



Assessment Of Magnitude Of Anticoagulation Use In Patients With Atrial Fibrillation For Primary Prophylaxis Of Stroke At St. Paul's Hospital Millennium Medical College Cardiac Clinic, Addis Ababa, Ethiopia.

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This thesis by **Bisrat Demeke(MD)** is accepted in its presented form by board of examiners in satisfying thesis requirement for the Specialty certificate in Internal Medicine.

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Abbreviations and Acronyms

ACC – American college of cardiology

AF- Atrial fibrillation

ASD – Atrial septal defect

CAD – coronary artery disease

CHA2DS2VASc - Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, Stroke /TIA, Age 65 -74, Vascular disease , Sex (female).

DCMP – Dilated cardiomyopathy

DM – Diabetes mellitus

ESC- European school of cardiology

ETB – Ethiopian Birr

HAS-BLED – HTN, Abnormal liver and renal test, Stroke, Bleeding, Labile INR, Elderly, Drugs (NSAIDS, Acetaminophen)

HTN –Hypertension

IHD – Ischemic heart disease

INR - International Normalized Ratio

LA – Left atrium

LAA – Left atrial appendage

LVH – left ventricular hypertrophy

MI – Myocardial ischemia

MS – Mitral stenosis

NOAC- Novel oral anticoagulant

OAC - Oral anticoagulant

OPD – Out patient department

RHD – Rheumatic heart disease

SPHMMC – St. Paul’s hospital millennium medical college

TASH – Tikur Anbessa Specialized Hospital

TIA – Transient ischemic attack

TTR - Time in therapeutic index

USA – United states of America

VKA – Vitamin K anticoagulant

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Abstract

Back ground- Atrial fibrillation increases a risk of stroke by five times as compared to a person without it. The best strategy to prevent stroke is to anticoagulate patients with atrial fibrillation based on their risk profile. Magnitude and the choice of anticoagulation is different at different institutions. Warfarin is a drugs of choice as primary prophylaxis in Ethiopia. Warfarin has much better efficacy than Aspirin but with narrow therapeutic index and needs frequent follow up with International normalized ratio(INR).

Objective - The objective of this study was to assess magnitude of anticoagulation use in patients with AF for primary prophylaxis of stroke at St. Paul's hospital cardiac clinic and to assess pattern of anticoagulation level among AF patients taking warfarin as primary prophylaxis for stroke.

Method- A prospective longitudinal study was done from March 1- June 30 on patients who visited cardiac clinics and additional data was collected from the patient charts. Descriptive analysis was done to estimate magnitude of anticoagulation use and pattern of anticoagulation level.

Results – In our study, from total of 145 study participants, females account 69% and mean age of study participants was 56.6 ± 11 . The magnitude of anticoagulation use was 79.3%. From those patients eligible to oral anticoagulant use 12.2% were not on oral anticoagulants, 9.8% were on Aspirin while 31.8% of ineligible patients were on warfarin. From patients taking warfarin 51.5% had sub therapeutic INR, 33.5% therapeutic and 15% supra therapeutic INR results during follow-up visits. The mean Time in Therapeutic Range (TTR) was 31.98%. Among patients on warfarin 20% had bleeding as a complication.

Conclusion - In our study magnitude of anticoagulation use was high which was comparable to better set ups but there is a discrepancy on initiation and choice of drug for primary prophylaxis of stroke from standard guidelines in patients with nonvalvular atrial fibrillation. Although frequency of follow up was good; patients level of anticoagulation measured as time spent in therapeutic range was less than acceptable range, which is 60%.

1.Introduction

1.1 Background

Atrial fibrillation is a common and important disturbance of electrical system of the heart (1). It is caused by chaotic electrical signals, which make the upper chambers of the heart (the atria) quiver, instead of properly contracting. During AF, blood pools in the atria, which can allow a clot to form. If a blood clot breaks free, it can enter the bloodstream and block an artery. Most seriously, this happens in an artery that leads to the brain causing a stroke (2).

Without treatment, the risk of stroke among people aged over 65 years with AF is about one in 20 per year, which is five to six times higher than of similar age without atrial fibrillation. The risk may be even higher if the AF is associated with damaged or diseased heart valves, or if the person has a history of high blood pressure, diabetes, heart failure or previous stroke (1).

A major goal of therapy in patients with AF is to prevent thromboembolic complications such as stroke (3). The decision about which therapy, if any, to use is based on an assessment of the level of stroke risk, which is usually classified as low, moderate or high using internationally recognized scales such as the CHA2DS2VASc score (4). In this risk score system, cardiac failure, hypertension, diabetes, vascular disease, 65 to 74 years of age, and female sex are worth 1 point each, whereas age 75 years or older and previous stroke or transient ischemic event are worth 2 points (3).

For patients with CHA2DS2VASc score of 0 the recent ESC guideline recommends no therapy while recent ACC guideline recommends Aspirin 81mg daily; for patients with risk score of 1 ESC recommends Oral anticoagulants and ACC recommends Aspirin 81mg or oral anticoagulants (exception female gender only); for patients with score 2 or more both ACC and ESC recommend OAC (4).

Although warfarin is clearly superior to antiplatelet agents, it has a relatively narrow therapeutic window and interacts with a variety of medications, foods and herbal products (5); in addition, there are pharmacogenetic differences in response between individuals (6). Due to these and other factors, responses to warfarin can vary widely between individuals, and therefore, routine monitoring and dose adjustment are required (7).

Even amongst patients who are eligible for warfarin therapy according to guidelines, the drug is underused (8). In addition, those receiving warfarin spend a significant proportion of time with levels of anticoagulation too low or too high for optimal efficacy and safety (8).

1.2. Statement of the problem

Atrial fibrillation is the most common cardiac arrhythmia with approximately 1% of the general population being diagnosed with the disease; however significant under diagnosis is likely. The risk of developing AF increases with age, and there is a 1:4 lifetime risk of the development of AF in men and women over 40 years of age (8).

Nonvalvular AF increases the risk of stroke 5 times and AF in the setting of mitral stenosis increases the risk of stroke 20 times over patients in sinus rhythm (9). One out of every 4 strokes is due to AF (2).

The prevention of stroke related to atrial fibrillation is a global public health priority. Strokes due to atrial fibrillation are common and frequently devastating ;70-80% of patients die or become disabled, yet they are largely preventable with anticoagulant therapy (64% reduction in the risk of stroke and 25% reduction in mortality) (10).

Evidence –based guidelines recommend the use of oral anticoagulant or antiplatelet therapy to reduce the incidence of stroke in patients with AF, regardless of the approach used to manage the arrhythmia (8).

The Updated 2017 AHA/ACC guidelines for the management of AF recommends: -

1. In patients with AF, antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute risks and relative risk of stroke and bleeding and the patient's values and preferences.
2. In patients with nonvalvular AF, the CHA₂DS₂-VASc score is recommended for assessment of stroke risk.
3. For patients with AF who have mechanical heart valves, warfarin is recommended, and the target INR intensity should be between 2.0 and 3.5 based on the type and location of the prosthesis (4).

Available data show that only 15–44% of eligible patients with AF are prescribed oral anticoagulant therapy with warfarin. Of such studies one study of Swedish practice revealed that 40% of eligible patients with a moderate to high risk of stroke received neither oral anticoagulant therapy nor aspirin (8).

Warfarin reduces the risk of stroke in these patients by 64%, whilst aspirin reduces this risk by 19%. Warfarin is also superior to dual antiplatelet therapy with aspirin and clopidogrel for the prevention of vascular events in patients with AF (8); but warfarin has a narrow therapeutic index, and its effectiveness and safety is a tight balance between risk of stroke and risk of bleeding (11).

The risk for bleeding with warfarin therapy in patients >80 years of age has been estimated to range anywhere from 1.63% to 13.1% per year. The risk for hemorrhage increases with an INR $\geq$ 4.0, older age and in the first 90 days of therapy (12).

1.3Significance of the study

Atrial fibrillation affects approximately 2.2 million patients in the United States. The proportion of ischemic strokes attributable to AF rises significantly with age, from 1.5% in those aged 50-59 years to 23.5% in those aged 80-89years (12). AF is independently associated with an increased risk of death. In the Framingham Heart Study, AF was associated with a 1.5 to 1.9 – fold increase in mortality over 40 years of follow-up (13).

The impact of AF on patients in Africa is not well characterized. Even in developed regions where high-quality health care is readily accessible, patients with AF are undertreated with anticoagulant therapy; similarly, data indicate that patients with AF in Africa receive suboptimal antithrombotic treatment to reduce their risk of stroke (13).

Little is known about the magnitude of anticoagulation use and level of anticoagulation in patients with AF as a primary prophylaxis for stroke in our country. This will be the first study to be done in Ethiopia with this title and help as a stepping stone for future further studies.

2. Literature review

Atrial fibrillation is the most common sustained arrhythmia and is the major public health problem. It is also the most common arrhythmia for which patients are hospitalized; approximately 33% of arrhythmia-related hospitalizations are for AF. AF is associated with an approximately fivefold increase in the risk for stroke and a twofold increase in the risk for all-cause mortality (13).

AF is a supraventricular arrhythmia which is characterized by disorganized, rapid, and irregular atrial activation with loss of atrial contraction and with an irregular ventricular rate that is determined by AV nodal conduction (14). On Echocardiography it is characterized by low-amplitude baseline oscillations (fibrillary or f waves) and an irregularly irregular ventricular rhythm. The f waves have a rate of 300 to 600beats/min and are variable in amplitude, shape and timing. In contrast, flutter waves have a rate of 250 to 350 beats/min and are constant in timing and morphology (3).

In 2010, the estimated number of men and women with AF worldwide were 20.9million and 12.6 million, respectively, with higher incidence and prevalence rates in developed countries. One in four middle-aged adults in Europe and the US will develop AF. By 2030,14–17 million AF patients are anticipated in the European Union, with 120 000–215 000 newly diagnosed patients per year. Estimates suggest an AF prevalence of approximately 3% in adults aged 20 years or older, with greater prevalence in older persons (15).

The mechanisms responsible for AF are complex. Triggering events may differ from maintenance mechanisms. In addition, the clinical phenotypes of paroxysmal, persistent, and longstanding persistent AF have different electrophysiology characteristics because of remodeling and different clinical modulators that affect the substrate, such as heart failure, atrial stretch and ischemia, sympathovagal influences, inflammation, and fibrosis (3).

AF is occasionally associated with an acute precipitating factor such as hyperthyroidism, acute alcohol intoxication, or an acute illness including MI or pulmonary embolism. AF occurs in up to 30% of patients recovering from cardiac surgery, associated with inflammatory pericarditis (14).

According to 2014 AHA/ACC guideline AF is classified as: -

1. Paroxysmal AF - AF that terminates spontaneously or with intervention within 07 days of

Onset. It may recur with variable frequency.

2. Persistent AF – Continuous AF that is sustained for more than 7 days.

3. Long standing persistent AF – Continuous AF for more than 12 months.

4. Permanent AF – It is used where there has been a joint decision by patient and physician to cease further attempts to restore and/or maintain sinus rhythm.

5. Nonvalvular AF – AF in the absence of rheumatic mitral stenosis, a mechanical or bio prosthetic heart valve, or mitral valve repair (9).

The strongest predictors of ischemic stroke and systemic thromboembolism are a history of stroke or a transient ischemic episode and mitral stenosis. When patients with AF and a previous ischemic stroke are treated with aspirin, the risk for another stroke is very high, in the range of 10% to 12% per year. At the other end of the risk spectrum are patients with lone AF, whose cumulative 15-year risk for stroke was reported to be in the range of 1% to 2%. Aside from previous stroke, the best-established risk factors for stroke in patients with nonvalvular AF are diabetes (relative risk, 1.7), hypertension (relative risk, 1.6), heart failure (relative risk, 1.4), and age 70 years or older (relative risk, 1.4 per decade) (3).

Risk of stroke is usually assessed using a scoring system called CHA₂DS₂-VASc. Which includes CHF, HTN, Age ≥ 75 , DM, Age 65 -74, Sex (Female), Vascular disease and previous stroke or TIA giving 2 points for stroke and Age ≥ 75 and the rest 1 point each (16).

2014 AHA/ACC guidelines recommend oral anticoagulant (OAC) therapy for AF patients with a CHA₂DS₂-VASc >2 (Class I recommendation) with either warfarin (Level of evidence A), dabigatran, rivaroxaban or apixaban (Level of evidence: B) and no antithrombotic therapy, OAC or aspirin (ASA) in patients with a CHA₂DS₂-VASc score of 1(9).

The CHA₂DS₂-VASc score appropriately designates age ≥ 75 years as a major risk factor (2 points), equivalent to a history of previous stroke/TIA, making anticoagulant therapy a Class I indication for this group of patients even in the absence of other risk factors (12).

Available data show that only 15–44% of eligible patients with AF are prescribed oral anticoagulant therapy with warfarin (17). Of such studies one study of Swedish practice revealed that 40% of eligible patients with a moderate to high risk of stroke received neither oral anticoagulant therapy nor aspirin (18). Another study done in china on patients with AF 31.7% of patients received oral anticoagulation while 61.2% of patients received antiplatelet treatment as primary prophylaxis for prevention of stroke (19).

In contrary, oral anticoagulation use in ESC (European society of cardiology) member countries was 67 and 49% in eligible and ineligible patients, respectively (20).

Because ~25% of strokes in those aged 80–89 years can be attributed to AF, it is especially important that the elderly receive adequate anticoagulation. However, warfarin is under-used in the elderly. In a study of 405 elderly patients with AF, 51% were prescribed warfarin. The remaining patients were deemed unsuitable for warfarin therapy, even though 83% had at least two major risk factors for stroke (8).

Antithrombotic medications prevent strokes and systemic emboli among patients with AF in part by reducing the formation of platelet-rich or thrombotic clots in the LA or LAA, from which they can embolize through the systemic circulation to the brain or other sites (9).

VKA therapy prevents stroke, systemic embolism, myocardial infarction, and vascular death better than single or dual antiplatelet therapy with aspirin and clopidogrel (annual risk of 5.6% for aspirin and clopidogrel vs. 3.9% with VKA therapy) (15).

Although warfarin is clearly superior to antiplatelet agents, it has a relatively narrow therapeutic window and interacts with a variety of medications, foods and herbal products (5); in addition, there are pharmacogenetic differences in response between patients (6). Due to these and other factors, responses to warfarin can vary widely between individuals, and therefore, routine monitoring and dose adjustment are required (7).

There have been several studies to estimate the risk/ benefit ratio of treating elderly AF patients with OAC, including the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study, which randomized individuals aged ≥ 75 years of age to aspirin or warfarin based on physician discretion. Stroke/systemic embolism (SE) occurred at a rate of 1.8%/year in warfarin-treated patients versus 3.8%/year in the aspirin group (hazard ratio [HR] 0.48; 95% confidence interval (CI), 0.28-0.80), with no difference in the rates of major hemorrhage (1.9 vs. 2.2%, resp.) (21).

A nested case-control study of the Anticoagulation and Risk Factors in Atrial fibrillation (ATRIA) population found that the risk of thromboembolism increased at INR levels < 1.8 (odds ratio (OR), 3.72) while the odds of intracranial hemorrhage (ICH) increased at INR values above 3.5 (22).

Intracranial hemorrhage (ICH) is the most dreaded type of hemorrhage in any patient on OAC. Though the risk of ICH increases with age, the absolute risk of warfarin-associated ICH is relatively low at around 0.2% to 0.6% per year (23).

Warfarin is recommended for patients with end stage renal disease (CrCl < 15 ml/min) or on hemodialysis (12).

The time the patients spend in therapeutic range is important to assess quality of anticoagulation. (24) A study done at Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia on quality of anticoagulation management with warfarin among outpatients showed that patients spent 52.2%, 29.0% and 18.8% of the time in sub-therapeutic, therapeutic and supra-therapeutic range, respectively (25) .

Another study done at urban hospital in cape town, south Africa on anticoagulation outcome of patients on anticoagulation therapy showed that only 48.5% of patients achieved target therapeutic range (26).

National assessment of warfarin anticoagulation therapy for stroke prevention in a AF of United states of America analyzed 2,683,674 INR results of 138,319 patients with AF over 02 years. Patients had a mean age of 74 years; 81% were ≥ 65 years of age, and 55% were ≥ 75 years of age. The mean time in the therapeutic range was 53.7% overall and improved with time on

treatment, increasing from 47.6% for patients with <6 months of testing to 57.5% for those with ≥ 6 months of testing ($P<0.0001$). Younger age, female sex, and lower income were also independently associated with poorer anticoagulant control (27).

In the above study younger individuals exhibited the poorest control and had a higher frequency of testing. The overall mean TTR for individuals <45 years of age was 45.5% compared with 53.9% for those ≥ 75 years of age ($P<0.001$). The relationship between TTR and age persisted beyond the first 6 months of INR measurement. Important differences in TTR were also evident by sex. Within every age category, women had lower TTR ($\approx 2\%$ – 3%) compared with men ($P<0.001$) and a higher frequency of INR testing. This relationship persisted beyond the initial 6-month period. Patients with the highest median incomes had higher mean TTR ($P<0.001$) (27).

A systemic review and meta-analysis of 21 studies (6,248 patients) showed; on average, in the four studies with a target INR range of 2 to 3, patients with AF receiving warfarin spent 61% of time within, 13% of time above, and 26% below the therapeutic range (28).

The stroke incidence is much higher in under anticoagulated patients (INR<2) with AF (7.4 events vs 1.3 events per 100 patient-years). Higher stroke incidence was observed in observational studies as compared with RCTs. Major bleeds were much more common in over anticoagulated patients (INR>3) with AF (3.7 events per 100 patient-years) than in normally anticoagulated patients (1.4 events per 100 patient years) (28).

The British Committee for Standards in Hematology (BCSH) and American College of Chest Physicians Antithrombotic guidelines recommend that INRs should be within target therapeutic range at least 60% of time (33,35)

3. Objectives

3.1. General objective

This study aimed to assess the magnitude of anticoagulation use as primary prophylaxis for stroke among patients with atrial fibrillation on follow up at St. Paul's hospital millennium medical college cardiac clinic, Addis Ababa, Ethiopia, from March 1- June 30, 2019G.C.

3.2. Specific objectives: -

1. To assess the magnitude of anticoagulation use as primary prophylaxis for stroke in patients with AF at St. Paul's hospital cardiac clinic.
2. To assess the pattern of anticoagulation level among atrial fibrillation patients who are taking warfarin as primary prophylaxis for stroke.

4. Methods

4.1 Study Area

The study was conducted in St. Paul's Hospital Millennium Medical College which is located at Gullele sub city at Swaziland street, Addis Ababa, Ethiopia. The hospital is the second largest public hospital in Ethiopia. It was built by Emperor Haile Selassie in 1961 to primarily give service at a low cost or even free of charge to those with low income. It currently has over 2000 clinical and non-clinical staff. The hospital added a medical college in 2007G.C. The outpatient service includes a number of clinics from each clinical department. Under the department of Internal Medicine, there are a number of subspecialty clinics. Cardiac clinic works three days per week and serves more than 150 patients every week. One of the clinics is assigned only for patients taking oral anticoagulants.

4.2 Study Period

This study was conducted from March 1– June 30, 2019 G.C.

4.3 Study Design

This is a prospective longitudinal study design intended to assess the magnitude of anticoagulation use in patients with AF as primary prophylaxis against stroke and assess the pattern of anticoagulation level among patients who are taking warfarin as primary prophylaxis for prevention of stroke; during the specified time.

4.4 Population

4.4.1 Source population

All patients who visited cardiac outpatient clinic during the specified study period and their chart.

4.4.2 Study population

All patients with atrial fibrillation who came for follow up at St. Paul's hospital during the study period.

4.5 Eligibility criteria

4.5.1 Inclusion criteria

All patients with atrial fibrillation who came for follow up at St. Paul's hospital during the study period.

4.5.2 Exclusion criteria

Patients with previous stroke.

Patients who are under 18 years of age.

4.6 Sampling method

All patients with AF who are on follow up at St. Paul's hospital cardiac clinic who fulfill the inclusion criteria were included.

4.7 Data collection methods and procedures

Data was collected using a questionnaire which was developed based on the parameters adopted from previous similar studies. The questionnaire (Annex V) has two parts. The first part is patient interview which includes socio - demographic and clinical information. The second part is chart review which includes Echocardiography findings, Organ function test, Complete blood count and INR (international normalized ratio) results. Patients' chart was also used to collect clinical and medication data. The data was collected by two general practitioners who were selected randomly from medical outpatient department (OPD). They were trained for two days ahead of data collection on how to collect the necessary data from patients and their chart. The data collection was supervised by internal medicine resident, who was trained ahead of data collection, using a checklist. Data collection was done from March 1 to June 30, 2019 during follow up visits at cardiac clinics. Patients who were taking warfarin as a primary prophylaxis for stroke were followed using their INR results to assess level of anticoagulation and they were assessed for possible complications from the warfarin on every visits they had during the study period. The level of anticoagulation was assessed by calculating the Time spent in Therapeutic Range (TTR) for individual patients.

4.8 Data processing and analysis

The data was analyzed by using SPSS version 23.0 software. The descriptive analysis was done using simple frequencies, proportions, mean and standard deviation. The results were presented by tables, pie charts and graphs.

4.9 Data quality control

Pretest of the questionnaire was done on 15 patients which was not included on the final analysis before the actual data collection started and modification was done based on feedback from the pretest. Data quality was controlled by rechecking the questionnaire to avoid duplications, incomplete information and invalid information during data collection. Regular checkup for completeness and consistency of the collected data was done using checklist by the supervisor. All data was examined and intensively cleaned before analysis.

4.10 Ethical considerations

Ethical clearance was obtained from institutional review board of St Paul's Hospital Millennium Medical College. Written Informed consent was obtained from each patient both in Amharic and English. It was translated to their native language for those who did not understand either language during interview by nurses who work at the cardiac clinics. Study participants were informed that participation was voluntary and they can discontinue the interview at any time and if they do not participate it will not affect their care. They were also told that their participation will not cause harm to them and those who volunteered were included in the study. Each patient's information was collected using a structured questionnaire and did not contain patients name. Moreover, the information was only used for this particular study and was kept confidential.

4.11 Operational definitions

Warfarin induced bleeding – any bleeding complaint that occurred during the study period which can be attributed to warfarin for those patients who are taking warfarin as primary prophylaxis for stroke; unless confirmed otherwise, was considered as warfarin induced.

Warfarin induced bleeding historically- any bleeding that can be attributed to warfarin which occurred before starting the study.

Time in therapeutic range – time in therapeutic range was calculated based on the traditional method which is by dividing the number of INR results within therapeutic range to the total INR results of individual patients. And it was used for patients with more than one INR result.

International normalized ratio: It is the ratio of a patient's PT to a normal (control) sample, raised to the power of international sensitivity index values used to determine the clotting tendency of blood in warfarin therapy (34,35)

Sub-therapeutic range: INR < 2.0, where patients are at increased risk for thrombosis (34,35)

Supra-therapeutic range: INR > 3.5, where patients are at increased risk for bleeding (9,34,35)

Therapeutic range: INR in the optimal range between 2.0 and 3.0 except for patients with mechanical heart valve which is 2.5- 3.5 (3,9,15) .

CHA2DS2VASc - Score for stroke risk assessment in Atrial fibrillation using: - Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, Stroke /TIA, Age 65 -74, Vascular disease, Sex (female).

HAS-BLED – Score for bleeding risk assessment in patients who are a candidate or taking anticoagulation: - HTN, Abnormal liver and renal test, Stroke, Bleeding, Labile INR, Elderly, Drugs (NSAIDS, Acetaminophen)

4.11 Dissemination of results

The study result will be submitted to Saint Paul's hospital millennium medical college department of internal medicine, post graduate coordinator office and shared to public health department. After accommodating the examiners comments, the findings will be published in locally accessible or international journals.

5. Results

Total of 145 patients fulfilled inclusion and exclusion criteria. They were followed over a period of 04months.

5.1 Socio-demographic and clinical characteristics

The age of participants ranged from 18-90years, with a mean age of 56.6 with a standard deviation of 11 and the median age was 60. Among 145 patients 100(69.0%) were female.

From 145 patients 69 (47.6%) patients were from Addis Ababa and 55 (37.9%) patients were from Oromia. Risk factors identified were HTN in 49 (33.8%) of patients, DM in 11 (7.6%) whereas only 3 (2.1%) of patients has renal problem (Table 1).

Table 1 Sociodemographic and clinical characteristics of AF patients who are taking primary prophylaxis for stroke at outpatient cardiac clinics of St. Paul's hospital, Addis Ababa Ethiopia, August 2019.

Characteristics	Frequency	Percent
Age (years)		
18-45	44	30.4
46-65	45	31.0
66-74	28	19.3
75-85	25	17.2
>85	3	2.1
Sex		
Male	45	31.0
Female	100	69.0
Address		
Addis Ababa	69	47.6
Oromia	55	37.9
Amhara	12	8.3
SNNP	9	6.2
HTN	49	33.8
DM	11	7.6
Renal disease	3	2.1

DM-diabetes mellitus, HTN-hypertension, SNNP- Southern nations and nationalities of peoples.

5.2 Types of AF

From the total of 145 patients 106 (73.1%) patients had Nonvalvular AF while 39 (26.9%) had valvular AF. From those patients with valvular AF 36 patients had Moderate-Severe Rheumatic MS while 3 patients had Prostatic heart valve (Table -3).

5.3 Distribution of primary prophylaxis use for stroke in AF patients

From 145 patients 113 (77.9%) patients were taking warfarin only, 23 (15.9%) patients were taking ASA, 1 (0.7%) patient was on rivaroxaban, 1 (0.7%) patient was on ASA+ warfarin the rest 7 (4.8%) patients were not taking primary prophylaxis for stroke (Figure-1).

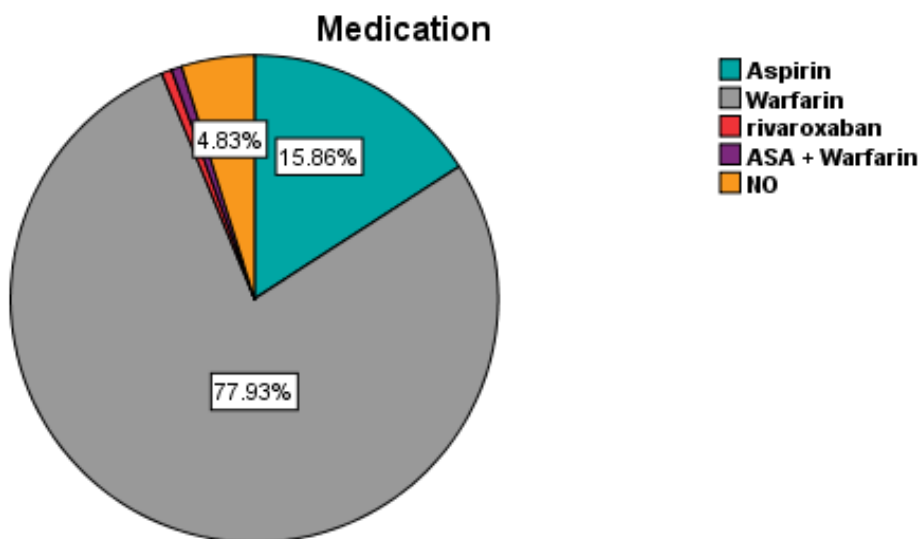


Figure 1 Frequencies of primary prophylaxis use for stroke among AF patients at outpatient cardiac clinics of St. Paul's hospital Addis Ababa, Ethiopia, 2019

5.4 Stroke and bleeding risk score of study participants

From total of 145 patients 106(73.1%) patients had nonvalvular AF. Among patients with nonvalvular AF 84(22-male and 62 female) patients had a CHA2DS2-VASc score of ≥ 2 while 22(12-male and 10 female) patients had a score of < 2 (Figure 2).

Among 145 patients 50(34.5%) patients had HAS-BLED score of 1 while 95(65.5%) patients had HAS-BLED score of 0(Table -3).

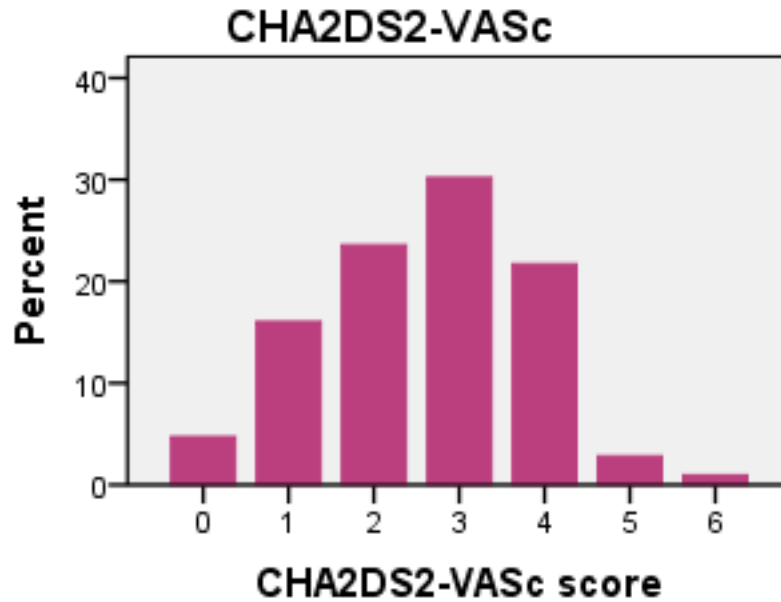


Figure 2 CHA2DS2-VASc score of patients with Nonvalvular AF at cardiac outpatient clinics of St. Paul's hospital, Addis Ababa, Ethiopia, 2019.

5.5 Magnitude of anticoagulation use in this study participants

In this study magnitude of use of primary prophylaxis for stroke among AF patients was 95.2%(138 patients) while 4.8%(7 patients) were not on any type of primary prophylaxis for stroke. From those patients who were taking primary prophylaxis for stroke majority 77.9% were on warfarin while 15.9% were taking ASA. One patient was on rivaroxaban and another one patient was on ASA + warfarin.

From the total 145 patients 123(84.8%) patients were eligible for oral anticoagulant therapy. The indication being having valvular AF 39 of patients and CHA2DS2-Vasc score of ≥ 2 for patients with Nonvalvular AF; 84 of the eligible for OAC patients.

Of the 39 patients that have valvular AF 28(71.8%) were female while 11(28.2%) were male with a mean age of 41years. From 84 eligible patients that have Nonvalvular AF 62(73.8%) were female while 22(26.2%) were male with a mean age of 66. Of 123 eligible patients to OAC 107(87%) were taking OAC, 12(9.8%) were taking ASA, 1 patient was on ASA + warfarin while 3 patients were not taking primary prophylaxis for stroke. Of 22 ineligible patients to OAC

11(50%) were taken ASA while 7((31.8%) were taking warfarin as primary prophylaxis for stroke (Table -2).

Table 2 Magnitude of anticoagulation use as primary prophylaxis for stroke among AF patients at St Paul's cardiac clinics, Addis Ababa, Ethiopia 2019.

Characteristics	Frequency	Percent
Eligible patients to OAC use	123	84.8
SEX		
Female	90	73.2
Male	33	26.8
Primary prophylaxis use		
OAC	107	87
ASA	12	9.8
Both ASA and warfarin	1	0.8
None	3	2.4
Type of AF		
Valvular	39	31.7
Non-valvular	84	68.3
Ineligible for OAC	22	15.2
SEX		
Female	10	44.5
Male	12	54.5
Primary prophylaxis use		
OAC	7	31.8
ASA	11	50
None	4	18.2

OAC-oral anticoagulant. ASA-aspirin, AF- Atrial fibrillation

5.6 Coagulation profile of study participants

From total of 114 patients on warfarin there was 427 INR results done during the study period visits. From these INR results 220(51.5%) were <2, 143(33.5%) were between 2-3, 59(13.8%) were >3-5.9, and 5(1.2%) were above or equal to 6. There were 32 visits where INR was not done. The mean TTR was 31.98%. 94(64.8%) of patients spent < 60% of time in therapeutic range while only 20(13.8) of patients spent $\geq$ 60% of time in therapeutic range. From the total

114 AF patients taking warfarin as primary prophylaxis for stroke 46(40.4%) of patients spent <25% of time in therapeutic range. (Table- 3).

5.7 Number of visits of patients taking OAC

From the total of 114 patients taking warfarin as primary prophylaxis for stroke 48(33.1%) patients had 04 visits during the study period while 23(15.9%) had 5 visits, 19(13.1%) had 3 visits, 13(9%) had 6 visits, 8(5.5%) had 2 visits and 3(2.1%) had only 1 visit (Table 3).

5.8 Complications of anticoagulant therapy

From a total of 115 patients who were taking oral anticoagulants for primary prophylaxis for stroke, 21(14.5%) patients had bleeding on previous visits, 1(0.7%) patient had bleeding during study period and 1(0.7%) patient had bleeding both on previous visits and during the study period while none of the patients had thromboembolic complications (Figure -3).

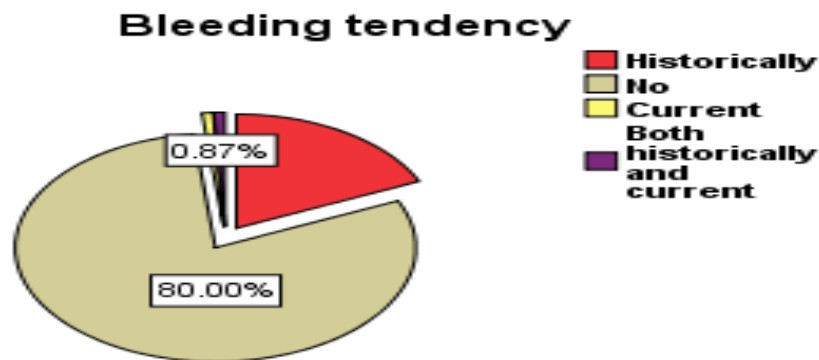


Figure 3 Frequency of bleeding tendency among AF patients taking oral anticoagulants as a primary prophylaxis for stroke at St. Paul's hospital cardiac clinics, Addis Ababa, Ethiopia, 2019.

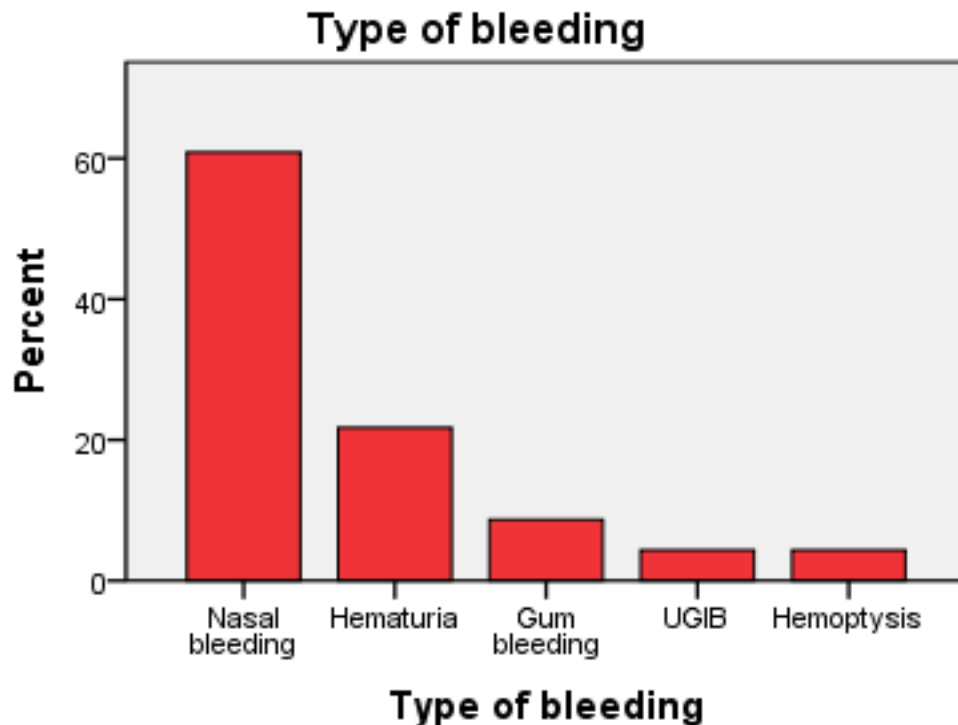


Figure 4 frequency of different types of bleeding among AF patients taking OAC for primary stroke prophylaxis at cardiac clinics of St. Paul's hospital, Addis Ababa, Ethiopia, 2019.

5.9 Drug discontinuation of patients taking Warfarin as primary prophylaxis

From the total of 114 patients taking warfarin as a primary prophylaxis for stroke 36(31.5%) had history of drug discontinuation during the study period. From those patients with history of drug discontinuation 19(52.7%) discontinued after physician advise due to high INR result during follow up, 6(16.7%) due to poor adherence ,6(16.7%) due to unavailability of the drug, 2 patients due to drug side effects, 2 due to financial reasons and one patient due to pregnancy.

5.10 Concurrent use of Warfarin with other medications with possible interaction

From the total of 114 patients taking warfarin 17 patients was taking statins, 12 patients PTU, 2 patents NSAIDs and 1 patient was taking Anti-TB.

5.11 Echocardiographic results of study participants

From the total of 145 study participants 144 had echocardiography which revealed Moderate-Severe Rheumatic MS in 36(27.1%) patients, prosthetic heart valve in 3(2.3%), degenerative valvular heart disease in 29(20%), LVH in 15(10.3%), corpulmonale in 14(9.7%), Non moderate-severe MS RHD in 12(8.3%), DCMP in 9(6.2%) and IHD in 4(2.8%) patients (Table 3).

Table 3- Frequency of type of AF, Echocardiography results, visits, HAS-BLED score and INR results of AF patients on primary prophylaxis for stroke at cardiac clinics of St Paul's hospital, Addis Ababa, Ethiopia, 2019.

Characteristic	Frequency	Percent
Type of AF		
Valvular	39	26.9
Moderate-severe MS	36	92.3
Prostatic valve	3	0.07
Non-valvular	106	73.1
Echocardiography		
Normal	11	7.6
Abnormal	133	91.7
Not done	1	0.7
Moderate-severe MS	36	27.1
Prostatic valve	3	2.3
Degenerative valvular heart disease	29	20
LVH	15	10.9
Corpulmonale	14	9.7
Non moderate- severe MS RHD	12	8.3
DCMP	9	6.2
IHD	4	2.8
Ebstein anomaly	3	2.1
ASD	1	0.7
Thrombus in LA/Appendage	1	0.7
Spontaneous echo contrast	1	0.7
Number of visits		

One	3	2.1
Two	8	5.5
Three	19	13.1
Four	48	33.1
Five	23	15.9
Six	13	9
HAS-BLED score		
0	95	65.5
1	50	34.5
INR results		
<2	220	51.5
2-3	143	33.5
2>3-5.9	59	13.8
≥ 6	5	1.2
TTR mean (%)		31.98

LA- left atrium, INR- international normalized ratio, MS- mitral stenosis, AF- atrial fibrillation. HAS-BLED [HTN, Abnormal liver/ renal function, elderly, stroke, labile INR, bleeding and drugs (NSAID, alcohol)].

5.12 financial burden of warfarin therapy

From the total of 114 AF patients taking warfarin as primary prophylaxis for stroke prevention 70(61.5%) had average monthly expense specific for warfarin use of <800 Birr while 44(38.5%) of patients spent ≥ 800 Birr per month. From those patients with ≥ 800-birr average monthly expenses 18 patients spent > 1000 birr, 1 patient 3000birr and another 1 patient 7500birr per month.

Those patients with 3000 and 7500birr average monthly expense had nonvalvular AF and were advised on the alternative use of rivaroxaban which was around 2000birr for a month supply as primary prophylaxis use for stroke prevention.

There were another 3 patients who requested transfer to other health care facilities which is near to their living area due to financial reasons. There were also 2 patients who discontinued the warfarin for more than 2 weeks due to financial reasons.

6. Discussion

This study was done to assess magnitude of anticoagulation use as primary prophylaxis for stroke in patients with AF and to assess pattern of anticoagulation level in patients taking warfarin for primary prophylaxis of stroke. Warfarin and ASA are the most commonly used drugs as primary prophylaxis for stroke in Ethiopia.

In this study the mean age was 56.6 ± 18 and median age was 60 years which was lower than other studies. A study done in china where mean age of study participants was 68.3 ± 11.9 (19); In the United States of America(USA) National assessment of warfarin therapy on AF patients where mean age was 74(27); In the Realise AF international cross-sectional survey where mean age was 66.6 ± 12.2 years (29) and in GLORIA- AF registry (patients from Europe, North America, Asia, Latin America and Middle east/Africa) median age was 71(30).

In this study 69% of study participants were female which is higher from other studies. In a study done on profile and outcome of patients on warfarin therapy in urban hospital in Cape town, South Africa females account 56.6% (26), study done in china where females account 46.9% of study participants (19), 45.5% in GLORIA-AF registry (30), and 43.6% in Realize survey (29).

In this study 26.9% had valvular AF which is higher from other studies. A study done in china had 14.4% of study participants with valvular AF (19). Most of the studies was done on Non-valvular AF. This may be due to the high epidemiological prevalence of Rheumatic heart disease in our country.

The magnitude of OAC use was 79.3% in our study which is higher from other studies. A study done in china on a total of 4161 patients only 31.7% received OAC as primary prophylaxis for stroke prevention in patients with AF. (19). In another study done in Sweden only 40% of patients with chronic AF were taking warfarin as primary prophylaxis for stroke prevention (18). Similarly, a literature review done in England showed warfarin use of 15%-44% in AF patients with no contraindication for warfarin (17).

Regarding ASA use, only 15.9% of our study participants were on ASA which is lower than other studies. In a study done in china 61.2% of study participants use ASA as primary prophylaxis for stroke prevention in patients with AF (19) In comparison to other studies OAC

use was high and ASA use was low in this study which is may be due to larger proportion of patients with valvular AF in our study.

The magnitude of OAC use was comparable to other studies done in Europe, North America and Asia. In the GLORIA-AF phase 2 global registry 79.9% of study participants were taking OAC as primary prophylaxis for stroke prevention. (30) Similarly, OAC use was 67% in members of European school of cardiology (20)

Regarding initiation of OAC based on standard guideline our study showed 12.2% of eligible patients for OAC were not taking OAC while 31.8% of ineligible for OAC therapy were on warfarin. ASA was given for 9.8% of eligible patients for OAC. Compared to other studies there is less discrepancy from standard guidelines in initiation of OAC as primary prophylaxis for stroke prevention in patients with AF. In a Realise AF international survey 47.4% of eligible patients for OAC were not given anticoagulation therapy while ASA was given for 66.7% of patients in Middle East/Africa, 55.3% in Europe, 43.9% in Latin America and 31.7% in Asia who were eligible for OAC (CHA2DS2-VASc score ≥ 2) (29). Similarly, in a study done in china 31.2% of Nonvalvular AF who had a CHA2DS2-Vasc score of 0 received OAC (19). In another study done in ESC member countries 49% of patients who were ineligible for anticoagulation therapy were on OAC therapy for primary prophylaxis for stroke prevention. (20)

The protective effect of warfarin from stroke and other thromboembolic complications is dependent on the time the patient spent on target therapeutic range(TTR). In our study the mean TTR was 31.98%. This result was comparable to a study done in our country on quality of anticoagulation management with warfarin at Tikur Anbesa hospital which showed the mean TTR of 29% (25). But it was higher from another study done at TASH on admitted patients where it was 21.4% (31). It was also comparable to the study done in china where TTR was 29.2%. (19) The TTR in our study was lower from other studies in Africa and much lower from studies with better set up like Australia, America and Europe. A study done in south Africa TTR was 48.5(26). In the USA national assessment of warfarin in a AF patient the TTR(mean) was 53.7(27). Similarly, studies done in Australia showed TTR of at least 70% up to 74% in trials. (11)

This difference can be attributed to better follow up with frequent INR monitoring and dose adjustment in countries with better health care system.

In our study patients in out of range were three times more likely to be in sub therapeutic range than supra therapeutic range. This result was similar with study done in south Africa which was 4 times more likely to be sub therapeutic range (26) and another study done at TASH medical ward which was 2.5 times more likely to be in sub therapeutic range. (31)

In our study there was 20.2%(23 patients) with bleeding complication with nasal bleeding being the most common compliant. Which is higher than other studies. In study done at TASH medical ward bleeding was the most common complication accounting 12.4% and epistaxis was the common compliant. (31) Similarly in a study done in south Africa there was 14% bleeding rate. (26)

American society of hematology, American college of chest physicians and American heart association suggest that INR should be monitored at interval of no longer than every 4 weeks for stable patients receiving warfarin (24,33,34). The average frequency of INR monitoring in our study was every 4 weeks which was in line with standard guideline recommendations. It was better from a study done at Tikur Anbessa Specialized Hospital where frequency of INR monitoring was every 8 weeks. (25)

7. Limitations of the study

1. The study was done only at one study area so it may be difficult to generalize the results.
2. The study did not account the possible difference in INR results from different laboratories.
3. The study duration was short which might affect some of the results.

8. Conclusion

In general, this study found that magnitude of anticoagulation use as a primary prophylaxis for stroke in patients with AF was high especially in patients with valvular AF. But for those patients with non-valvular AF stroke risk assessment and initiation of oral anticoagulation as primary prophylaxis for stroke prevention was poor. There was deviation from standard guidelines in initiation of primary prophylaxis and choice of drug as primary prophylaxis for stroke prevention. There was good frequency of follow up and INR monitoring even though most of the patients has very poor anticoagulation with most patients spending in sub therapeutic range. In spite of most patients being in sub therapeutic range there was significant number of patients with complications mostly nasal bleeding. There was also significant number of drug discontinuation mostly due to high INR and poor adherence. The financial burden of warfarin therapy was high in some patients to the extent that resulted in drug discontinuation.

9.Recommendation

Based on the results found the following points are recommended to improve our patient follow up.

1. For health professionals

- Stroke risk assessment should be done regularly for patients with non valvular AF.
- For those patients who are a candidate for oral anticoagulation bleeding risk assessment should be done before initiation of oral anticoagulants.
- Initiation of anticoagulation as primary prophylaxis for stroke prevention should be in line with standard guidelines.
- Patients on oral anticoagulation should have frequent follow up based on patient requirement.
- Patients on warfarin should be advised on drug adherence and possible drug side effects.
- Financial burden of frequent follow ups should be assessed for each patient and appropriate measure should be taken based on the results.

2. For health institutions and Ministry of health

- Patients with AF who are taking warfarin should be followed regularly based on patient requirement. And since it requires frequent monitoring the necessary investigations and trained professional should be available widely.
- Warfarin should be available easily if possible in public hospitals at low cost. So we can improve our patient follow up and decrease the financial burden on the patients.

3. For researchers

- Further studies should be done at multiple sites for prolonged duration to assess the factors associated with poor anticoagulation level that was found in this and other similar studies in our country.

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የፍቃደኝነት ፎርም

ይህ ፎርም በውስጥ ደዌ ህክምና ክፍል በልብ ምትና ተያያዥ ችግሮች ዙሪያ በልብ ህመማን ላይ ያሉ ችግሮች ዙሪያ የሚያጠና መሆኑን በመረዳት፣ በእኔ ላይ ምንም ችግር እንደሌለው በመረዳት ፍቃደኝነቴን እገልጻለሁ፡፡

የፍቃደኝነት ፊርማ:.....

ለማንኛውም ጥያቄ ቢፈልጉን

ዶ/ር ብስራት ደመቀ 09-12-76-63-32/ bisratdemeke27@gmail.com

ANNEX II-Consent form- English version

In signing this document, I am giving my consent to participate in the study titled **magnitude of anticoagulation use in patients with AF as primary prophylaxis of stroke in cardiac clinic**. I have been informed that the purpose of this study to assess **magnitude and level of anticoagulation use in AF patients as primary prophylaxis of stroke at cardiac clinic** SPHMMC. I have understood that participation in this study is entirely voluntarily. I have been told that my answers to the questions will not be given to anyone else and no reports of this study ever identify me in any way. I have also been informed that my participation or non-participation or my refusal to answer questions will have no effect on me. I understood that participation in this study does not involve risks.

I understood that Dr. Bisrat Demeke is the contact person if I have questions about the study or about my rights as a study participant.

Investigator :Dr. Bisrat Demeke

Cell phone: +251 912766332

E-mail: bisratdemeke27@gmail.com

Participant's signature and date: _____

የመረጃ ቅፅ

በቅዱስ ጳውሎስ ሆስፒታል ሚሊኒየም ሜዲካል ኮሌጅ በውስጥ ደዌ ተመላላሽ ህክምና ክፍል በልብ ምትና ተያያዥ ችግሮች ዙሪያ ለማጥናት የተዘጋጀ መጠይቅ፡፡

ጤና ይስጥልኝ

ስሜ.....ይባላል፡፡

ዛሬ እዚህ የተገኘሁት የልብ ምትና ተያያዥ ችግሮች ዙሪያ በልብ ህመማን ላይ የሚደረገው ጥናት መረጃ ለመሰብሰብ ነው፡፡ ጥናቱን በዋናነት የሚያካሂዱት በቅዱስ ጳውሎስ ሆስፒታል ባልደረባ የሆኑት ዶ/ር ብስራት ደመቀ ናቸው፡፡ የጥናቱ ዓላማ በልብ ምትና ተያያዥ ችግሮች ዙሪያ በልብ ህመማን ላይ ያሉ ችግሮችን ማጥናት ነው፡፡ ስለሆነም የጥናቱ ተሳታፊ እንድትሆን/ኚ እና ለሚጠየቁ ጥያቄዎች ተገቢ ምላሽ እንድትሰጡ/ጩ በትህትና እጠይቃለሁ፡፡

የተሳታፊ ፊርማ _____

ለማንኛውም ጥያቄ ቢፈልጉን

ዶ/ር ብስራት ደመቀ 09-12-76-63-32/ bisratdemeke27@gmail.com

ANNEX IV: Information sheet

**St. Paul's Hospital Millennium Medical College Department of Internal medicine
individual consent form for the study on: Assessments of the magnitude of anticoagulation
use as primary prophylaxis for stroke in patients with Atrial Fibrillation who are on follow
up at SPHMMC cardiac clinic on 2018/19.**

My name is _____. I am working with the research team of St. Paul's Hospital Millennium Medical College. We would like to assure you your name will not be mentioned in the questionnaire and the information that you will give us will be kept confidential and only used for research purpose. You have full right to refuse to take part or to interrupt the interview at any time. But the information that you will give us is quite useful to achieve the objective of the study and to bring change in atrial fibrillation managements.

Are you willing to participate in the study? 1- Yes 2 - No

If the answer is yes, thanks! Conduct the interview. If the answer is no, Thanks!

Don't force or reinforce an individual to participate in the survey

Interviewer's: name ----- signature -----

Date of interview ----- date -----month/2018/19 G. C.

Checked on ----- date-----month/2018/19 G.C

Complete 1 Incomplete 2 other (specify) -----

ANNEX V. Data Collection Format

Part I – Patient interview

Date –

Code number _____

Section 1 – Sociodemographic and clinical data

1. Age of the patient in years _____

2. Sex

A. Male

B. Female

3. Address

A. Addis Ababa

B. Oromia

C. Amhara

D.SNNP

Others, Specify _____

4. Have you been told to have HTN?

A. Yes

B. NO

5. Have you been told to have DM?

A. Yes

B. NO

6. How many years have you been told to have rhythm problem? _

7. Have you been told to have a renal problem?

A. Yes

B.NO

Section II – Medication history

8. Are you taking aspirin as primary prophylaxis for stroke?

A. Yes

B. NO

9. Are you taking warfarin as primary prophylaxis for stroke?

A. Yes

B.NO

10. If your answer is yes for the above question, for how long have you been taking warfarin?

11. Was there any bleeding tendency while you were taking warfarin?

12. If your answer is yes for the above question, what was the type of bleeding?

A. Nasal bleeding

B. Hematuria

C. Intracerebral hemorrhage

D. Other, specify _____

13. What was your INR level at the time of bleeding?

Section III – Financial history

14. What is your average monthly income?

15. What is the average amount you spend on medication (warfarin) monthly?

16. What is the average amount you spend on laboratory for INR monthly?

17. What is the average amount you spend for transportation during follow up for a single visit?

18. Is there any income that you will lose during your hospital visits?

A. Yes

B.NO

19. If the answer is yes for the above question, what is the average amount per single visit?

20. Do you have other financial issue that was not mentioned above?

A. Yes

B. NO

21. If the answer is yes for the above question, specify with the estimated amount that the patient spend per visit?

PART II – Chart Review

22. What is the type of atrial fibrillation?

A. Valvular

B. Non-valvular

23.If the answer for the above question is non-valvular what is the CHA2DS2-Vasc score?

24.If the answer for the above question is 2 and above, what is the HAS BLED score.

25.Is the patient taking primary prophylaxis for stroke?

A. Yes

B. NO

26. If the answer for the above question is yes, what is the medication?

A. Aspirin

B. Warfarin

C. Other, specify _____

27.If the answer for the above question is warfarin, for how long was the patient taking warfarin?

28.If the patient is taking warfarin, what is the INR result?

29.Was there any drug discontinuation?

A. YES

B. NO

30.. If the answer for the above question is yes, for how long was the drug discontinued?

31. What was the reason for drug discontinuation?

A. Poor adherence

B. Unavailability of the drug

C. Drug side effect

D, Other, specify

32. Was there a diagnosis of thromboembolic event other than stroke while the patient was taking prophylaxis?

A. Yes

B. NO

33. If the answer for the above question is yes, what was the medication?

A. Aspirin

B. Warfarin

34.If the patient was taking warfarin, what was the INR result at that time?

35.Types of medications the patient is taking currently?

A. Aspirin

B. Warfarin

C. Angiotensin converting enzyme inhibitors

D. Beta blockers

E. Digoxin

F. Dihydropyridine calcium channel blockers

G. Diuretics

H. Statins

I. NSAIDS

J. Anti-acids

k. Others, specify

Investigation results

36. Renal function test

A. Creatinine

B. BUN

37. Liver function test

A. Normal

B. Abnormal

38.Complete blood count:

A. Hemoglobin

B. Platelet

Echocardiography

39.left atrial diameter(mm)

40. Spontaneous echo contrast present

A. Yes

B. NO

41. Thrombus in left atrium or appendage

A. Yes

B. NO

42. If the patient has valvular AF, what is the diagnosis?

A. Moderate – severe Rheumatic MS

B. Prosthetic heart valve/s

43. Echocardiography result of patients with non-valvular AF?

A. Rheumatic heart disease – non moderate-severe rheumatic MS.

B. Ischemic heart disease

C. Dilated cardiomyopathy

D. Left ventricular hypertrophy

F. Degenerative valvular heart disease

G. Portal hypertension

H. Other, specify