PERCENTAGE OF TIME IN THERAPEUTIC RANGE AND PROPORTION OF THROMBOEMBOLIC EVENT IN NONVALVULAR ATRIAL FIBRILLATION PATIENT ON WARFARIN

BY

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LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
CCB	Calcium Chanel Blocker
CKD	Chronic Kidney Diseases
CI	Confidence Interval
CRP	C-Reactive Protein
HUSM	Hospital Universiti Sains Malaysia
IHD	Ischemic Heart Diseases
INR	International Normalized Ratio
NOAC	New Oral Anticoagulant
OAC	Oral Anticoagulant
TTR	Time in Therapeutic Range

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ABSTRAK (VERSI BAHASA MELAYU)

Pengenalan : Fibrilasi atrium (AF) adalah aritmia jantung berterusan yang paling biasa. Penggunaan warfarin dapat mengurangkan kadar strok iskemia pada pesakit yang mengidap penyakit nonvalvular AF, akan tetapi memerlukan pemantauan yang kerap dan pemantauan dos. Sasaran INR sering tidak dicapai, dan risiko trombosis, pendarahan dan kematian mungkin berkaitan dengan kawalan INR.

Kaedah :

Kami menganalisis hubungan antara kawalan INR dan kadar tromboembolik, pendarahan dan juga faktor klinikal yang berkaitan dengan masa dalam julat terapeutik (TTR), diantara 73 pesakit fibrilasi atrium nonvalvular. Pesakit telah dibahagikan kepada 2 kumpulan (mereka yang mempunyai kawalan yang baik TTR ≥ 60% dan mereka yang kawalan lemah TTR <60%), sesuai dengan waktu peratusan dengan INR daripada 2.0 hingga 3.0. Hasil dibandingkan mengikut kawalan INR. Hasil utama adalah bahagian trombotik, dan pendarahan.

Keputusan :

Peratusan purata TTR mewakili pesakit di negeri Kelantan adalah 40% dengan kumpulan kawalan lemah mempunyai kadar pendarahan lebih tinggi (kemungkinan nisbah, 5.01; 95% CI 1,30-19,39; p = 0.02) berbanding dengan kumpulan kawalan yang baik. Beberapa faktor klinikal telah dikanal pasti termaksuklah trigliserida (nisbah kemungkinan, 10.60; 95% CI 1,64-68,39; p = 0,013), jenis AF - kekal (nisbah kemungkinan, 6.81; 95% CI 1,22-38,11; p =

0.029) dan pendarahan (nisbah kemungkinan, 9.98; 95% CI 1,65-60,22; p = 0.012) yang mempunyai kaitan dengan TTR <60%.

Kesimpulan :

Dalam pesakit fibrilasi atrium nonvalvular yang mengambil warfarin, risiko pendarahan berkait rapat dengan kawalan lemah TTR. Kawalan INR baik adalah penting untuk meningkatkan kualiti pesakit.

ABSTRACT (ENGLISH VERSION)

Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. The use of warfarin reduces the rate of ischemic stroke in patients with nonvalvular AF, but requires frequent monitoring and dose adjustment. Target INR are frequently not achieved, and the risk of thrombosis, bleeding and death may be related to INR control.

Methods :

We analyzed the relationship between the INR control and the proportion of thromboembolic event, bleeding and clinical factors associated with time in therapeutic range (TTR) , among 73 patients with nonvalvular atrial fibrillation. Patient were divided into 2 groups (those with good control TTR ≥ 60% and those with poor control TTR < 60 %), according to the percentage time with an INR of 2.0 to 3.0. Outcomes were compared according to INR control. The main outcome measures were thrombotic event, and bleeding.

Result :

The mean TTR in Kelantan patient is 40% with poor control group had higher rates of bleeding (odds ratio, 5.01; 95% CI 1.30 to 19.39; p = 0.02) compared with the good control group. Several clinical factors were identified incliding triglyceride (odds ratio, 10.60;95% CI 1.64 to 68.39; p = 0.013), type of AF – permanent (odds ratio, 6.81; 95% CI 1.22 to 38.11; p = 0.029) and bleeding (odds ratio, 9.98; 95% CI 1.65 to 60.22; p = 0.012) significantly associated with TTR < 60%.

Conclusion :

In patient with nonvalvular atrial fibrillation taking warfarin, the risk of bleeding is related to poor control of TTR. Good INR control is important to improve patient outcome.

CHAPTER ONE
INTRODUCTION

1. INTRODUCTION

Atrial Fibrillation (AF) is the most common persistent cardiac arrhythmia. It is an arrhythmia of atria causing cessation of atrial contraction as they begin to fibrillate leading to ineffective filling to the ventricles. Hence, the heart would be inefficient as a pump and consequently end up as having reduced cardiac output. When sinus rhythm fails to act as the driven force for the heart, the ventricular response also becomes irregular, reflecting the erratic atrial electrical signal. The irregular contraction of the ventricles manifested clinically as irregularly irregular pulse would become either too fast or too slow and more commonly the former causing a variety of symptoms as a result of these hemodynamic variances (Sra, Dhala et al. 2000).

In Malaysia, reported prevalence in single center was 2.8% amongst acute medical admission (Freestone, Rajaratnam et al. 2003). In the west, one study revealed the crude incidence of AF was between 6.7 to 3.0 per 1000 person per year, and showing variation in terms sex, race and age group with more incidence in white male (above 70 year old) and lowest incidence in African-American women (Alonso, Agarwal et al. 2009). In short, atrial fibrillation affects 1 in 25 adults of 60 years or older and nearly 1 in 10 adults of 80 years or older (Go, Hylek et al. 2001)

CHAPTER TWO

LITERATURE REVIEW

2. Atrial Fibrillation (AF)

2.1 Background

The latest European Society Cardiology (ESC) 2010 guidelines defined AF as a cardiac arrhythmia with the following characteristics (Camm, Kirchhof et al. 2010) :

a. The surface ECG show 'absolutely' irregular RR intervals (AF is therefor sometimes known as *arrhythmia absoluta)*, i.e RR interval that do not follow a repetitive pattern.

b. There are not distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.

c. The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and < 200 ms (>300bpm).

AF may be classified based on etiology. In cases of no identifiable etiology recognized in patient with a structurally normal heart; it would be classified as lone AF. While others will depend on the underlying etiology such as complications of hypertensive, valvular or other structural heart diseases. However the classification system based on the temporal pattern of the arrhythmia is currently recommended (Camm, Kirchhof et al. 2010). There are five types of AF based on the presentation and duration of the arrhythmia: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent AF.Any

patients presenting to medical attention may have a first detected episode of AF and this is termed first *diagnosed* AF, irrespective of duration and the symptoms. While paroxysmal AF is self-terminating, usually within 48 hours; the paroxysm may continue beyond 48 hours and last within seven days. Forty eight hour time limit is important as after this the chance of spontaneous termination is low and anticoagulation must be considered. Arrhythmia that persist after 7 days up to period of 1 year and continues requiring electrical or pharmacological cardioversion for termination is call persistent AF. Longstanding (> 1 year duration) AF; when it is decided for rhythm control and management is known as long-standing persistent AF. AF that cannot be successfully terminated by cardioversion or where cardioversion is not pursued or indicated or has not been attempted and when the patient as well as the physician has already accepted the arrhythmia, it is termed permanent AF. At any time during period of permanent AF, when rhythm management is pursued then the classification will be changed to long-standing persistent AF.

The pathology of AF is usually associated with underlying heart diseases. Condition that lead to atrial enlargement, an elevation in atrial pressure, or infiltration or inflammation of the atria almost invariably end up with AF. A prospective evaluation of the echocardiographic predictors of AF in individual without rheumatic heart diseases was performed in the Framingham Heart Study and showed that the left atrial enlargement precede and predisposes to AF (Vaziri, Larson et al. 1995). Other echocardiographic risk factors for AF were increased left ventricular wall thickness and reduced left ventricular fractional shortening.

2.2 Conditions associated with AF

a. Age

The risk of developing AF increases with age, possibly through age-dependent loss and isolation of atrial myocardium and associated conduction disturbances (Alonso, Agarwal et al. 2009)

b. Hypertension

Hypertension is the most common condition associated with AF and a risk factor for incident (first diagnosed) AF (Nieuwlaat, Capucci et al. 2005). It is also a major risk for AF-related complications such as stroke and systemic thrombo-embolism.

c. Coronary artery disease

About 20% or more of AF patient's population were found to have coronary artery disease (Nieuwlaat, Capucci et al. 2005), (Nabauer, Gerth et al. 2009). It is uncertain whether uncomplicated coronary artery disease per se (atrial ischemia) predispose to AF or by unknown interaction between AF and coronary perfusion (Goette, Bukowska et al. 2009).

d. Diabetes mellitus

Diabetes mellitus requiring medical treatment is found in about 20% of AF patient. The effects of diabetes causing AF still a topic of ongoing research. These are the possible mechanism known so far ; inflammation with the role of C-reactive protein (CRP) promoting myocardial fibrosis and diastolic dysfunction ; diabetes may lead to atrial

enlargement; the effect of neural remodeling that occurs in diabetes, the high risk of coronary artery diseases and consequently congestive cardiac failure in people with diabetes and the association of obesity in diabetes with high risk of obstructive sleep apnea (OSA) may contribute to atrial fibrillation (Dublin, Glazer et al. 2010).

e. Obesity

In the same European survey, obesity is found in 25% of AF patients (Nabauer, Gerth et al. 2009). The mean body mass index was 27.5 kg/m2 in a large, German AF registry (equivalent to moderately obese). In one study, obesity is an important, potentially modifiable risk factor for AF with possibly relationship on left atrial diameter (Wang, Parise et al. 2004) .

f. Thyroid disorder

Overt thyroid dysfunction may be the only cause of AF and can lead to AF-related complications. In 2 major Europeans surveys, thyroid disorders was found to be relatively uncommon in AF populations although it was up to 12% in AF population (Nieuwlaat, Capucci et al. 2005, Nabauer, Gerth et al. 2009). However subclinical thyroid dysfunction may contribute to AF. Data from General Hospital Kuala Lumpur by Freestone and colleagues in 2003 reveled 3 out of 40 (7.5%) AF patients were found to have thyroid disorders.

g. Heart failure

Thirty percent (30%) of AF patients were found to have symptomatic heart failure [New York Heart Association (NYHA) classes II-IV] (Nabauer, Gerth et al. 2009, Kirchhof, Lip et al. 2011). Interestingly, up to 30-40% of heart failure patients also were

found to have AF, depending on the underlying cause and severity of heart failure. It is well known that heart failure can be both a consequences of AF (e.g. tachycardiomyopathy or decompensation in acute onset AF) and a cause of the arrhythmia due to volume overload and increased atrial pressure load, secondary to valvular dysfunction, or chronic neurohormonal stimulation (Lubitz, Benjamin et al. 2010).

h. Valvular heart disease

Valvular heart disease is common associated with AF and found in about 30% of AF patients (Nieuwlaat, Capucci et al. 2005, Nabauer, Gerth et al. 2009). AF is found as an early manifestation of mitral stenosis and is caused by left atrial distension. AF occurs in later stages of aortic valve diseases. While 'rheumatic AF' is rare in western countries, it is becoming a diseases burden in the developing nations.

i. Cardiomyopathies

Cardiomyopathies, including primary electrical cardiac diseases (Maron, Towbin et al. 2006), carry an increased risk for AF , especially in young patients. Relatively rare cardiomyopathies are found in 10% of AF patient (Kirchhof, Auricchio et al. 2007).

2.3 Oral anticoagulant in managing atrial fibrillation.

With regards to the important aspect of AF management which is stroke prevention, the use of oral anti coagulation (OAC) is based on estimated risk of stroke using well validated scores such as $CHADS_2$ and CHA_2DS_2-VASC. The scores are most widely studied and used in stroke prevention AF patients. The proper order was CHA_2DS_2-VAS_c score was applied when the $CHADS_2$ score lessthen 2 (Camm, Kirchhof et al. 2010).

The latest guidelines encourage the use of anticoagulants in all patient except lone AF and score of 0. Patients with score of 1 should be preferably on warfarin rather than antiplatelet(aspirin or clopidogrel). Any score of 2 and above warranted the use of OAC if no contraindications. Caution should be exercised when the risk of bleeding is significant. Bleeding risk in AF patient can be estimated by using HAS-BLED score. Score> 3 out of 9 total scores is considered ‘ high risk’, hence requiring careful titration of OAC and regular monitoring (Pisters, Lane et al. 2010).

Table 2.3.0 : $CHADS_2$ score

	CONDITIONS	POINT
C	Congestive heart failure	1
H	Hypertension : blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A	Age ≥ 75 year old	1
D	Dibetes mellitus	1
S_2	Previous Stroke or Tia or Thromboembolism	2

Table 2.3.1 : Annual risk of stroke based on $CHADS_2$ score.

Annual Stroke Risk		
$CHADS_2$ Score	**Stroke Risk %**	**95% CI**
0	1.9	1.2–3.0
1	2.8	2.0–3.8
2	4.0	3.1–5.1
3	5.9	4.6–7.3
4	8.5	6.3–11.1
5	12.5	8.2–17.5
6	18.2	10.5–27.4

Table 2.3.2 : CHA_2DS_2-VAS_C score.

	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

Table 2.3.3: Annual Stroke Risk based on CHA_2DS_2-VAS_c score.

Annual Stroke Risk.		
CHA_2DS_2-VASc Score	**Stroke Risk %**	**95% CI**
0	0	-
1	1.3	-
2	2.2	-
3	3.2	-
4	4.0	-
5	6.7	-
6	9.8	-
7	9.6	-
8	12.0	-
9	15.2	-

Over 90 percent of strokes that occur in AF patients are caused by blood clots formed in the left atrial appendage due to fibrillation (Manning and Douglas 1998). The clots can subsequently dislodge and travel through the arterial system, ending up in the blood vessels of the brain, causing a stroke. Not only does AF predispose patients to stroke, but AF patients also tended to have more severe strokes than non-AF patients.

The vitamin K antagonist, warfarin has long been used in reducing stroke risk in AF patients (Hart, Pearce et al. 2007). However, the safety and efficacy of warfarin is highly dependent on maintaining international normalized ratios (INRs) within a very narrow therapeutic range of between 2 and 3(Oake, Fergusson et al. 2007). Maintaining the appropriate INR requires regular monitoring, which has proven difficult and varied across different countries, according to a global AF registry available from the European Society of Cardiology. Among the regions compared in the registry, only an average of 38 percent of patients in Asia had INR within 2.0-3.0 (Singer, Hellkamp et al. 2013)

The risk of ischemic stroke increases with INR levels < 1.8, and the risk of intracranial hemorrhage increases sharply at INR levels > 3.5(Chiang, Zhang et al. 2013). These results are particularly alarming in light of the differences in intracranial hemorrhage risk with warfarin use among AF patients of different ethnicities: Asian AF patients are four times more likely than whites to suffer intracranial hemorrhage(Shen, Chen et al. 2008).

Besides hemorrhagic complications with warfarin, it has also been found that warfarin use tends to be discontinued across patients of all ages between 40 and over 85 years, in as little as 2 years after initiation of treatment(Gallagher, Rietbrock et al. 2008). These findings support the standard “therapeutic “ INR range of 2.0 to 3.0 for nonvulvular AF.

2.4 Quality of warfarin treatment assessment.

The quality of warfarin treatment assessmentis determine bythe percent Time in Therapeutic Range (TTR). Three different methods to calculate TTR were identified :

- Percent of Visits in Range (Traditional Method) This looks at how many visits had INR results in range, and divides by the total number of visits. If the patient has had 8 visits, and 6 had readings within their therapeutic range, then the patient is considered in range 75% of the time.
- Percent of Visits in Range on Given Date (Cross Section Method)This method takes a specific date in time, and all patients are evaluated on the last reading prior to that date to see if they were within range. The number of patients in range (on their last reading) is taken as a percentage of the total active patients on that date.

- Percent of Days in Range (Rosendaal Method) This is the most complex of the calculations, as it looks at the amount of time between visits to determine how long the patient might have been within their therapeutic range. If a patient has a therapeutic range of 2.0 - 3.0, and on May 1st tested at 2.5, then tested 3.5 on May 31st, then we can determine how many days were in range. Since there were 30

days between tests, we assume that the patient slowly moved from 2.5 to 3.5 over those 30 days, so around May 15th, the patient was probably over 3.0, and therefore was out of range. Therefore, we estimate that 15 days were in range, and 15 days were out of range (within the 30 day time period), which means the patient is within range 50% of the time.

A commonly used summary of the quality of warfarin is the linearly interpolated percent time in therapeutic range (Rosendaal Method) (Schmitt, Speckman et al. 2003), and this method will beuse in this study.

For the analysis of the relationship between INR control and the rates of stroke, systemic embolization, and bleeding, we divided into two groups which are TTR < 60% defined as poor control group and TTR ≥ 60% defined as good control group, (White, Gruber et al. 2007).

2.5 Justification of the study.

The main justification in this study is to evaluate the effectiveness and safety of warfarin in term of thromboembolic prevention in nonvalvular atrial fibrillation. There is also no current benchmark regarding time in therapeutic range being set up in Malaysia. Moreover, this study is trying to explore the association factors that influencethe target INR, and tying to determine whether a minimum TTR is needed to achieve a benefit from OAC in nonvalvular AF. In the presence of New Oral Anti Coagulant (NOAC), cost is still one of the reason warfarin is commonly used in Malaysia.

CHAPTER THREE

OBJECTIVES

3.1 General Objective

To evaluate the mean of Time Therapeutic Range in nonvalvular atrial fibrillation patients on warfarin who are attending INR clinic HUSM

3.2 Specific objectives

1. To determine the proportion of thromboembolic event between good control group (TTR ≥ 60%) and poor control group (TTR < 60%)
2. To determine the proportion of bleeding event between good control group (TTR ≥ 60%) and poor control group (TTR < 60%)
3. To evaluate association between clinical factors and percentage of TTR.

3.3 Research Hypothesis

Objective 1

The proportion of thromboembolic event in TTR ≥ 60% is lower than TTR < 60%

Objective 2

The proportion of bleeding event in TTR ≥ 60% is lower than TTR < 60 %

Objective 3

Clinical data and demographic characteristics influenced the percentage of TTR.

CHAPTER FOUR

METHODOLOGY

4.1 Study Design

This is a retrospective cohort study

4.2 Study approval

This study was approved by the Research and Ethic Committee, UniversitiSains Malaysia.

4.3 Study setting and population

This study was conducted between January 2012 until December 2012 in the International Normalized Ration (INR) clinic, Hospital UniversitiSains Malaysia (HUSM) and record department HUSM, KubangKerian, Kelantan. There were estimated about 30 patients who came to the INR clinic on Sunday every week to monitor their coagulation profile. These include patients with atrial fibrillation, prosthetic valve, valvular or septal defects and patients with previous history of deep vein thrombosis and pulmonary embolism.

4.4 Data collection

Patient record files were traced from the Record Department of HUSM and screened for the eligibility of the criteria.

4.5 Sampling method

All patients on warfarin came for INR follow up from January 2012 till December 2012 with every 3 monthly interval were selected by systematic random sampling.

4.6 Inclusion criteria

1. Age > 18 years old and above

2. Nonvalvular atrial fibrillation

3. On warfarin at least 30 days since 1st January 2012

5. INR monitoring within 3 month interval

4.7 Exclusion criteria

1. Age < 18 years old

2. Valvular heart disease

3. On warfarin less than 30 days in 1st January 2012

4. Taking warfarin less than 1 year

5. INR monitoring more than 3 months interval.

4.8 Sample size determination

Sample size was calculated using single proportion formula using Epi Info (TM) version 3.5.1 for general objective :

- Based on Daniel E.Singer et al.(2013) a proportion of 5% with target was achieved.
- Values of absolutes precision calculated at 5%
- Based on the software calculation at 5% precision (95% CI) – the estimated sample size would be 73 patients.

Calculation of sample size for secondary objectives.

Objective 1 : Proportion of thromboembolic event in TTR (TTR ≥ 60% and TTR < 60%) using the PS Software (version 3.0.43) with two proportion formula :

Level of significant (α) = 0.05

Power ($1 - \beta$) = 0.8

Prevalence (Po) of thromboembolic event in TTR > 60% = 0.01 (base on Harvey D. et al 2007)

Prevalence (P1) of thromboembolic event in TTR < 60% = 0.2 (base on expert opinion)

m = 1

Sample size n : 83 subject.

Objective 2 : Proportion of bleeding event in TTR (TTR ≥ 60% and TTR < 60%) using two proportion formula :

Level of significant (α) = 0.05

Power ($1 - \beta$) = 0.8

Prevalence (Po) of bleeding event in TTR > 60% = 0.16 (base on Harvey D. et al 2007)

Prevalence (P1) of bleeding event in TTR < 60% = 0.35 (base on expert opinion)

m = 1

Sample size n : 44 subject.

4.9 Variables recorded in data entry form

Data would be obtain from patient record folder after get approval from ethic committee. The following variables were recorded in the data entry form (appendix 2).

- Patient identification number, age , sex, race, and occupation status
- Physical examination including blood pressure, heart rate, body mass index, height and weight.
- Underlying medical problems or co-morbidities such as diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, ischemic heart disease, heart failure, thyroid diseases, peripheral vascular disease, previous stroke or transient ischemic attack, and others.
- Date diagnosis of AF
- Type of AF whether paroxysmal, persistent or permanent.

- The presence of stroke either ischemic stroke or hemorrhagic stroke
- The presence of systemic emboli
- The presence of bleeding whether minor or major bleeding
- The CHADS and CHADS-VASC scores would be score on the base on the above findings
- The list of current patient medications
- Blood investigation result
- Previous echocardiography findings especially the ejection fraction by Teichholz's method, diastolic dysfunction, hypokinetic wall and thrombus.
- Warfarin dose for 4 INR clinic visits (3 monthly interval)
- INR values for 4 visit (3 monthly interval)
- Individual TTR
- TTR either $\geq 60\%$ or $< 60\%$

4.10 Operational definition

1) Diabetes mellitus type I and type II (DM)

   Patients were categorized as diabetes mellitus if they vave been previously diagnosed as diabetes mellitus type I or type II with or without medications.

2) Hypertension

   Patient were categorized as hypertensive if they have been previously diagnosed as hypertension or elevated blood pressure $\geq$ 140/90 mmHg during the visit with or without antihypertensive

3) Ischemic heart diseases

Ischemic heart diseases was noted to be present when the patient had undergone coronary angiogram or history of previous myocardial infarction or positive stress test or recurrent admission with unstable angina/non ST elevation myocardial infarction awaiting/refused angiogram. The presence of previous or recurrent positive ischemic change on ECG indicated by ST depression $\geq$ 0.5 mm in 2 or more contiguous leads or deep symmetrical T-wave inversion would further support the diagnosis.

4) Hyperlipidemia

Patients were documented to have hyperlipidemia based on the diagnosis of hyperlipidemia in the HUSM folder with or without lipid lowering agents and also if they presented with serum TG > 1.7 mmol/l or HDL-C < 1.3 mmol/l (female) or < 1.0 mmol/l (male), LDL-C > 2.6 mmol/l (NCEP ATPIII guidelines, 2001).

5) Thyroid disease

Thyroid disease was present when it had been documented in the folder and patients had received treatment which including thyroidectomy, radioactive iodine ablation and anti-thyroid medications (carbimazole or propythiouracil). These include patients who has history of thyrotoxicosis and subsequently became hypothyroid as a result of the thyroidectomy or radioactive iodine ablation treatment and on thyroxine supplements.

6) $CHADS_2$ score

$CHADS_2$ stands for the presence cardiac failure, hypertension, age $\geq$ 75, diabetes mellitus and stroke (2 points). Each carries 1 point except stroke. This is the primary risk stratification tool for stroke and thromboembolism.

7) CHA_2DS_2-VASc score

CHA_2DS_2-VASc score stands for the congestive heart failure, hypertension, age ≥ 75 (double), diabetes, stroke (double), vascular diseases, age 65-75 and sex category (female). This scoring system is an important tool for the risk of stroke and thromboembolism.

8) INR

INR stands for international normalized ration. It refer to the ratio of patient prothrombin time (PT) in seconds over the control PT and it raised to the power of International Sensitivity Index (ISI) of the tissue factor reagent used in the test. It is used for the monitoring the therapeutic window of warfarin. INR target for prevention of stroke in nonvulvular AF was between 2 to 3. higher INR at ≥ 4.0 will increase risk of bleeding and low INR at ≤ 2 will increase risk of thrombosis (Hylek, Evans-Molina et al. 2007).

9) TTR

TTR is stand for therapeutic time in range, is a widely cited measure of the quality of warfarin therapy. The percentage of TTR can tell how well the patient's intensity of anticoagulation is maintained within the therapeutic range, since and increased in TTR is associated with a reduction in hemorrhagic and thromboembolism. TTR ≥ 60% is consider good control and TTR < 60% is consider poor control (White, Gruber et al. 2007)

10) Stroke

The diagnosis of stroke was confirmed by a clinical history of the sudden development of a major neurological deficit lasting more than 24 hours that was correlated with a

cerebrovascular terrority, with confirmed by computed tomography (CT) scan or magnetic resonant imaging (MRI), and patients were taking warfarin at the time of the stroke.

11) Previous stroke

A diagnosis of previous stroke recorded in the medical record. In all instances, previous strokes occurred before the beginning of anticoagulant therapy.

12) Systemic emboli

Systemic emboli was defined as abrupt vascular insufficiency associated with clinical and radiological evidence of arterial occlusion in the absence of the another problem mechanism. In the presence of the atherosclerotic peripheral vascular diseases, diagnosis of embolism needed angiographic demonstration of acute arterial occlusion.

13) Bleeding

Bleeding event can be divided into two, whether major bleeding or minor bleeding. Major bleeding defined as fatal bleeding or clinically overt bleeding associated with a reduction in hemoglobin 20 g/L or greater, or clinically overt blood loss need transfusion 2 U or more of whole blood or erythrocytes or bleeding involving critical anatomical sites(Rao, Eikelboom et al. 2009) :

- Intracranial hemorrhage
- Intraspinalhemorrhage
- Intraocular hemorrhage
- Retroperitoneal hemorrhage
- Pericardial hemorrhage

- Atraumaticintra-articular hemorrhage

Minor bleeding defined as :

- Gross hematuria not associated with trauma (e.g, from instrumentation)
- Epistaxis that is prolonged, is repeated, or requires plugging or intervention
- Hemoptysis
- Subconjunctival hemorrhage
- Hematoma >5 cm or leading to prolonged or new hospitalization
- Clinically overt bleeding, causing a decrease in hemoglobin of 2 to 3 g/dL

4.11Statistical analysis

Data was analyses by using IBM Statistical Package for Social Science (SPSS) version 22 and STATA version 11. The data was analyses by using univariable and multivariable logistic regression. There are six steps that were followed for this statistical analysis :

- Data exploration and cleaning
- Univariables analysis
- Multivariable analysis (Preliminary main effect model)
- Interaction and multicollinearity checking (Preliminary final model)
- Overall goodness of fit of the model
- Interpretation , presentation and write up