PROPORTION OF SUB THERAPEUTIC INTERNATIONAL NORMALIZED RATIO AND ASSOCIATED FACTORS AMONG PATIENTS ON WARFARIN AT JIMMA MEDICAL CENTER, JIMMA, SOUTHWEST 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 target, Sub therapeutic level increases both the risk and severity of thromboembolism. Despite thrombotic consequences of Sub therapeutic INR, little is known about its prevalence.

Objective: This study assessed the proportion and factor associated with Sub therapeutic INR among patients on warfarin at Jimma medical center (JMC).

Method- Institution based prospective Cross-sectional study was done from October 1, 2021-December 30, 2021 among 196 patients on warfarin following chronic follow up at Jimma Medical Center. The collected data was entered into a computer by EpiData software version 3.1 and analyzed using statistical package for the social sciences (SPSS) software version 25. A descriptive statistics was used to describe categorical variables as frequencies and percentages while continuous data was described using mean, median, standard deviation. Binary and multivariate logistic regression was used to identify statistical significance at p value of <0.05.

Result: The Majority (84.7%) of the respondents has Time in therapeutic range (TTR) below sixty percent. In this study, poor adherence to warfarin, presence of comorbidity and shorter duration of warfarin were significantly associated with sub therapeutic INR at P-value less than 0.05. Additionally, the independent predictors of sub-therapeutic INR were non adherence to warfarin (AOR 6.13 (95% CI ((3.31-28.10), being widowed and divorced (AOR 2.95 (95% CI (1.50-56.60).

Conclusion and Recommendation: Proportion of Sub therapeutic INR among patients on warfarin at Jimma Medical center is very high as reflected by low TTR and high level of low INR. Poor adherence to warfarin, presence of comorbidity and shorter duration of warfarin were significantly associated with sub therapeutic INR. Therefore, we recommend the physician to give proper warfarin adherence advice and management of comorbidity.

Key words: *Proportion* of *Sub therapeutic INR, Warfarin, Anticoagulation*

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LIST OF ABBREVIATIONS AND ACRONYMS

AF: Atrial Fibrillation

BMI: body mass index

CVD: Cardiovascular disease

DVT: Deep vein thrombosis

INR: International normalized ratio

JMC: Jimma Medical Center

MMAS-8: Morisky Medication Adherence Scale-8

PTE: Pulmonary thromboembolism

PVT: Portal venous thrombosis

SPSS: Statistical package for the social sciences

TTR: Time in therapeutic range

VHD: Valvular Heart Disease

VKA: Vitamin K antagonist

VTE: Venous thromboembolism

CHAPTER ONE: INTRODUCTION

1.1. Back ground

Vitamin K antagonists (VKAs) are among the most commonly prescribed drugs globally. They are used by approximately 2% of the population in USA (1, 2). 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(3). 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 (3, 4, 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 (6,7,8,9). 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.

Despite intensive monitoring by specialized anticoagulation clinics, the INR is within the target range only 65-75% of time (7, 8). 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.

1.2. Statement of the problem

Anticoagulants are prescribed for the prevention and treatment of deep vein thrombosis, pulmonary embolism, atrial fibrillation, myocardial infarction, rheumatic heart disease and therefore decrease the burden of CVD by reducing thromboembolic phenomenon (11,12). Cardiovascular disease (CVD) and stroke produce enormous health and economic burdens worldwide. CVD is becoming the second common causes of death in most African countries following infectious disease estimated to account to 20% of total death in 2020. Reducing thrombotic complications are possible by optimization of the given anticoagulants.

Warfarin is the most commonly used medication for reducing thrombotic complications despite its challenge to attain intended therapeutic target (INR 2-3). Some studies have demonstrated that low INR is associated with attenuation of the protective effects of anticoagulation therapy, as would be expected. The time spent out therapeutic range especially, the Subtherapetic INR range is very high as demonstrated in most studies. This significantly affects the efficacy for which warfarin is prescribed leading to thromboembolic complication like DVT, PTE, Stroke. As a result, it affects patients' quality of life due to its comorbidities and increased costs of care. Despite these, globally there is gap on knowledge of proportion of Subtherapetic INR as most literatures focuses on prevalence and factor associated with supratherapitic INR and its complication although we frequently observe number of Subtherapetic INR despite repeated the drug adjustment. Especially in developing countries like ours where warfarin is most commonly used anticoagulants and we expect the burden of Subtherapetic INR to be high, there is limited number of data regarding the proportion and factor associated with of Subtherapetic INR. So with this study we aim to measure the level of Subtherapeutic INR and its associated factors among patients on warfarin in Jimma medical center, Ethiopia

1.3. Significance of the study

By this study we are going to assess proportion of sub therapeutic INR considering thresh hold of INR 2, below which the risk of thromboembolism rises most acutely. With this, types of patients and factors that contribute to increased risk of Subtherapetic INR will be identified. This will help to know the overall burden of the problem as it is understudied topic in our setup and in our country in general. The result from this study will serve as the beginning of an effort to reduce the incidence of

Subtherapeutic INR and its thromboembolic consequences by working on the identified factors both at patient, hospital and community level. Hence, our study can serve as the beginning of an effort to understand burden of Subtherapeutic INR, address factor associated with it and reduce the thromboembolic complication by optimization anticoagulation in our setup.

CHAPTER TWO: LITERATURE REVIEW

2.1. Prevalence of low INR

Despite frequent monitoring of the INR, sub therapeutic anticoagulation is common. In prospectively collected data from 47 community-based clinics that involved 4489 patients throughout the United States from 2000 to 2002, 34% had at least one low INR considering INR below 2 as cut point (13). In systematic review of 148 studies were included, Subtherapeutic INR was reported 37 % and 63% in AF and venous thromboembolism respectively.

Data from department of Thrombosis and Haemostasis at the Leiden University Medical Center in Leiden, Netherlands, Occurrence of a low INR depended on indication for anticoagulant therapy, with the highest risk in patients who used anticoagulants as prophylaxis and the lowest risk in patients with mechanical heart valves (14) (66.5 % and 36 %) respectively . In 30% of cases the sub therapeutic INR was preceded by an event necessitating vitamin K or discontinuation of the anticoagulant drug. Retrospective surveys of newly hospitalized Korean patients on continuous warfarin therapy, Percent TTR of INR were used to evaluate anticoagulant effect in the study (15). The mean percent TTR was 38.4 ± 28.4% and the range of TTR was 5.8 to 91.7%. None of the centers achieved a mean TTR of >60%. Of all INR measurements, 41.7% were <2.0. Long-term warfarin therapy group (≥ 3 years) had higher percent TTR than control group (< 3 years).

In a cross-sectional evaluation of five warfarin anticoagulation services in Uganda and South Africa which reviewed 229 patients clinical records, most common indications for warfarin were venous thrombo-embolism in 112/229 (49%), atrial fibrillation in 74/229 (32%) and valvular heart disease in 30/229 (13%)(16). Anticoagulation control was poor at all included clinics with median TTR of 41% (interquartile range 14% to 69%). In cross sectional study at Tertiary hospital in Addis Ababa patients spent 52.2%, 29.0% and 18.8% of the time in sub-therapeutic, therapeutic and supra-therapeutic ranges, respectively (17). From medical records review of 202 patients treated with warfarin between June 1, 2016, and May 30, 2018, at the University of Gondar comprehensive specialized hospital, the median time spent in the therapeutic range was 37.91. More than two-third (70.8%)) of participants had poor anticoagulation quality. Logistic regression analysis showed that potential medication interaction and presence of co-morbidity were significantly associated with quality of anticoagulation (18)

2.2. Factors associated with low INR

Even though, the causes of sub therapeutic anticoagulation are less well understood, It is known that low international normalized ratio (INR < 2) is a risk factor for thromboembolism in patients receiving warfarin. Compared with men, women had an increased incidence of low INR. Compared with patients anticoagulated for atrial fibrillation, patients anticoagulated for venous thromboembolism had an increased incidence of low INR. In prospective study in 47 clinics in united states the 5 most common reasons for low INR were nonadherence (17%), interruptions for procedures (16%), recent dose reductions (15%), no reason apparent after questioning (15%), and second or greater consecutive low INR (13%). In addition, in the initial phase of oral anticoagulant therapy patients spend more time below the target range than during long-term use, since it usually takes some time before stable anticoagulation is achieved(19).

Patients aged younger than 50 years had a slightly increased risk of a low INR. Occurrence of a sub therapeutic INR also depended on indication for treatment, with the highest risk in patients who used oral anticoagulants as prophylaxis for VTE and the lowest risk in patients with mechanical heart valves(20). A low INR was preceded by an event necessitating discontinuation of treatment in 30% of cases. These were mainly invasive procedures (11.2% of cases, 1.0% of controls), surgical admissions (6.5% of cases, 1.6% of controls) and hemorrhages (5.9% of cases and 1.7% of controls (21).

Few studies have been reported relationship between dietary vitamin K and anticoagulant effect. It has been reported that higher vitamin K intake is significantly associated with higher percent Subtherapeutic INR (22). A study on the correlation between Mediterranean diet and quality of anticoagulation confirmed that Mediterranean diet is not associated with changes in TTR (23). When restricting vitamin K intake excessively, fluctuation of vitamin K intake can be increased and cause instability of INR (24). In cohort study, on 146 patients with mechanical heart valve, Khat chewing is associated with mean low INR as compared to non-chewer with an average of 0.2 on first and second visit (25). Systemic review from one experimental pharmacokinetic study and 12 cross sectional study involving 1240 patients suggested that smoking was associated increase in warfarin requirement per week as compared with nonsmokers (26). In retrospective cohort study in King Abdulaziz Medical City, Riyadh, Saudi Arabia, between January 2014 and June 2017 Out of 211 patients included; therapeutic INR was achieved in 71.1%, 42.3%, 38% of normal body, obese

patients and of morbidly obese patients respectively. Moreover, morbidly obese and obese patients required a higher average daily dose of warfarin compared to patients with normal weight (27).

In hospital-based cross sectional study conducted between November 1, 2019 and October 31, 2020 at University of Gondar hospital on total of 338 study subjects, 33% of study subjects achieved the desired INRs (INR=2.0-3.0), while 13% of patients attained optimal INR control (TTR≥65%). There were no significant association of socio-demographic characteristics including age, gender, educational level and monthly income with optimal INR control. Likewise, clinical characteristics including dose of warfarin, warfarin adherence, frequency of INR determination, other concomitant drug intake, co-existing comorbidities, consumption of green leafy vegetables and alcohol intake didn't show significant association with optimal INR control (28).

3.3. Conceptual framework

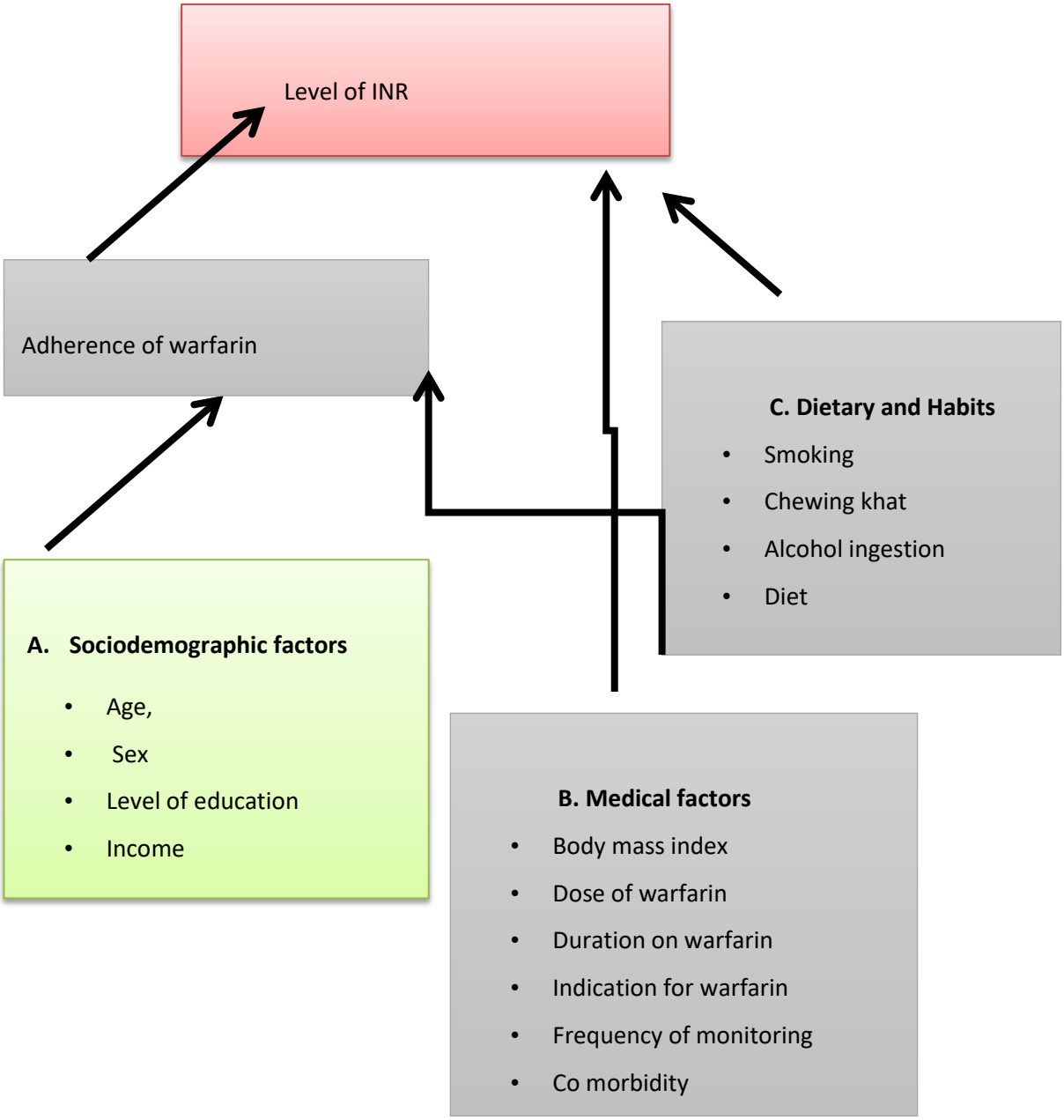

Figure 1: Aims to show relation between level of INR and warfarin adherence and other associated factors

CHAPTER THREE: OBJECTIVES

3.1. General Objective:

- To assess proportion and factors associated with sub therapeutic INR in patients on warfarin attending chronic follow up at JUMC from October 1, 2021-December 30, 2021

3.2. Specific objectives:

- To measure proportion of INR in patients on Warfarin.
- To identify factors associated with low INR in patients on warfarin.

CHAPTER FOUR: METHODS AND MATERIALS

4.1. Study area and study period

The study was conducted from October 1, 2021 – December 30, 2021 in JMC at chronic follow up , which is located in Jimma zone. Jimma zone comprises Jimma town and its nearby woredas. It is located in South West of Ethiopia, Oromia regional state, with an estimated population of 2,486,155 (based on 2007 census conducted by the central statistical agency of Ethiopia). The town is located 346 KM from the capital, Addis Ababa. Jimma medical center is the only teaching and referral hospital for the southwest population in the country. The hospital gives health services at the inpatient and outpatient levels as a referral Hospital for 15 million populations in the South West of the country. Under the Department of Internal medicine, it has general medical wards, sub-specialty units with a total of 120 beds and chronic follow-up clinics. The chronic follow up provides services for about 2400- 2800 patients over a period of a month both from Jimma town and from the surroundings. Of these patients, about 400 were on warfarin for DVT, AF or stoke during 2013 of follow up.

4.2. Study design

Hospital based prospective cross-sectional study design was used.

4.3. Source population:

All patients on Warfarin at chronic follow up clinic of JUMC

4.4. Study population:

All patients on warfarin at chronic follow up clinic of JMC from October 1, 2021- December 30, 2021.

4.5. Illegibility criteria

4.5.1. Inclusion criteria

1. Patients on warfarin for at least 1 months

4.5.2. Exclusion criteria

1. Patients who has Less than 3 INR determination
2. Patients who has incomplete chart or information

4.6. Sample size determination and sampling technique

4.6.1. Sample size

The sample size is determined by using single population proportion formula and the proportion was taken as 52.2 % as the prevalence of Subtherapeutic INR in Tikur anbessa hospital, Tertiary hospital in Addis Ababa. Thus, by considering 95 % confidence interval (CI) and 5% marginal error the sample size is calculated as follows:

n = N*X / (X + N – 1)

Where,

n- Required sample size

N-the population size (400)

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

z- Standard deviation from normal value at 95% ci which is 1.96

p- Proportion of Subtherapeutic INR of patients on warfarin at black lion hospital (52.5%)

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

Therefore,

n = 196

4.6.2. Sampling technique:

Non randomized convenient sampling method on participants who met eligibility criteria was used until maximum size is achieved.

4.7.1 Instrument

A questionnaire was used for data collection with the following contents: Chart number, age, sex, height, weight, level of education, monthly income, and area of residence, Alcohol, tobacco, khat chewing habits, dietary adherence to health care provider advice, indication, duration and adherence of warfarin, during warfarin therapy, co-administered medications, co morbidity, INR, Frequency of follow up.

4.7.2. Study variables

4.7.2.1. Dependent variables

- Level of INR

4.7.2.2 Independent variables

A. Sociodemographic factors

- Age
- Sex
- Marital status
- Level of educational
- Occupation
- Income
- Place of residence

C. Dietary and Habits

- Smoking
- Chewing khat
- Alcohol ingestion
- Diet

B. Medical factors

- Body mass index
- Dose of warfarin
- Adherence to warfarin
- Duration on warfarin
- Indication for warfarin
- Frequency of monitoring
- Comorbidity

4.8. Operational Definition

Thromboembolic events: Disease state that includes DVT, PTE and stroke that result from occlusion of blood vessel as result of exaggerated clotting of blood. (1 ,2)

Frequency of INR monitoring: Time gap in days between each INR result (7)

Vitamin K rich Diet: Diet, which has high contents of vitamin K such as avocado, leafy green vegetables, Cabbage, lettuce during the patient was on warfarin (23)

Time in therapeutic range: Percentage of target range INR number to total number of INR while patients are on warfarin (29).

Comorbidity: A Medical condition that simultaneously presents in addition to primary disease (31)

Chewing khat: An act of chawing khat while the patient is on warfarin therapy. (32)

Sub therapeutic INR: Level of INR less than 2 or TTR of < sixty percent (33)

Anticoagulant: Drugs that prevent or reduce coagulation of blood prolonging the clotting time (34).

4.9. Data collection procedure and management

4.9.1. Data collectors

Data required for study was collected by four nurses after they received training. Interviewer administered questionnaire and reviewing patients' charts was used for data collection. The charts of respondents were reviewed simultaneously while they were interviewed for information that cannot be received with interview.

4.9.2. Data collection instruments

The data abstraction format was developed by principal investigator by reviewing relevant literatures and articles that can address the objective of the study. The abstraction format is generally designed to include information about Sociodemographic data, habit and dietary factors and medical conditions of the respondents (16-18, 25-28).

4.10. Data quality management

Data was collected using a uniform data collection format. All data collectors and supervisors were trained on the standardized study protocol and data collection format before initiation of the study. Questionnaires prepared in English, translated into Afan Oromo/Amharic, and translated back into English to check its consistency. The Afan Oromo /Amharic versions were used for data collection after pretesting on 5% of the actual sample size before the data collection. To ensure quality pre-test was conducted on patients attending Shenan Gibe general hospital and we proceed to data collection. The collected data was checked for completeness and consistency on each day of collection. The principal investigator led the overall activities during the data collection period.

4.11. Data processing and analysis

After checking for data completeness manually, data was entered using EpiData version 3.1 software applications. Then data analysis was done using SPSS version 25. Before analysis data cleaning and recoding was done. Descriptive statistics was used to describe Categorical variables by frequencies and proportion, while continuous variables data was summarized using mean, median, standard deviation, or interquartile range. Multinomial logistic regression was used to identify significantly associated variables with the outcome. First bivariate analysis was done to nominate variables for multivariable analysis; using p value < 0.25 as a cutoff point, variables with less cut point was entered in to multivariable analysis. Then, nominated variables were entered in to multivariable analysis and p value <0.05 and 95% CI was used to ascertain significant association.

4.12. Ethical issues

After ethical clearance from the institutional review board of institute of health permission was obtained from the hospital to collect data. Verbal consent was received from patients during data collection. Patients' confidentiality was ensured during the study period. No risky procedures applied and respondents were treated with warfarin and other medication according to existing guideline. For patients who cannot afford for their INR laboratory fee was paid. All possible

necessary precautions were employed to minimize COVID -19 exposures during patients were interviewed.

4.13. Dissemination of result

The paper will be submitted to all relevant stakeholders like faculty of medical sciences, departments of internal medicine and libraries. The finding of this study will be addressed for researchers and others through presentation on Seminars and publications. Publications in peer-reviewed, national or international journals will also be considered

CHAPTER FIVE: RESULTS

5.1. Sociodemographic and economic characteristics of the respondents

A total of 196 patients on warfarin for various reasons were included in this study. More than half, 121(61.7%) of them were female. Of the total 196 participants nearly a third 66(33.7 %) and 63(32.1%) aged in the ranges of 36-50 and 35 and less years of age respectively. The majority of them 121(61.7 %) lives in rural areas. More than two third, 132(67.9%) of the participants are Muslim while 21 (10.7%) are protestant. Nearly a third 60(30.6 %) of the respondents are underweight while 18(9.2 %) of them are overweight. Among the total participants half 98(50 %) of them does not have formal education while only 20 (10.2%) of respondents attended college or university level. The majority of them are farmers which account for 88(44.9 %) while and government workers account for only 33(16%). More than half 101 (51.5 %)and 54(27.6%) of them has monthly income of less than 1500 while only 8.7 % get monthly income of 5,500- 10,000ETB (Table 1).

Table 1: Sociodemographic and economic characteristics of patients on warfarin at JMC follow up clinic, JMC, 2021.

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^2	<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
Religion	Muslim	132	67.3
	Orthodox	43	21.9
	Protestant	21	10.7

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
	Merchant	26	13.3
	Government employed	33	16.8
	Jobless	49	25
Income/month	< 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

5.2. Behavioral and dietary factors

Among the respondents more than quarter 51(26 %) were actively chewing khat. Majority of them 22(42.3%) chew Khat weekly. Eight (4.1 %) have history smoking of which 3(37.5%) are current smoker. Only 6(3.1 %) has history of ingesting alcohol almost two third 4(66.7%) of them are currently alcoholic. Majority 107(54.6%) patients were advised on dietary selection while on warfarin by their care providers and almost two third 70(65.4%) of them were adherent to the advice. Majority 118(60.2%) of them were poorly adherence according to MMAS-8. Only 22(11.2%) of patients have discontinued their warfarin during the last 1 month of follow up for more than one week. More than two third of 15(68.2%) and 4(18.2%) of them discontinued warfarin for financial reason (Table 2).

Table 2: dietary and habit characteristics of patients on warfarin at JMC follow up clinic, JMC, 2021.

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	Yes	22	11.2
last month	No	174	88.8
Reason for discontinuation	For financial	17	77.3
	For high INR and surgery	54	22.7

5.3. Clinical profile of respondents

Of the total respondents 116 (59.2%) were AF patients while Only 5 (2.6 %) and 4(2 %) were patients with PVT and PTE respectively. Of them 139 (70.9 %) have comorbidity: heart failure accounts for more than third 70 (35.7%), while tuberculosis, malignancy, anemia and epilepsy

accounts for 23(16.5 %) of comorbidities together. Almost all 136(97.8%) of them were on treatment for their comorbidity. They were on warfarin for mean duration of 15.53 ±18.922 [1 to 90 months]. Among them more than two third 135(68.9%) were on warfarin for 12 months. During follow up while the mean number of documented INR was 6.99± 4.57 [3 to 29] the majority 123(62.8%) of respondents had less than six documented INR. Almost three quarter 146(74.5%) of the patients took 35-70 mg of warfarin per week while only 4(2%) took the higher dose. Of the respondents almost half 99(50.5%) every month while 12(6.1 %) have INR done every 3 months. Considering the latest INR majority 109(55.6%) of the respondents has sub therapeutic INR while 21(10.7) were in sub therapeutic range. While the mean TTR of respondents were 25.03±24.17 % [0 to 80%] the majority 166(84.7%) of them has TTR of INR below 60% (Table 3)

Table 3: Medical characteristics of patients on warfarin at JMC follow up clinic, JMC, 2021.

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=<70	146	74.5
	>=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	Up to 6 documented INR	123	62.8

INR	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	Less than 60%	166	84.7
range	60% and above	30	15.3
Has comorbidity	Yes	139	70.9
	No	57	29.1
	Heart failure	70	50.4
Type of comorbidity	HTN	30	21.6
	Thyrotoxicosis	16	11.5
	Others	23	16.5
Treatment	Yes	136	97.8
	No	3	2.2.

5.4. Pattern of the latest international normalized ratio

Finding of this study showed that among 196 patients on warfarin at chronic follow up clinic of Jimma medical center (JMC), 109(55.6%), 66(33.7 %) and 21(10.7 %) are in Sub therapeutic, therapeutic and sub therapeutic range respectively considering the latest INR on the day of data collection. (Figure: 2)

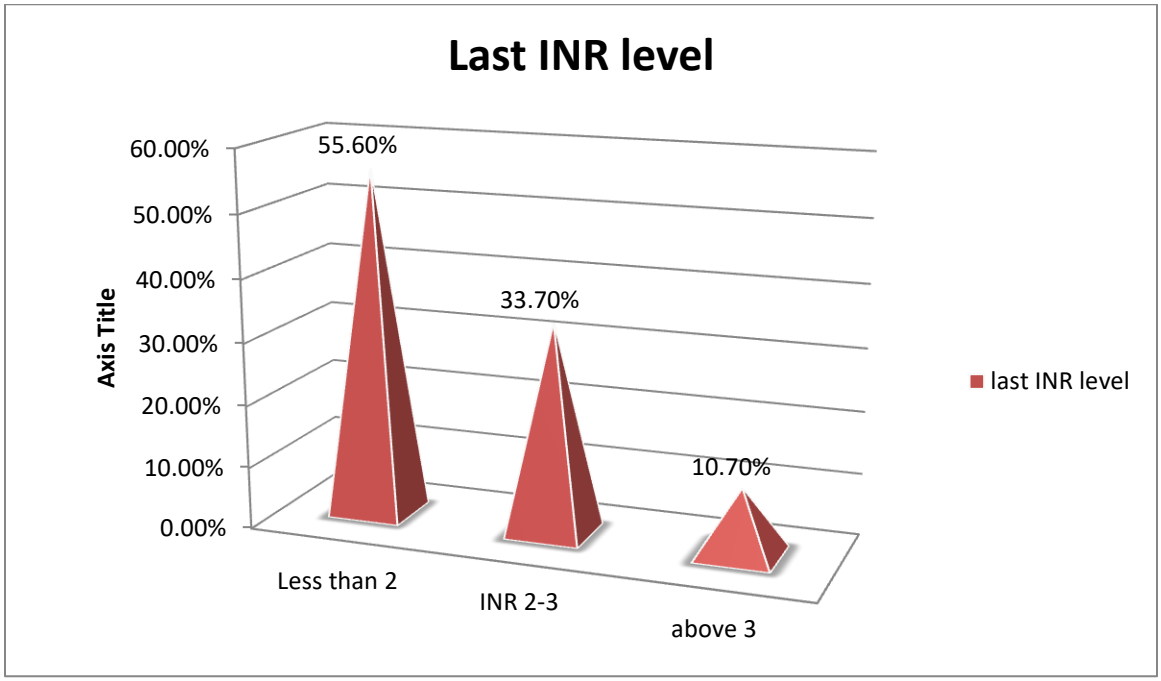

Figure 2: Pattern of the latest INR among patients on warfarin at chronic follow up clinic, JMC, 2021.

On other hand, finding of this study also showed that among 196 patients on warfarin at chronic follow up clinic of JMC 166(84.7 %) have TTR of less than 60 percent, the target below which most guidelines consider as poor anticoagulation (figure 3)

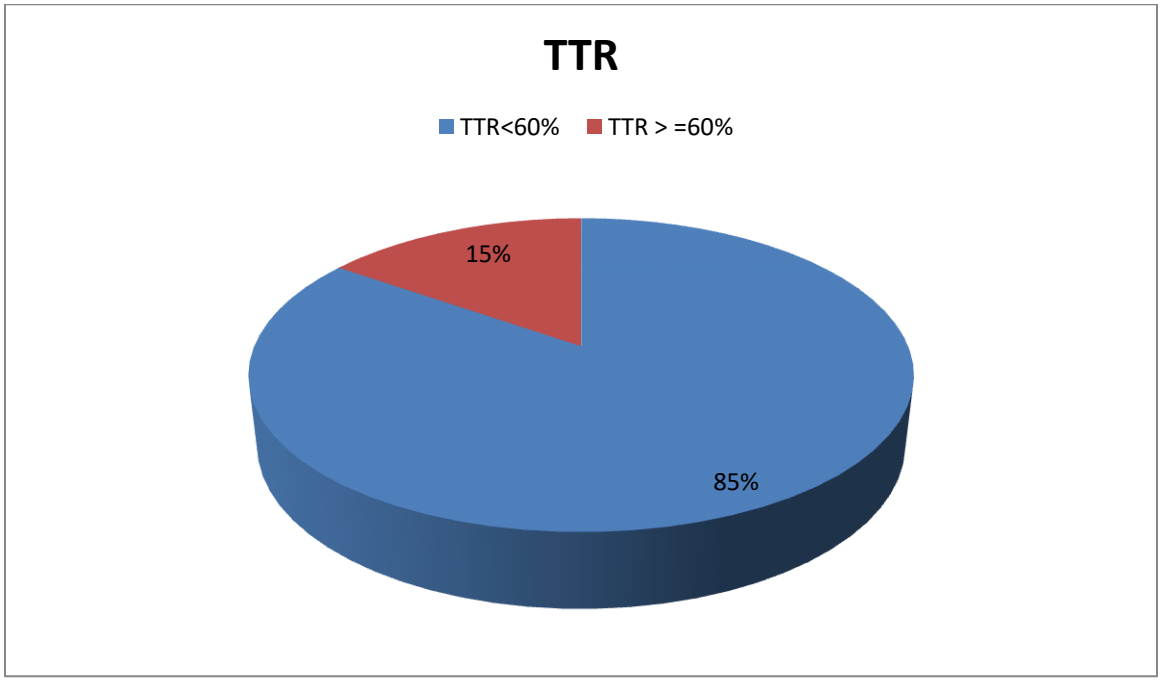

Figure 3: Proportion of time in therapeutic range INR among patients on warfarin at chronic follow up clinic, JMC, 2021

5.5. Factors associated with Sub therapeutic international normalized ratio

In this study factors affecting INR were identified of which chat chewing, alcohol ingestion, smoking, level of education, monthly income and religion were not associated on bivariable analysis at P-value less than 0.25. Therefore, these variables were excluded from multivariable analysis. It was observed from a data of multivariate analysis that adherence to warfarin, shorter duration of warfarin and presence of comorbidity were significantly associated with sub therapeutic INR at P-value less than 0.05.

The odd of developing Sub therapeutic INR among patients who were none adherent to warfarin were about 6 times more likely than its counterpart [AOR 6.13 (95% CI ((3.31-28.10)].Patients who had no comorbidity were about 96.5% less likely to develop Sub therapeutic INR as compared to their counterpart [AOR 0.035 (95% CI (.004 -0.323)].It's also found that patients who were on warfarin for more than 12 months were 89.6% less likely to be in sub therapeutic range than those who were on follow up for less than 12 months[AOR .104(95% C.I .012-.875)]. The other independent predictors of Sub therapeutic INR being widowed and divorced with nearly three times odd of having sub therapeutic INR [AOR 2.95 (95% CI (1.50-56.60)].

On other hand non adherent to dietary advice [AOR 3.93 (95% CI ((.82-18.82)], being overweight [AOR 14.69 (95% CI (.72-300.80)] and target weight (AOR 4.92 [95% CI (.27-90.40)], living in rural area [AOR 3.875(95% C.I .699-21.486)] occupation: being merchant (AOR 3.96 (95% CI ((.47-33.00), being jobless [AOR 3.64 (95% CI (.14-95.40) and frequency of INR follow up [AOR 3.243(. (95% C.I (.430-24.437)] didn't show any association with sub therapeutic INR as compared to their counterparts.
(Table 4).

Table 4: Binary and multivariate logistic regression analysis of factors associated with sub therapeutic INR among patients on warfarin at JMC, 2021.

Variables		TTR		COR (95% CI)	AOR (95% CI)	P value
		<60%	≥60%			
Sex	Male	65(86.7)	10(13.30	1		
	Female	101(83.5)	20(16.5)	.777(.342-1.765)	.288(.054-1.545)	.146
Age	<=35	50(79.4)	13(19.60	1		.309
	36-50	56(84.8)	10(15.2)	2.229(.826 − 6.013)	.364(.037-3.542)	.384
	>50	60(89.6)	7(10.4)	1.531(.545 − 4.297)	.197(.025-1.576)	.126
BMI(Kg/m2)	<18.5	50(83.3)	10(16.7)	1		
	18.5-24.9	101(85.6)	17(14.4)	1.0(.243 − 4.110)	4.922(.268-90.439)	.283
	>=25	15(83.3)	3(16.7)	.842(.220 − 3.220)	14.690(.717-300.8)	.081
Residence	Urban	61(81.3)	14(18.7)	1		
	Rural	105(86.3)	16(13.7)	1.506(.688 − 3.297)	3.875(.699-21.486)	.121
Marital status	Married	134(85.6)	23(14.4)	1		.250
	Single	19(79.9)	5(20.8)	1.116(.236 − 5.272)	.447(.042-4.699)	.502
	Others	13(86.7)	2(13.3)	1.711(.287 −10.19)	2.945(.153-56.60)	.474
Occupation	Farmer	79(89.7)	9(10.3)	1		.296
	Merchant	22(84.6)	4(15.4)	1.003(.316 − 3.178)	3.961(.475-33.0)	.203
	Government employed	21(63.6)	12(36.40)	1.600(.390 −6.559)	.572(.025-13.27)	.727
	Others	44(89.7)	5(10.3)	5.0(1.568 − 16.131)	3.638(.139-95.41)	.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(.821-18.82)	.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)	<.0001

Dose of warfarin per week in mg	<35mg	42(91.3)	4(8.7)	1		
	35-70mg	124(82.7)	26(17.3)	.454(.150- 1.377)	.520(.087-3.110)	.474
Number of documented INR	<= 6 documented INR	107(87.0)	16(13.0)	1		
	> 6 documented INR	59(80.2)	14(19.8)	.630(.288-1.381)	.968(.198-4.731)	.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(.430-24.437)	.254
Duration on warfarin	<=12 months	113(68.0)	53(32.0)	1		
	12 months	22(73.3)	8(26.7)	1.290(.539 - 3.08)	.104(.012-.875)	.037
Indication for warfarin	AF	102(87.9)	14(12.1)	1		.160
	DVT	56(81.2)	13(18.8)	.366(.087- 1.544)	.296(.025-3.540)	.337
	Others	8(72.7)	3(27.3)	.619(.144 - 2.659)	.059(.003-1.157)	.062
Has comorbidity	Yes	127(90.0)	12(10.0)	1		
	No	39(68.4)	18(31.6)	.205(.091-.462)	.035(.004-.323)	.003

CHAPTER SIX: DISCUSSION

The finding of this study showed that the proportion of sub therapeutic INR was 55.6% among patients on warfarin at Jimma medical center chronic follow up clinic considering the latest INR results. Majority of the respondents 84.7 % have TTR of less than 60 %with only TTR of 15.3%. Presence of comorbidity, duration on warfarin, level of adherence to warfarin and was found to be significantly associated with sub therapeutic INR.

The finding of this study was significantly higher than previous study conducted in developed country, USA (37%) in AF and (63 %) in DVT (13) and Nederland (35%) in patients anticoagulated for prosthetic valves (14). The discrepancy may be due to residence in rural area in most of our patients, poor adherence and less frequent INR determination. It might be due to difference in study design. The previous studies were systematic review study design unlike the current study which is prospective cross sectional study design. In deed it may be due to study period deference between current and previous study. Similarly proportion of sub therapeutic INR was higher than which was done in newly admitted Korean hospital (41%)South African and Ugandan hospital (59%)(15,16).The discrepancies might be due to difference in study design in which the Korean, South African and Ugandan study was retrospective cohort study design. In our study, it's also found that patients who were on warfarin for more than 12 months were 89.6% less likely to be in sub therapeutic range than their counterparts which is congruent with study done in Korea whose being on warfarin therapy for ≥ 3 years had higher percent TTR than their counterparts. The discrepancy might also due difference in duration of warfarin treatment.

Comparing the last INR level, the result of our study was comparable to study done in black lion referral hospital where sub therapeutic INR is 52.2 %(17). The TTR in our study is also significantly lower as compared to study done in university of Gonder (70.8%) (18). The discrepancy might be due to the lack of hospital based INR determination in our set up which affect the frequency of patients follow up.

The majority of patients with sub therapeutic INR range (TTR of <60%) in this study were patients 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 in Gonder (18). This is

probably due the fact that patients with comorbidity has higher pill burden that affect the adherence and drug interaction.

In this study, poor level of adherence to warfarin was associated with sub therapeutic INR. The odd of having TTR of <60% was nearly six times higher among those with poor adherence to warfarin as compared to highly adherent patients. This is congruent with previous study done in 47 clinics throughout United States where non adherence was among five causes of sub therapeutic INR (19).

In this study age didn't show any association with level of INR as cross sectional study done in Spain study showing patients with younger than 50 years with a slight increased risk of a low INR (20, 21). This might be because of significance difference in age of study population (Mean age was 73.6 years in Spain while its 46.42(±16.45 years) in our study.

This study also indicates that non adherence to dietary advice was associated with nearly four times likely be in sub therapeutic INR level compared to those who are well adherent to the advice. This finding was similar to previous few studies were patients who took vitamin K rich diet was associated with sub therapeutic INR (22).

In this study, having higher BMI didn't show association with Sub therapeutic INR which is incongruent to retrospective cohort study in King Abdulaziz Medical City, Riyadh, Saudi Arabia, between January 2014 and June 2017 on 211 patients included where therapeutic INR was achieved in 71.1%, 42.3%, 38% of normal body, obese patients and of morbidly obese patients respectively (27).

Furthermore, our study showed association of warfarin adherence, which is incongruent with cross sectional study done in university of Gondar were no significant association was found (28).

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATION

7.1. Conclusion

Finding of this study pointed out that the proportion of sub therapeutic INR among patients on warfarin at JMC follow up clinic was very high. Comorbidity, adherence to warfarin and duration on warfarin and had shown statistically significant association with sub therapeutic INR. Furthermore, being overweight, being widowed or divorced, living in rural area, being jobless and having less frequent INR follow up were independent predictors of sub therapeutic INR.

7.2. Recommendation

As per the result of this study, the following recommendations were forwarded.

For physician: to give proper adherence advice to warfarin and diet and medications that interacts with warfarin while monitoring INR to achieve therapeutic range.

For hospital administrative: to avail the laboratory to have proper INR follow up as almost all of the results were from private sector which most of our patients cannot afford and might affect the adherence.

For researchers: Finally we recommend a future study dealing with larger multicenter study to know additional factors and the outcomes of the patients with sub therapeutic INR while on warfarin.

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Annex II Information Sheet and Consent Form

A. Information Sheet

Research title

PROPORTION OF SUBTHERAPEUTIC INTERNATIONAL NORMALIZED RATIO AND ASSOCIATED FACTORS AMONG PATIENTS ON WARFARIN AT JIMMA MEDICAL CENTER, JIMMA, SOUTHWEST ETHIOPIA

Name of the organization: -

Jimma University, Institute of health, Faculty of medical sciences, Department of Internal Medicine

Purpose of the study

To assess the proportion of sub therapeutic INR and associated factors among patients on warfarin at Jimma medical center, Jimma, southwest of Ethiopia.

Confidentiality

Any information is obtained about you will be kept confidential. This is assured by avoiding use of any identifier about you and information will be recorded with code number and will be used only for purpose of this study.

Voluntary participation

Participation on this study is voluntary basis of participant while have the right to refuse on participation at any time. I would like to inform you that ethical clearance was obtained from Jimma University Research Ethical Review board. At end, if you have a query you can ask us any questions at any time. Here are addresses of investigator who you can contact:

Name of investigator: Dr. Abdulkadir Urgessa - Principal Investigator

Name of advisors: - Dr. Belete Habte (Internist, Assistant Professor) – Co investigator

Dr. Gashahun Mokonnen (Internist, Assistant Professor) –Co investigator

Mrs. Chaltu Fikru (MPH, Assistant Professor)- Co investigator

B. Consent Form (English version)

Participant identification number_____

Greetings!

My name is _____a physician/nurse working at this hospital. We are conducting a research on proportion of Subtherapeutic INR and associated factors on clients who are taking warfarin at JMC.We hope you will be one of the participants. The aim of this research is to know the burden of this problem which if conducted will guide us on the way we may tackle it. There will not be any intervention and you will be treated according to existing guideline. Therefore there will not be any harm to you and all information you provide will be kept confidential if you are willing to be participant. Are you willing to participate in our research?

A. Yes B. NO

I_____ have read the information sheet fully in my own language (informed) and understood its content well. have given my consent freely for the participation on the study on assessment of the proportion of sub therapeutic INR among patients on warfarin at Jimma Medical center, Jimma, southwest of Ethiopia, 2021.

Participant signature_____Date_____

Data collector name: _____ Signature: ____Date: _____

Witnesses

1. Name: _____ signature: _____Date: _____
2. Name: _____ Signature: _____ Date: _____
3. Name _____ Signature _____Date_____

B. Guca fedhii qorannoo irratti hirmaachuu ittiin gaafatamu (Afan Oromo version)

Lakkofsa kaardii hirmaataa_____

Nagaya jirtuu!

Maqaan koo _____jedhama. Ogeeassa/ogeettii fayyaa giddugala fayyaa jimmaati.Qorannoo waa'ee "**hamma INR yeroo yaaliin kennamu ta'uu qabuu gadi (proportion of Subtherapeutic INR) fi wantootawalqabatan"** jedhuhojjachuufdeemna.Qorannoon kun Onkololeessa 10, 2014hangaMuddee 10, 2014 kan adeemsifamuu fi hamma rakkinichaa baruuf kan nu fayyaduu fi gara fulduraaf akkamitti akka irratti hojjachuu akka qabnuuf kan karaa saaquu dha. Qorannoo kana yeroo raawwannu wanti addaa kan isinniif kennamu waan hin jirreef midhaan tokkollee kan isinirra gahu hin jiru. Akkasumas ragaan isin nuuf kennitan icciitiin kan kayamuudha. Hirmachuuf fedhii qabdanii?

A. Eeyyeen B. Miti

Maqaan koo_____ jedhama.Qorannaa armaan olotti ibsame erga afaan kootiin dubbisee hubadhee booda fedhii kootiin hirmachuuf murteesseera.Isa kana dirqama tokko malee ta'uu isaa mallattoo kootiin mirkaneessa.

Mallattoo hirmaataa_____guyyaa_____

Maqaa nama daataa funaanuu: _____ mallattoo ____ guyyaa: _____

Ragaa

1. Maqaa: _____ mallattoo: _____guyyaa: _____
2. Maqaa: _____ mallattoo: _____ guyyaa: _____
3. Maqaa_____ mallattoo_____guyyaa_____

B. የፊቃደኝነትፎርም (አማርኛቬርሽን)

ኮድ_____

ጤናይስጥልኝ!

እኔ_____እባላለዉ.።የጅማጤናማዕከልሰራተኛነኝ። ከሚጠበቀዉበታችየሀነአይኤኒአሪመጠንናምክናቶችየሚልጥናትእያካደንነዉ።ጥናቱከጥቅምት 10, 2014 - ተሕሳስ 10, 2014 የሚካሄደዉስሆንለጥናቱፍቃደነቶንለመጠየቅነዉ። ምርሚሩየችግሩንመጠንለማወቅየሚጠቅመንሲሆንየዚህቃለመጠየቅግዜየሚሰጡንመረጃለምርሚሩዉ ጤትብቻየሚንጠቀመዉናለሌላወገንየማናካፍለዉይሆናል፡ እንድሁምመደበኛየሚወስዱትመዳሃኒትላይየሚጨመርናየሚቀነስሲለሌለዉምንምጉዳትአይደርስቦትም። ቃለመጠየቁላይለመሳተፍፍቃደኛኖት?

ሀ. አዎ(ወደቀጣይ)

ለ. አይ (ጥያቄያቁሙ)

እኔ_____
ቃለመጠየቁላይለመሳተፍፍቃደኛመሆኔንበፍርማዬአረጋግጣለዉ።

የተሳታፍዉፍርማ_____ ቀን_____

ቃለመጠየቅአድራጊስም_____ ፍርማ_____ ቀን _____

ሚስክር

1. ስም: _____ ፍርማ: _____ቀን: _____

2. ስም: _____ ፍርማ _____ ቀን: _____

3.ስም_____ ፍርማ_____ቀን_____

Annex III: Questionnaire

Date of data collection---------/-------/----------

European date month year

First, I would like ask you some question about yourself

Card no: ----------Code----------

Region---------- Zone ----------woreda----------

A. Sociodemographic factors

1. Sex of patient.
   A. Male
   B. Female
2. What your age? _____
3. Weight_____Height_____
4. What is your current address?
   A. Urban
   B. Rural
5. What is your religion?
   A. Muslim
   B. Orthodox
   C. Protestant
   D. Catholic
   E. Others (specify)----------
6. What is your marital status?
   A. Married
   B. Single
   C. widowed
   D. Divorced
7. What is your highest level of education you have completed?
   A. Illiterate or informal education
   B. Primary (1-8)
   C. Secondary (9-12)
   4. Diploma +
8. What is your occupation?
   A. Farmer
   B. Merchant
   C. Government worker (specify) ----------
   D. Jobless
   E. Other -----

8. How much is your estimated annual income?_____

B. Dietary and behavioral factors

9. Have you ever smoke any tobacco product?
   A. Yes
   B. No
10. If Yes to Q 9, do you currently smoke any tobacco?
    A. Yes
    B. No
11. Have you ever consumed alcohol?
    A. Yes
    B. No
12. If yes to question number 11, have you consumed any alcohol in the past 12 months?
    A. Yes
    B. No
13. If yes to Q12, how frequently, have you had at least one standard drink?
    A. Less than once per month
    B. 1-3 days per month
    C. 1-2 days per week
    D. 3-4 days per week
    E. 5-6 days per week
14. Did you ever chew chat?
    A. Yes
    B. No

15. If yes to Q14, how frequently do you chew khat after you started warfarin?
    A. Daily
    B. Biweekly
    C. Weekly
    D. Monthly
16. Did you get dietary advice while you are on warfarin?
    A. Yes
    B. No
17. If yes to Question no 16, are you following your caring health professional?
    A. Yes
    B. No

C. Medical factors

18. Level adherent to your warfarin dose? (Use MMAS-8 scale)

Chart MMAS-8 (Result for each)	**0**	**1**
1. Do you sometimes forget to take your warfarin?	0	1
2. Over the past two weeks, were there any days when you did not take your warfarin	0	1
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?	0	1
4. When you travel or leave home, do you sometimes forget to bring along your medications?	0	1
5. Did you take your warfarin yesterday?	0	1
6. When you feel like your INR is under control (INR of 2-3), do you sometimes stop taking your medicine?	0	1
7. Do you ever feel irritated about sticking to your disease treatment plan?	0	1
8. How often do you have difficulty remembering to take all your warfarin? Never/Sometimes/Quite Often/Always	Other (0)	Never (1)
MMAS-8 score	-	-

19. Did you discontinue warfarin with the last month?
    A. Yes
    B. NO
20. If yes to question number 19, why?
    A. Discontinued for surgery
    B. Discontinued for financial reason

C. Dose reduced in reaction to high INR or bleeding
D. Other ---

21. Any known Co morbidity?

A. Yes
B. No

22. If yes to Question no 21, which comorbidity was identified?

F. RVI
G. Epilepsy
H. Malignancy

23. If you have any of the co morbidity, are you on treatment?

A. Yes
B. No

24. If yes for Question no 23, which medication are you getting? List them_____

25. What is the Indication for warfarin?

A. Atrial Fibrillation
B. DVT
C. PTE
D. Prostatic valve
E. Prior stroke

26. Dose of warfarin per/week in milligram _____

A. Heart failure
B. Diabetes mellitus
C. Renal failure
D. Asthma /COPD
E. TB

27. Duration of warfarin treatment _____.

28. How frequently do you have your INR followed?

A. Weekly
B. Monthly
C. Every 2 months
D. Every 3 months

29. What is the number of INR results during follow up? _____

30. The last INR result_____

31. What is number in the following ranges?

A. < 2 _____
B. 2-3 _____
C. >3 _____

Annex IV: Declaration

I, the undersigned, internal medicine 3rd year resident declare that this thesis is my original work in the partial fulfillment of the requirements of specialty certificate in Internal Medicine

Name: Dr. Abdulkadir Urgessa Jada

Signature: _____

Place of submission: Jimma University Institute of Health, faculty of Medical sciences, Department of Internal Medicine.

Date of Submission: _____

This thesis has been approved by the university advisors.

Advisors Name	Signature
1._____	_____
2._____	_____
3. _____	_____