (PhD student in Social and Administrative Pharmacy) at the Department of Social and Administrative Pharmacy, School of Pharmacy, Addis Ababa University. To establish a clinic in the hospital, it is crucial to have information on the current service status, the gaps/challenges that may exist, how to improve it, and ways to improve overall anticoagulation management services in hospitals. The information you provide is very important, and therefore, kindly be frank in your responses. I assure you that the information you provide will be handled with strict confidentiality, and at no time will you be required to identify yourself by name. To participate in this study, you must have been involved in the management of patients requiring anticoagulation therapy. The entire interview process will take a maximum of 40 minutes.

Would you be volunteer to participate in the study? □ Yes □ No

If yes, the study participant signature _____ Date _____

Signature _____ Date _____

Investigator Name _____

Signature _____ Date _____

If you any enquey regarding this study, please do not hesitate to contact:

Principal Investigator: Tamrat Assefa Department of Social and Administrative Pharmacy, School of Pharmacy, Addis Ababa University Mobile No: 0912023382 Email: tamrat.assefa@aaau.edu.et	Advisors: Prof. Teferi Gedif Dr. Legese Chelkeba Dr. Dejuma Yadeta Dr. Amha Gebremedhin

Appendix 8: Key informant interview guide with healthcare professionals (Qualitative study)

I) Socio-demographic data

1. Age ---------- years

2. Sex: □ Male □Female

3. Profession/Specialty/Position

□ Internist	□ Hematologist	□ Head of Pharmacy
□ Adult cardiologist	□ Pulmonologist	□Head of Lab
□ Cardiothoracic surgeon	□ Neurologist	
□ Orthopedic Surgeon	□ Emergency Medicine Specialist	
□ Pediatric cardiologist	□ Oncologist	
□ Gynecologists and Obstetrician		

4. Year of experience in managing patients who need anticoagulation:

a) <2 years b) 2-5 years c) >5-10 years d) >10 years

5. Do you think the current set-up of your working area in the hospital is suitable for providing appropriate anticoagulation management services (AMS)?

□ If yes, explain why it is a comfortable setup.

□ If not, explain, what is missing.

II. Practice of anticoagulant Management service

1. Do your clinic/unit/ward have the following functional protocols? □Yes. □ No

Please circle choices all that apply to your clinic/ward.

a. Standardized warfarin initiation dosing protocol
b. Standardized warfarin maintenance dosing protocol
c. Indication of warfarin/anticoagulant with target INR and duration of anticoagulation
d. Frequency of INR monitoring for both new and stable patient on warfarin
e. Risk stratification for VTE development Assessment
f. Protocol on VTE prophylaxis and treatment
g. Risk stratification for Bleeding Assessment
h. Contraindications to warfarin and other anticoagulants therapy
i. List of drugs interact with warfarin and their management

j. Warfarin reversal protocol for elevated INR with without bleeding

k. Patients education on anticoagulation protocol

l. Anticoagulation management during pre and post operative (any surgical procedures)

m. Other (Specify)_____

If not, what are the reasons for not having important anticoagulation specific protocols to your unit/clinic in the hospital?

2. What are the main challenges of anticoagulation management services in this hospital, particularly in your clinic/ward?

3. What are the solutions you suggest for solving the above challenges/service gaps?

4. How do you describe the regular availability of:

a. INR testing
b. Anticoagulants (both warfarin and parenteral)
c. Waiting time for INR test results
d. Reliability of INR values:
e. Regular patient follow up and appointment

5. In general, how do you describe the quality of anticoagulation management service at this hospital?

6. If apharmacist-led anticoagulation clinic is established in this hospital, what do you think its advantageous for increasing patient safety and improving the quality of anticoagulation therapy in the hospital?

7. How do you describe the need of working together (with the pharmacy team) in the clinic? Will your unit assign physicians and nurses to this teamwork if a need arises?

8. What do you think the involvement of clinical pharmacists in anticoagulation clinic in terms of their contribution to improve/solve the current AMS challenges in the hospital?

9. If you have any, other comments to add regarding our point of discussion.

Appendix 9: Key informant interview guide for in-depth interview with the head of pharmacy Department of TASH (qualitative study)

1. Are anticoagulants at hospital pharmacy regularly available in the required quantity and in the strength/dose rangse that are easy for patients to take?
    - If no, why?
2. How do you describe the effects of anticoagulants drugs shortages on patient treatment outcomes?
3. How do you describe the quality of patient counseling on warfarin therapy in outpatient pharmacies of hospital in terms of informing patients about the name and dose of warfarin, its indication, when to take warfarin, warfarin-foods/drugs/traditional medications interaction, side effects of warfarin, labeling and availability of dispensing aid tools, and so on?
    - If counseling is not enough regarding warfarin therapy what are the reasons behind this?
4. Do pharmacy department work with different units that deliver anticoagulation management services to improve the quality of the service in the hospital?
    - If yes, what are the roles of pharmacy professional in the team?
    - If no, why? Are there any efforts by the department to work with these units?
5. What is the plan of the pharmacy department to improve the quality of the current warfarin therapy practice in hospital?
6. If in the hospital pharmacist-led anticoagulation clinic is established, what benefits do you think for patients, pharmacy professionals and the hospital?
7. Do hospital pharmacy department allow the pharmacists to work in the clinic?
8. How do you describe the quality of anticoagulation management services in the hospital?
9. Is there anything more you would like to add regarding our points of discussion?

Appendix 10: Key Informant Interview Guide for In-depth Interview with Head of Laboratory (Qualitative Study)

1. How do you describe about INR testing in this hospital?
2. Does the hospital consistently have INR testing machines, reagents, and other necessary supplies available?
   - If not, how do you describe the impact on patient satisfaction?
3. What are the current practices regarding the availability, affordability and waiting time for INR test?
4. How do you perceive the reliability of the test results and their effects on patient treatment?
5. What would you suggest to improve the quality of INR testing?
6. What do you think the establishment of anticoagulation clinic will add to the quality of INR testing?
7. Is there anything you would like to add to our discussion?

Addis Ababa University

College of Health Sciences School of Pharmacy

Appendix 11: Study information sheet for participants to involve in knowledge, adherence, and satisfaction with warfarin therapy

Knowledge, Adherence and Satisfaction among Ambulatory Patients Receiving Warfarin at Tikur Anbessa Specialized Hospital, Ethiopia

We would like to invite you to participate in this original postgraduate research project. You should only participate if you want; choosing not to participate will not disadvantage you in any way and will not be connected to your current treatment. Before you decide whether you want to participate, you must understand why the research is being conducted and what participation will involve. Please take time to read the following information carefully and discuss it with others: ask us if there is anything that is unclear or if you would like more information. This study is conducted as a PhD requirement in Social and Administrative Pharmacy at the Department of Social and Administrative Pharmacy, Addis Ababa University, Ethiopia.

Aims of the research/description of the study: This study aimed to assess the patients' knowledge, adherence, and satisfaction with warfarin therapy among those attending cardiac and hematology clinics (CHCs) of Tikur Anbessa Specialized Hospital (TASH).

What would happen if you agreed to participate?

You will also be asked a few questions in a one-to-one interview about your knowledge of warfarin therapy, adherence to warfarin therapy, and satisfaction with anticoagulation management. The interviews will be conducted in a private room in the outpatient department of the Tikur Anbessa Specialized Hospital. The interview will last approximately 40 minutes.

Risks and Discomforts of being in the study: We did not expect any risks to be associated with this study. However, if there is any unanticipated harm to patients, they will be linked to consultant cardiologists and hematologists. If you are not comfortable participating in the study or answering some questions, you are not obliged to do so. If you are distressed during an interview, it can be stopped.

Possible benefits: We hope that the information obtained will help improve the anticoagulation management service provided at the outpatient department of Tikur Anbessa Specialized

Hospital. After completion of the study, the findings will be shared with you, either by inviting you to the meeting or by giving you a leaflet.

Confidentiality: If you participated in this study, we will make sure that the data collected does not include your name or identifying information. It is kept on a locked cupboard and/or closed using a password on a computer. Once the collected data are analyzed, they will be discarded. Only principal researcher knows that the information belonged to you.

Voluntary participation or withdrawal from the study: It is up to you to decide whether to participate. If you decide to participate, you will be free to withdraw at any time without providing a reason.

Contacts:

- Main researcher: Tamrat Assefa under the supervision of Prof. Teferi Gedif, Dr. Legese Chelkeba Dr. Dejuma Yadeta and Dr. Amha Gebremedhin.
- The principal investigator can be contacted at:+251912023382.
- If this study has harmed you in any way, you can contact the Institutional Review Board of the College of Health Science Addis Ababa University using the details below for further advice and information.
- Institutional Review Board, College of Health Sciences, Addis, Addis Ababa University Mobile number: +251947339272; email: chs.irb@aau.edu.et

Addis Ababa University

College of Health Sciences School of Pharmacy

Appendix 12: Written consent form for Interview based cross-sectional study (English Version)

Written Consent Form for data collection on Knowledge, Adherence and Satisfaction among Ambulatory Patients Receiving Warfarin at Tikur Anbessa Specialized Hospital, Ethiopia

Greetings,

My name is _____. I am working as a data collector with a team carrying out a PhD study on the topic "Pharmacist-Led Anticoagulation Services and Patient Knowledge, Adherence, and Satisfaction with Warfarin Therapy" at the School of Pharmacy, College of Health Sciences, Addis Ababa University. In this study, participants will be asked about their knowledge of the anticoagulation therapy (warfarin) they are receiving, adherence to warfarin therapy, and satisfaction with anticoagulation treatment. Your participation in this study is voluntary, and you can refuse to participate or you are free to withdraw yourself from the study at any time. Participation in this study will not affect the services that you receive from the hospital. The information you provide will be handled with strict confidentiality and at no time will you be required to identify yourself by name. The information you provide is important to improve anticoagulation management services in hospitals. You may skip any questions you do not want to answer. The entire process of this questionnaire took a maximum of 40 minutes.

Would you be volunteer to participate in the study? □ Yes □ No

If yes, the study participant signature _____ Date _____.

Principal Investigator: Tamrat Assefa Mobile No: 0912023382 Email: tamrat.assefa@aaau.edu.et	Advisors: Prof. Teferi Gedif Dr. Legese Chelkeba Dr. Dejuma Yadeta Dr. Amha Gebremedhin

Appendix 13: Data collection tool collecting sociodemographic characteristics of study participants

SN	**Sociodemographic characteristics**			
1	Patient I-Care Number: _____ Phone No: _____			
2	Sex: ☐Male	☐Female		
3	Age: _____years			
4	Marital status	☐ Single ☐ Married	☐ Divorced ☐ Separated	☐ Widowed
5	Religion	☐ Orthodox Christian ☐ Catholic	☐ Muslim ☐ Others (Specify)	☐Protestant
6	Highest educational status	☐ Unable to read and write ☐ Able to read and write	☐ Primary school (Grade 1-8) ☐Secondary school (Grade 9-12)	☐ Certificate/ Diploma ☐ Degree and above
7	Place of residence	☐ Addis Ababa	☐ Out of Addis Ababa	
8	Monthly family income (in ETB**)**	☐ ------Birr	☐ No income	
9	Employment status	☐Employed (paid work) ☐ Self-employed	☐ Housewife ☐ Student	☐ Retired Not working
10	With whom do you live?	☐ Family	☐ Alone	
11	Social drug use	Do you drink Alcohol?	Do you smoke cigarette?	Do you chew chat?
		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
12	Medical service payment method:	☐Free ☐Out of pocket	☐Insurance	☐ Other
13	Duration since on warfarin	---------- (Write in years or months)		

Appendix 14: Data collection tool for oral anticoagulation knowledge assessment in patients receiving warfarin therapy at the TASH

Anticoagulation knowledge assessment Questionnaires

1. What is the use of warfarin?

A. Lower hear rate

B. Thinning the blood

C. Thickening the blood

D. I don't know its use

2. For how long do you need to take warfarin once it is started?

A. Six months

B. One year

C. Lifelong

D. It depends on each person's indication

3. Which of the following food items would interfere with your warfarin?

A. Banana

B. Cabbage

C. Carrot

D. Tomato

4. The best time of day for you to take your warfarin is—

A. At lunchtime

B. In the evening

C. The morning before breakfast

D. Any time of day when you remember

5. While out with friends for dinner, you have just finished your third glass of wine. This amount of alcohol consumed in a single evening will:

A. Cause a decrease in your warfarin effect

B. Cause an increase in your warfarin effect

C. Does not affect you or your warfarin dose in any way

D. Make you sick when taking warfarin medication

6. On warfarin, you

A. Should not eat green leafy vegetables

B. Can eat green leafy vegetables once a month

C. Can eat as many green leafy vegetables as you would like whenever you would like.

D. Can eat green leafy vegetables but needs to eat the same amount regularly every week.

7. You just remember that you forgot to take your evening warfarin dose the previous night. You would—

A. Skip the dose of warfarin you missed and take the current dose

B. Take the missed warfarin dose right now

C. Wait and take two doses of warfarin this evening

D. Take half of the missed dose of warfarin right now

8. Which of the following activities is risky when taking warfarin?

A. Playing football because you can hit your head

B. Taking a bath because soap interacts with warfarin

C. Playing cards because using your hands a lot will cause a blood clot

D. Walking a lot because exercise is not good for you while taking warfarin.

9. On warfarin, which of the following would you go directly to the emergency room?

A. Small bruises

B. Your appetite dramatically increases

C. Nosebleed, which will not stop bleeding

D. Gums that bleed for a few seconds after brushing teeth

10. If you ran out of your warfarin prescription, you would—

A. Borrow warfarin from a friend, as long as it is the same dose as yours

B. Call and ask for refills for that day so you do not miss a dose of warfarin

C. Wait until your next appointment that is just a few days away to get a new prescription

D. Do nothing because you have taken warfarin long enough; otherwise, there would be more refills on your prescription.

11. The results of the PT/INR test indicate that

A. How thick or thin is your blood while taking warfarin

B. How well do your kidneys work after taking warfarin

C. What is your average blood sugar level after taking warfarin?

D. How much alcohol have you consumed since you started taking warfarin?

12. When making a dental appointment while taking warfarin, what you need to remember?

A. Cannot have procedures done on your teeth while taking warfarin

B. Must tell your dentist you are taking warfarin in advance of having any procedure done

C. Can have procedures done, and there is no need to tell the dentist about warfarin.

D. Can the dental procedure be performed if you arrive at your dental appointment. Tell the dentist you are taking warfarin

13. What is your target INR range?

A. 2-3

B. 2.5-3.5

C. I don't know

14. Your neighbor brings over this great ''all natural'' herbal supplement that she bought from a traditional healer. She swears that this helps all her aches and pains, and recommends that you take it when you ache. Your decision is to?

A. Take her advice, realizing that you could use this herbal supplement

B. Start taking the herbal supplement and tell your pharmacist at the next office visit

C. Ask your pharmacist/doctor if the herbal supplement interacts with your medication before you take it.

D. Avoid taking herbal supplements altogether because all medications interact with warfarin

15. Which of the following may have a significant effect on how your warfarin works?

A. Changes in your mood.

B. Changes in sleep habits.

C. How much water your drink.

D. Using over the counter medications

16. Occasionally eating a large amount of leafy greens vegetables while taking warfarin can:

A. increase your risk of bleeding from warfarin.

B. reduce the effectiveness of the warfarin.

C. cause upset stomach and vomiting.

D. reduce your risk of having a blood clot

17. If your INR value is above the “goal range”:

A. you are at an increased risk of having a clot.

B. you are more likely to have drowsiness and fatigue from warfarin.

C. you are at an increased risk of bleeding.

D. you are less likely to experience side effects from warfarin

18. When is it safe to take a medication that interacts with warfarin?

A. If you take the warfarin in the morning and the interacting medication at night.

B. If your healthcare provide is aware of the interaction and checks your INR regularly.

C. If you take your warfarin every other day.

D. It is never safe to take a medication that interacts with warfarin.

Appendix 15: Adherence to oral anticoagulation treatment (warfarin) assessment using the Morisky Green Levine Scale (MGLS)

Section I: Morisky Green Levine Scale (MGLS) questions

SN	Items	Yes	No
1	Do you ever forget to take your warfarin?		
2	Are you careless at times about taking your medicine?		
3	When you feel better do you sometimes stop taking your medicine (warfarin)?		
4	Sometimes of you feel worse when you take the medicine (warfarin), do you stop taking it?		

Section II: Reasons for poor medication Adherence

Tick all boxes that apply to each patient

Forgetfulness	□	Feeling Worsening when taking the drug	□
Fear of drug adverse events	□	I am taking many drugs which create confusion	□
Inadequate instruction on how to take	□	Cost of medication too expensive	□
I can't get the drug		Disbelief in drug effectiveness	
Difficulty during administration	□	Feeling better	□
Due to work load/busy		Other (Please specify) ----------	
Finished the medicine before my appointement	□		□

Appendix 16: Patient satisfaction with anticoagulant treatment using the anticlot treatment scale (ACTS)

Patients will be asked to rate their experiences of anticoagulant treatment during the past four weeks on a five-point scale of intensity (1 = not at all, 2 = a little, 3 = moderately, 4 = quite a bit, 5 = extremely). Reverse coding is adopted to calculate the burden scale so that higher scores indicated higher satisfaction. The Burden subscale score ranged from 12 to 60 and the Benefit subscale score ranged from 3 to 15, with a total range of 15–75 for all 17 items.

1	How much does the possibility of bleeding as a result of your anticlot treatment limit you from doing physical activity?	**1**	**2**	**3**	**4**	**5**
2	How much does the possibility of bleeding as a result of your anticlot treatment limit you from taking part in your usual activities?					
3	How bothered are you by the possibility of bruising as a result of your anticlot treatment?					
4	How bothered are you by having to avoid other medicines as a result of your anticlot treatment?					
5	How much does your anticlot treatment limit what you eat and drink?					
6	How much of a hassle(inconvenience) are the daily aspects of your anticlot treatment? (e.g., remembering to take your medicine at a certain time, taking the correct dose of your medicine, following a diet, limiting alcohol, etc.)					
7	How much of a hassle (inconvenience) are the occasional aspects of your anticlot treatment? (e.g., the need for blood tests, going to or contacting the clinic/doctor, making arrangements for treatment while travelling, etc.).					
8	How difficult is it to follow your anticlot treatment?					
9	How time-consuming is your anticlot treatment?					

10	How much do you worry about your anticlot treatment?					
11	How frustrating is your anticlot treatment?					
12	How much of a burden is your anticlot treatment?					
13	Overall, how much of a negative impact has your anticlot treatment had on your life?					
14	How confident are you that your anticlot treatment will protect your health?					
15	How reassured do you feel because of your anticlot treatment?					
16	How satisfied are you with your anticlot treatment?					
17	Overall, how much of a positive impact has your anticlot treatment had on your life?					

አዲስ አበባ ዩኒቨርሲቲ፣ ጤና ሳይንስ ኮሌጅ

ፋርማሲ ትምህርት ቤት

Appendix 17: Study Information sheet for [Amharic version]

የጥናቱ ተሳታፊዎች የመረጃ ቅፅ

በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል ዋርፋሪን ለሚወስዱ ተመላላሽ ታካሚዎች ላይ ስለ መድሃኒቱ(ዋርፋሪን) እውቀት ፡ በአግባቡ ስለመዉሰድ እና በአገልግሎቱ ስለሚኖራቸዉ እርካታ ላይ ያመጣዉን ተጽኖ ለማጥናት የተዘጋጀ ጥናት።

በዚህ በአይነቱ የመጀመሪያ በሆነ የጥናትና ምርምር ፕሮጀክት እንዲሳተፉ በትህትና እንጋብዝዎታለን፡፡ በጥናቱ ለመሳተፍ መወሰን ያለብዎት ለመሳተፍ ከፈለጉ ብቻ ነው፡፡ ላለመሳተፍ በመወሰንዎ በማንኛውም መልኩ የሚደርስብዎት ጉዳት ወይም የሚያጡት ጥቅም አይኖርም (አሁን እየወሰዱ ካለት ህክምና ጋር ምንም አይነት ግንኙነት የለዉም፡፡ በጥናቱ ለመሳተፍ ከመወሰንዎ በፊት ጥናቱ ለምን እንደሚካሄዴና የእርስዎ ተሳትፎ ምን እንደሆነ መገንዘብዎ አስፈሊጊ ነው። እባክዎ ትንሽ ጊዜ ይወስዱና የሚከተለውን መረጃ በጥንቃቄ ያንብቡ፡፡ ግልፅ ያልሆነለዎት ነገር ካለ ወይም ተጨማሪ መረጃ ከፈለጉ ይጠይቁን፡፡ ይህ ጥናት በአዲስ አበባ ዩኒቨርስቲ ጤና ሳይንስ ኮሌጅ ፋርማሲ ት/ቤት በፋርማስዩትክስ እና ሶሻል ፋርማሲ ትምህርት ክፍል የዶክትሪት ዲግሪ ማሙያ የሚካሄድ ነው፡፡

የጥናቱ አላማ:

የዚህ ጥናት ዋና አላማ በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል ዋርፋሪን በሚወስዱ ተመላላሽ ታካሚዎች ላይ ስለ መድሃኒቱ(ዋርፋሪን) እውቀት፡ በአግባቡ ስለመዉሰድ እና በአገልግሎቱ ስለሚኖራቸዉ እርካታ ለምዳስስ ነዉ፡፡በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል የደም ማቅጠኛ አገልግሎት በልብ እና ሄማቶሎጅ ክሊኒኮች ህክምና በመከታተል ላይ የሚገኙ ሕመምተኞችና እንደዉም ዋርፋሪን እየወሰዱ ያሉት ታካምዎች በዚህ ጥናት እንዲሳተፉ የሚመረጡ ይሆናል፡፡

በዚህ ጥናት ለመሳተፍ ከተስማሙ ምን ይጠበቅብዎታል?

አንደ ለአንድ በሆነ ቃለ-መጠይቅ ታካሚዎች ስለምወስዱት መድሃኒት(ዋርፋሪን) ያላቸዉን እዉቀት፡ በአግባቡ ስለመዉሰድ እንደውም ስለ ደም ማቅጠኛ አገልግሎት በአገልግሎት ስለሚኖራቸዉ እርካታ ጉዳዮች የተወስኑ ይጠየቃሉ፡ ፡ ቃለ-መጠይቁ በዚህ ሆስፒታል ተመላለሽ ህክምና ክፍል ውስጥ የሚካሄድ ይሆናል፡፡ ቃለ-መጠይቁ ወደ 40 ደቂቃዎች ይወስዳል፡፡

በጥናቱ በመሳተፍዎ የሚደርስብዎ ጉዳት: ውይይቱ ማንኛውም አይነት ችግር ያደርስብዎታል ብለን አናስብም፡፡ ምናልባት አልፎ አልፎ ሰዎች በሚጠየቁት ጥያቄዎች ቅር ሊሰኙ ይችላሉ፡፡ ምናልባት ከጥያቄዎቹ መካከል አንዳንድ ጥያቄዎች የማይመችዎት ከሆኑ ጥያቄዎች አለመመለስ (መልስ አለመስጠት) ይችላሉ ወይም በማንኛውም ጊዜ ጥያቄዎቹ የማይመችዎት ከሆኑ ሊቆም ይችላሉ።

ልገኙ የሚችሉ ጠቀሜታዎች: ከዚህ ጥናት የሚገኘው መረጃ በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል የደም ማቅጠኛ አገልግሎት ለማሻሻል ያስችላል፡፡ በአጠቃላይ ጥናቱ ከተጠናቀቀ በኋላ በጥናቱ የተደረሰባቸውን ግኝቶች በስብሰባ ወይም ደግሞ በበራሪ ወረቀት የምናሳውቅ ይሆናል፡፡

የሚሰጡት መረጃ እንድት ይያዛል? በዝህ ጥናት ውስጥ ስምዎት ወይም ማንነትዎን ሊገልፅ የሚችሉ መረጃ እንዲይሰፍር እናደርጋለን፡፡ የተሰበሰበ መርጃ ሳጥን ውስጥ የሚቆልፍባቸው ይሆናል እንደዉም መረጃው ከተቀናበረ በኋለ እንዲወገዱ ይደረጋል፡፡ ከዋና ጥናት አድራጊው በስተቀር መረጃው የእርስዎ መሆኑን ማንም እንዲያውቅ አይደረግም፡፡

ስለ ተሳትፎ ሁኔታ፡ በዚህ ጥናት ለመሳተፍ ወይም ላለመሳተፍ ሙሉ በሙሉ የእርስዎ ውሳኔ ነው፡፡ ለመሳተፍ ከወሰኑ በማንኛውም ጊዜ ምንም አይነት ምክንያት መስጠት ሳያስፈልግዎ ተሳትፎዎን ማቋረጥ ይችላሉ፡፡

ዋና ተመራማሪ ታምራት አሰፋ በ ፕ/ር ተፈሪ ገድፍ፤ ዶ/ር ለገስ ጨልቀባ ፤ ዶ/ር ደጁማ ያደታ እና ዶ/ር አመሃ ገብረመድን አማካሪነት

ዋና ተመራማሪ የበስልክ ቁጥር፡ 251912023382

ጥናት በማንኛውም መልኩ ጉዳት ካደረሰብዎ ወይም ለተጨማሪ መረጃና ምክር በአዱስ አበባ ዩኒቨርስቲ ጤና ሳይንስ ኮሌጅ ተቋማዊ ግምገማ ቦርድ በሚከተለው አድራሻ ማግኘት ይችላሉ፡፡

ስልክ ቁጥር፡ +251947339272 ወይም በኢመይል: chs.irb@aau.edu.et

አዲስ አበባ ዩኒቨርሲቲ፣ ጤና ሳይንስ ኮሌጅ
ፋርማሲ ትምህርት ቤት

Appendix 18: Amharic version of Written Consent Form

አባሪ ተሳታፊዎች በጥናቱ ላይ ለመሳተፍ ፍቃደኝነታቸዉን ይሚገፁበት ቅፅ

Research Title: በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል ዋርፋሪን በሚወስዱ ተመላላሽ ታካሚዎች ስለ ዋርፋሪን ያላቸዉ እዉቀት፡ በአግባቡ ስለመዉሰድ እና ባገልግሎቱ ስለሚኖራቸዉ እርካታ የሚዳስስ ጥናት።

ጤና ይስጥልኝ _____ እባላለሁ። በአዲስ አበባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅ ፋርማሲ ትምህርት ቤት የፒኤችዲ ጥናት: በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል በፋርማሲስት የሚመራ የደም ማቅጠኛ አገልግሎት ዋርፋሪን በሚወስዱ ተመላላሽ ታካሚዎች ስለ ዋርፋሪን ያላቸዉ እዉቀት እዉቀት፡ በአግባቡ ስለመዉሰድ እና በአገልግሎቱ ስለሚኖራቸዉ እርካታ የምዳስስ የፒኤችዲ ጥናት ላይ መረጃ ሰብሳቢ ሆኜ እየሰራሁ እገኛለሁ።

በዚህ ጥናት ላይ ታካሚዎች ስለሚዎስዱት መድሃኒት(ዋርፋሪን) ያላቸዉን ዕዉቀት፤መዳሃኒቱን በአግባቡ ስለመዉሰድ ና ስለደም ማቅጠኛ ህክምና ያላቸዉን እርካታ የሚዳስስ ጥናት ነዉ፡፡ በዚህ ጥናት ውስጥ ያለዎት ተሳትፎ ሙሉ በሙሉ በፈቃደኝነት ላይ የተመሰረተ ሲሆን፤ በዚህ ጥናት መሳተፍም ሆነ አለመሳተፍ በሆስፒታሉ ዉስጥ በሚየገኙት አገልግሎት ላይ ምንም አይነት ተፅእኖ የማይኖረዉ ሲሆን ቃለመጠይቁን ማቋረጥ ወይም ጥያቄዎችን አለመመለስ ይችላሉ፡፡ በጥናቱ ዉስጥ የሚስጡአቸዉ መልሶች ሙሉ በሙሉ በሚስጥር የሚተበቁ ሲሆን የእርሰዎ ስም በማንኛዉም መልኩ በጥናቱ ዉስጥ አይገለፅም፡፡ የሚሰጡት መረጃ በሆስፒታሉ የደም ማቅጠኛ አገልግሎትን ለማሻሻል ይጠቅማል፡፡ የዚህ መጠይቅ አጠቃላይ ሂደት ቢበዛ 40 ደቂቃዎችን ይወስዳል።

በጥናቱ ለመሳተፍ ፈቃደኛ ነዎት ☐ አዎ ☐ አይደለሁም

አዎ ከሆነ፣ የጥናት ተሳታፊ ፊርማ _____ ቀን _____

ዋና ተመራማሪ፡ ታምራት አሰፋ
ስልክ ቁጥር፡ 0912023382
E-mail: tamrat.assefa@aau.edu.et

አማካሪዎች፡ ፕ/ር ተፈሪ ገድፍ
ዶ/ር ለገስ ጨልቀባ
ዶ/ር ደጁማ ያደታ
ዶ/ር አመሃ ገብረመድን

Appendix 19 : Amharic version of the data collection tool for oral anticoagulation knowledge assessment in patients receiving warfarin at TASH

<u>አባሪ:</u> በጥቁር አንበሳ ስፔሻላዝድ ሆስፒታል ዋርፋሪን የሚወስዱ ታካሚዎች ስለመድሃኒቱ ያላቸውን እውቀት ለመገምገም የተዘጋጀ ቅጽ።

ክፍል-1: ስለ ማህበራዊ መረጃ የሚመለከቱ ጥያቄዎች					
1	የታካሚ I-Care ቁጥር፡- _____ ስልክ ቁጥር: _____				
2	ፆታ	☐ ወንድ ☐ ሴት			
3	እድሜ _____ ዐመት				
4	የጋብቻ ሁኔታ	☐ ያላገባ/ች ☐ ያገባ/ች	☐ የተፋታ/ች ☐ የተለያየ/ች	☐ የሞተበት/ባት	
5	ሃይማኖት	☐ ኦርቶዶክስ ☐ ካቶሊክ	☐ ሙስሊም ☐ሌላ[ይጥቀሱ]_____	☐ ፕሮቴስታንት	
6	የትምህርት ደረጃ	☐ ማንበብና መጻፍ የማይችል ☐ ማንበብና መጻፍ የሚችል	☐ አንደኛ ደረጃ (1-8) ☐ ሁለተኛ ደረጃ (9-12)	☐ ቴክኒክና ሙያ/ዲፕሎማ ☐ ድግሪ እና ከዚያ በላይ	
7	የመኖሪያ ቦታ	☐ አድስ አባባ	☐ ከአድስ አባባ ውጭ		
8	የቤተሰብው ወርሐዊ ገቢ ስንት ነው? (በብር)	☐ ---------- ብር	☐ ገቢ የለኝም		
9	የስራ ሁኔታ	☐ ተቀጣሪ ☐ የግለ ስራ	☐ የቤት አመቤት ☐ ተማሪ	☐ ጡረተኛ ☐ ስራ የሌለዉ	
10	ከማን ጋር ነው የሚኖሩት?	☐ከቤተሰብ ጋር	☐ ብቻዬን		
11	ደባል ሱስ ሁኔታ የሚግልጽ	አልኮል ይጣሉ?	ጫት ትቅማለህ?	ሲጋራ ታጨሳለህ?	
		☐ አዎ ☐ አልጠጣም	☐ አዎ ☐ አልቅምም	☐ አዎ ☐ አላጨስም	
12	የህክምና አገልግሎት የክፍያ ዘዴ	☐ በነጻ	☐ በክፍያ	☐ በጤና መድህን	☐ ሌላ _____
13	የዋርፋሪን ለምን ያክል ጊዜ ውስድዋል	_____(በዓመታት ወይም በወር ይፃፉ)			
15	ይምታወቅ ይኩላልት ህመም አለቦት	☐ አዎ ☐ የለብኝም			
16	ይምታወቅ ይጉበት ህመም አለቦት	☐ አዎ ☐ የለብኝም			
17	ከዝይ በፍት ከፍታኘ የሆነ መድማት ኢጋጥሞት ያውቃል?	☐ አዎ ☐ የለብኝም			

	(ለምሳሌ ወደ ጭንቅላት/ሆድ ውስ፤ሆስፕታል መተኛት፤ ደም መውሰድ)	

ክፍል-2*:* ስለ ደም ማቅጠኛ መድሀኒት ያለዎትን እውቀት የሚገመግም መጠይቅ

1. የዋርፋሪን ጥቅም ምንድ ነው?

ሀ. የልብ ምት መቀነስ

ለ. ደሙ ማቅጥን

ሐ. ደሙ ማወፈር

መ. ጥቅሙን አላቀውም

2. ዋርፋሪን አንዴ መውሰድ፥ ከጀመሩ ለምን ያህል ጊዜ መውሰድ ያስፈልግዎታል?

ሀ. ስድስት ወር

ለ. አንድ አመት

ሐ. የዕድሜ ልክ

መ. ይህ የሚወሰነው በእያንዳንዱ ታካሚ የህመም ሁኔታ አይነት ነው

ሰ. አላውቅም

3. ከሚከተሉት ምግቦች ውስጥ የትኛው ከዋርፋሪን ጋር ይጋጫል?

ሀ. ብሮኮሊ

ለ. ሙዝ

ሐ. ካሮት

መ. ቲማቲም

ሰ. አላውቅም

4. ዋርፋሪንን ለመውሰድ እጅግ ተመራጭ የሚሆነው ግዜ የትኛዉ ነው?

ሀ. በምሳ ሰአት

ለ. በምሽት

ሐ. ጠዋት ከቁርስ በፊት

መ. በቀን ውስጥ በሚያስታውሱበት በማንኛውም ሰዓት

5. በአንድ የአራት ምሽት ሶስት ብርጭቆ ቢራ ቢጠጡ፣ በአንድ ምሽት ይህ ያክል የአልኮል መጠን መውሰድዎ?

ሀ. የወሰዱትን ዋርፋሪን ውጤታማነት ይቀንሳል

ለ. የወሰዱትን ዋርፋሪን ውጤታማነት ይጨምራል

ሐ. የወሰዱትን ዋርፋሪን ውጤታማነት ላይ ምንም አይነት ተጽእኖ አይኖረውም

መ. የዋርፋሪን በሚወስዱበት ጊዜ ህመም እንድሰማዎት ያደርጋል

ሠ . አላውቅም

6. ዋርፋሪን እየወሰዱ ሳሉ

ሀ. አረንጓዴ ቅጠላማ አትክልቶችን መብላት የለበትም

ለ. በወር አንድ ጊዜ አረንጓዴ ቅጠላማ አትክልቶችን መመገብ ይችላል

ሐ. በፈለጉት ጊዜ የፈለጉትን ያህል አረንጓዴ ቅጠላማ አትክልቶችን መመገብ ይችላሉ

መ. አረንጓዴ ቅጠላማ አትክልቶችን መመገብ ይችላል ነገር ግን በየሳምንቱ ተመሳሳይ መጠን በመደበኛነት መብላት ይኖርበታል

7. ትናንት ምሽት መውሰድ የነበረበዎተ ዋርፋሪን እንክባ እረሱት እንበል፣ ነገር ግን አለመዉሰደዎን አሁን ቢያስታዉሱ ምን ያደርጋሉ

ሀ. የተረሳውን የዋርፋሪን መጠን ይዘሉ እና የዛሬውን መጠን እወስዳለሁ

ለ. ያልወሰድኩትን የዋርፋሪን መጠን አሁኑኑ እወስዳለሁ

ሐ. የዛሬ ምሽት ጠብቄ እና ሁለት መጠን ዋርፋሪን እወስዳለሁ

መ. ያልወሰድኩትን የዋርፋሪን መጠን ግማሽ ያህሉን አሁኑኑ እወስዳለሁ

8. ከሚከተሉት ተግባራት ውስጥ ዋርፋሪን በሚወስዱበት ጊዜ የበለጠ አደገኛ የሆኑት ተግባራት የትኞቹ ናቸው?

ሀ. እግር ኳስ መጫወት፣ ምክንያቱም ጭንቅላትዎ ግጭት ሊደርስበት ስለሚችል

ለ. ገላ መታጠብ፣ ምክንያቱም ሳሙና ከዋርፋሪን ጋር ስለሚጋጭ

ሐ. ካርታ መጫወት ምክንያቱም እጆችዎን አብስቶ መጠቀም የደም መርጋት ያስከትላል

መ. ብዙ የእግር ጉዞ ማዲረግ ምክንያቱም ዋርፋሪን እየወሰዱ የአካል ብቃት እንቅስቃሴ ማድረግ ለእርስዎ ጥሩ ስላልሆነ

9. ዋርፋሪን እየወሰዱ ባሉበት ጊዜ ከሚከተሉት ውስጥ በቀጥታ ቢያጋጥመዎት ወደ ህክምና ይሄዳሉ?

ሀ. በቆዳ ላይ ትንንሽ ቁስሎች

ለ. የምግብ ፍላጎትህ በከፍተኛ ሁኔታ ሲጨምር

ሐ. የማይቆም መንሰር ሲያጋትመዎት

መ. ጥርስዎን ከተቦረሸ በኋላ ለጥቂት ሰኮንዶች የሚደማ ድድ

10. በእጅዎ ላይ ያለው የዋርፋሪን ቢያልክብዎት

ሀ. እርስዎ የሚዎስዱት መጠን ጋር ተመሳሳይ እስከሆነ ድረስ ዋርፋሪንን ከጓደኛዎ መዋስ

ለ. የሚያስፈልገዎትን የዋርፋሪን መጠን እንዳይረጥቦዎት ለዚያ ቀን ወደ ህክምና ቦታ ሂደው መጠየቅ

ሐ. ቀጣዩ ቀጠሮ ጥቂት ቀናት ብቻ የሚቀረው በመሆኑ አዲስ የሐኪም ማዘዣ ለማግኘት እስከዚያው ድረስ መጠበቅ

መ. ምንም አለማድረግ፥ ምክንያቱም ዋርፋሪን በቂ ጊዜ የወሰዱ ስለሆነ; ያለበለዚያ መድሃኒት ከመጠን በላይ ስለሚሆንብዎ።

11. የእርስዎ INR ምርመራ ውጤት ለህኪሙ የሚሰጠው መረጃ

ሀ. ዋርፋሪን በሚወስዱበት ጊዜ ደምዎን ዉፍረት/ቅጭኔት መጠን

ለ. ዋርፋሪን እወሰዱ ኩላሊቶዎ በአግባቡ የመስራት አቅም

ሐ. ዋርፋሪን ከወሰዱ በኋላ የደምዎ አማካይ የስኳር መጠን ምን ያህል እንድሆነ

መ. ዋርፋሪን ከወሰዱ በኋላ የሚጠጡትን አልኮሆን መጠን ምን ያህል እንድሆነ

12. ዋርፋሪን በሚወስዱበት ጊዜ የጥርስ ህክምና ቀጠሮ ሲይዙ(ለምሳሌ፥ጥርስ ማውጣት፡ማሳጠብ፤ ይተቦረቦረ ለማስተካከል) ምን ማድረግ ያስፈልግዎታል?

ሀ.ዋርፋሪን በሚወስዱበት ጊዜ በጥርስዎ ላይ ምንም አይነት የጥርስ ህክምና አለማድረግ

ለ. ማንኛውንም አይነት የጥርስ ህክምና ከማድረግዎ በፊት ለጥርስ ህኪምዎ ዋርፋሪን እንደሚወስዱ መንገር አለብዎት

ሐ. የጥርስ ህክምና ማድረግ ይችላል እና ስለ ዋርፋሪን ለጥርስ ህኪሙ መንገር አያስፈልግም

መ. የጥርስ ህክምና ቀጠሮዎ ቦታ ሲደርሱ ዋርፋሪን እንደሚወስዱ ለጥርስ ህኪሙ ከነገሩት የጥርስ ህክምናውን ሊሰራ ይችላል

13. የእርስዎ ተገቢ የINR መጠን ከስንት ኣስከ ስንት ነው?

ሀ. 2-3 ለ. 2.5-3.5 ሐ. አላቀውም

14. የእርስውዎ ጎረቤት ባህላዊ መድሃኒት ገዝተው እየተጠቀሙ በመሆኑ፥ ለእርስዎም ህመም እንደሚጠቅም ምክር ቢለግስዎት፥ውሳኔዎ ምን ይሆናል?

ሀ. ይህ የባህል መድሃኒት ለእርስዎም እንደሚጠቅም በማመን ምክሩን እቀበላለሁ።

ለ. ባህላዊ መድሃኒቱን መዉሰድ ይጀምሩ እና በሚከተለዉ ከጠሮ ጉዳዩን ለፋርማሲስቱ/ህኪሙ ያስረዳሉ።

ሐ.ባህላዊ መድሃኒቱን ከመዉሰድዎ በፊት እርስዎ ከሚወስዱት ዋርፋሪን ጋር ይጋጭ እንደሆነ ፋርማሲስትዎን/ዶክተርዎን ይጠይቃሉ

መ. ማንኛውንም የባህል መድሃኒት አለመውሰድ፥ ምክንያቱም ሁሉም ባህላዊ መድሃኒቶች ከዋርፋሪን ስለሚጋጩ።

15. ከሚከተሉት ውስጥ የዋርፋሪን ውጤታማነት ላይ ተጽእኖ የሚኖረው የቱ ነው?

ሀ. የስሜት መቀያየር

ለ. የእንቅልፍ መዛባት

ሐ. የሚጠጡት የውሃ መጠን

መ. ያለማዣ የሚወሰዱ መድሃኒቶችን መጠቀም

ሠ. አላውቅም

16. ዋርፋሪን በመውሰድ ላይ እያሉ አልፎ አልፎ አረንጓዴ ቅጠላማ አትክልቶችን በከፍተኛ መጠን መመገብ፥

ሀ. የደም መፍሰስን አደጋ ይጨምራል

ለ. የዋርፋሪን ውጤታማነትን እንድቀንስ ሊያደርግ ይችላል

ሐ. የጨጓራ መታወክ እና ትውከት ያስከትላል

መ. የደም መርጋት ችግርን ሊቀንስልውት ይችላል

17. እርስዎ የINR ምርምራ ውጤት ከሚፈለገው በላይ ከሆነ

ሀ. ለደም መርጋት አደጋ ይጨምራል

ለ. ከዋርፋሪን ጋር ተያይዞ የድብርት እና ድካም ስሜት ይጨምራል

ሐ. የመድማትዎ አደጋ ይጨምራል

መ. ከዋርፋሪን ጋር የሚታዩ የጎንዮሽ ጉዳቶችን የመከሰት እድል ይከንሳል

18. ከዋርፋሪን ጋር የሚጋጩ መዲሃኒቶችን ለመውሰድ ተገቢ የሚሆነው በምን አይነት ሁኔታ/መቼ ሲወስዱ ነው?

ሀ. ዋርፋሪን ጠዋት ወስዶ የተጓዳኝ መድሃኒት ማታ መውሰድ

ለ. ክትትል የሚያደርግለዎት የጤና ባለሙያ ስለመድሃኒቶቹ ግጭት የሚያዉቅ ከሆነ እና በቋሚነት የINR ምርመራ ብያደርግሎዎ

ሐ. ዋርፋሪን አንድ ቀን እያለፍ የሚወስዱ ከሆነ

መ. ከዋርፋሪን ጋር የሚጋጩ መድሃኒቶች በፍጹም አለመውሰድ

Appendix 20: Amharic version of the data collection tool on the Morisky Green Levine Scale (MGLS) to assess patient adherence to warfarin therapy

<u>አባሪ: የሞሪስኪ ግሪን ሌቪን መስፈርት (በጥቁር አንበሳ ስፔሻላዝድ ሆስፒታል ዋርፋሪን የሚወስዱ ታካሚዎች መድሃኒቱ በታዘዘው መሰረት በአግባቡ መውሰዳቻውን ለማርጋገጥ የሚያገለግል መለኪያ/መስፈርት</u>

ተ.ቁ	**የሞሪስኪ ግሪን ሌቪን መስፈርት (Morisky Green Levine scale (MGL)**	**አዎ**	**በፍጹም**
1	መድሃኒቶን (ዋርፋሪን) መውሰድ ረስተዉ ቀርተዉ ያውቃሉ?		
2	አንዳንድ ጊዜ መድሃኒትዎን (<u>ዋርፋሪን</u>) ለመውሰድ ቸልተኛ ነዎት?		
3	አንዳንድ ጊዜ ጥሩ ስሜት ሲሰማዎት (ዋርፋሪን) መውሰድ ያቆማሉ?		
4	አንዳንድ ጊዜ ዋርፋሪን ሲወስዱ የከፋ ስሜት ከተሰማዎት: መድሃኒቱን መውሰድ ያቆማሉ?		

መዳሃኒቱን በአግበቡ ካልወሰድ እባክዎ ምክንያቱን ይግለጹ (ከ አንድ በላይ መልስ መምረጥ ይቻላል)

ረስቸው/ስለምረሳው	☐	መዳሃኒቱን ስወስድ ህመሜ ስለሚባባስበኝ	☐
የጎኒዮሽ ጉዳትን((ሳይዶኢፌክት) በመፍራት	☐	የምወስዲቸው መድሃኒቶች ብዙና ግራ የሚያጋቡ ስለ ሆኑ	☐
ስለመዳሃኒቱን አወሳሰድ በቂ መረጃ ስለሌለኝ	☐	መዳሃኒቱ ውድ ስለ ሆነብኝ	☐
መዳሃኒቱን ማግኘት ስላልቻልኩ	☐	ይጠቅመኛል ብዬ ስለማላምን/ስላማላስብ	☐
መዳሃኒቱን ስውጠው ስለምያስቸገረኝ	☐	ተሽሎኛል ብዬ ስላሰብኩ	☐
ስራ ስለምበዛብኝ	☐	በሌላ ምክንያት (ይግለፁት)…….....	☐
መዳሃኒቱን ከቀጠሮ በፍት ስለ አለቀብኝ	☐		

Appendix 21: Amharic version of data collection tool on patient satisfaction with anticoagulant treatment using the anticlot treatment scale (ACTS)

<u>አባሪ: ህመምተኞች ስለ ደም መቅጠኛ መድኃኒት (በዋርፋሪን ህክምና) ላይ ያለችውን እርካታ ለመለካት የተዘጋጀ መጠይቅ (አንት ክሎት ትሪትምንት ስኬል)</u>

<u>ህመምተ</u>ኛው ላለፉት አራት ሳምንታት ውስጥ ያልውን ከዋርፋሪን ጋር የተያያዘ ተሞክሮ ከ1 እስከ 5 ደረጃ በማዉጣት የሚጠየቁትን ጥያቄዎች ይመልሳል፡፡

1: በጭራሽ **2:** በትንሹ **3:** መለስተኛ **4:** በሚገባ **5:** እጅግ በጣም

ቁ.	ጥያቄዎች	በጭራሽ (1)	በትንሹ (2)	መለስተኛ (3)	በሚገባ (4)	እጅግ በጣም (5)
1	የደም መቅጠኛ መድኃኒት (ዋርፋሪን) በመውሰዶ ምክንያት ሊከሰት በሚችል መድማት ምን ያህል አካላዊ እንቅስቃሴ ከማድረግ ይገድቦታል?					
2	የደም መቅጠኛ መድኃኒት (ዋርፋሪን) በመውሰዶ ምክንያት ሊከሰት በሚችል መድማት ምን ያህል በተለመደው እንቅስቃሴዎት እንዳይሳተፉ ይገድቦታል?					
3	የደም መቅጠኛ መድኃኒት (ዋርፋሪን) በመውሰዶ ምክንያት ለከሰት የሚችል የቆዳ ለይ መብልዝ ምን ያህል ያሳስቦታል/ ይርበሾታል?					
4	የደም መቅጠኛ መድኃኒት (ዋርፋሪን) በመውሰዶ ምክንያት ሌሎች መድሀኒቶችን ላለመውሰድ ምን ያህል ተቸግረዋል/ይርበሾታል?					
5	የደም መቅጠኛ መድኃኒት(ዋርፋሪን) በመውሰዶ የምበሉት እና የምጠጡት ነገሮች በምን ያህል ተገድቦል?					
6	የደም መቅጠኛ መድኃኒት (ዋርፋሪን) ህክምናዎ ጋር ተያይዞ በዕለት ተዕለት ሁኔታዎች/ክንዋኔዎች ምን ያህል ያቸገራሉ?(ለምሳሌ፤ መድሃኒትዎን በተወሰነ ጊዜ መውሰድዎን መስታወስ፤ ትክክለኛውን የመድሃኒት መጠን መውሰድ፤ የተነገሮትን አመጋገብን መከተል፤ ከአልኮል መገደብ፣ ወዘተ)					
7	የደም መቅጠኛ መድኃኒት(ዋርፋሪን) ህክምናዎ ጋር ተያይዞ አልፎ አልፎ በሚደረጉ ታግባራት ምን ያህል ይቸገራሉ? (ለምሳሌ የደም ምርመራ/INR አስፈላጊነት፤ ወደ ሆስፕታል መሄድ/ህክም መገናኘት፤ጉዞ ላይ ሳሉ ለህክምናን ማመቻችት ወዘተ.)					

8	የደም መቅጠኛ ህክምናዎን መከተል ምን ያህል ያስቸግራል/ከባድ ነው?					
9	የደም መቅጠኛ ህክምናዎ ምን ያህል ሰዓቶን/ጊዜዎን ይወስዳል/ጊዜ የሚወስድ ነው?					
10	ስለደም መቅጠኛ መድኃኒት/ ህክምና ምን ያህል ይጨነቃሉ?					
11	የደም መቅጠኛ ህክምናዎ ምን ያህል ተስፋ አስቆራጭ ነው?					
12	ደም መቅጠኛ ህክምናዎ ምን ያህል ጫና / ሸክም አለዉ ነው?					
13	በአጠቃላይ የደም መቅጠኛ ህክምናዎ በሕይወቶ ላይ ምን ያህል አሉታዊ (negative) ተጽዕኖ አሳድሯል/አለው?					
14	የደም መቅጠኛ ህክምናዎ ጤንነትዎን እንደሚጠብቅ ምን ያህል እርግጠኛ ነዎት/ይተማመናሉ?					
15	በየደም መቅጠኛ/በዋርፋርን ህክምናዎ/ምክንያት ምን ያህል መረጋጋት ይሰማዎታል?					
16	በደም መቅጠኛ በዋርፋርን ህክምናዎ ምን ያህል ረክተዋል?					
17	በአጠቃላይ የደም መቅጠኛ ህክምናዎ በሕይወቶ ላይ ምን ያህል አዉንታዊ (positive) ተጽዕኖ አሳድሯል/አለው?					

Appendix 22: Data collection tool on sociodemographic and clinical characteristics for the comparison study

A. **Sociodemographic characteristics**

1. Patient I-Care Number: _____

2. Sex: ☐ Male	☐ Female	Age: ----------years

B. Disease and Medication Related (clinical characteristics) questions

3. Presence of comorbidities which don't have warfarin indication: Yes ☐ No ☐ (If yes tick all box that apply)

Hypertension	☐	Renal disease (AKI/CKD)	☐
Heart Failure	☐	Diabetes mellitus	☐
Gastric Illness/ peptic ulcer disease	☐	Seizure Disorder	☐
Atrial fibrillation (that don't need warfarin)	☐	HIV/AIDS	☐
Liver disease	☐	Gynecological disorder	☐
Dermatology condition	☐	Peripheral artery disease	☐
Degenerative valvular heart disease	☐	CRVHD that don't need warfarin	☐
Hypertensive heart disease	☐	Hyperthyroidism	☐
Asthma	☐	Hypothyroidism	☐
Dyslipidemia	☐	Tuberculosis	☐
History of ischemic stroke	☐	History of hemorrhagic stroke	☐
History of coronary artery disease/ ischemic heart disease	☐	COVID-19	☐
Cancer	☐	Rheumatologic disorder	☐
Inflammatory bowel disease	☐	Prior myocardial infarction	☐

Chronic obstructive pulmonary disease	☐	Psychiatric disorder	☐
Benign prostatic hyperplasia	☐	Other (Specify):	

Assessment of Stroke **(CHA_2DS_2-VASc)** and Bleeding Risk **(HAS-BLED)** in AF patients for prescribing warfarin

CHA_2DS_2-VASc		**Score**	**HAS-BLED**		**Score**
C	Congestive Heart Failure	1	**H**	Hypertension	1
H	Hypertension	1	**A**	Abnormal renal and liver function (1 point	1or 2
A	Age 75years or older	2	**S**	Stroke	1
D	Diabetes Mellitus	1	**B**	Bleeding tendency/predisposition	1
S	Stroke, TIA or TEE	2	**L**	Labile INRs	1
V	Vascular disease (prior MI, PAD, aortic	1	**E**	Elderly (eg, age >65 years)	1
A	Age 65 to or 74 years older	1	**D**	Drugs or alcohol (1 point each)	1 or 2
S	Sex category (i.e., female)	1			
	Maximum score	**9**		**Maximum score**	**9**

CHA_2DS_2-VASc score=0, No antithrombotic		HAS-BLED score of ≥3 indicates that caution is warranted when prescribing oral anticoagulation and regular review is required
CHA_2DS_2-VASc score=1, Antithrombotic with oral anticoagulation or antiplatelet therapy, Use oral		
CHA_2DS_2-VASc score ≥2, Antithrombotic with oral anticoagulation		

C. Warfarin Anticoagulation related information

Indication for warfarin therapy (Tick all that apply):

AF (Valvular) or (Non valvular)	☐	Atrial flutter	☐
CRVHD	☐		☐
Cardioembolism(includes sardioembolic stroke,	☐	Cardiac thrombus (includes left ventricular/apical/arterial thrombus)	☐

peripheral artery embolism), other site embolism), or non-embolic stroke (ischemic stroke				
Post mechanical MVR	☐	Post mechanical TVR	☐	
Post mechanical AVR	☐	Cardiomyopathy	☐	
Bioprosthetic valve replacement/repair	☐	Deep vein thrombosis		
Post-percutaneous mitrla ballon valvotomy	☐	Post mycordial infarction	☐	
Pulmonary hypertension	☐	Chronic pulmonary embolism	☐	
IHD and atrial/ventricular thrombus	☐	Others (Write the indication (_____)	☐	
Portal vein thrombosis	☐		☐	

4. Expected Duration of therapy: 3months ☐ 3-6months ☐ 6months☐ lifelong☐ Others☐

Target INR: ☐ 2-3	☐ 2.5-3.5	☐ Other Target:

Warfarin anticoagulation management follow- up form

SN	Follow up date	INR value	Anticoagulation Status	Weekly warfarin dose (Write the actual prescription)	Action on dosing	Next Visit date	Drug Interaction (Yes/No). If yes, list them in Q9	Sign of bleeding (Yes/No)	Additional Note
1									
2									
3									
4									
5									
6									
7									

8										
9										
10										

10. Warfarin Interacting drugs (Tick all that apply)

Interacting drug		**Interacting drug**		**Interacting drug**	
Aspirin	☐	Estrogen/COC		Paracetamol	☐
Allopurinol	☐	Erythromycin	☐	Phenobarbitone	☐
Amiodarone	☐	Fluconazole	☐	Phenytoin	☐
Azithromycin	☐	Ibuprofen	☐	Prednisolone	☐
Carbamazepine	☐	Indomethacin	☐	Propylthiouracil	☐
Ceftriaxone	☐	Isoniazid	☐	Protease Inhibitors	☐
Cimetidine	☐	Ketoconazole	☐	Rifampin	☐
Ciprofloxacin	☐	Levothyroxine	☐	Rosuvastatin	☐
Clarithromycin	☐	Lopinavir/ritonavir	☐	Simvastatin	☐
Clopidogrel	☐	Methimazole	☐	Sulfamethoxazole/trimethoprim	☐
Cloxacillin	☐	Metronidazole	☐	Tramadol	☐
Diclofenac	☐	Miconazole	☐	Valproic acid	☐
Doxycycline	☐	Nevirapine	☐	Omeprazole	☐
Efavirenz	☐				☐

11.Number of co-medications (Write them by number): _____

12. Number of hospital admission during study period (follow up) (if yes, admssion fill the date of visit)): _____

Admission	Date of Admission	Reasons of Admission	Admission	Date of Admission	Reasons of Admission	If yes, write reason(s)(e.g warfarin-related)
Admission 1			Admission 3			
Admission 2			Admission 4			

13. Number of emergency room during study period (follow up (if yes, number of visitst): _____

ERV	Date of visit	Reasons of visit	ERV	Date of visit	Reasons of visit	If yes, write reason (e.g warfarin-related)and date of ED visit1
Visit 1			Visit 3			
Visit 2			Visit 4			

14. Incidence of thromboembolic events during study period (follow up (Write them by number and fill the date event occurred): _____

Event	Date Occurred	INR value	Event	Date Occurred	INR value	If yes, write type of TEEs(any strokes types, TIA, etc) and date of incidence
Event 1			Event 3			
Event 2			Event 4			

Appendix 23: Manual/Protocol of Pharmacist Led-Anticoagulation Clinic at Tikur Anbessa Specialized Hospital

ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

Tikur Anbessa Specialized Hospital

Prepared by: Anticoagulation Team

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Acronyms

AC ----------Anticoagulation Clinic

ACCP---------- American College of Chest Physicians

AVK ----------Antivitamin K

DOAC ----------Direct oral anticoagulant

INR ----------International normalization ratio

PLAC ----------Pharmacist led anticoagulation clinic

TASH ----------Tikur Anbessa Specialized hospital

TTR ---------- Total therapeutic range

UFH ---------- Unfractionated heparin

UMC ---------- Usual medical care

VTE ---------- Venous thromboembolism

WMTAC ---------- Warfarin medication therapy adherence clinic

1. Introduction

Pharmacist-Led Anticoagulation Clinic (PLAC) is a specialized healthcare service where clinical pharmacists take a central role in managing anticoagulation therapy for patients. These clinics are designed to optimize the outcomes of anticoagulation therapy, improve patient safety, and ensure high-quality care. Below is an overview of the key features and benefits of PLAC.

Materials, premises, and personnel needed to establish PLAC

1.1. Materials and premises

To establish an anticoagulation clinic, the following should be met:

1. **Staffing requirements**:
    - One anticoagulation clinician (preferably a cardiologist).
    - At least two clinical pharmacists.
    - Two nurses.
    - One laboratory technologist.
2. **Facility and equipment**:
    - A consultation room sufficient for patient visits.
    - An examination room equipped with at least five chairs and tables.
    - An office room furnished with three chairs and tables.
    - Computers with internet access and anticoagulation database software for documentation.
    - A point-of-care device for INR testing in the examination room, or a prepared laboratory test site.
3. **Database Setup**:
    - A functional database must be established for patient management and record-keeping.
    -

2.2 Personnel

An anticoagulation clinic requires a team of trained healthcare professionals. The team should include at least two clinical pharmacists trained in anticoagulation therapy management, one cardiologist, one nurse, and one laboratory technician.

A. Clinical pharmacist

Qualification: Trained in anticoagulation therapy management.

Roles and responsibilities:

- Coordinate with the pharmacy directorate to procure necessary materials.
- Organize seminars and training sessions for healthcare professionals.
- Carefully review patient medication charts when referred to the anticoagulation clinic.
- Conduct patient interviews to gather essential information.
- Document patient information on the pharmacy sheet and sign off.
- Order INR tests, review results, and adjust doses per protocol when necessary.
- Refill warfarin prescriptions if no dose adjustment is needed.
- Educate patients on:
    - Anticoagulants and their indications.
    - Dosage, timing, and duration of therapy.
    - INR testing frequency and target INR range.
    - Managing missed doses.
    - Drug, food, and herbal interactions (e.g., with green leafy vegetables).
    - Side effects of warfarin and when to seek emergency care.
    - Lifestyle considerations such as alcohol consumption and physical activity.
- Consult with the cardiologist if challenges arise in patient management.
- Share clinic findings with hospital administration and the public.

B. Anticoagulation clinician

Qualification: Cardiologist or cardiology fellow.

Roles and Responsibilities:

- Collaborate with clinical pharmacists and provide consultations as needed.
- Conduct patient interviews and physical examinations to establish diagnoses.
- Order laboratory and imaging tests as necessary.
- Liaise with other physicians about the clinic's activities and share findings.
- Ensure sufficient physician staffing for the anticoagulation clinic.
- Participate in regular meetings, workshops, training sessions, and seminars.

C. Laboratory technologist

Qualification: Trained in INR laboratory testing and point-of-care devices.

Roles and Responsibilities:

- Prepare materials for laboratory testing, including INR tests.

- Communicate results to the clinical pharmacist or anticoagulation clinician.
- Coordinate with the biomedical department to resolve issues with test results or equipment malfunctions.
- Participate in training sessions and seminars.
- Regularly request materials and equipment from the pharmacy directorate.
- Report INR results from the lab or point-of-care testing.

D. Nurse

Qualification: Bachelor of Science in Clinical Nursing with training in anticoagulation protocols.

Roles and responsibilities:

- Prepare the examination room and necessary equipment, such as blood pressure apparatus and documentation materials.
- Arrange and facilitate patient examinations.
- Schedule patient appointments.

This structured team ensures the efficient operation of the anticoagulation clinic and high-quality patient care.

3.Scope of care of Anticoagulation service

Patient enrolment to PLAC and referral

- All patients currently receiving anticoagulants from the cardiac and hematology units of TASH will be included.
- New patients starting anticoagulant therapy for the first time in these clinics and related outpatient units will be referred to the PLAC.
- Patients discharged from various medical and surgical wards who require long-term anticoagulation therapy for post-operative conditions will be referred to the PLAC, where anticoagulants are prescribed.
- Referrals should be made in writing.
- Each referral should state the reason for anticoagulant use, the desired treatment intensity, and the planned duration of treatment. If the physician has already prescribed a dosage of the anticoagulant, the specific strength and daily dosage should be indicated.
- The physician referring the patient to the anticoagulation clinic must document the following information in the patient's medical chart.
  - Name, sex, age, weight, height of patient

- Current medications, including prescription and nonprescription
- medical history: known diseases and surgeries, drug allergies and reactions
- Conditions relating current medication regimen, surgical history, and hospitalizations.
- Indication for anticoagulation therapy
- Target INR range and planned duration of therapy
- If already receiving anticoagulation therapy include: start date, current dose
- History of bleeding including major and minor (dates and outcomes)
- Physician name and signature

- All referrals to the PLAC must include a supervising physician who is responsible for regularly assessing the patient's ongoing need for anticoagulation therapy, as well as managing any medical or surgical issues.
- The discontinuation of anticoagulation therapy will only happen based on the physician's order. Once the desired length of treatment is achieved, the PLAC clinician is authorized to discontinue the medication and discharge the patient from the clinic.

4. Scheduling patients

- Patients are scheduled by a nurse working in the PLAC (Patient Liaison and Care Center). The anticoagulation clinician and clinical pharmacist will conduct follow-up appointments, accept new consultations, and make necessary changes to the care plan.
- For hospital patients who are enrolled after discharge, appointments must be scheduled within one week of their discharge date.
- Once patients are stable, their appointments should be no more than two months apart, unless they encounter difficulties during that period.
- Patients should arrive 1-2 hours prior to their laboratory testing, which includes tests such as INR and CBC. If they have additional diagnostic tests or assessments that require more time, they should coordinate with laboratory personnel to arrive even earlier to ensure these tests are completed.
- The pharmacist will document each visit in a pharmacy follow-up chart (see Appendix 7) or in the designated database, if available. The documentation for each patient include the following information:
  - Visit date, indication for anticoagulation, co-morbidities, other drugs patients are receiving, therapeutic INR goal, the expected duration of therapy, visit day INR

value, warfarin dosing plan, any patient assessment information as deemed appropriate, frequency of INR monitoring after each visit, consumption status of food high in vitamin K, adherence status, warfarin related encountered side effects

5. Standardized warfarin dosing protocol

- Warfarin is adjusted based on current INR measurements. Prior to making a dose adjustment assessment for any missed doses, drug interactions, diet, documentation of bleeding, or other changes that may affect INR is mandatory for each patient in every PLAC visit.
- Increased dietary intake of vitamin K can reduce the anticoagulation effect of warfarin.

Table 1: Warfarin maintenance dosing protocol

Maintenance Dosing Protocol		
Target INR 2-3		Target INR 2.5-3.5
INR	**Dose Adjustment Plan Until Next INR/ visit**	**INR**
< 1.5	Increase weekly dose by 10-20%	< 2
1.5-1.9	Increase weekly dose by 5-10%	2-2.4
2-3	No change	2.5-3.5
3.1-3.5	Decrease weekly dose by 5-10%	3.6-4.0
3.6-4.9	Hold one dose, then decrease the weekly dose by 10-20%	4.1-4.9
5-9	Hold 2 doses, then decrease weekly dose by 10-20%	5-9
>9.0	Hold and follow daily INRs (also see reversal protocol if needed)	> 9

6. Frequency of INR monitoring for both initiation and maintenance of warfarin protocol

Table 2: Frequency of INR Monitoring for Maintenance of Warfarin

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

Every 6-12 weeks	If the patient maintained on same stable dose for at least 6 months

7. Risk of stroke development in patients with atrial fibrillation

The CHA2DS2VASc scoring system is a simple system that can be used to assess the annual risk of stroke and the need for anticoagulation in non-rheumatic AF. Treatment with warfarin is recommended for CHA2DS2VASc scores equal to or greater than 2. The CHA2DS2VASc score (see Table 3) includes the most common stroke risk factors in everyday clinical practice and has been validated in multiple cohorts (Table 3).

Table 3: CHA2DS2-VASc scoring system

CHA2DS2-VASc Clinical characteristics		**Points**
	Congestive Heart Failure	1
H	History of Hypertension	1
A	Age 75 years or older	2
D	Diabetes Mellitus	1
S	History of stroke or transient ischemic attack	2
V	Vascular disease	1
A	Age 65-74 years or older	1
S	Sex category female	1
	Total Score (Maximum points=9)	

8. Risk of bleeding

To assess the appropriateness of anticoagulant therapy, the risk of stroke should be weighed against the risk of bleeding. The risk of bleeding can be assessed using the HAS-BLED scoring system (Table10) where a bleeding risk score of ≥ 3 indicates a high-risk. Assessments may identify reversible risks that can be managed before the initiation of warfarin therapy (Table 4).

Table 4: HAS-BLED Scoring System.

HAS-BLED Clinical characteristics		Add points
H	Hypertension (uncontrolled, greater than 160 mmHg systolic)	1
A	Abnormal renal and liver function(1 point each)	1 or2
S	Stroke (previous history, particularly lacunar)	1
B	Bleeding (history or predisposition e.g. anemia)	1
L	Labile INRs (i.e. time in the therapeutic range is less than 60 percent)	1

E	Elderly (older than 65 years)	1
D	Drugs (e.g. non-steroidal anti-inflammatory or antiplatelet drugs, heparin or thrombolysis) or alcohol (1point each)	1 or 2
	TOTAL SCORE (Maximum points=9)	

9. Contraindication to the warfarin therapy protocol

In determining whether to start warfarin, absolute and relative contraindications must be considered. The lists below are not exhaustive.

Absolute contraindications to warfarin therapy include:

- Known large esophageal varices
- Significant thrombocytopenia (platelet count less than 50x109/L)
- Within 72 hours of major surgery with risk of severe bleeding: defer and reassess postoperatively
- Previously documented hypersensitivity (e.g. priapism or ischemic necrosis)
- Acute clinically significant bleed–defer and reassess stroke versus bleeding risk within three months
- Decompensated liver disease or deranged baseline clotting screen (initial INR Greater than 1.5)
- Pregnancy and within 48 hours postpartum. Warfarin is teratogenic and causes fetal bleeding. It is also associated with spontaneous abortions and perinatal bleeding

Relative contraindications to warfarin therapy include:

- Previous history of intracranial hemorrhage–seek specialist opinion
- Recent major extracranial bleeding within the last six months where the cause has not been identified or treated, defer the decision for warfarin therapy
- Peptic ulcer within the last three months: defer until peptic ulcer treatment is completed. Ensure peptic ulcer preventive therapy is initiated while on the anticoagulant therapy.
- Recent history of recurrent falls in patients at higher risk of bleeding (i.e. HAS-BLED Score greater than or equal to 3
- Dementia or marked cognitive impairment with poor medicine adherence and no care support
- Chronic alcohol abuse, especially if binge drinking
- Untreated or poorly controlled hypertension, consistently greater than 160/90 mm/Hg.
- Warfarin may be used during breastfeeding. It has not been detected in breast milk at doses upto12 mg per day. Therefore, higher doses may require periodic INR monitoring in infant

10. List of drugs that interact with warfarin

Warfarin is metabolized by the cytochrome P450 system (2C9, 3A4, and 1A isoenzymes). Drugs that are either hepatic enzyme inducers or inhibitors may affect INR. Table 5 summarizes a comprehensive list of drugs that potentiate or inhibit the anticoagulant effect of warfarin, which is rated according to the interaction direction, clinical severity, and quality of evidence, and developed lists of warfarin drug interactions considered highly probable, probable, possible, and highly improbable. When a potential warfarin-drug interaction is detected, healthcare professionals should determine the management of oral anticoagulation.

Severity of interaction

Major interaction: The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects, or the drugs are contraindicated for current use

Moderate interaction: The interaction may result in an exacerbation of the patient's condition and/or require an alteration in therapy

Table 5: Clinically Significant warfarin-Drug Interactions

Major interaction	
Allopurinol	Fluoxetine
Amiodarone	Gatifloxacin
Amoxicillin	Gemcitabine
Ampicillin	Gemifloxacin
Aspirin	Itraconazole
Azithromycin	Ketoconazole
Bicalutamide	Levofloxacin
Carboplatin	Linezolid
Cefepime	Mercaptopurine
Cefixime	Methotrexate
Cefotaxime	Metronidazole
Cefotaxime [Systemic}	Miconazole (Non-Systemic)
Ceftazidime	Moxifloxacin
Cephalexin	Nilotinib
Ciprofloxacin	Norfloxacin
Clarithromycin	NSAIDS
Clopidogrel	Oxaliplatin
Cloxacillin	Paroxetine
Cyclophosphamide	Penicillin G [Systemic]

Doxorubicin	Piperacillin -Tazobactam
Efavirenz	Rosuvastatin
Enoxaparin	Sertraline
Erythromycin	Simvastatin
Etoposide	Sulfamethoxazole/Cotrimoxazole
Fluconazole	Tamoxifen
Fluorouracil	Valproic Acid/Sodium Valproate
Moderate Interaction	
Amitriptyline	Imipramine
Atazanavir	Lopinavir
Atenolol	Lovastatin
Carbamazepine	Pantoprazole
Ceftriaxone	Paracetamol
Chlordiazepoxide	Phenobarbital
Cimetidine	Phenytoin
Cisplatin	Prednisolone
Combine oral contraceptive	PTU
Doxycycline	Ritonavir
Fluvastatin	Tetracycline
Glibenclamide	Thyroxin
Griseofulvin	

11. Warfarin reversal protocol for elevated INR with or without bleeding

An INR ≥ 5 significantly increases the risk of bleeding. Please refer to Table 6 for recommended actions regarding high INR results. Assess whether a patient with a high INR needs to be admitted to the hospital for specialized treatment, such as blood products, and monitoring purposes.

Major bleeding

Major bleeds are those that result in death, are life-threatening, cause chronic sequelae, or consume major healthcare resources. It includes

- Fatal bleeding, and/or
- 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
- Bleeding causing a fall in hemoglobin level of 20 g/L or 1.24 mmol /L) or more, or leading to transfusion of two or more units of whole blood or red cells

Minor bleeding

Minor bleeding includes access site, gastrointestinal, epistaxis, hematuria, gingival, and bleeding not stated under major bleeding.

Table 6: Warfarin reversal recommendation

INR level	**Recommendation if Rapid Reversal is NOT necessary**
INR greater than the therapeutic range but less than 4.5 and **No** bleeding	• Reduce or hold the next warfarin dose and/or reduce subsequent doses. • Resume a lower dose of warfarin once INR approaches therapeutic range. No need for vitamin K
4.5-10, **No** evidence of bleeding	• Hold warfarin. Consider oral vitamin K (1–2 mg) if the patient is at high risk of bleeding. • Check INR within 24 hours. Resume a lower dose of warfarin once INR approaches therapeutic range.
>10, no evidence of bleeding	Hold warfarin. Administer oral vitamin K (2.5–5 mg). May need to repeat Recheck INR in 24 hours.
INR Level	**Rapid Reversal Indicated**
Elevated, with a need for an urgent (but not lifesaving) procedure	Hold warfarin, give oral vitamin K 2.5-5mg
Elevated, with non-life threatening bleeding	Hold warfarin, give vitamin K 5-10mg IV by slow infusion, give fresh frozen plasma (FFP), or consider Prothrombin Complex Concentrates (PCCs)
Elevated, with the need for lifesaving procedure	Hold anticoagulation, give Vitamin K 5-10mg IV, give PCC
Elevated, with life-threatening, major bleeding	Hold anticoagulation, give Vitamin K 5-10mg IV, give PCC

12. Patient education on Anticoagulation protocol

Each patient enrolled in the PLAC receives counseling regarding the appropriate use of anticoagulation therapy. The pharmacist provides verbal and/or written educational material to new patients. Patients are comprehensively educated at their initial encounter(s) and briefly educated at each subsequent visit to reduce complications and improve the quality of care.

Patient education on anticoagulation therapy includes the following:

• The purpose of anticoagulation therapy and its relation to clot formation.

- Names of anticoagulant medications, their strengths, descriptions (such as color), and daily dosages (amount/number of tablets).

- How anticoagulant medications work.
- Potential implications of too much or too little anticoagulation.
- Reasons for the necessity of regular blood tests.
- The meaning of INR (International Normalized Ratio) and the desired INR range appropriate for the patient's treatment.
- The importance of close monitoring and adherence to the therapeutic plan.
- Common symptoms and signs of bleeding.
- Common symptoms and signs of thromboembolism (e.g., stroke, deep vein thrombosis, pulmonary embolism).
- Precautionary measures to reduce trauma and the risk of bleeding.
- Dietary, drug, and alcohol use patterns that may cause complications with anticoagulation therapy.
- The impact of disease processes (e.g., fever and diarrhea) on the response to anticoagulation therapy.

The necessity of informing healthcare providers about current anticoagulation therapy during scheduled or unexpected

Table 7: Addis Ababa University, College of Health Sciences, Tikur Anbessa Specialized Hospital (TASH)
Pharmacist –Led Anticoagulation Clinic (PLAC)
Warfarin Therapy/Anticoagulation Follow-Up Form

Name_____Age _____Sex____ MRN._____
Tel. No_____ Region/SubCity/Zone (Woreda):_____
Referring Physician: Dr_____Underlying Cardiac Problem_____
PLAC enrollment date:_____Warfarin Indication_____Target INR:

Keys:

			Warfarin dose:														
Follow up Date	**INR value**	***Anticoagulation Status**	**M**	**T**	**W**	**T**	**F**	**S**	**S**	****Action on warfarin dosing**	**Missed dose**	**Change in diet**	**Warfarin interacting drug(s)**	**Sign of bleeding (Yes/No)**	**Detail Notes**	**Next appointment date**	**Name and signature of pharmacist**

*** Anticoagulation Status:** Sub-therapeutic range, In therapeutic range, Supra therapeutic range
**** Action: Decrease, Continue the same, Increase, Omit, Omit and then decrease, Omit and then continue,**

ስለ ደም ማቅጠኛ መድሃኒት(ዋርፋሪን) ለታካምዎች ያምሰጥ

የተለያዩ የልብ ችግር በተለይም የሪሁማቲክ የልብ ችግር ያላቸዉ ታክምዎች በልብ ዉስጥ የደም መጓገል ሊያጋጥማቸዉ ይችላል፡፡ የጓገለ ደም ልብ ደም ሲረጭ ወደተለያዩ የሰዉነት ክፍሎች በመሄድ፣ የተለያዩ ችግሮች ያመጣል፡፡ የጓገለ ደም ከሚሰራጭባቸዉ የሠዉነት ክፍሎች ዉስጥ አንጓል፣ እግር ወይም እጅ እና ኩላሊት ዋናዎቹ ናቸዉ፡፡ ወደ ጭንቅላት ሲሄድ ስትሮክ (Stroke) ማለትም ድንገተኛ የሰዉነት ክፍል መዛል (ፓራላይዝ) መሆን ሲያመጣ፣ ወደ እግር ወይም እጅ ሲሄድ ድንገተኛ የእጅ ወይም የእግር መጥቆር (ጋንግሪን) ያመጣል፡፡ ይህንን ለመከላከልና ከተከሰተም ድጋሚ እንዳይወጣ የደም ማቅጠኛ መድኃኒቶች ይወሰዳሉ፡፡ የተለያዩ የደም ማቅጠኛ መድኃኒቶች ያሉ ሲሆን፣ በብዛት የሚወሰደዉ ዋርፋሪን (Warfarin)ተብሎ የሚጠራዉ መድኃኒት ነዉ፡፡ ይህ መድኃኒት ደም ቀጥኖ አደገኛ ደም እንዳይፈስና የሚፈለገዉ የደም ቅጥነት እንዲመጣ ፅኑ ክትትል ያስፈልገዋል፡፡ ክትትል የሚደረገዉ በናሙና ደም ምርመራ (INR) ሲሆን መጀመሪያ አካባቢ ይህ ምርመራ (INR) ቶሎ ቶሎ የሚሰራ ሲሆን፣ የሚበቃዉ የመድኃኒት መጠን ከታወቀ በኋላ ግን የINR ምርመራው ይምደረግበት በየአንድ ወር በላይ ልሆን ይችላል፡፡ ስለሆነም የሚያስፈልገዉ ዉጤት በመድሃኒቱ እንዲገኝና አደጋ የሆነ የደም መፍሰስ እንዳያጋጥም ታካምዉ ከፍተኛ ትኩረት ሰጥቶ መድኃኒቱን መዉሰድና ለክትትሉ እገዛ ማድረግ አለበት፡፡

የደም ከመጠን በላይ መቅጠን ምልክቶች

- ነስር፤ የሽንት ከወትሮ በላይ መቅላትና ደም መምሰል፤በደም አክታ መምጣት
- ሰዉነታችን በቀላሉ መድማትና መርፌ ስንወጋ ወይም ትንሽ ጉዳት ሲደርስ የደም ቶሎ ያለመቆም
- ድንገተኛ የመገጣጠሚያ እብጠት
- ቅጥነቱ የበዛ ሲሆን ጭንቅላት ዉስጥ ደም መፍሰስና የሠዉነት መዛል እንዲሁም ራስን መሳት

እነዚህ ምልክቶች ሲታዩና የደም ናሙና ምርመራ (INR) በጣም ከፍ ማለት (ከ 4.5 በላይ መሆን) ካለ ቶሎ ወደሕክምና ተቋም መሄድ ያስፈልጋል፡፡

ዋርፋሪን ሲወሰድ የሚደረጉ ተግባራት

- የታዘዘዉን የመድኃኒት መጠን ከሐኪሙና ከፋርማሲ ባለሙያ መረዳትና ትክክለኛዉን መጠን መዉሰድ
- መድኃኒቱን ሁልጊዜ በተመሳሳይ ሠዓት መዉሰድ (ምሽት ላይ ቢሆን ይመረጣል) ፡፡
- ከላይ የተጠቀሱትን አደገኛ ጉንዮሽ ጉዳት ሲኖር ቶሎ ሐኪም ቤት መሔድ፡፡
- የደም ናሙና ምርመራዉን በተመሳሳይ ጊዜ መስጠት (ማለትም ጠዋት ጠዋት)፡፡
- ከመድሃኒቱ ጋር የሚጋጩ መድኃኒቶች ብዙ ስለሆኑ ማንኛዉንም መድኃኒት ስታዝዝ ለሐኪሙ የደም ማቅጠኛ እንደሚወስድ መናገር፡፡
- መድኃኒቱ ከምንበላቸዉ ምግቦች ጋርም ስለሚጋጭ፣ አረንጓዴ ቅጠላማ አትክልቶችን መመገብ በየሳምንቱ ተመሳሳይ መጠን በመደበኛነት መብላት ይኖርበታል፡፡
- የማይበሉ ምግቦችን አለመመገብ፣የሚከለከሉት ምግቦች አረንጋዴ ቅጠላማ አትክልቶች ናቸዉ፡፡
- የደም ማቅጠኛ መድኃኒት ያለመደበኛ የደም ናሙና ክትትል መዉሰድ አደገኛነቱ ስለሚነላ ተገቢዉን የደም ናሙና ክትትል (INR) ማድረግ ይገባል፡፡

<u>የደም ማቅጠኛ መድሃኒት (ዋርፋርን) መከታተያ ቅጽ</u>

(የተጀመረበት ቀን_____) የምፈለገው INR መጠን_____

የዛሬው ክትትል ቀን	የINR መጠን	**<u>ዋርፋርን (</u>**Warfarin) tab_____mg በቀን የሚወሰድ የእንክብል መጠን							ቀጣይ ቀጠሮ የባለሙያ ስምና ፊርማ
		ሰኞ	ማ	ረ	ሐ	ዓ	ቅ	እ	