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ANTICOAGULATION MANAGEMENT PRACTICE, AND ASSOCIATED FACTORS IN ATRIAL FIBRILLATION PATIENTS ON WARFARIN THERAPY AT ST. PAUL HOSPITAL MILLENNIUM MEDICAL COLLEGE

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Anticoagulation Management Practice, and Associated Factors in Atrial Fibrillation Patients on Warfarin Therapy at Saint Paul Hospital Millennium Medical College

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A Thesis submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in Partial Fulfillment for the Requirements of Master of Science Degree in Pharmacy Practice.

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This is to certify that the thesis prepared by Nuredin Shiferaw, entitled with: Anticoagulation Management Practice, and Associated Factors in Atrial Fibrillation Patients on Warfarin Therapy at Saint Paul Hospital Millennium Medical College. Submitted in partial fulfillment of the requirements for the degree of Master of Science in Pharmacy Practice complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

Anticoagulation Management Practice, and Associated Factors in Atrial Fibrillation Patients on Warfarin Therapy at Saint Paul Hospital Millennium Medical College

Nuredin Shiferaw, Addis Ababa University, 2021

Anticoagulants are cornerstones in management of Atrial Fibrillation to prevent stroke. Monitoring of warfarin depends on time in therapeutic range, frequency of international normalization range measurements, warfarin dose adjustments, warfarin drug interaction and bleeding adverse event. This study aimed to assess the anticoagulation management, and factors affecting anticoagulation management in atrial fibrillation patients taking warfarin. Institutional-based Retrospective Cross-Sectional study was conducted from August to October 2019 at St. Paul Hospital Millennium Medical College. Data were collected retrospectively from a total of 300 patient medical records. Patients who have taken warfarin as an indication of primary prevention of atrial fibrillation were included in the study. A systematic random sampling technique was employed while recruiting the study participants. The data were entered to Statistical Package for Social Science window version 25 for analysis. Descriptive summaries were presented by using frequencies and percentages. Time in therapeutic range was calculated using the Rosendaal method, international normalization range frequency and drug interaction with warfarin were assessed and warfarin dose adjustments were also checked. Univariate and multivariate analysis were used to determine factors affecting time in therapeutic range and bleeding events. *P*-value ≤0.05 was considered as statistically significant. The mean age of the patient was 56.37 years and 65.3% of the study participants were females. Percent time in therapeutic range was found to be 42.03 ± 18.75. Only 12.67% patients had a time in the therapeutic range above 65%. Out of the 3162 INR tests, only 1094(34.60%) tests were within the therapeutic range. Bleeding event was recorded on 62 (20.70%) of the patients. Poor time in therapeutic range was associated with only age between 65 and 74, number of comedication of 1 and 2 and presence of congestive heart failure. Anticoagulation management was found to be poor in this study compared to other studies.

Key words: Warfarin, Bleeding, Time in Therapeutic range, Stroke, Atrial Fibrillation

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Contents

Abbreviations and Acronyms

AF	Atrial Fibrillation
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
$CHADS_2$	Congestive Heart failure, Hypertension, Age 75 years and above, Diabetes Mellitus, Prior stroke or transient ischemic attack
CHA_2DS_2- VASc	Congestive Heart failure, Hypertension, Age 75 years and above, Diabetes Mellitus, Prior stroke or transient ischemic attack, Vascular disease, Age 65-74 years, Sex category
CER	Comparative Effectiveness Review
ESC	European Society of Cardiology
GARFIELD-AF	Global Anticoagulant Registry in the Field–Atrial Fibrillation
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or Alcohol
$HEMORR_2HAGES$	History of bleeding, Hepatic or renal disease, Alcohol abuse, Malignancy, Older age, Reduced platelet count or function, Hypertension, Anemia, Genetic predisposition, Excessive fall risk, Stroke
INR	International Normalization Ratio
NVAF	Nonvalvular AF
NOACs	Non-Vitamin K Antagonists
OAC	Oral Anticoagulants
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
RCTs	Randomized Controlled Trials
SPHMMC	Saint Paul Hospital Millennium Medical College
TTR	Time in Therapeutic Range
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
WDI	Warfarin Drug Interaction

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1. Introduction

1.1. Background

One of the emerging major global health burdens is atrial fibrillation (AF). Atrial Fibrillation, an abnormal rate or rhythm of the heart, is the most common type of arrhythmia. It can lead to an increase in the risk of stroke (Akinboboye, 2015).

More than 1% of the adult population is affected in general population. But the actual prevalence may be higher due to many patients with AF remain undiagnosed. The prevalence of AF is increasing along with aging in the developed world, and it is associated with a fivefold increased risk of stroke, with 20% of all strokes associated with AF. In developed countries, coronary artery disease and hypertensive heart disease are the two most common causes for AF, while the large incidence of undertreated streptococcal infections in Africa contributes to the high burden of valvular AF associated with rheumatic heart disease (RHD) (Stambler and Ngunga, 2015; Al-Shamkhani, Ayetey and Lip, 2018). Although RHD is the major cause of AF in sub-Saharan Africa, non-valvular cardiac causes are rising due to epidemiological transition in the region (Nguyen, Hilmer and Cumming, 2013). AF may depend on additional risk factors, such as heart failure, hypertension, older age, diabetes, prior stroke, vascular disease, and female sex (Lip et al., 2010; Furie et al., 2012; Lau et al., 2017). Strokes related to AF tend to be associated with greater morbidity and mortality compared with non-AF-related strokes (Taggar and Marı, 2008).

Treatment options for patients with AF aim to control irregular heart rate or rhythm and prevent stroke (Kabra, Girotra and Sarrazin, 2016). Anticoagulation therapy is used to reduce the risk of stroke in patients with AF. Therefore, most AF patients will be on life-long oral anticoagulation therapy (Lip *et al.*, 2015; Lehto *et al.*, 2017).

The increase in warfarin usage over the last decade can undoubtedly be traced to overwhelming evidence of its effectiveness in preventing embolic strokes in patients with atrial fibrillation. A pooled analysis showed risk reduction for recurrent ischemic stroke for warfarin versus placebo of 64% (OR 0.36, 95% CI 0.20–0.65) (Klijn *et al.*, 2019). Despite this, its narrow therapeutic index makes it difficult to maintain patients within a defined anticoagulation range.

The quality of anticoagulation control, as reflected by the mean individual time in therapeutic range (TTR) is a major determinant of efficacy and safety of the Vitamin K antagonists (VKAs).

Indeed, if the TTR is >65%, the rates of stroke and major bleeding on VKA are low (Lip, 2015). In order to achieve the optimal clinical outcome, the TTR should be at least 65% or, while a 2020 European Cardiac Society guideline suggested ≥70% (Lip *et al.*, 2018; Hindricks *et al.*, 2020).

A meta-analysis showed the quality of anticoagulation control with VKAs has proven to be poor; with an estimated time spent in the therapeutic INR range (TTR) 55%. Thromboembolic events may occur more frequently at an INR <2.0 and major hemorrhagic events at an INR >3.0. Overall, 44% (39%–49%) of hemorrhages occurred when INRs were above the therapeutic range, and 48% (41%–55%) of thromboemboli took place when below it (Oake *et al.*, 2007; Baker, 2009; Klijn *et al.*, 2019).

Management decisions need to be individualized when considering thromboprophylaxis, balancing the risk of stroke against the risk of serious hemorrhage. This has led to the analysis of net clinical benefit comparing ischemic stroke with intracranial hemorrhage, at least for vitamin K antagonist (VKA; eg, warfarin) therapy (Singer *et al.*, 2009; Nielsen *et al.*, 2015). A pooled analysis showed an increase of major bleeding in patients treated with warfarin compared to placebo (OR 4.31, 95% CI 1.21–15.35) (Klijn *et al.*, 2019).

1.2. Statement of the problem

Achieving high-quality anticoagulation control can often be difficult and labor-intensive with warfarin due to its indirect mode of action and a large number of factors that influence its pharmacokinetics and pharmacodynamics (Baker, 2009) and close monitoring of the anticoagulant effect (international normalized ratio (INR) measures) between 2 and 3 (Singer *et al.*, 2009; Gallagher *et al.*, 2014). It is essential to aim for adequate therapeutic anticoagulation while limiting the risk of hemorrhagic complications (Vallakati and Lewis, 2016).

A meta-analysis conducted in US has reported that patients spend only about one-half the time within therapeutic INR (Baker, 2009). In clinical trials, the time in therapeutic range (TTR) for patients taking warfarin ranges between 55% and 66%, however, in real world clinical practice, the reported TTR is typically less than 60% even in developed countries. In Asian countries, the situation is even worse with TTR typically less than 40% (Dlott *et al.*, 2014; Chan *et al.*, 2016; Vallakati and Lewis, 2016). Reduced anticoagulation control in warfarin users has been associated with an increased risk of stroke and mortality (Gallagher *et al.*, 2011).

A 10% increase in time spent out of TTR is associated with a 29% increase in the risk of mortality, and a 10 to 12% increase in the risk of an ischemic stroke and other thromboembolic events (Jones *et al.*, 2005). In the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF) study, patients with TTR <65% had a 2.6-fold higher risk of stroke, 1.5-fold higher risk of major bleeding, and 2.4-fold higher risk of all-cause mortality (Haas *et al.*, 2016). A recent meta-analysis of 31 studies confirmed that increasing mean TTR is associated with a lower rate of both major bleeding and stroke/systemic embolism (Vestergaard *et al.*, 2017).

Despite the clear net clinical benefit of OACs in patients with AF at risk for stroke, major bleeding events, especially intracranial bleeds, may be devastating. Warfarin is the second most common cause of adverse drug events in emergency departments, and the overall risk of major bleeding averages 7-8% per year (Michel, 2009; Senoo, Lane and Lip, 2014). Raymond et al. showed that major bleeding events occurred in 41 out of 100 patients at a median of 19 months following warfarin initiation. (Seet *et al.*, 2014). Even though there is a study that includes all indications of warfarin, no such study was done only in AF patients taking warfarin in Ethiopia,

and findings of this study will assist treatment decisions in St. Paul Hospital Millennium Medical College (SPHMMC).

1.3. Significance of the study

Warfarin is still widely used anticoagulant in AF patients. Maintaining the quality of warfarin therapy by maintaining INR value is very difficult. This study focused on AF patients and tried to assess anticoagulation monitoring practice by calculating TTR. INR measurements were also assessed according to target INR ranges. This may help physicians to develop a mechanism in which patients may have a good therapeutic outcome.

Furthermore, the findings of this study may help in identifying predictive factors that affect TTR so that physicians can give much emphasis to improve patients' TTR value that may have a direct correlation with risk of stroke and bleeding.

The result of this study insight physicians and health professionals to use the risk of stroke scores regularly on each patient. It also helps to develop strategies to decrease the risk of bleeding and achieve optimal TTR. It also helps other researchers to have further investigations.

2. Literature review

2.1. Introduction

Atrial fibrillation (AF) is one of the major common and chronic disorders in modern cardiology. Due to its loss of heart rate control, diminished atrial contraction, and especially its propensity to thrombogenesis, AF can cause ischaemic stroke and systemic thromboembolism, heart failure, impaired quality of life, and frequent prolonged hospitalizations (A. John Camm *et al.*, 2012; Schwanda and Gruber, 2019).

2.2. Classification of Atrial Fibrillation

AF may be classified based on etiology, depending on whether it occurs without identifiable etiology in patients with a structurally normal heart, or whether it complicates hypertensive, valvular, or other structural heart disease. Hypertensive, valvular, ischaemic, and other types of structural heart disease underlie most cases of persistent and permanent AF (Kirchhof *et al.*, 2012; Prescott *et al.*, 2017).

Traditionally, AF in sub-Saharan Africa is related to rheumatic valvular heart disease (RVHD). However, with economic transition AF risk factors and complications are likely to change. A survey on a rural in-hospital population diagnosed with AF in west Shewa region, Ethiopia showed RVHD was found in 38.9% of patients, especially in females (41.1%) and young patients, whereas hypertension (HTN) and degenerative valvular disease were predisposing to AF in old patients (Bregani, Valcarenghi and Conti, 2019). Similar studies done in other parts of Ethiopia also reported that RVHD accounted for 2184(34.6%) (Yadeta *et al.*, 2017) and 74(35%) of cases (Endewunet *et al.*, 2020).

A classification system based on the temporal pattern of the arrhythmia has been recently recommended. Patients presenting to medical attention may have a first detected episode of AF or, if previous episodes have been documented, recurrent arrhythmia. Episodes themselves may be paroxysmal, if they terminate spontaneously, usually within seven days, or persistent if the arrhythmia continues requiring electrical or pharmacological cardioversion for termination. AF that cannot be successfully terminated by cardioversion, and longstanding (> 1 year) AF, where cardioversion is not indicated or has not been attempted, is termed permanent. Whereas, NVAF is AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or

mitral valve repair (Markides and Schilling, 2003; Kirchhof *et al.*, 2012; Craig T. January *et al.*, 2014).

2.3. Pathophysiology of Atrial Fibrillation

The pathogenesis of AF is now thought to involve an interaction between initiating triggers, often in the form of rapidly firing ectopic foci located inside one or more pulmonary veins, and an abnormal atrial tissue substrate capable of maintaining the arrhythmia. Although structural heart disease underlies many cases of AF, the pathogenesis of AF in apparently normal hearts is less well understood. Although there is considerable overlap, pulmonary vein triggers may play a dominant role in younger patients with relatively normal hearts and short paroxysms of AF, whereas an abnormal atrial tissue substrate may play a more important role in patients with structural heart disease and persistent or permanent AF (Markides and Schilling, 2003; Iwasaki *et al.*, 2011).

The determinants of the Virchow triad, including stasis, endothelial damage, and coagulation properties, are centrally involved in AF-related thrombus formation. Blood stasis, particularly in the blind-pouch atrial appendage, is the most important determinant. AF impairs atrial contractile function through multiple mechanisms, including reduced Ca^{2-} stores because of decreased APD and reduced ICaL, altered intracellular Ca^{2-} handling, and abnormal myofilament protein phosphorylation. Delayed return of contractile function after cardioversion results in late thromboemboli. Biomarkers suggest a prothrombotic role for local inflammation, along with coagulation system changes (Nattel and Opie, 2006; Watson, Shantsila and Lip, 2009; Wakili *et al.*, 2010; Pellman and Sheikh, 2015).

2.4. Risk of stroke in AF patients

The most serious and disabling complication of AF is thromboembolic stroke; AF serves as an independent risk factor for stroke. Estimates suggest that about 15% to 20% of US strokes can be attributed each year to AF (Prescott *et al.*, 2017).

Several studies have reported risk factors for stroke in patients with AF. A meta-analysis, with a total of 58,883 patients have found characteristics associated with a higher relative risk of stroke while on an OAC such as age ≥75 years, female sex, previous stroke/transient ischemic attack,

VKA naive status, moderate and severe renal impairment, aspirin use, and Asian race (Albertsen *et al.*, 2013; Yaghi and Kamel, 2017).

Over the years several stroke risk stratification systems have been developed using common and validated stroke risk factors in patients with AF, to aid decision-making for thromboprophylaxis. In 2010, a revised clinical risk stratification tool for predicting stroke and thromboembolism in AF provided some improvement in the predictive value of the existing $CHADS_2$ (1point for congestive cardiac failure, hypertension, age 75 years and above and diabetes mellitus. Prior stroke or transient ischemic attack is assigned 2 points) schema by including age 65–74 years, vascular disease and female gender to form the CHA_2DS_2 -VASc score (*Table 1*). Hence European Society of Cardiology (ESC) guidelines recommend OACs to male patients with AF and CHA_2DS_2-VASc score ≥ 2 and female patients with CHA_2DS_2-VASc ≥ 3, and to consider OACs for those patients with intermediate-risk (i.e., males with CHA_2DS_2-VASc ≥ 1 and females with CHA_2DS_2-VASc ≥ 2 (Kirchhof *et al.*, 2016). The 2019 American Heart Association/ American College of Cardiology/Heart Rhythm Society guidelines recommend oral anticoagulation for patients with a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered and no therapy for those with a CHA_2DS_2-VASc score of 0 in men and 1 in women. For patients with AF who have moderate-to-severe mitral stenosis or mechanical heart valves, warfarin is recommended (A. John Camm *et al.*, 2012; Craig T. January *et al.*, 2014; Lip *et al.*, 2015; January *et al.*, 2019).

A 2017 Comparative Effectiveness Review evaluated questions related to stroke prevention in patients with AF and atrial flutter and CHA_2DS_2-VASc scores have the best prediction ability for stroke events in patients with AF. Recent guidelines also recommend use of CHA_2DS_2-VASc scores as a simple clinical based stroke risk score to initially identify ‘low stroke risk’ patients that should not be offered antithrombotic therapy to prevent stroke and reduce mortality (AHRQ, 2017; Lip *et al.*, 2018).

Table 1: Risk of stroke scores for Atrial Fibrillation

CHA_2DS_2-VASc Clinical characteristics		Add points
C	Congestive Heart Failure	1
H	History of Hypertension	1
A	Age 75years or older	2
D	Diabetes Mellitus	1
S_2	History of Stroke or Transient Ischaemic Attack	2
V	Vascular disease	1
A	Age 65 years or older	1
Sc	Sex category female	1
	TOTAL SCORE (max9)	

Low risk- 0, Moderate risk -1 and high risk ≥2

2.5. Management of Atrial Fibrillation

Stroke prevention is the principal priority in the holistic approach to AF management. AF management requires patient centered and symptom directed decisions on rate or rhythm control ('Better symptom management') as well as 'Cardiovascular and other risk factor, and lifestyle management' (Lip *et al.*, 2018; Hindricks *et al.*, 2020). Rate control in AF is an important strategy. It impacts quality of life, reduces morbidity, and decreases the potential for developing tachycardia-induced cardiomyopathy. Multiple agents, including beta blockers, non-dihydropyridine calcium channel blockers, digoxin, and certain antiarrhythmic drugs, including amiodarone and sotalol, have been evaluated with regard to efficacy in attaining rate control. AV nodal ablation with permanent pacemaker implantation effectively controls and regularizes ventricular heart rate and, in selected patients, improves symptoms. Long-term AF management may attempt to restore and maintain sinus rhythm, commonly referred to as "a rhythm-control strategy," using a combination of approaches, including cardioversion, antiarrhythmic drugs, and radiofrequency catheter ablation in the setting of appropriate anticoagulation and rate control (Craig T. January *et al.*, 2014; Staerk *et al.*, 2017; January *et al.*, 2019). Anticoagulant therapy should be individualized on the basis of shared decision- making after discussion of the absolute

risks and relative risks of stroke and bleeding, as well as the patient's values and preferences. Recent guidelines recommended Novel Oral Anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, and edoxaban over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve). But warfarin is still the most commonly used oral anticoagulant in many countries (January *et al.*, 2019).

2.6. Pharmacology of warfarin

Vitamin K antagonists (VKAs) such as warfarin, produces their anticoagulant effect by inhibiting vitamin K epoxy reductase, which is required for the conversion of vitamin K to its active form vitamin KH2 (reduced form of vitamin K). Vitamin K dependent proteins such as clotting factors II, VII, IX, and X require c-carboxylation by vitamin KH2 for biological activity (Ageno *et al.*, 2012). The relationship between the dose of warfarin and the response varies between patients and is modified by genetic and environmental factors (dietary intake, drug interactions, critical illness, etc.) that can influence the absorption of warfarin, its pharmacokinetics, and its pharmacodynamics (Holbrook *et al.*, 2012).

Warfarin is effective for the primary and secondary prevention of Venous Thromboembolism (VTE), for the prevention of systemic embolism in patients with prosthetic heart valves or AF, acute myocardial infarction in high-risk patients; and stroke, or recurrent infarction, in patients with acute myocardial infarction (Garcia *et al.*, 2012).

2.7. Anticoagulation Management in Atrial Fibrillation

The use of oral anticoagulation (OAC) therapy resulted in a 64% reduction in stroke and a 26% reduction in all-cause mortality compared with control/placebo (Lip *et al.*, 2012) and while aspirin use was associated with a non-significant 19% risk reduction, with no impact on mortality (Craig T January *et al.*, 2014; Senoo, Lane and Lip, 2014). Randomized controlled trials (RCTs) have demonstrated that dose-adjusted warfarin reduces the risk of an ischemic stroke by up to 68% compared with no therapy (Han *et al.*, 2013).

An ideal quality indicator for outpatient oral anticoagulation would have several characteristics: it would be easy to abstract, calculate, and understand; improvement would be possible; and there would be strong evidence linking it to important outcomes, such as stroke, venous

thromboembolism, and major hemorrhage. Percent TTR has many of these characteristics (Rose *et al.*, 2011; Gateman, Trojnar and Agarwal, 2017). TTR is interpreted to be a reflection of the overall quality of anticoagulation achieved on warfarin in clinical practice as well as in pharmaceutical trials. TTR, by taking into account multiple INR values from contiguous visits, is used to reflect anticoagulation control over time (Farsad *et al.*, 2016).

There are three commonly accepted methods for calculating TTR; these are the Rosendaal (number of days in range divided by total monitored days); traditional (number of in-range visits divided by total number of visits) and cross-sectional (number of patients in range on last visit divided by number of patients) methods. The Rosendaal method assumes a linear progression of change in INR between a patient's visits; in other words, it assumes that the INR changes the same amount each day. Meanwhile, the traditional and cross-sectional methods do not treat INR as a dynamic value that changes over time. Instead, these methods consider each individual INR value to be static and binary, either in or out of range (Loeliger, 1985; Rosendaal *et al.*, 1993; Schmitt, Speckman and Ansell, 2003).

The efficacy and safety of VKA therapy is closely associated with the quality of OAC management, as reflected by the average percentage of TTR of the INR 2.0–3.0, the frequency of INR measurements, warfarin dose adjustments based on INR measurements, and number of drug interactions. Indeed, various studies have shown how a high TTR translates into a lower risk of stroke and bleeding, whilst on OAC. Experts have suggested that the minimum target TTR should be no less than 65 % (Ageno *et al.*, 2012; Mearns *et al.*, 2014).

Reports from the prospective multicenter FANTASIIA and ORBIT-AF registries found that mean TTR was 61.5% and 65%, respectively (Pokorney *et al.*, 2015; Esteve-Pastor *et al.*, 2017). A retrospective cohort study in ambulatory care clinics at tertiary care hospital in Saudi Arabia have found that the mean TTR was 59.0 ± 24.1%. Of 110 patients, 32.7% had poor anticoagulation control (Rosendaal TTR <50%), 40.9% had good control (TTR 50–75%), and only 26.4% had excellent anticoagulation control (TTR >75%) (Alyousif and Alsaileek, 2016).

Another study conducted in nine primary health care centers in Lithuania also found the mean time in therapeutic range (TTR) was 40.0% with only 20% of patients had TTR of > 65% (Urbonas *et al.*, 2019). Lower TTR values reported amongst 1,428 Chinese AF patients taking

warfarin in which mean and median TTR values were 38.2±24.4% (Chan *et al.*, 2016). Lower TTR values were also reported in Namibia (29.4% (Jonkman *et al.*, 2019), Botswana (30.8%) (Mwita *et al.*, 2018), and Ethiopia studies (29%) (Fenta, Assefa and Alemayehu, 2017)

For better outcomes, INR results should be kept within target range. But it is difficult to achieve this. Higher percentage of INR values within the therapeutic range and lower percentage below and above therapeutic range were reported in studies done in Portugal, Brazil, Kuwait, Jordan and South Africa (Zubaid *et al.*, 2013; Caldeira *et al.*, 2014; Sonuga *et al.*, 2016; Al-Momany *et al.*, 2019; Silva *et al.*, 2020). In a private setting study performed in Patients with NVAF in Brazil, 49.1 per cent of all INR values assessed were within the therapeutic range (2.0–3.0), while 26.1 per cent of all INR values were < 2.0 and 24.8 per cent were > 3.0. (Silva *et al.*, 2020). In a Kuwait study with NVAF patients, in 1808(48%) of the patients achieved the therapeutic range while the subtherapeutic range INR was 1429(38%) and the rest 533(14%), INR values were categorized under supratherapeutic range (Zubaid *et al.*, 2013). A South African study reported that out of 136 patients, 66 (48.5%) had INR values within the target range. It also showed that a total of 51.5% of the patients were out-of-range; of which 41.2% were sub-therapeutic, while 10.3% were supra-therapeutic (Sonuga *et al.*, 2016). The average percentage of time that patients remained above (INR > 3.0) and below the target INR (INR < 2.0) were 16.5% and 23.2%, respectively in Portuguese study patients in which more than 90% of study participants had AF (Caldeira *et al.*, 2014). A Jordanian study has shown a much higher percentage of INR values between therapeutic range (71.2%), while 14% were subtherapeutic and 8.1% were supratherapeutic (Al-Momany *et al.*, 2019).

A Namibian study reported lower percentage in which of all the INR values reported in the patients' records, 25.2% were within, 54.6% were below, and 20.1% were above the INR target (Jonkman *et al.*, 2019). A previous study in Tikur Anbessa, Ethiopia, only 971(43.2%) INR values were within the therapeutic range, while 873(38.9%) values were below therapeutic range while 401(17.9%) were above range. (Fenta, Assefa and Alemayehu, 2017).

Among patients treated with warfarin, the international normalized ratio (INR) should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable (January *et al.*, 2019). Alyousif and Alsaileek have

found that INR determination was done every 35 days in a study done in Saudi Arabia (Alyousif and Alsaileek, 2016). Longer INR monitoring was reported in Ethiopia in which the mean frequency of INR monitoring per patient was every 62.9 days (range 17.7–143.7 days) irrespective of patients' INR targets (Fenta, Assefa and Alemayehu, 2017).

Urbonas et al. have found that warfarin dose was not properly adjusted based on patients INR value. In about 40% of the cases with INR values outside the target range, no dose corrections were implemented. About 27% of decisions on warfarin dose adjustment were not consistent with the recommended warfarin posology (Urbonas *et al.*, 2019).

A number of factors were associated with poor anticoagulation control. FANTASIIA registry reported that Diabetes mellitus [odds ratio (q =OR) 1.38; P = 0.008], peripheral artery disease (PAD, OR 1.62; P = 0.048), and HAS-BLED (OR 1.13; P = 0.022) were independently associated with TTR < 70%. Patients with TTR < 70% had high risk of bleeding events (21.7 vs. 16.8%; P = 0.021) (Esteve-Pastor *et al.*, 2017).

A similar result has been reported from an ORBIT-AF registry study in U. S that patients with renal dysfunction, advanced heart failure, frailty, prior valve surgery and higher risk for bleeding (ATRIA) or stroke (CHA_2DS_2-VASc score) had significantly lowest TTR ($p<0.0001$ for all). Patients treated at anticoagulation clinics had only slightly higher median TTR (69%) than those not (66%) ($p<0.0001$) (Pokorney *et al.*, 2015). A Lithuanian study found that in the multivariate regression model, gender, HAS-BLED score, and warfarin treatment duration were associated with a TTR of ≥65% (Urbonas *et al.*, 2019).

Contradicting the above studies poor anticoagulation control was not associated with age, female sex, or duration of anticoagulation in a Saudi Arabian study. By contrast, there was a significant trend towards worse anticoagulation control in patients with higher $CHADS_2$ score ($p = 0.043$). Thirty-one patients (28.2%) had a history of prior stroke. The overall quality of anticoagulation was not significantly different between patients with and without stroke (TTR was 56.3% and 60.1%, respectively; $p = 0.46$) (Alyousif and Alsaileek, 2016).

VKAs are among the medications with the highest incidence of drug-related life-threatening events and top the list of interactions with foods, herbal supplements, prescribed drugs and over-

the counter medications. Interactions resulting in over- or under-anticoagulation drastically increase the risk of major hemorrhagic or thrombotic event (Ageno *et al.*, 2012). The most common class of drugs that interact with warfarin include anti-infectives (such as fluroquinolones, azole antifungals, protease inhibitors), anti-inflammatory drugs and cardiovascular drugs (Di Minno *et al.*, 2017).

A study done in Black Lion Hospital; Ethiopia identified a total of 76 (21.1%) WDIs using Micromedex online drug reference analysis. Moderate type of interaction was accounted for 75.4% of the total drug interactions and the remaining were the major type of interactions. Propranolol 24.7 (6.7%), and omeprazole 10 (2.8%) were among the most frequent drugs interacted with warfarin (Tadesse and Woldu, 2018). In another study done in South Africa, a total of 87 patients were on concurrent medications with possible drug interactions with warfarin. The most commonly used among such medications are simvastatin (57) and aspirin (35). Other medications with potential drug interactions that were used concurrently with warfarin include amiodarone (7), sodium valproate (3), methotrexate (1), allopurinol (8), SSRIs (1) and digoxin (12) (Sonuga *et al.*, 2016).

Bleeding is the most serious complication associated with anticoagulation therapy. Warfarin treatment confers a substantial risk of bleeding, and the reduction in thrombo-embolic events must be carefully weighed against the risk of bleeding for each individual patient. Non-modifiable and partially modifiable bleeding risks are important drivers of bleeding events in synergy with modifiable factors. These risk factors have been used to formulate various bleeding risk scores generally with a modest predictive ability for bleeding events. From bleeding risk prediction, the HAS-BLED score (Table 2)had the best evidence for predicting bleeding risk (moderate strength of evidence) (Lip *et al.*, 2012; Hoehmann, Gravina and Cuoco, 2017; Hindricks *et al.*, 2020)

In 4273 patients from two centers in Sweden, the frequency of major bleeding was 2.6. There was a correlation between age and the risk of major bleeding ($P < 0.001$) (Wieloch *et al.*, 2011). Observations from the 4060 patients in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial have shown a major bleeding occurred in 260 patients, an annual incidence of approximately 2% per year. Increased age, heart failure, hepatic or renal disease, diabetes, first AF episode, warfarin use, and aspirin use were significantly associated with major

bleeding. Minor bleeding was common with 738 patients reporting this problem in one or more visits (Dimarco *et al.*, 2005).

In another study done in Jordan the frequency of major bleeding events among all AF patients was 1.7%. Gastrointestinal bleeding was the major type of bleeding, which accounts for 68% (n = 17) of the cases. High PT-INR value was found in 96.3% (n = 28) of the patients, thereby making it the primary predictor of bleeding events. Other predictors including, advanced age, other comorbidities such as hypertension and multiple anticoagulation therapy were also observed to be significant (M Matalqah, Yehya and Al-Taani, 2019).

Table 2: Clinical risk factors in the HAS-BLED score

Risk factors and definitions		Add points
H	Uncontrolled hypertension SBP >160 mmHg	1
A	Abnormal renal and/or hepatic function Dialysis, transplant, serum creatinine >200 mmol/L, cirrhosis, bilirubin ≥2 upper limit of normal, AST/ALT/ALP ≥3 upper limit of normal	1point for each
S	Stroke Previous ischaemic or hemorrhagic[a] stroke	2
B	Bleeding history or predisposition Previous major hemorrhage or anemia or severe thrombocytopenia	1
L	Labile INR[b] TTR <60% in patient receiving VKA	2
E	Elderly Aged >65 years or extreme frailty	1
D	Drugs or excessive alcohol drinking Concomitant use of antiplatelet or NSAID; and/or excessive[c] alcohol per week	1point each
	TOTAL SCORE (max9)	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SBP = systolic blood pressure; INR = international normalized ratio; NSAID = Non-steroidal anti-inflammatory drug; TTR = time in therapeutic range; VKA = vitamin K antagonist.
a Hemorrhagic stroke would also score 1 point under the 'B' criterion.
b Only relevant if patient receiving a VKA.
c Alcohol excess or abuse refers to a high intake (e.g., >14 units per week), where the clinician assesses there would be an impact on health or bleeding risk.

3. Objective

3.1. General objective

To assess anticoagulation management and associated factors in AF patients on warfarin therapy at St. Paul Hospital Millennium Medical College

3.2. Specific objectives

- To determine the time in therapeutic range of INR among AF patients taking warfarin therapy
- To assess warfarin dose adjustments among AF patients taking warfarin therapy
- To identify predictive factors affecting time in therapeutic range among AF patients taking warfarin therapy
- To determine bleeding events and predictive factors range among AF patients taking warfarin therapy

4. Methods

4.1. Study Setting

The study was conducted at St' Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia. The hospital was established in 1968 GC, while the medical school opened in 2007 GC. It has a bed capacity of about 700. It provides services at emergency, inpatient and outpatient departments. It sees an average of 1200 emergency and outpatient clients daily. The outpatient departments have many specialty clinics and the cardiac clinic is one of them that serves patients with many cardiovascular disease conditions. It has more than 8 cardiologists and nurses (Geletu *et al.*, 2018).

4.2. Study design and period

Institutional based retrospective cross-sectional study was conducted from August 1st to October 31th 2019 at SPHMMC. The data were collected retrospectively from the medical records of patients.

4.3. Source and study population

4.3.1. Source population

All AF patients who were on warfarin and have follow up at cardiac clinic at SPHMMC were considered as source population.

4.3.2. Study population

AF patients' medical records who were on warfarin and had follow up at the cardiac clinic at SPHMMC from January 1 2017 to December 31, 2018 constituted the study population, and those patients who fulfilled the inclusion criteria were the sample population.

4.4. Sample size determination

The sample size was estimated using a single population proportion formula. Since there is no similar study, taking P-value of 0.5, 95% confidence interval, and 1.96 for Z and 5% for d, the sample size will be:

$$n = \frac{Z^2_{a/2}\, P\,(1-P)}{d^2}$$

The calculated sample size using this formula is 384. Since the anticoagulation clinic works every Wednesday morning and on average 9 patients with AF visits the clinic, the expected number of source population in the study period (N), would be 9* 104 weeks which is 936. The sample size was adjusted and calculated using the correction formula for N less than 10,000; $\boldsymbol{n \times N / n + N \sim 273}$. Adding a 10% contingency, thus final sample size used in this study was **300**.

A systematic random sampling technique was used to recruit samples for the data collection process. The actual sampling fraction (k^{th}) was calculated by dividing the total number of source population attending the clinic during the study period (936) by the corrected sample size (300) which is 3. Thus, every 3 patient's charts were reviewed.

4.5. Inclusion and exclusion criteria

4.5.1. Inclusion criteria

- Age greater than 18 years
- Patients who are on warfarin for at least 1month
- Patients who have at least 2 INR records

4.5.2. Exclusion criteria

Patient's chart with incomplete records of INR measurements and corresponding warfarin dose at the time of visit

4.6. Study variables

4.6.1. Dependent variables

- TTR value
- Bleeding events

4.6.2. Independent variables

- Age
- Sex
- Duration of warfarin therapy
- Dose and frequency of warfarin
- Concomitant medication
- INR value
- Presence of comorbid illnesses
- Any interacting drugs with warfarin

4.7. Data Collection Procedure

A pre tested tool was employed after reviewing similar articles that assessed Anticoagulation management in AF patients who were on warfarin therapy. The instrument includes variables included in the CHA_2DS_2-VASc score. These include socio-demographic characteristics, comorbid conditions such as hypertension, congestive heart failure, diabetes mellitus, stroke/transient ischemic attack, laboratory values such as INR, and any bleeding record. CHA_2DS_2-VASc score was calculated for each patient and TTR was calculated using Rosendaal's (Rosendaal *et al.*, 1993) method. The required information included the dates and results of all INR measurements during the observation time, as well as the dates of all bleeding events and INR values at the time of the event. Percentages of patients on subtherapeutic and supratherapeutic INR value would be described. The frequency of INR measurement was also assessed for optimal therapy.

A total of four (two pharmacists and two nurses) were recruited as data collectors. Before the actual data collection, data collectors were trained on how to collect the necessary data from the patient's chart using the data collection instrument, and sampling techniques, the ethical

principles and data management. Pre-testing was done and all necessary modifications were made on the data collection instrument.

Throughout the data collection process, close supervision was made by the principal investigator. The collected data were checked regularly for completeness and consistency.

4.8. Data analysis and interpretation

First, the data was checked for completeness and consistency. Then, data was exported to Statistical Package for Social Science (SPSS) window version 25 for analysis. A descriptive summary was presented by using frequencies and percentages. Univariate and multivariate analysis was used to measure the association of dependent and independent variables where 95% confidence interval (CI) and P-value of 0.05 was utilized to determine statistical significance. Micromedex online database was used to analyze drug interaction between warfarin and other drug prescribed for patients (*Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare.*, 2018).

4.9. Ethical considerations

Prior to study initiation, ethical clearance was obtained from Addis Ababa University, School of Pharmacy ethical review committee (reference number: ERB/SOP/1220/09/2019) and SPHMMC (reference number: PW123/12. Only numerical identification was used as a reference. Confidentiality and anonymity of subjects were maintained by not recording identifying details, such as name or any other personal identifiers. No disclosure of any name of the patients, the healthcare provider was made with the findings.

4.10. Operational definitions

Time in Therapeutic Range (TTR): a measure of quality of anticoagulation intensity and expressed as how much time the patient spent in the therapeutic range of INR. It is used as a surrogate marker to assess outcomes and an increased TTR is associated with a reduction in hemorrhage and thromboembolism.

Poor TTR: if a patient had a TTR value of <65% by calculating using the Rosendaal method

Minor bleeding: any bleeding events that did not cause fatality and not requiring a blood transfusion or hospitalization. This may include easy bruising and prolonged bleeding from minor cuts and injuries are common side effects of warfarin. Extensive large bruises, especially without a known cause, or bleeding that takes an unusually long time to stop, Nosebleeds, bleeding gums, and heavy menstrual periods are other common types of bleeding.

Major bleeding: any bleeding events that need medical attention. Experiencing red or black tarry stool, or red or dark brown urine, vomiting blood or coffee ground-like material, and coughing up blood are signs of major bleeding

Major drug interaction: the interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects.

Moderate drug interaction: the interaction may result in exacerbation of the patient's conditions and/or require an alteration in therapy.

5. Results

5.1. Socio-demography and clinical characteristics

Among the study participants, 65.3% were females and the mean age of the patients was 56.4 ±16.6 years old (20 -90 years range). (Table2)

Table 3: Socio-demographic characteristics of patients with AF taking warfarin at SPHMMC, Addis Ababa, Ethiopia, from January 2017-December 2018 (N= 300).

Variables		**N**	**%**
Sex	Male	104	34.7
	Female	196	65.3
Age	18-40	64	21.3
	41-64	108	36.0
	65-74	74	24.7
	≥ 75	54	18.0

Regarding the type of AF, 64% had non-valvular type AF. The most common comorbid conditions were chronic rheumatoid valvular heart disease (CRVHD). The mean number of medications prescribed along with warfarin was 3.1 ± 1.2 (1-9 range).

Table 4: Clinical characteristics of patients with AF taking warfarin at SPHMMC, Addis Ababa, Ethiopia, from January 2017-December 2018 (N= 300).

		Frequency	Percent
Type of AF	Non-valvular	192	64
	Valvular	108	36
Comorbid conditions	CHF	192	64
	CRVHD	186	62
	Hypertension	98	32.67
	Stroke	72	24
	Degenerative valvular Heart Disease	35	11.67
	Pulmonary hypertension	34	11.33
	Cardiomyopathy	26	8.67
	Hypertensive Heart Disease	22	7.33
	Hyperthyroidism	20	6.67
	Valve replacement	18	6
	DM	18	6
	Acute coronary syndrome	10	3.33
	Asthma	10	3.33
	Others*	27	9
$CHADS_2$-VA_2SC score	Score 1	16	5.3
	Score 2	72	24.0
	Score 3 and above	104	34.7
Number of medications	1 and 2	80	26.7
prescribed per patient	3-4	192	64.0
	5 and above	28	9.3

**include other cardiovascular diseases, DVT, Chronic Kidney disease, Epilepsy*

5.2. Time in therapeutic range

On average patients were on warfarin for 332.81 (63-691) days. The mean percentage TTR according to Rosendaal's method is 42.03 ± 18.75D. Patients spent on average 155.5 days below range, but only in 37.7 days, they spent above range. Among the 300 patients, only 38(12.67%) had spent their time in the therapeutic range above 65%.

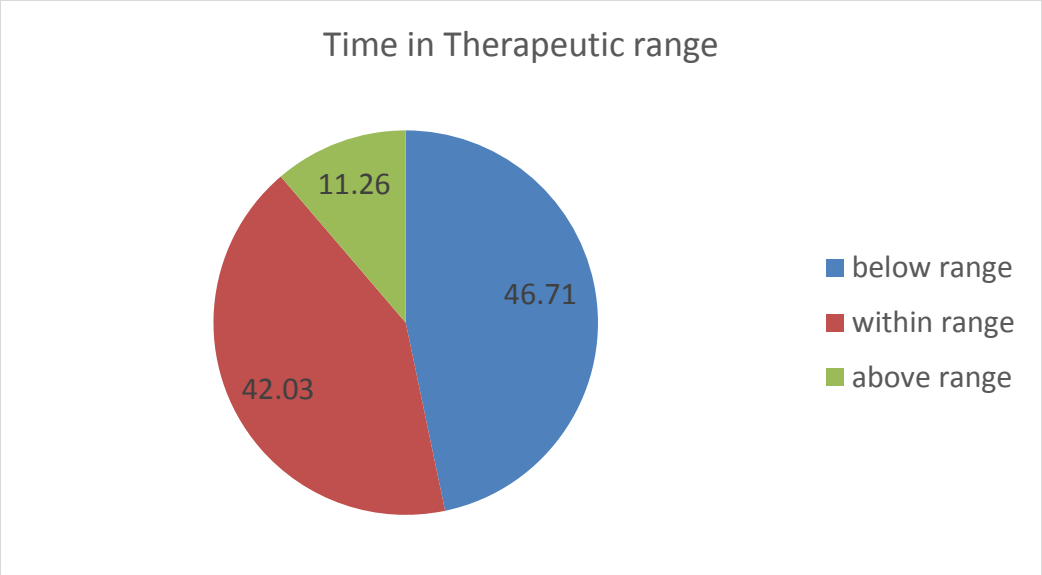

Fig 1: Percent TTR values of AF patients taking warfarin at SPHMMC, Addis Ababa, Ethiopia, from January 2017-December 2018 (N= 300).

5.3. INR Monitoring Practice

5.3.1. INR frequency

With regard to target INR range, 282 patients had a target range between 2.0-3.0, while the rest (18) patients had 2.5-3.5. On average, INR has been done every 35 days (16.3-67.2 days). Seventy (23.3%) patients had a mean INR measurement less than a month, while 183 (61) and 47 (15.6%) patients, INR was done between 4-6 weeks and above 6 weeks, respectively.

A total of 3162 INR tests with a mean of 10.54 ±4.27(range 3-18 INR tests) were determined during two years follow up for these patients. Among these only 1094 (34.6%) tests were within the therapeutic range. One thousand six hundred eight (50.85%) and 460 (14.55%) were below

and above therapeutic ranges respectively. None of the patients had all tests within the target range.

5.3.2. INR distribution

5.3.2.1. For target range of 2.0-3.0

The number of patients that had a target therapeutic range of 2.0-3.0 was 282. A total of 2902 INR tests were done, of which, 1020(35.15%) INR tests were within the therapeutic range. Among these tests, 1438(49.55%) were subtherapeutic, while 444(15.23%) were supratherapeutic.

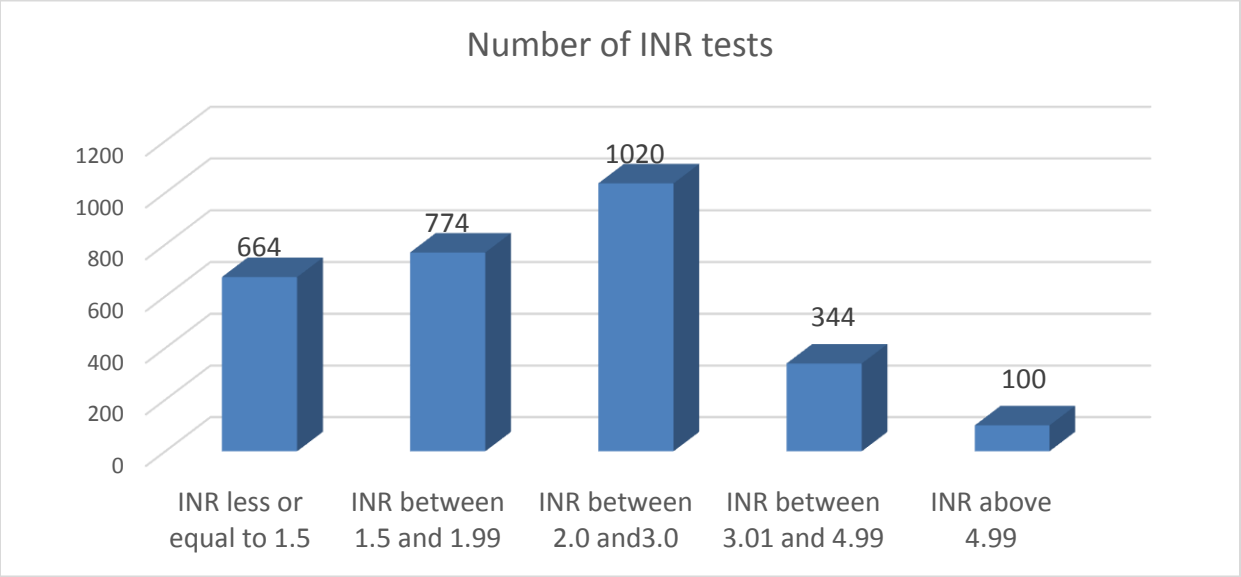

Fig 2: INR values distributions within different intervals of AF patients taking warfarin with a target range of 2.0-3.0 at SPHMMC, Addis Ababa, Ethiopia, from January 2017-December 2018 (N= 282).

5.3.2.2. For target range of 2.5-3.5

A total of 18 patients who underwent mechanical valve replacements were followed. There was a total of 260 INR tests done, of these, 74 tests were within the therapeutic range. Of tests done, 170 and 16 INR tests were subtherapeutic and supratherapeutic, respectively.

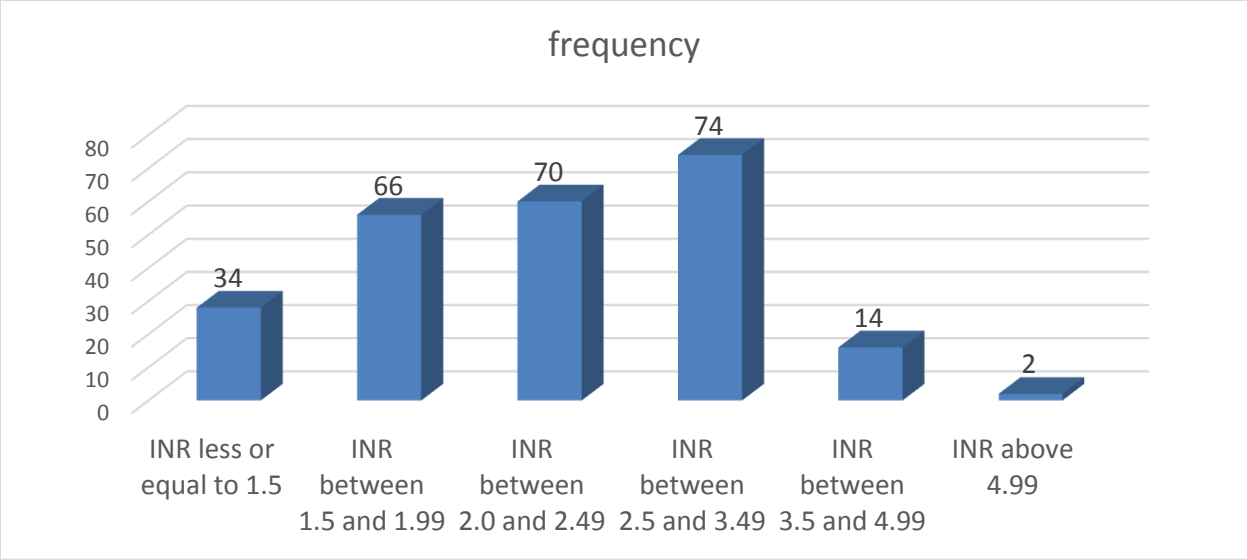

Fig 3: INR values distributions within different intervals of AF patients taking warfarin with a target range of 2.5-3.5 at SPHMMC, Addis Ababa, Ethiopia, from January 2017-December 2018 (N= 18).

5.4. Warfarin dose adjustment

Warfarin dose adjustment was needed 2064 times. But in only 1006(54.85%) times warfarin was dose adjusted. Of these, 682(67.79%) dose adjustments were done for subtherapeutic INR values, while the rest accounts for supratherapeutic INR values. For INR value below the therapeutic range, only 682(84.41%) were dose increments. But for supratherapeutic INR values, in 254 (69.09%) cases the dose was decreased while in 70 cases warfarin dose was stopped for up to 1 week.

Table 5: Out of range INR and corresponding warfarin dose adjustments of patients with AF taking warfarin at SPHMMC, Addis Ababa, Ethiopia, from January 2017-December 2018 (N= 300).

	number	Percent
below INR range but no change in warfarin	800	49.69
below INR range and warfarin was increased	682	45.94
below INR range but warfarin was decreased	126	4.37
above INR range but no change in warfarin dose	132	31.05
above INR range and warfarin was decreased	254	53.18
above INR range and warfarin was omitted/stopped and decreased	70	15.92

5.5. Types of drugs prescribed with Warfarin

Several medications were prescribed with warfarin concomitantly. The most common drug was frusemide in which 196 patients were taking it. Metoprolol and enalapril were given to 170 and 106 patients, respectively.

A total of 198 warfarin drug interactions (WDI) was found on 132 (44%) patients. Only 26 (19.39%) patients had two WDIs while 106 (81.61%) had only one WDIs. When checked for drug interaction using Micromedex Aspirin, Benzanthin Penicillin had major drug interactions, while atenolol, omeprazole and propranolol had moderate type of interactions. Only carbamazepine and phenobarbitone had decrease in effect of warfarin, while the rest potentiates and had higher risk of bleeding.

Table 6: Types of drugs prescribes with warfarin of patients with AF taking warfarin at SPHMMC, Addis Ababa, Ethiopia, from January 2017-December 2018 (N= 300).

Drug name	Frequency	Percent	Type of Drug interaction
Frusemide	196	65.3	
Metoprolol	170	56.7	
Enalapril	106	35.3	
Benzanthin Penicillin	72	24	Major
Spironolactone	66	22	
Atenolol	66	22	Moderate
Atorvastatin	62	20.7	
Digoxin	32	10.7	
Amlodipine	22	7.33	
Propylthiouracil	20	6.67	Moderate
Omeprazole	12	4	Moderate
Aspirin	10	3.3	Major
Metformin	10	3.3	
Hydrochlorothiazide	10	3.3	
Carvedilol	8	2.67	
Salbutamol	8	2.67	
Propranolol	6	2	Moderate
Simvastatin	4	1.33	Major
Insulin (NPH)	4	1.33	
Amiodarone	2	0.67	Major
Phenobarbitone	2	0.67	Moderate
Carbamazepine	2	0.67	Moderate
Indomethacin	2	0.67	Moderate
Others*	16		

*includes Alfuzosin, Beclomethasone aerosol, Telmisartan, Ferrous fumarate,

5.6. Predictive factors for the time in therapeutic range

All clinically relevant variables were entered into multivariate analysis and checked for association with poor time in therapeutic range (TTR less than 65%). Only number of comedication of 1 and 2 and the presence of CHF had shown significant association.

Association with predictive factors was checked first using univariate analysis. Considering p ≤0.25; age, number of medications, hypertension and diabetes melitus have shown statistical association. Taking these variables and adding CHF and stroke, since it is clinically significant variable, to multivariate analysis, only taking 1 or 2 medications along with warfarin was found to be protective by 81.1% than taking more than 2 medications (AOR=0.189 CI= 0.052-0.691, P=0.012). Similarly, the presence of CHF had 2.69 times the risk of having poor therapeutic outcomes (AOR =2.694; CI = 1.108-6.550, P=0.029).

Table 7: Predictive factors associated with poor time in therapeutic range of patients with AF taking warfarin at SPHMMC, Addis Ababa, Ethiopia, from January 2017-December 2018 (N= 300).

		TTR <65%	TTR ≥65%	COR	P- value	AOR	P- value
Age	18-40	59	5	0.68(0.19-2.36)	0.541	0.56(0.14-2.21)	0.409
	41-64	95	13	1.09(0.39-3.06)	0.863	1.32(0.44-3.40)	0.619
	65-74	60	14	**1.87(0.67-5.22)**	**0.234**	1.84(0.61-5.55)	0.278
	≥75	48	6	1		1	
Number of medications	1and2	74	6	**0.20(0.06-0.65)**	**0.007**	**0.19(0.05-0.69)**	**0.012***
	3 and 4	168	24	**0.36(0.14-0.90)**	**0.029**	0.51(0.17-1.53)	0.229

	≥5	28	8		1	1	
CHF	Yes	166	26	**1.25(0.60-2.59)**	**0.544**	**2.69(1.11-6.55)**	**0.029***
	No	96	12		1	1	
Hypertension	Yes	82	16	**0.63(0.31-1.25)**	**0.187**	1.54(0.70-3.39)	0.279
	No	180	22		1	1	
Stroke/TIA	Yes	62	10	0.87(0.40-1.89	0.721	2.19(0.95-5.07)	0.065
	No	200	28		1	1	
DM	Yes	14	4	**0.48(0.15-1.54)**	**0.218**	2.60(0.62-10.9)	0.192
	No	248	34			1	

5.7. Bleeding events

In this study, bleeding event was recorded in 62 (20.7%) patients. Among these, 5 of them had more than one (4 patients with 2 episodes and 1 patient with 3 episodes) episodes of bleeding events. At the time of bleeding events, 14 patients had INR value within therapeutic range, while 20 of them had INR range between 3.01 and 4.99 and 28 patients had INR range above 5.0. Among patients with bleeding, 14 of them had stroke. When checked for an association, the bleeding event was associated with sex, the presence of DM, and taking aspirin on both univariate and multivariate analysis. Female sex was associated with bleeding events than males (A-OR=0.353; C.I.= 0.184-0.674; p-0.002). Presence of DM as a comorbid condition and taking aspirin were associated with 5- and 10-times having bleeding events than vice versa (AOR =5.192 C.I.= 1.645-16.390; p-0.005 and AOR= 10.678; C.I. =2.499-45.636; p-0.001), respectively.

Table 8: Predictive factors associated with Bleeding of patients with AF taking warfarin at SPHMMC, Addis Ababa, Ethiopia, from January 2017-December 2018 (N= 300).

		Bleeding		C-OR		A-OR	
		Yes	No		P-value		P- value
Sex	Female	32	164	**0.48(0.27-0.85)**	**0.012**	**0.35 (0.18-0.67)**	**0.002***
	Male	30	74	1		1	
DM	Yes	8	10	**3.38(1.27-8.96)**	**0.014***	**5.19 (1.64-16.39)**	**0.005***
	No	54	228	1		1	
Aspirin use	Yes	6	4	**6.23(1.71-22.96)**	**0.006***	**10.68 (2.45-45.64)**	**0.001***
	No	56	234	1		1	

6. Discussion

The present study aimed to assess anticoagulation management practice and factors affecting anticoagulation management in AF patients on warfarin therapy at St. Paul Hospital Millennium Medical College. In doing so a total of 300 medical records of patients diagnosed with Atrial Fibrillation and treated with warfarin were assessed.

The mean age of patients was 56.37 years and the majority of the study participants (65%) were females. This finding was consistent with a study done in south Africa (Ebrahim *et al.*, 2018) but much lower than studies done in Europe and the USA(Rose *et al.*, 2011; Cotte *et al.*, 2014). This might be due to the high prevalence of rheumatic heart disease in younger patients; and female sex in this study and south African studies.

TTR was found to be 42.03%, with just 12.67% having TTR over 65 per cent. This is lower than the ESC guideline (Hindricks *et al.*, 2020), but comparable to the studies done in Chinese AF

patients (38.2%), Lithuania (40%) and Turkey (42.3%) (Turk *et al.*, 2015; Chan *et al.*, 2016; Urbonas *et al.*, 2019). This showed anticoagulation management in these countries were poor and difficult to manage.

Higher TTR values have also been reported than this finding. FANTASIIA and ORBIT-AF registries reported that TTR was 61.5% and 65% respectively (Pokorney *et al.*, 2015; Esteve-Pastor *et al.*, 2017). The discrepancy might be due to these studies only included patients with NVAF diagnosis and they had a study design of cohort. Other studies done in Saudi Arabia, Iran and Kuwait and Brazil also showed that the mean TTR was 59.0%, 54.9%, 52.6% and 56.6% respectively (Zubaid *et al.*, 2013; Alyousif and Alsaileek, 2016; Farsad *et al.*, 2016; Silva *et al.*, 2020). Even though higher than this study, these studies showed that, managing warfarin in real world practice is difficult.

Cotte et al., evaluated the TTRs of 6250 patients in four European countries (France, Germany, Italy, and United Kingdom) with atrial fibrillation who had been prescribed vitamin K antagonists. They concluded that 47.8%, 44.2%, 46.1%, and 65.4% of the evaluated patients had TTRs >70% in France, Germany, Italy, and the United Kingdom, respectively (Cotte *et al.*, 2014). Good control was also reported in Iranian (37.3%) and Brazil (31%) studies (Farsad *et al.*, 2016; Silva *et al.*, 2020) as compared to with just 12.67% in this study and a Lithuania study (20%) (Urbonas *et al.*, 2019).

On the other hand, a lower TTR values were reported in Namibia (29.4% (Jonkman *et al.*, 2019), Botswana (30.8%) (Mwita *et al.*, 2018), and Ethiopia studies (29%) (Fenta, Assefa and Alemayehu, 2017). This discrepancy may be clarified by these studies, which involve not only patients with atrial fibrillation but also other conditions for which warfarin was indicated.

In this study, it was found that only 1094(34.60%) INR tests were between therapeutic range, while 1608 (50.85%) and 460 (14.55%) INR tests were below and above therapeutic ranges respectively. This finding was much similar to a Namibian study in which of all the INR values reported in the patients' records, 54.6% were below, 25.2% were within, and 20.1% were above the INR target (Jonkman *et al.*, 2019). The lower percentage of patients with INR above the goal range in this study could be due to longer INR periods and lack of resources. A previous study in Tikur Anbessa, Ethiopia, 873(38.9%) values were below therapeutic range while 401(17.9%).

Only 971(43.2%) INR values were within the therapeutic range. But this study included not only AF patients but also other indications for warfarin (Fenta, Assefa and Alemayehu, 2017).

Higher percentage of INR values within the therapeutic range and lower percentage below and above therapeutic range were reported in studies done in Portugal, Brazil, Kuwait, Jordan and South Africa (Zubaid *et al.*, 2013; Caldeira *et al.*, 2014; Sonuga *et al.*, 2016; Al-Momany *et al.*, 2019; Silva *et al.*, 2020). In a private setting study performed in Patients with NVAF in Brazil, 49.1 per cent of all INR values assessed were within the therapeutic range (2.0–3.0), while 26.1 per cent of all INR values were < 2.0 and 24.8 per cent were > 3.0. (Silva *et al.*, 2020). In a Kuwait study with NVAF patients, the subtherapeutic range INR was 1429(38%), while in 1808(48%) of the patients achieved the therapeutic range and the rest 533(14%), INR values were categorized under supratherapeutic range (Zubaid *et al.*, 2013). A South African study reported that out of 136 patients, 66 (48.5%) had INR values within the target range. It also showed that a total of 51.5% of the patients were out-of-range; of which 41.2% were sub-therapeutic, while 10.3% were supra-therapeutic (Sonuga *et al.*, 2016). The average percentage of time that patients remained above (INR > 3.0) and below the target INR (INR < 2.0) were 16.5% and 23.2%, respectively in Portuguese study patients in which more than 90% of study participants had AF (Caldeira *et al.*, 2014). A Jordanian study has shown a much higher percentage of INR values between therapeutic range (71.2%); of which, 14% were subtherapeutic and 8.1% were supratherapeutic (Al-Momany *et al.*, 2019).

In this study, Warfarin dose needed to be adjusted 2064 times. But in 932(45.15%), warfarin dose was not adjusted despite the need for adjustment. The anticoagulation services are being provided once in a week. This would influence the management of non-therapeutic INRs and warfarin dose adjustment. But still, this is higher than the study in Namibia, which reported just 38.7% (Jonkman *et al.*, 2019). But this study didn't include characteristics that may have a significant impact on the anticoagulant response to warfarin (e.g. co-morbidities, concurrent medications, diet, alcohol use, smoking, and missed or extra doses). In Lithuania in which, in about 40% of cases of INR outside the target range, no dose corrections were implemented (Urbonas *et al.*, 2019). But similar to study done at Tikur Anbessa hospital, Ethiopia which reported 658(51.65%) (Fenta, Assefa and Alemayehu, 2017). INR should be monitored within a week after the occurrences of non-therapeutic ranges to adjust daily warfarin dose accordingly

(Holbrook *et al.*, 2012). Taking other alternative actions such as recommending non-pharmacological actions and managing warfarin interacting medications could be the reasons for providers' poor response on warfarin dose adjustment for patients in non-therapeutic INR ranges.

For supratherapeutic INR values, 304 (69.09%) warfarin dose was either decreased or omitted/stopped, while in 136 (30.91%) of cases warfarin dose was not changed. Similarly, a Namibian study also found that, in patients whose INR was supra-therapeutic, the warfarin dose was decreased in 62% of the patients, did not change in 23% (Jonkman *et al.*, 2019). As opposed to this study, warfarin dose was increased in 6% of cases. A higher proportion of improper dose modification was found in a study performed in Ethiopia in which only 218 (54.4%) warfarin doses were decreased and 123 (30.7%) and 60 (14.9%) warfarin doses were not adjusted and increased respectively (Fenta, Assefa and Alemayehu, 2017). Only limited patient information (age, gender, and indication for warfarin treatment) was available for analysis. But, in these studies, no information was available on important factors that could significantly affect warfarin anticoagulation control, such as diet, drug interactions, alcohol and tobacco use. Moreover, patient records were handwritten, which could have led to errors not only during clinical care, but also during transcription of the raw data to an electronic format for analysis. In a study done in Lithuania, warfarin dose was decreased in 276(61.1%) cases, while no dose correction was made in 169(37.4%) and the dose increased in 7(1.6%) patients (Urbonas *et al.*, 2019).

For INR value below the therapeutic range, out of 1602 dose adjustments, only 736(45.94%) were dose increments. Surprisingly 796(49.69%) and 70(4.37%) warfarin dose was not changed and even decreased respectively, despite being in the subtherapeutic range. These findings were similar to another study done in Ethiopia that found out of subtherapeutic range INR values, increased in 398 (45.6%) cases, unchanged in 343(39.3%) and decreased in 132(15.1%) cases. This study had much better achievement than in a study done in South Africa which reported the warfarin dose was increased in 26% of the patients, not changed in 44%, and decreased in 12% (Fenta, Assefa and Alemayehu, 2017; Jonkman *et al.*, 2019). Only 804(55.8%) cases warfarin was increased, while in 602(41.8%) and 34(2.4%) either no dose correction was made or dose decreased (Urbonas *et al.*, 2019).

In this study 44% of patients had WDIs. This is higher than a study done on Tikur Anbessa hospital which reported 21.1% (Tadesse and Woldu, 2018). This might be due to inconsistencies in practice and presence of higher comorbid conditions. Another study done on Ayder Referral hospital, Ethiopia reported that almost all (99.2%) of patients had WDIs (Teklay *et al.*, 2014). This higher rate might be due to the study was done in inpatients that needed intensive care. Furthermore, outpatients usually have few co-morbidities requiring less polypharmacy as they are relatively stabilized in which many interventions were made to optimize treatment outcome. In this study major WDIs accounted for 75% of all WDIs as opposed to studies done in Ethiopia (Teklay *et al.*, 2014; Tadesse and Woldu, 2018). This might be due to the high prevalence of use of antibiotics (Benzanthin Penicillin) in this study for the secondary prevention in CRVHD patients.

In this study, poor TTR was found to be affected by age and number of medications a patient taking. Conflicting findings have been published with respect to age. In comparison to this study, studies in South Africa have shown that older patients ≥55 years of age are more likely to have a therapeutic INR than younger patients. (Sonuga *et al.*, 2016; Ebrahim *et al.*, 2018). A Swedish study also found a correlation between improved TTR and older age (Wieloch *et al.*, 2011). However the efficiency of the anticoagulation was poor in the older population and there was a negative association between age and TTR levels in a study in Turkey (Turk *et al.*, 2015). Furthermore, many previous studies that focused on AF population found old age to be associated with lower TTR (Melamed *et al.*, 2011; Nelson *et al.*, 2013). Possible explanations of the negative correlation between age and TTR are age related changes in drug metabolism, higher prevalence of co-morbidities in older patients and decline in cognitive function with increasing age.

Comorbid conditions have been reported to affect TTR in previous literatures. The most common reported disease conditions were diabetes, CKD, CHF, and prior stroke (Nelson *et al.*, 2013; Silva *et al.*, 2020). This study was consistent with these findings in which CHF has a negative effect on TTR. This might be due to the more comorbid conditions, the more drugs needed to treat them which may have a drug interaction with warfarin. Apart from these, other variables were not found to affect TTR in this study. But other studies reported female sex had lower TTR values than males (Caldeira *et al.*, 2014; Silva *et al.*, 2020).

The most common complication of warfarin therapy was bleeding. This study found that 20.7% of patients had at least one episode of non-major bleeding. This was similar to the study that found 313(19.4%) patients had bleeding events of which 28(1.7%) had major bleeding (M Matalqah, Yehya and Al-Taani, 2019). However, a higher percentage of minor bleeding events recorded in a WATER registry in Turkey were found in 222 (38.8%) cases and significant bleeding was 29 (5.1%) (Turk *et al.*, 2015). Even though this study didn't assess the prevalence of major bleeding, due to the cross-sectional method used, many studies reported a life threatening Intracranial Hemorrhages and gastrointestinal bleeding events (Dimarco *et al.*, 2005; Turk *et al.*, 2015).

In this study, 48 (77.4%) patients that had bleeding, had elevated INR measurements, of which 20 (41.7%) of them had INR range between 3.01 and 4.99 and 28 (58.3%) patients had INR range above 5.0. This is higher than a study that reported Overall, 44% of hemorrhages occurred at INRs above the therapeutic range (Oake *et al.*, 2007). This is expected as INR levels increased so as risk of bleeding. However, bleeding might also happen even in target INR range. With this regard, 14(22.6%) patients had bleeding events even though their INR was within target range.

An AFFIRM study reported that Increased age, heart failure, hepatic or renal disease, diabetes, first AF episode, warfarin use, and aspirin use were significantly associated with major bleeding (Dimarco *et al.*, 2005). This aligns with the finding of the present study in which female sex, diabetes, and aspirin use were associated with bleeding.

7. Limitation of the study

The present study is not without limitations. While auditing patients' charts retrospectively, extract the necessary information was a continuous challenge. This was mainly due to poor organization in documenting of patients' history chronologically and; also, illegible physician handwriting. Moreover, the incompleteness of the patient charts hindered the ability to identify the number of bleeding or thromboembolic events from the study population. Only limited patient information (age, gender, and indication for warfarin treatment, drug interaction and comorbid conditions) was available for analysis. No information was available on important factors that could significantly affect warfarin anticoagulation control, such as diet, alcohol use, and nonpharmacologic interventions. The retrospective cross-sectional study design makes it difficult to show the direction of association of factors affecting TTR. The study conducted on a single-center; hence generalization to other patients treated for in other recent centers may not be possible

8. Conclusion

The time spent in therapeutic range among patients taking warfarin for atrial fibrillation is poor. Most of the time patients spent out of their target INR range. Warfarin dose adjustments were not done in most of the time. This study also showed that WDI is significant and the most common drug was Benzanthin Penicillin. Age, number of medications, and presence of HF as comorbid conditions were associated with poor TTR. The bleeding event was high in this study and was affected by male sex, presence of DM, and aspirin use.

9. Recommendation

Time in therapeutic besides INR values can be considered as an additional target for outcome assessment.

Standardized and/or hospital-based warfarin initiation and maintenance algorithms should be prepared and be availed at clinics

Emphasis should be given to patient education and awareness to increase patient knowledge

Bleeding events are common adverse events of warfarin therapy and could be fatal, so guidelines should be prepared for reporting and management of bleeding

Pharmacist managed anticoagulation clinics are nowadays available in most countries with better TTR, hence shifting towards it should be considered.

Other newer oral anticoagulants can be considered in selected patients who can afford to take them.

10. References

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11. Annex

Annex I: Data abstraction format

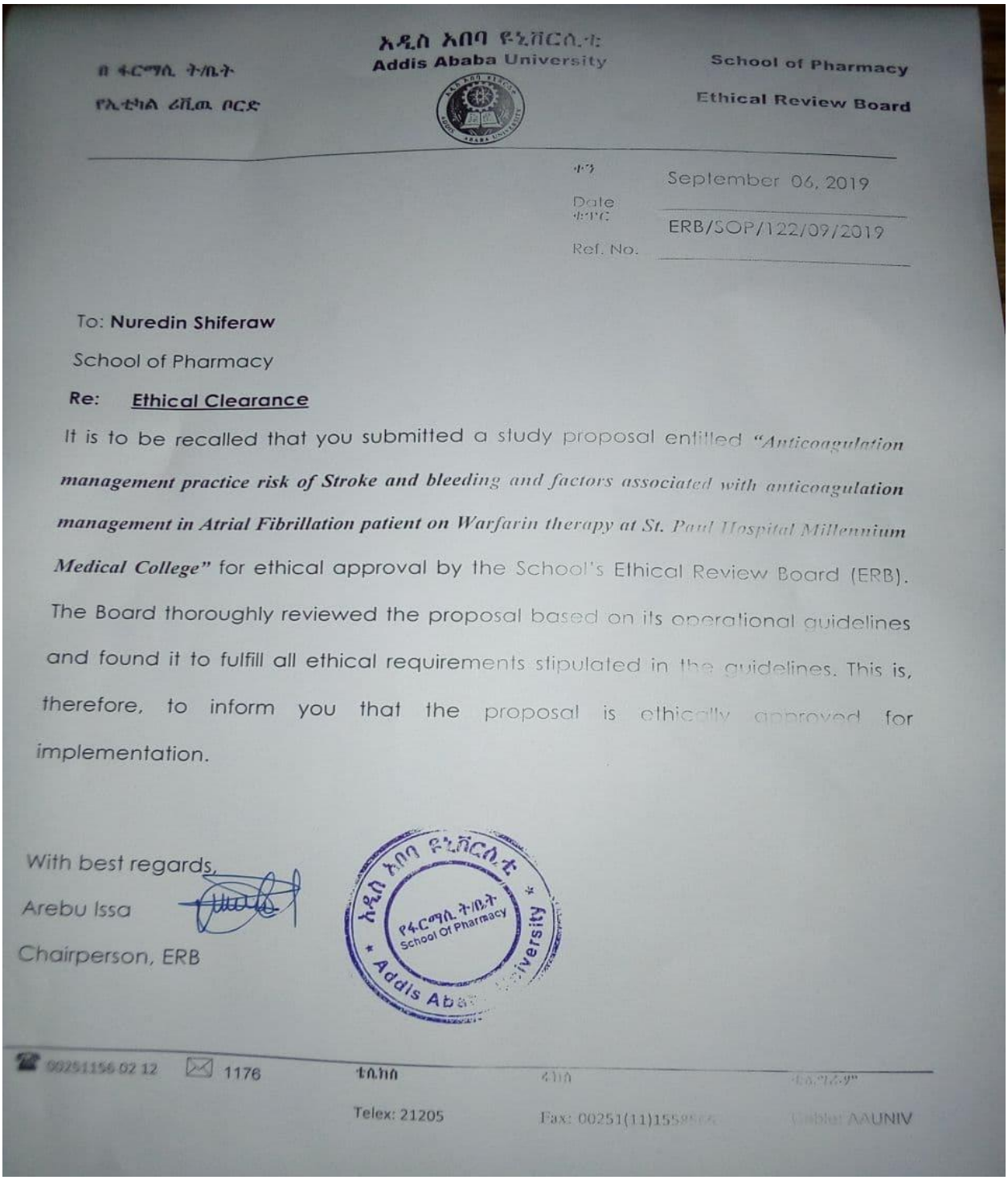
No	Question	
101	Code of the data collector	
102	Code of patient card	
103	Age of patient in years	
104	Sex of patient	1. M 2. F
105	Type of AF	1. Non valvular AF 2. Valvular AF (presence of severe mitral stenosis or valve placement) AF

106	Comorbid conditions	1.Hypertension 2.Congestive Heart Failure 3.Stroke/Transient Ischemic Attack 4.Diabetes Mellitus 5.Coronary Artery disease 6.Peripheral Artery disease 7.Chronic Rheumatoid Valvular Heart Disease 8.Others (specify) _____		
107.	INR value and dose of Warfarin	Day	INR value	Dose of Warfarin in mg /day
		Day1:	INR1:	
		Day2:	INR2:	
		Day3:	INR3:	
		Day4:	INR4:	
		Day5:	INR5:	
		Day6:	INR6:	
		Day7:	INR7:	
		Day8:	INR8:	
		Day9:	INR9:	
		Day10:	INR10:	
		Day11:	INR11:	
		Day12:	INR12:	
		Day13:	INR13:	
		Day 14:	INR14:	
		Day 15:	INR15:	
108	Medications other than warfarin	1.---------- 2. ---------- 3. ---------- 4.---------- 5.---------- 6.---------- 7.---------- 8.---------- 9.---------- 10.----------		
109	Any bleeding event	Event:	INR value	Warfarin dose
		Event1:		
		Event2:		
		Event3:		
		Event4:		
		Event5:		
		Event6:		
		Event7:		
110	Calculated CHA_2DS_2-VASc			

Annex II: Sample template for Rosendaal method of Time in Therapeutic Range calculation

test date	Inr	days since last date	inr diff	previous inr within range	current inr within range	scenario	inr diff above range	inr diff within range	inr diff below range	days within range since last test	days below range since last test	%days within range since last test	warfarin dose
1	2.09				in range								5
2	2.48	35	0.39	in range	in range	in range	0	0.39	0	35.00	0.00	100.00	5
3	1.63	49	-0.85	in range	below	calculate	0	0.48	0.37	27.67	21.33	56.47	2.5
4	1.43	35	-0.2	below	below	below	0	0	0.2	0.00	35.00	0.00	2.5
5	1.2	91	-0.23	below	below	below	0	0	0.23	0.00	91.00	0.00	2.5
6	3.3	28	2.1	below	above	calculate	0.3	1	0.8	13.33	10.67	47.62	5
7	1.58	56	-1.72	above	below	calculate	0.3	1	0.42	32.56	13.67	58.14	2.5
8	1.94	14	0.36	below	below	below	0	0	0.36	0.00	14.00	0.00	5
9	1.25	70	-0.69	below	below	below	0	0	0.69	0.00	70.00	0.00	5
10	4.67	56	3.42	below	above	calculate	1.67	1	0.75	16.37	12.28	29.24	7.5
11	1.3	14	-3.37	above	below	calculate	1.67	1	0.7	4.15	2.91	29.67	Omit
12	2.2	91	0.9	below	in range	calculate	0	0.2	0.7	20.22	70.78	22.22	5
13	1.29	63	-0.91	in range	below	calculate	0	0.2	0.71	13.85	49.15	21.98	5
Total		602								163.16	390.79	365.34	

Annex III: Ethical clearance



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Addis Ababa University

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School of Pharmacy
Ethical Review Board

ቀን Date: September 06, 2019

ቁጥር Ref. No.: ERB/SOP/122/09/2019

To: **Nuredin Shiferaw**

School of Pharmacy

Re: **Ethical Clearance**

It is to be recalled that you submitted a study proposal entitled *"Anticoagulation management practice risk of Stroke and bleeding and factors associated with anticoagulation management in Atrial Fibrillation patient on Warfarin therapy at St. Paul Hospital Millennium Medical College"* for ethical approval by the School's Ethical Review Board (ERB). The Board thoroughly reviewed the proposal based on its operational guidelines and found it to fulfill all ethical requirements stipulated in the guidelines. This is, therefore, to inform you that the proposal is ethically approved for implementation.

With best regards,

Arebu Issa

Chairperson, ERB

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