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Anticoagulation Control, Outcomes, and Associated Factors in Patients with Atrial Fibrillation Receiving Warfarin at Tertiary Care Hospital in Ethiopia

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Abstract

Anticoagulation is the cornerstone in the prevention of stroke in atrial fibrillation. This study aimed at assessing the anticoagulation control and outcome and predictive factors in atrial fibrillation patients on warfarin therapy. A retrospective chart review was used to evaluate patients with atrial fibrillation who were on warfarin during two years follow up at the anticoagulation clinic of the hospital. The time in therapeutic range (TTR) was calculated using Rosendaal's method. Data were analyzed using SPSS software version 25. Univariable and multivariable analyses were computed to determine factors affecting TTR and bleeding events. We included 300 patients in this study. The mean percentage TTR was 42.03 ± 18.75. Only 38 (12.67%) patients achieved a TTR of above 65%. The average international normalized ratio (INR) testing frequency was 35 days (16.3-67.2 days). Taking 1 or 2 drugs along with warfarin was found to be better in achieving good TTR as compared to taking more than two drugs ($p = .014$). Having heart failure was associated with a 2.45 times odds of poor anticoagulation control (TTR< 65%) ($p = .047$). Male study participants were 2.53 times more likely of developing bleeding events than females ($p = .009$). Bleeding events were observed in 62 (20.67%) patients. Study participants, who didn't have Diabetic Mellitus and those not receiving aspirin were at lower odds developing bleeding events (AOR = .196; C.I. = .060-.638; p−.007 and AOR = .099; CI. = .024-.416; p−.02), respectively. In summary, the time spent in the therapeutic range was minimal in this population of patients with AF on warfarin managed at a hospital run anticoagulation clinic in Ethiopia. Moreover, the number of co-prescribed medications, and having heart failure were associated with poor TTR. Bleeding events were high and affected by male sex, having DM comorbidity, and using aspirin.

Keywords

anticoagulation, atrial fibrillation, warfarin, international normalized ratio, time in therapeutic range, Ethiopia

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Background

According to the Global Burden of Disease project estimation, the worldwide prevalence of atrial fibrillation (AF) was around 46.3 million individuals in 2016.[1] The actual prevalence might be higher because many patients with AF remain undiagnosed.[2,3] The occurrence of AF is increasing along with age, and it is associated with a fivefold increased risk of stroke.[4] AF is an independent risk factor for developing stroke and about 15% to 20% of US strokes were attributed each year to AF.[5]

Stroke related to AF tends to be associated with higher morbidity and mortality than non-AF-related stroke.[6] Treatment for patients with AF aims to control rhythm irregularity and prevent stroke.[6,7] Anticoagulants are among the commonly used treatment options for patients with AF. They are capable of reducing the risk of stroke in patients with AF and most patients are on life-long oral anticoagulation.[7,8] The effectiveness of warfarin in preventing embolic strokes in AF patients is well documented.[9,10] Despite that, its narrow therapeutic index makes it challenging to maintain patients within a defined anticoagulation range.[11]

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The quality of vitamin K antagonists (VKAs) is reflected by the mean individual time in the therapeutic range (TTR). In patients on VKAs, achieving the TTR of ≥65% results in optimal anticoagulation with reduced risk of stroke and bleeding.[12] The recent European Society of Cardiology (ESC) guideline recommends a TTR of >70% for AF to ensure good quality of VKA treatment.[13] Anticoagulation with VKAs is considered to be poor when an estimated TTR is less than 55%.[14] Achieving high-quality anticoagulation can often be challenging and labor-intensive with warfarin due to various factors related to its narrow therapeutic index.[11] In clinical practice, the reported TTR is typically less than 60% even in developed countries.[15] In Asian countries, the situation is even worse, with TTR typically less than 40%.[8–10] Reduced anticoagulation control in warfarin users is associated with an increased risk of stroke and mortality.[16] Another challenge with TTR is it doesn't remain stable over time as reported elsewhere by many studies.[17–19]

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.[20] A meta-analysis of 31 studies confirmed that increasing mean TTR is associated with a lower rate of major bleeding and stroke/systemic embolism.[21] When the time spent out of the therapeutic range increases by 10%, there is 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.[22]

Despite the apparent clinical benefit of VKAs 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 to 8% per year.[23,24] Raymond *et al.* showed that major bleeding events occurred in 41 out of 100 patients at a median of 19 months following warfarin initiation.[25] There are minimal published studies evaluating anticoagulation control in Ethiopian populations. However, a study at a tertiary care teaching hospital reported a TTR of 29% in patients who received warfarin for many indications.[11] However, no study addressed AF patients taking warfarin, and hence, the current study is the first of its kind. This study focused on AF patients and tried to assess anticoagulation monitoring practice by calculating TTR and INR levels and their corresponding target ranges. The results will help physicians to give more emphasis to improve patients' TTR value and to use the risk of stroke scores regularly for each patient which may in turn help to decrease the risk of stroke and bleeding. Therefore, the current study assessed the anticoagulation management practice and associated factors in patients with AF on warfarin therapy at Saint Paul's Hospital Millennium Medical College (SPHHMC), Ethiopia.

Materials and Methods

Study Setting

This study was conducted at Saint Paul's Hospital Millennium Medical College (SPHMMC) which is governed by a board under the Federal Ministry of Health, Addis Ababa, Ethiopia. This largest teaching hospital has about 700 beds with an average of 1200 emergency and outpatient visits daily.[26]

Study Design and Period

The current study was a single-centered retrospective study conducted on patients with AF who visited the anticoagulation clinic of the hospital from January 1, 2017, to December 31, 2018 (two years). Patients' charts were reviewed for data collection.

Inclusion and Exclusion Criteria

Patients on warfarin (≥1 month), who have ≥2 INR records, and age of >18 years were included in this study. However, those with incomplete records on INR measurements and corresponding warfarin dose; and other relevant clinical information were not eligible for the study.

Sample Size and Sampling Technique

The sample size was estimated using a single population proportion formula by taking estimating prevalence of .5 as there was no similar study in AF and then the sample size was calculated to be 384. Since the anticoagulation clinic of the studied hospital works once a week and on average nine patients with AF visit the clinic. The expected number of the study population (N) in the study period was approximately 936 (9*104). The sample size was adjusted and calculated using the correction formula for N less than 10 000; $n \times N/n + N \sim 273$. Adding a 10% contingency, the final sample size used in this study was 300. By using a systematic random sampling technique, we selected samples for the data collection process. The actual sampling fraction (k^{th}) was determined by dividing the total number of source population attending the clinic during the study period (936) by the corrected sample size (300). Thus, the sample fraction was determined as 3.

Study Variables

Time in therapeutic range value and bleeding events were the dependent variables. Independent variables were age, sex, duration of warfarin therapy, dose and frequency of warfarin, concomitant medication, INR value, presence of comorbid illnesses, and any interacting drugs with warfarin in this study.

Data Collection Tool

The data collection tool that was prepared after reviewing similar articles that assessed anticoagulation management in AF patients on warfarin therapy was utilized in this study. The instrument includes a revised clinical risk stratification tool for predicting stroke (ie CHA_2DS_2 -VASc score) which

allocates (1 point for heart failure, hypertension, diabetes mellitus, and vascular diseases; 2points for age ≥ 75 years and prior stroke/transient or ischemic attack)[27] and other clinical characteristics such as INR values, and any bleeding record. We calculated the CHA_2DS_2-VASc score for each patient and TTR was computed using Rosendaal's method. This method adds each patient's time within the therapeutic range and divides it by the total time of observation. This assumes that between-test INR varies linearly.[28] The recorded data include INR values and their determination dates; and the bleeding events and their dates of occurrence. 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.[29]

Data Collection and Quality Management

A total of four personnel (two pharmacists and two nurses) collected the data. Before conducting the data collection, training was provided to the data collectors on data collection procedures (how to extract the required information from patients' charts) using the data collection tool. We pre-tested the tool and included all the necessary modifications before using it for actual data collection. The completeness and consistency of the data were regularly monitored and supervised throughout the data collection process.

Data Analysis

Data was entered and analyzed by the Statistical Package for Social Science (SPSS) Version 25 software. Frequencies and percentages were used to express the descriptive analysis parameters. Univariable and multivariable analyses were computed to measure the association of dependent and independent variables, and a 95% confidence interval (CI) and *P*-value of .05 were used to determine statistical significance. A Micromedex online database was employed to check for a drug-drug interaction between warfarin and other co-prescribed drugs (s) for patients.[30]

Ethical Considerations

Addis Ababa University, School of Pharmacy, Ethical Review Committee, and SPHMMC granted ethical clearance for this study with a reference number of ERB/SOP/1220/09/2019 and PW123/12, respectively. Study participants' confidentiality and anonymity were kept by omitting patient identifiers, such as names or other personal identifiers.

Results

Socio-Demographic and Clinical Characteristics

Among the study participants, 65.3% were females. The mean age of the patients was 56.4 ± 16.6 years. About two-third of patients (64%) had a non-valvular type of AF. The most common comorbid conditions were heart failure and chronic rheumatic valvular heart disease. The mean number of medications prescribed with warfarin was 3.1 ± 1.2 (1-9 range). The overall results on socio-demographic and clinical characteristics were presented in Table 1.

INR Monitoring Practice

INR Frequency

A total of 3162 INR tests with a mean of 10.54 ± 4.27 were determined per patient during the two years' follow-up.

Table 1. Sociodemographic and Clinical Characteristics of Patients with AF taking Warfarin at SPHMMC (*N* = 300).

Socio-demographic and clinical characteristics		Number (*N*)	Percent (%)
Sex	Male	104	34.7
	Female	196	65.3
Age	18 to 40	64	21.3
	41 to 64	108	36
	65 to 74	74	24.7
	≥ 75	54	18
Type of AF	Non-valvular	192	64
	Valvular	108	36
Comorbid Conditions	Heart Failure	192	64
	Chronic rheumatic valvular heart disease	186	62
	Hypertension	98	32.7
	Stroke	72	24
	Degenerative valvular heart disease	35	11.7
	Pulmonary Hypertension	34	11.3
	Cardiomyopathy	26	8.7
	Hypertensive Heart Disease	22	7.3
	Hyperthyroidism	20	6.7
	Valve Replacement	18	6
	Diabetic Mellitus	18	6
	Ischemic Heart disease*	10	3.3
	Asthma	10	3.3
	Others**	27	9
CHA_2DS_2-VASc Score	1	28	9.3
	2	108	36
	≥ 3	164	54.7
Number of Medications Prescribed per patient	1 to 2	80	26.7
	3 to 4	192	64
	≥ 5	28	9.3

*Include acute and coronary syndrome and peripheral artery disease; **include other cardiovascular diseases, deep vein thrombosis, chronic kidney disease, and Epilepsy.

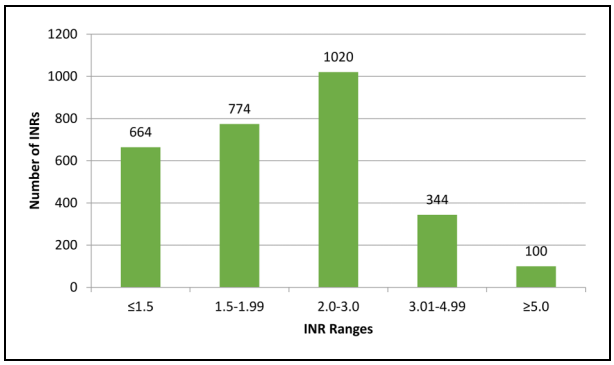

Figure 1. INR values distributions within different intervals among patients with AF taking warfarin at SPHMMC for achieving INR 2.0 to 3.0 ($N = 2902$).

Among them, 1094 (34.6%), 1608 (50.85%), and 460 (14.55%) were within the therapeutic range, below, and above therapeutic ranges, respectively. None of the patients had all tests within the target ranges. The average rate of INR testing was 35 days (16.3-67.2 days). In most of the study participants (61%), INRs were determined in the interval of four to six weeks. In 23.3% and 15.6% of patients, INR monitoring was made within four weeks and above six weeks, respectively.

INR Distribution

Regarding the target INR range, 282 patients had a target range between 2.0 to 3.0, and only 18 patients had 2.5 to 3.5 target ranges. For the 2 to 3 target range, out of 2902 INR tests, 1020 (35.15%) INR tests were within the therapeutic range. The remaining 1438 (49.55%) and 444 (15.23%) INR tests were sub-therapeutic and supra-therapeutic INRs, respectively (Figure 1).

Among eighteen patients who had mechanical valve replacements and need to achieve INR of 2.5 to 3.5, a total of 260 INR tests were determined. The majority of INRs being subtherapeutic, only 74 (28.46%) INRs were within the therapeutic ranges and the INRs distributions were illustrated in Figure 2.

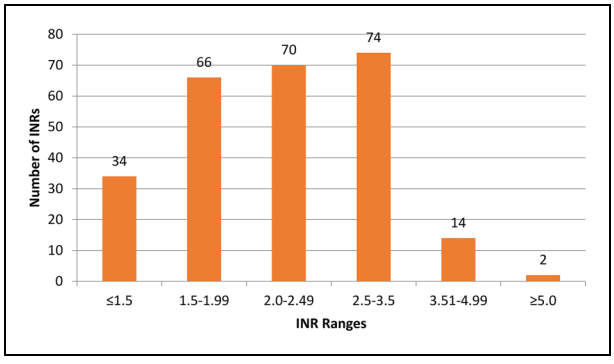

Figure 2. INR values distributions within different intervals among patients with AF taking warfarin at SPHMMC for achieving INR 2.5 to 3.5 ($N = 260$).

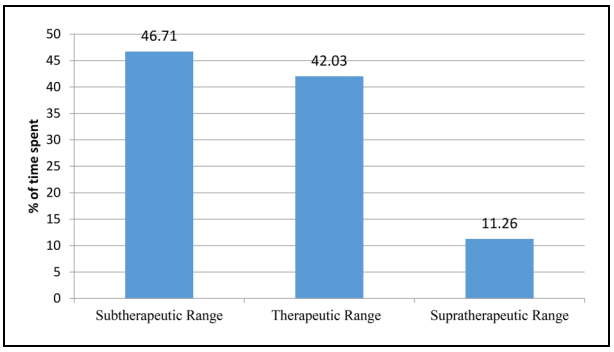

Figure 3. Time spent in different INR ranges in patients with AF receiving warfarin at SPHMMC ($N = 300$).

Time in Therapeutic Range (TTR)

The mean percentage TTR according to Rosendaal's method is 42.03 ± 18.75 SD (Figure 3). Only 38 (12.67%) patients had spent their TTR of $\geq 65\%$.

In this study, a higher number of patients were recorded in intermediate and higher stroke risk groups in both TTR cut-off ranges (TTR $< 65\%$ and TTR $\geq 65\%$). Table 2 shows TTR ranges according to CHA_2DS_2-VASc score groups.

Warfarin Dose Adjustment

In this study, warfarin dose adjustment was required 2064 times for non-therapeutic INRs. However, for only 1132 (54.74%) non-therapeutic INRs, warfarin dose was adjusted in this study. From the adjusted ones, 808 (71.38%) and 324 (28.62%) were for sub-therapeutic and supra-therapeutic INR values, respectively (Table 3).

Co-Prescribing After Warfarin

Out of large numbers of co-prescribed drugs, 176 of them have interaction with warfarin in 132 (44%) patients. Eight (6.06%) patients had two warfarin drug interactions (WDIs), while 124 (93.94%) had only one WDI. The specific types of WDIs (only major and moderate interactions) were indicated based on the Micromedex interaction checker in Table 4.

TTR Predictor Factors

In all variables with $p < .25$, unilateral analysis was entered into multivariate analysis and checked for association with poor

Table 2. TTR ranges according to CHA_2DS_2-VASc Score.

		TTR Ranges		
		TTR < 65%	TTR ≥ 65%	Total
CHA_2DS_2-VASc Score	1	26	4	30
	2	98	10	108
	≥ 3	138	24	162
Total		262	38	300

TTR (< 65%). Receiving one or two drugs and having heart failure were the only variables significantly associated with TTR in this study. Accordingly, taking 1 or 2 drugs along with warfarin was found better in achieving good TTR when compared with receiving more than two drugs (AOR = .194; CI- .052-.717, $P = .014$) in achieving better TTR Similarly, heart failure comorbidity had 2.467 times the risk of having poor therapeutic outcomes (AOR = 2.467; CI - 1.014-6.005, $P = .047$) (Table 5).

Table 3. Non-therapeutic INRs and warfarin dose adjustment in patients with AF taking Warfarin at SPHMMC ($N = 300$).

Number of Non-therapeutic INRs	Dose Decreased *N* (%)	No Dose Adjustment *N* (%)	Dose Increased *N* (%)
Sub-therapeutic INR Values ($N = 1608$)	126 (7.84)	800 (49.5)	682 (42.41)
Supra-therapeutic INR Values ($N = 460$)	254 (55.22)	136 (29.57)	70 (15.21)

Table 4. Drug Interactions with warfarin in patients with AF taking warfarin at SPHMMC ($N = 132$).

Type of WDIs	Co-prescribed Drugs	Number	Percent
Major	Benzathine Penicillin	72	54.54
	Aspirin	10	7.57
	Simvastatin	4	3.03
	Amiodarone	2	1.51
Moderate	Propylthiouracil	20	15.15
	Omeprazole	12	9.09
	Propranolol	6	4.54
	Phenobarbitone	2	1.51
	Carbamazepine	2	1.51
	Indomethacin	2	1.51

Bleeding Events

In this study, major/minor bleeding events were observed in 62 (20.67%) patients. Among these, 5 of them had more than one (4 patients with two episodes and one patient with three episodes) episode of bleeding events. At the time of bleeding events, 14 patients had INR value within the therapeutic range, while 20 of them had an INR range between 3.01 and 4.99, and 28 patients had an INR range above 5.0. Among patients with bleeding, 14 had intracranial hemorrhage. Sex, having Diabetes Mellitus, and taking aspirin had an association with bleeding events when entered into multivariate analysis. Male sex was 2.53 times at risk of having bleeding events than females (CI - 1.261-5.079; $p-.009$). Patients who didn't have Diabetic Mellitus and those not receiving aspirin were at were less likely to develop bleeding events (AOR = .196; C.I. = .060-.638; $p-.007$ and AOR = .099; CI. = .024-.416; $p-.02$), respectively (Table 6).

Discussion

The present study reviewed 300 medical records of patients diagnosed with AF and treated with warfarin. We also determined

Table 5. Predictor factors associated with poor TTR in patients with AF taking warfarin at SPHMMC ($N = 300$).

Variables		TTR 65%	TTR ≥ 65%	*P*-value	AOR
Sex	Female	174	22	.453	.720 (.305- 1699)
	Male	88	16		1
Age in years	18 to 40	59	5	.477	.596 (.143- 2.478)
	41 to 64	95	13	.807	1.152 (.371- 3.571)
	65 to 74	60	14	.223	1.977 (.661- 5.916)
	≥ 75	48	6		1
Number of Medications Prescribed per Patient	1 to 2	74	6	.014	.194 (.052- .717)
	3 to 4	168	24	.115	.408 (.134- 1.242)
	≥ 5	28	8		1
CHA_2DS_2-VASc Score	1	26	4	.638	1.432 (.321- 6.384)
	2	98	10	.229	.560 (.218- 1.439)
	≥ 3	138	24		1
Heart failure	Yes	166	26	.047	2.467 (1.014- 6.005)
	No	96	12		1
Hypertension	Yes	82	16	.127	1.874 (.837- 4.195)
	No	180	22		1
Stroke/transient ischemic attack	Yes	62	10	.359	1.542 (.612- 3.886)
	No	200	28		1
Diabetes mellitus	Yes	14	4	.430	1.836 (.406- 8.315)
	No	248	34		1
Hyperthyroidism	Yes	18	4	.342	1.871 (.514- 6.814)
	No	244	34		1
Cardiomyopathy	Yes	24	2	.151	.294 (.055- 1.561)
	No	238	36		

AOR: adjusted odds ratio, TIA: transient ischemic attack.

Table 6. Predictive factors associated with bleeding in patients with AF taking warfarin at SPHMMC ($N = 300$).

Predictive Factors		Bleeding			
		Yes	No	*P*-value	AOR
Sex	Female	32	164	1	
	Male	30	74	.009	2.531 (1.261-5.079)
Age	18 to 40	14	50	1	
	41 to 64	20	88	.990	.993 (.347- 2.843)
	65 to 74	14	60	.884	1.068 (.439- 2.600)
	≥ 75	14	40	.807	1.122 (.444- 2.836)
Number of Medications Prescribed per Patient	1 to 2	12	68	1	
	3 to 4	44	148	.626	.734 (.212- 2.539)
	≥ 5	6	22	.110	.394 (.125- 1.236)
CHA_2DS_2-VASc Score	1	10	20	1	
	2	16	92	.485	.669 (.216- 2.069)
	≥ 3	36	126	.426	1.386 (.620- 3.098)
CHF	Yes	36	156	1	
	No	26	82	.543	1.277 (.581- 2.809)
Hypertension	Yes	20	78	1	
	No	42	160	.569	1.255 (.574- 2.746)
Stroke/TIA	Yes	14	58	1	
	No	48	180	.626	1.229 (.536- 2.819)
DM	Yes	8	10	1	
	No	54	228	.007	.196 (.060- .638)
Aspirin Use	Yes	6	4	1	
	No	56	234	.002	.099 (.024- .416)

predictive factors that are associated with TTR and bleeding events.

The present study observed a TTR of 42.02% in the entire cohort with only 12.7% of patients achieving a TTR ≥ of 65%. The result was comparable with findings from AF patients in Chinese (38.2%),[9] Lithuanian (40%),[31] and Turkish (42.3%)[25] studies. However, higher TTR values of 61.5% and 65% were reported by the FANTASIIA[12] and ORBIT-AF[32] registries respectively. The discrepancy might be because those studies included only patients with non-valvular AF patients. Other similar studies from Saudi Arabia, Iran, Kuwait, and Brazil also found the mean TTR between 52.6% to 59%.[33–36] Even though the TTR values are higher than the current study, these studies indicated the challenges in managing warfarin in real-case scenarios.

A study by Cotté *et al.* evaluated the TTRs in four European countries in AF patients and found that 44.2% to 47.8% of patients achieved TTR of above 70% and with a higher percentage (65.4%) in United Kingdom patients.[37] Similarly, the Lithuanian (20%),[31] Iranian (37.3%),[34] and Brazilian (31%)[36] studies reported a higher number of patients who achieved TTR of above 65% as compared to just 12.67% in our study. On the other hand, studies from Namibia (29.4%),[14] Botswana (30.8%),[15] and Ethiopia (29%)[11] published lower TTR values. The inclusion of other warfarin indications conditions (not only AF) might be the possible reason for these small discrepancies.

In our study, only 34.6% of INR tests were within the therapeutic range, and the remaining 50.85% and 14.55% INR values were below and above the expected therapeutic ranges, respectively. Lower therapeutic INR values were also reported from a Namibian study (25.2%)[14] and another study in Ethiopia (43.2%).[11] Unlike the current research, studies conducted elsewhere found higher rates of INR values within therapeutic ranges with a lower percentage of INRs below and above therapeutic ranges.[10,38]

In this study, warfarin dose adjustment was needed 2068 times (65.4%) but it was adjusted in 54.74% occurrences. The current warfarin dose adjustment rate was comparable with another study in an Ethiopian university teaching hospital (51.65%)[11] and lower than that of the Namibian study report (61.3%).[14] In the Lithuania study, there was no warfarin dose adjustment done even though 40% of the INRs were out of the therapeutic range.[31] The relatable setup in these Ethiopian two tertiary teaching hospitals might contribute similarity in dose adjustment rates. In this study setting, the anticoagulation management service was provided once per week, which might influence the management of non-therapeutic INRs and warfarin dose adjustment. INR monitoring should be within a week after the occurrences of non-therapeutic INR ranges to adjust daily warfarin dose accordingly.[20] Taking other alternative actions such as recommending non-pharmacological methods and managing warfarin interacting medications, counseling on the importance of adherence to warfarin could be reasons for providers not adjusting warfarin for patients with non-therapeutic INRs.[11]

We reported a higher prevalence of warfarin drug interactions (WDIs) (44%) than other similar studies done in the Ethiopian setting (21.1%).[21] The deviations might be due to practice-related gaps and more prevalent comorbid cases in

the study of the present work. Another study conducted in Ayder Referral Hospital of Ethiopia reported a 99.2% WDIs prevalence.[22] The higher rate of WDIs can be associated with the study participants being critical inpatients. Furthermore, outpatients usually have few co-morbidities requiring less polypharmacy to optimize treatment outcomes. Major WDIs accounted for 75% of all WDIs and differed from similar studies in Ethiopia.[21,22]

In this study, taking more than 2 drugs and heart failure were associated with poor TTR. Various literature works showed controversial results on age association with poor TTR. In comparison to this study, studies in South Africa have shown that older patients ≥ 55 years of age were more likely to have a therapeutic INR than younger ones.[16,23] In the same way, a Swedish study also found a correlation between improved TTR and older age.[24] However, the quality of anticoagulation was minimal in the aged population, and there was a negative association between age and TTR levels in a Turkish study.[25] Furthermore, many previous studies on the AF population found old age to be associated with lower TTR.[39–41] 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.

Effect of comorbid conditions (diabetes, chronic kidney disease, heart failure, prior stroke) on TTR was reported elsewhere.[36,41] Our study was consistent with those findings in which heart failure.[39] and diabetes mellitus,[42] negatively affected TTR. The possible justification could be patients with comorbidities require more drugs/polypharmacy for their management, which makes the patients more vulnerable to WDIs, which in turn, affect optimal anticoagulation. Even though other studies supported female sex association with lower TTR than the male sex, it was not significant in our survey.[36,43]

The most common complication of warfarin therapy was bleeding. In our study, 62 (20.67%) of patients had at least one episode of bleeding, and similar (19.4%) prevalence was documented in another study with 1.7% being major bleeding.[30] However, a higher percentage of minor (38.8%) and major (5.1%) bleeding events was reported in another study.[25] From previous works, many studies reported life-threatening intracranial hemorrhages and gastrointestinal bleeding events.[25,44] In this study, out of 62 patients with bleeding events, 48 (77.42%) had elevated INR values (ie above target INRs) which were higher than Oake *et al.*'s study that reported 44% of bleeding events occurred at INR values above the therapeutic range.[45] However, bleeding might also happen even at sub-therapeutic and the target INRs. With this regard, 14 (22.6%) patients had bleeding events even though their INR was within the target range. An AFFIRM study reported that increased age, having heart failure, hepatic or renal disease, diabetes, first AF episode, and aspirin use were significantly associated with major bleeding.[44] Similarly, our study revealed a statistically significant association of male sex, diabetes mellitus, and aspirin use with bleeding.

Limitation of the Study

Poor organization in documenting patients' history and illegible handwriting were difficulties while reviewing charts which might affect the quality of data in some instances. Only limited patient information (age, gender, and indication for warfarin treatment, drug interaction, and comorbid conditions) was available for analysis without including other factors (diet, alcohol use, adherence status, and non-pharmacologic interventions) that could affect warfarin anticoagulation control as we couldn't get this information from retrospective chart review. The study is a single-center one, which limits results generalizability.

Conclusions

In summary, the time spent in the therapeutic range was minimal in this population of patients with AF on warfarin managed at a hospital run anticoagulation clinic in Ethiopia. The time spent in the therapeutic range among patients taking warfarin for atrial fibrillation was suboptimal. Moreover, number of medications, and comorbid heart failure were associated with poor TTR. The bleeding events were high in this study and affected by male sex, diabetes mellitus comorbidity, and aspirin use.

Abbreviations

AOR: adjusted odds Ratio; AF: atrial fibrillation; CHA2DS2-VASc: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category); CI: confidence interval; INR: international normalization ratio; SPHMMC: Saint Paul's Hospital Millennium Medical College; SD: standard deviation; TTR: time in therapeutic range; VKA: vitamin K antagonist; WDI: warfarin-drug interaction

Data Sharing Statement

The original dataset supporting the finding of the present study will be available from the corresponding author upon a reasonable request.

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Authors' Contributions

All authors made a significant contribution to this work. NSY conceived the study idea, developed the study design, conducted the study, and analyzed data. Then, TAT and SUH enriched it. Finally, AAA and TAT did critical revisions of the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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