

# Attainment of Target in Therapeutic Range of International Normalized Ratio and Correlates Among Patients on Warfarin Therapy at Jimma Medical Center, Jimma, Ethiopia

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## Abstract

**Background:** Warfarin is a highly effective therapy to prevent thromboembolic complications of venous thromboembolism (VTE), atrial fibrillation (AF), cardiac thrombus and valvular heart disease. While its optimum effect is achieved when international normalized ratio (INR) is in the target range, Subtherapeutic level increases both the risk and complication of thromboembolism. This study was aimed to assess the attainment of target to therapeutic range, proportion and factor associated with subtherapeutic level of INR among patients on warfarin therapy at Jimma Medical Center.

**Methodology:** a hospital-based cross-sectional study was conducted at Jimma Medical Center from October 1st to December 30th, 2021. All patients on warfarin therapy, visiting medical chronic follow up clinics during the study period were included. Data was collected using structured questionnaires and then entered into Epi-data version 3.1 for analysis. Chi-square tests and logistic regression models were used to see relationships between variables.

**Results:** Among 196 patients on warfarin therapy, female accounts for 61.7%, with mean age of  $43 \pm 7$  years. Half of the participants didn't attend formal education and hence can't read and write, and most of them (61.7%), live in rural areas, of whom 44.9 % of them farm to earn a living. Most of the study participants (51.5%), were those with very low monthly income of less than 50USD. Among the study participants, a quarter of them chew Khat, a very few (4.1 %) were smokers, and even lower number (3.1 %) were alcoholic. Majority 107(54.6%) patients were advised on dietary selection while on warfarin from whom about two third 70(65.4%) were adherent to the advice. Majority 118 (60.2%) of them were poorly adherent and more than two third of them discontinued warfarin for financial reason. Warfarin therapy was prescribed for AF in about 116 (59.2%), while chronic pulmonary embolism and portal vein thrombosis were other documented reasons for warfarin therapy. Heart failure was the most common co-morbidity accounting more than a third 70 (35.7%), followed by tuberculosis, malignancy, anemia and epilepsy, all together accounts for 23(16.5 %) of comorbidities. The mean duration of warfarin therapy was  $15.53 \pm 18.922$  months [1 to 90 months], about two-thirds took 35-70mg of warfarin per week. The mean number of documented INR was  $6.99 \pm 4.57$  [3 to 29], of which half of them had monthly determination. The majority 109(55.6%) of the respondents had subtherapeutic INR while 21(10.7) were in supratherapeutic range. While the mean TTR was  $25.03 \pm 24.17$  % [0 to 80%], in the majority 166(84.7%), it was below 60%. Poor adherence [AOR 6.13 (95% CI ((3.31-28.10))], shorter duration of warfarin, less than 12 months [AOR .104(95% C.I .012-.875)] and presence of comorbidity [AOR 0.035 (95% CI (.004 -0.323))] were significantly associated with subtherapeutic INR.

**Conclusion:** attainment of therapeutic INR among patients on warfarin therapy is suboptimal. This was evidenced by significant number of patients with low TTR as well as INR. Poor adherence to warfarin therapy, shorter duration since initiation of warfarin and presence of co-morbid illnesses were significantly associated with subtherapeutic INR. This may lead to complications of venous thromboembolism, further leading to morbidity, increased mortality and poor quality of life. Therefore, providing health education and treatment of comorbidity may improve adherence which may also improve attainment of therapeutic INR that reduce complications and improve quality of life.

**Keywords:** Anticoagulation, Warfarin, International Normalized Ratio, Target Therapeutic Range, Jimma Medical Center

## 1. Introduction

Vitamin K antagonists (VKAs) are among the most commonly prescribed drugs globally. They are used by approximately 2% of the population in USA. This number has kept growing over the past decade and warfarin is most commonly prescribed VKA. VKAs are used to treat and prevent thrombosis. It produces an anticoagulant effect by interfering with the regeneration of vitamin K hydroquinone from vitamin K epoxide which inhibits the reductase enzymes in the vitamin K cycle. The international normalized ratio (INR) is used to monitor the effectiveness of the anticoagulant. Their effectiveness for various indications has been proven in many well-designed studies. Indications include atrial fibrillation, deep vein thrombosis, pulmonary embolism and heart valve prostheses [1-5].

Unfortunately, therapy with VKAs is not without drawbacks. One important limitation is their narrow therapeutic window. When on the one hand, the intensity of anticoagulation, expressed as the INR is too low, the risk of thrombosis increases up to that of untreated patients. On the other hand, if the INR is too high, the risk of bleeding complications increases sharply. A second limitation of VKAs is the considerable variability in anticoagulant response. Not only does the required dose vary significantly between patients, but also VKAs are subject to interactions with drugs and diet, and various disease states, so the anticoagulant response for a particular patient often fluctuates over time. Because of these properties the INR needs to be monitored closely and dose adjustments often need to be made [6-9].

Despite intensive monitoring by specialized anticoagulation clinics, the INR is within the target range only 65-75% of time. Time in therapeutic range (TTR) has been widely used to measure the quality of INR control as it reflects the percentage of time within a therapeutic INR range. A minimum target of TTR  $\geq 60\%$  is recommended by the experts to ensure the effectiveness and safety of warfarin [9]. While the narrow therapeutic window is inherent to treatment with VKAs, the variability in anticoagulant response can be influenced by several factors such as age, alcohol consumption, smoking, diet, exercise, concomitant medications, and environmental changes [10]. Dietary vitamin K is an independent factor that influences changes in INR and knowledge about these interactions is essential to improve quality of treatment. High sub therapeutic INR range affects the efficacy for which warfarin is prescribed leading to thromboembolic complication like DVT, PTE and Stroke. These will lead to increased morbidity, mortality and compromised quality of life.

## 2. Material and methods

### 2.1. Study Design and setting

A quantitative prospective observational hospital-based study was conducted at Jimma Medical Center, Ethiopia, from October 1st to December 30th, 2021. Jimma Medical Center is a tertiary teaching hospital located in Jimma Town, Oromia region of Ethiopia serving a population of over 20 million population catchment areas. The medical center has over 1500 healthcare providers, serving about 160,000 outpatients, 11,000 emergency cases and more than 4700 deliveries per year. The chronic follow up provides services for about 2400- 2800 patients over a period of a month both from Jimma town and the surroundings. Of these patients, about 400 were on warfarin for DVT, AF or stroke during 2013 Ethiopian Academic year follow up.

The hospital also provides coronary care services, including at outpatient follow up Clinics, Emergency care services especially for spectrums of acute coronary syndromes and inpatient services with laboratories including coagulation profiles, organ function tests, Electrocardiogram, Echocardiography and stress testing services for patients with Heart failure, and other major facilities among which diabetes care and follow up, dialysis and higher imaging services including Computed Tomography and MRI are listed. The set up also has installed a catheterization machine, which is a brand new of its kind and to start on both diagnostic and interventional angiography very soon.

### 2.2 Inclusion and exclusion criteria

All patients on warfarin therapy for at least 1 month and on follow up at Medical Chronic follow up clinic of Jimma Medical Center within the study period, willing to participate in the study were included. Those patients with INR determination of less than three times, those patients whom their charts are incomplete, as well as those who declined to participate in the study were excluded.

### 2.3 Sample Size determination

Single population proportion sample size determination formula was employed, based on the previous study conducted in a similar setting, Tikur Anbessa Tertiary Hospital in the Addis Ababa, Capital of Ethiopia, which reported the proportion as 52.2%, was taken [11]. Assuming a 95% confidence level and a 5% margin of error, the sample size was calculated using the following formula:

$$n = N \cdot X / (X + N - 1)$$

Where,

n- sample size

N-population size (400)

$$x = Z_{\alpha/2}^2 \cdot p \cdot (1-p) / MOE^2 = 384$$

z- Standard deviation from normal value at 95% Confidence Interval

p- Proportion of subtherapeutic INR of patients on warfarin (0.52%)

MOE- Possible margin of error that can be tolerated which is 5% (0.05)

1-p- proportion of population that do not possess character of interest

n = 196

## 2.4. Data collection

A structured data collection format, which was tested for consistency prior to the data collection, was used including the Socio-demographic characteristics (age, sex, chart number, marital status, level of education, monthly income, and area of residence) and clinical profiles of the patients with Acute ischemic stroke with especial focus on time of onset of their symptoms and time of arrival. The charts of the patients were collected and reviewed for additional data regarding the previous patient care, type and kind of medication the patients taking, previous history of admission and the possible reason and management provided in the current presentation. The data collectors used personal protective equipment like alcohol-based hand sanitizer, and face mask to reduce any risk of transmitting infections from the patients to the data collectors and vice-versa.

## 2.5. Data analysis

Data were analyzed using Epidata manager version 3.1 and then transported to SPSS version 25 for analysis. Demographic characteristics of the study subjects were analyzed descriptively. Categorical data was analyzed using frequencies (n) and percentages (%) and represented in graphs and pie charts. Continu-

ous data was analyzed using mean (SD) for normally distributed data or median (IQR) for skewed data. Chi-square, Fischer's exact, students were used in bi-variate analysis while binary logistic was used to conduct multivariate analysis. Fischer's exact was used when cell frequency was less than five ( $n < 5$ ) while Chi-square test was used for cell frequency ( $n > 5$ ). Significance level required was  $< 0.05$ . Odds ratio was used to show direction of association between the independent and dependent variables.

## 2.6. Study limitation

Since this study is a cross-sectional study, it is impossible to analyze causal relationship between variables of the study. In addition to the small sample size, it makes difficult to find factors associated with those on follow up at clinic with respect to admitted cases. Also, this is a finding from a single institution.

## 2.7. Results

### 2.7. 1. Socio-demographic characteristics

All 196 patients who were on warfarin therapy for various reasons and on follow up at Medical Follow up Clinics of Jimma Medical Center, Ethiopia, during the study period were interviewed and enrolled into the study, with a 100% response rate. Most of the study participants were female (61.7%, Ratio of male to female being 1:1.6), with mean age of  $43 \pm 7$  (range 35 to 85) years. Half of the study participants didn't attend formal education and hence can't read and write, and most of them 121(61.7%), reported as They are from rural area, of whom most of them farm to earn a living. Most of the study participants were those with very low monthly income of less than 50USD. Most of the patients (80.1%) were married and were living with their family Table 1.

Variable		Frequency	Percent
Sex	Male	75	38.3
	Female	121	61.7
Age in years	less than equal to 35	63	32.1
	36-50	66	33.7
	51 and above	67	34.2
BMI in Kg/m <sup>2</sup>	<18.5	60	30.6
	18.5-24.9	118	60.2
	25 and above	18	9.2
Residence	Urban	75	38.3
	Rural	121	61.7
Marital status	Married	157	80.1
	Single	24	12.2
	Others	15	7.6
Educational status	No formal education	98	50.0
	Elementary	45	23.0
	high school	33	16.8
	Diploma and above	20	10.2
Occupation			
	Farmer	88	44.9

Income/month	Merchant	26	13.3
	Government employed	33	16.8
	Jobless	49	25
	< 1,500	101	51.5
	1,500-3,500	54	27.6
	3,500-5,500	24	12.2
	5,500-10,000	17	8.7

**Table 1: Socio-demographic characteristics of patients on warfarin therapy on follow up at Jimma Medical Center, 2021**

### 3. Dietary and Behavioral Characteristics of the Study participants:

Of the study participants, nearly a quarter 51(26 %) of them actively chew khat, 4.1% of them were smokers, while about 3% of them were alcoholic. Majority 107(54.6%) of the study participants were advised on dietary selection while on warfa-

rin therapy by their healthcare providers, of whom about two third 70(65.4%) of them were adherent to the advice. However, overall adherence was poor in majority 118 (60.2%) of the study participants according to MMAS-8. Only about 10% of the study participants had discontinued their warfarin during the last 1 month of follow up, mainly due to financial reason Table 2.

Variable		Frequency	Percent
Smoking history	Yes	8	4.1
	No	188	95.9
Current smoker	Yes	3	37.5
	No	5	62.5
History of alcohol ingestion	Yes	6	3.1
	No	190	96.9
Current use	Yes	4	66.7
	No	2	33.3
Current khat chewing	Yes	51	26.0
	No	145	74.0
Frequency of khat chewing	Daily	6	11.5
	Twice per week	12	23.1
	Weekly	22	42.3
	Monthly	12	23.1
Got dietary advice	Ye	107	54.6
	No	89	45.4
Followed the advice	Yes	70	65.4
	No	37	34.6
MMAS-8 adherence level	Adherent	78	39.8
	Non adherent	118	60.2
Discontinued warfarin last month	Yes	22	11.2
	No	174	88.8
Reason for discontinuation	For financial	17	77.3
	For high INR and surgery	54	22.7

**Table 2: Dietary and behavioral characteristics of patients on warfarin therapy at follow up clinic, Jimma Medical Center, Ethiopia, 2021**

### 4. Clinical profiles, patterns and factors associated with sub-therapeutic INR among the study participants

Atrial fibrillation-related risk of thromboembolism was the commonest indication for warfarin therapy, accounting nearly 60% (116), while portal vein thrombosis and pulmonary thromboem-

bolism take the subsequent lead. Heart failure was the leading comorbidity as it was found in 70 (35.7%), while tuberculosis, malignancy, anemia and epilepsy accounted for 23(16.5 %) altogether. Almost all 136(97.8%) of them were on treatment for their comorbid illnesses. The average weekly dose of warfarin

in about two-third, 146(74.5%), of the patients was 35-70 mg, in which monthly determination was done in about half of the study population. The mean duration of warfarin therapy was 15.53  $\pm$  18.922 [1 to 90 months], while the mean number of documented INR was 6.99  $\pm$  4.57 [3 to 29]. Considering the latest INR, majority 109(55.6%) of the study participants had subtherapeutic range. Furthermore, the mean TTR was 25.03  $\pm$  24.17 % [0 to 80%], with the majority 166(84.7%) of them having TTR below 60% (Table 3, Figures 1 and 2) On other hand, Low level of

adherence, [AOR 6.13 (95% CI ((3.31-28.10)), shorter duration since initiation of warfarin therapy, [ AOR .104(95% C.I .012-.875)], and presence of comorbidity, [AOR 0.035 (95% CI (.004-.323))], were found to be factors significantly associated with subtherapeutic INR. Living alone was also found to significantly affect attainment of target INR, as being widowed and divorced ones were nearly three times odd of having sub therapeutic INR [AOR 2.95 (95% CI (1.50-56.60))], in this study Table 4.

Variables		Frequency	Percent
Indication for warfarin	AF	117	59.7
	DVT	71	36.2
	PTE and PVT	8	4.1
Dose of warfarin per week in mg	<35mg	46	23.5
	35= $\leq$ 70	146	74.5
	$\geq$ 70	4	2.0
Duration on warfarin	Less or equal to 12 months	135	68.9
	Greater than 12 months	61	31.1
Frequency of follow up	Weekly	40	20.4
	Monthly	99	50.5
	Every two month	45	23.0
	Every three month*	12	6.1
Number of documented INR	Up to 6 documented INR	123	62.8
	Above 6 documented INR	73	37.2
Latest INR Value	Less than 2	109	55.6
	2-3	66	33.7
	Above 3	21	10.7
Time in therapeutic range	Less than 60%	166	84.7
	60% and above	30	15.3
Has comorbidity	Yes	139	70.9
	No	57	29.1
Type of comorbidity	Heart failure	70	50.4
	HTN	30	21.6
	Thyrototoxicosis	16	11.5
	Others	23	16.5
Treatment	Yes	136	97.8
	No	3	2.2.

**Table 3: Medical characteristics of patients on warfarin therapy at follow up clinic of Jimma Medical Center, Jimma Ethiopia 2021**

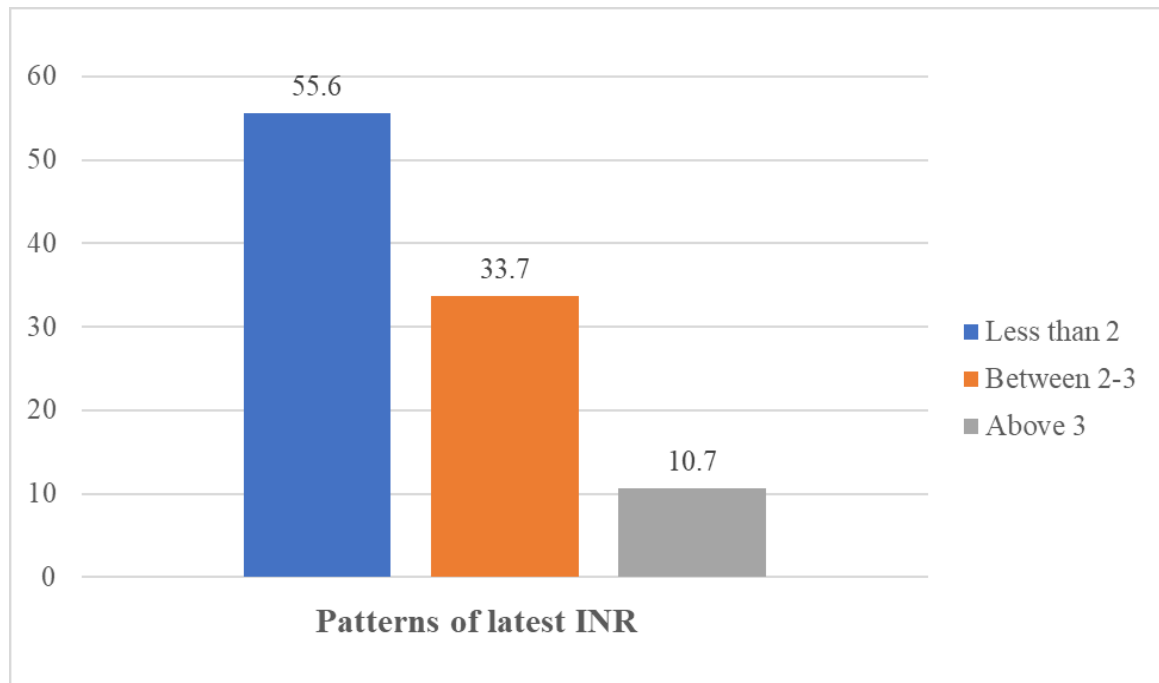
Variables		TTR		COR (95%CI)	AOR (95%CI)	p-value
		<60%	$\geq$ 60%			
Sex	Male	65(86.7)	10(13.30)	1		
	Female	101(83.5)	20(16.5)	0.777(0.342-1.765)	0.288(0.054-1.545)	0.146
Age	$\leq$ 35	50(79.4)	13(19.60)	1		0.309

	36-50	56(84.8)	10(15.2)	2.229(0.826 – 6.013)	0.364(0.037-3.542)	0.384
	>50	60(89.6)	7(10.4)	1.531(0.545 – 4.297)	0.197(0.025-1.576)	0.126
BMI(Kg/m <sup>2</sup> )	<18.5	50(83.3)	10(16.7)	1		
	18.5-24.9	101(85.6)	17(14.4)	1.0(0.243 – 4.110)	4.922(0.268-90.439)	0.283
	>=25	15(83.3)	3(16.7)	0.842(0.220 – 3.220)	14.690(0.717-300.8)	0.081
Residence	Urban	61(81.3)	14(18.7)	1		
	Rural	105(86.3)	16(13.7)	1.506(0.688 – 3.297)	3.875(0.699-21.486)	0.121
Marital status	Married	134(85.6)	23(14.4)	1		0.250
	Single	19(79.9)	5(20.8)	1.116(0.236 – 5.272)	0.447(0.042-4.699)	0.502
	Others	13(86.7)	2(13.3)	1.711(0.287 – 10.19)	2.945(0.153-56.60)	0.474
Occupation	Farmer	79(89.7)	9(10.3)	1	1	0.296
	Merchant	22(84.6)	4(15.4)	1.003(0.316 – 3.178)	3.961(0.475-33.0)	0.203
	Government employed	21(63.6)	12(36.40)	1.600(0.390 – 6.559)	0.572(0.025-13.27)	0.727
	Others	44(89.7)	5(10.3)	5.0(1.568 – 16.131)	3.638(0.139-95.41)	0.439
Followed the Dietary advice	Yes	51(75.0)	17(25.0)	1		
	No	36(97.3)	1(2.7)	12.0(1.527 – 94.2)	3.930(0.821-18.82)	0.047
MMAS-8 adherence level	Adherent	51(65.4)	27(34.6)	1		
	Non adherent	115(97.4)	3(2.6)	7.294(5.9 – 69.95)	6.128(3.31-28.10)	<0.0001
Dose of warfarin per week in mg	<35mg	42(91.3)	4(8.7)	1		
	35-70mg	124(82.7)	26(17.3)	0.454(0.150- 1.377)	0.520(0.087-3.110)	0.474
Number of documented INR	<= 6 documented INR	107(87.0)	16(13.0)	1		
	> 6 documented INR	59(80.2)	14(19.8)	0.630(0.288-1.381)	0.968(0.198-4.731)	0.968
Frequency of INR follow up	Less than Monthly	113(81.3)	26(18.7)	1		
	Monthly or less frequently	53(93.0)	4(7.0)	3.049(1.013-9.178)	3.243(0.430-24.437)	0.254
Duration on warfarin	<=12 months	113(68.0)	53(32.0)	1		
	12 months	22(73.3)	8(26.7)	1.290(0.539 - 3.08)	0.104(0.012-0.875)	0.037
Indication for warfarin	AF	102(87.9)	14(12.1)	1		0.160
	DVT	56(81.2)	13(18.8)	0.366(0.087- 1.544)	0.296(0.025-3.540)	0.337
	Others	8(72.7)	3(27.3)	0.619(0.144 - 2.659)	0.059(0.003-1.157)	0.062

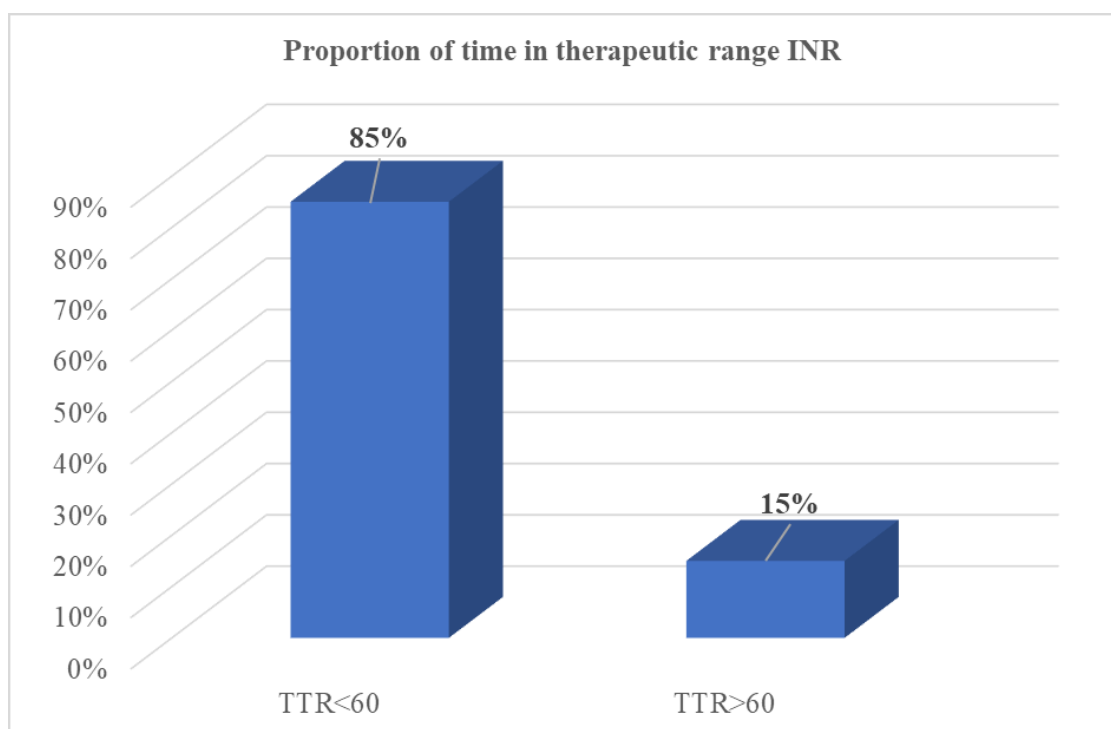


Has comorbidity	Yes	127(90.0)	12(10.0)	1		
	No	39(68.4)	18(31.6)	0.205(0.091-0.462)	0.035(0.004-0.323)	0.003

**Table 4. Association between variables and subtherapeutic INR among patients on warfarin therapy at medical follow up clinics of Jimma Medical Center,2021**



**Figure 1:** Patterns of INR level attained among patients on warfarin therapy at medical follow up clinics of Jimma Medical Center,2021



**Figure 2:** Proportion of Time in therapeutic range of INR among patients on warfarin therapy at medical follow up clinics of Jimma Medical Center, 2021

## 5. Discussion

Most of the study participants were female (61.7%, Ratio of Male to female being 1:1.6), with mean age of  $43 \pm 7$  (range 35 to 85) years. The proportion of subtherapeutic INR in this study was low, 55.6%. The time in therapeutic range (TTR) was also less than 60% in the majority (84.7%) of study participants. This is significantly higher than the previous studies conducted in the USA, which reported 37% of TTR of warfarin therapy used in AF, 63 % of TTR used in DVT and, in the Netherlands, which reported TTR of 35% of warfarin therapy used in patients with prosthetic valves. The discrepancy may be due to the difference in the study design, which were systematic reviews as opposed to our study, which was prospective cross-sectional. Furthermore, residence of rural area leading to less frequent INR determination masking the real attainment may be another reason for the high record [12, 13].

The majority 109(55.6%) of the study participants had subtherapeutic range of INR. However, this was even higher when compared to studies done on newly admitted patients to Korean Hospital reporting INR of 41%, and similar studies from South Africa and Ugandan Hospital showing INR level of 59%. The discrepancies might be due to difference in study designs in which the Korean, South African and Ugandan studies were retrospective cohort study designs [14, 15].

The TTR in this study was also significantly lower as compared to the study done in University of Gonder which reported the TTR of 70.8% [16]. Presence of comorbidity, duration on warfarin, and level of adherence to warfarin therapy was found to be significantly associated with subtherapeutic INR. This was evidenced as the majority of patients with subtherapeutic INR range (TTR of <60%) in this study those with comorbidities. They were about 96.5% higher likely to develop Subtherapeutic INR as compared to their counterpart. This finding was similar to study done in University of Gonder [16]. This is probably due to the fact that patients with comorbidity have higher pill burden that affect the adherence and drug interaction. Furthermore, patients who were on warfarin therapy for more than 12 months were 89.6% more likely to be in therapeutic range compared to those on warfarin therapy for less than 12 months. This was also similar with the study done in Korea which showed that participants on warfarin therapy for  $\geq 3$  years had higher percentage of TTR than their counterparts. Regarding the adherence, the odd of having TTR of <60% was nearly six times higher among those with poor adherence to warfarin therapy as compared to those adherents to the standard. This negative association was also reported in the study in 47 clinics of the United States where nonadherence was among five causes of sub therapeutic INR [17].

## 6. Conclusion

Attainment of therapeutic INR among patients on warfarin therapy in this study is suboptimal. This was evidenced by significant number of patients with low TTR as well as INR. Poor adherence to warfarin therapy, shorter duration since initiation of warfarin and presence of co-morbid illnesses were significantly associated with subtherapeutic INR. This may

lead to complications of venous thromboembolism, further leading to morbidity, increased mortality and poor quality of life. Therefore, providing health education and treatment of comorbidity may improve adherence which may also improve attainment of therapeutic INR that reduce complications and improve quality of life.

## Data sharing Statement

All data is available within the article.

## Ethical Approval

Ethical clearance was obtained from the Institutional Review board (IRB) of the Institute of Health. A formal support letter was obtained from the respective administrations. All the study participants and respective stakeholders were informed about the purpose of the study, and written informed consent was obtained from all participants. We used an impartial witness during the entire informed consent process and data collection period for those participants who were unable to read/write. The study was conducted per the declaration of Helsinki. Confidentiality of participants' information was kept using unique codes rather than personal identification.

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## Author Contributions

KNT, GMD and KHJ participated in the conception of the idea, designing the study, data collection and analysis, and write up the draft results. KNT, BHM, AUJ, EGA and KNT reanalyzed the data, drafted, edited and revised the manuscript. All authors agree to take responsibility and be accountable for the contents of the article as well as agreed on the journal to which the article will be submitted. All authors read and approved the final manuscript.

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## Disclosure

The authors report no conflicts of interest in this work.

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