THE CLINICAL OUTCOME EVALUATION ON THE ATRIAL FIBRILLATION PATIENTS RECEIVING WARFARIN FOR SECONDARY STROKE PREVENTION IN THE MEDICATION THERAPY ADHERENCE CLINIC IN SERDANG AND SEREMBAN HOSPITALS

MOCHAMAD DJUNAEDI

UNIVERSITI SAINS MALAYSIA

2016

THE CLINICAL OUTCOME EVALUATION ON THE ATRIAL FIBRILLATION PATIENTS RECEIVING WARFARIN FOR SECONDARY STROKE PREVENTION IN THE MEDICATION THERAPY ADHERENCE CLINIC IN SERDANG AND SEREMBAN HOSPITALS

by

MOCHAMAD DJUNAEDI

Thesis submitted in fulfillment of the requirements
for the degree of
Doctor of Philosophy

September 2016

ACKNOWLEDGMENT

First of all, my deepest gratitude to the Almighty Allah for his great help, blessing and spiritual guidance in completing this study.

In this precious opportunity, I wish to express sincere appreciation to my main supervisor, Prof. Dr. Syed Azhar Syed Sulaiman. Thank you for the endless guidance throughout the completion of my dissertation. His guidance and wisdom have helped me to overcome the challenges in this journey. Without his continuous motivation and patience, this study would not have achieved fruitful results. He has willingly took his time and attention to help me in the successful completion of this study.

I wish to dedicate special appreciation to my field supervisor, Dr. Abdul Kahar Abdul Ghapar who is the Head in Cardiology Department in Hospital Serdang for his encouragement and support during the process of my study.

My sincere thanks also goes to Dato' Dr. Ardi Haji Awang and Dr. Jaafar Che Mat, directors of Serdang Hospital and Seremban Hospital respectively, for giving me the opportunities to collect the data needed for my study.

I am grateful to the heads of Pharmacy Department and all fellow pharmacists at Hospital Serdang and Hospital Tuanku Ja'afar Seremban, as well as nursing staffs and medical assistants who have expanded my point of view from my first visit to the clinics until the completion of my study.

To the honorable Dato' Dr. Chang Kian Meng, the Chairman of Medical Research and Ethics Committee, Ministry of Health Malaysia, thank you for giving me the opportunity to validate my research data.

I would like to say thank you to Dr. Goh Bak Leong, Head of Clinical Research Center (CRC) in Serdang Hospital and Dr. Lee Ming Lee, Head of Clinical Research Center (CRC) in Seremban Hospital for the facilities provided to complete my study.

Also, my gratitude goes to Assoc. Prof. Mohd. Shukri Yahaya, Head of Statistical Advisory Service, Institute of Postgraduate Studies, Universiti Sains Malaysia, who is very persistent and careful in giving guidance on the application of statistical analysis in this study.

Last but not least, I would like to thank my family: my mother Drs Hj. Masturah, for giving birth to me and supporting me spiritually throughout my life; my wife Dra. Hj. Wiwik Nafiroh; and my children, Shofa, Marwah, Huda, and Elok for their unconditional love and support throughout this journey.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
ACTIVE	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Event
ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
AFASAK	Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation Study
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AFI	Atrial Fibrillation Investigator
AHA	Americam Heart Association
ARP	Atrial Refractory Period
ATC	Anticoagulation clinic or antithrombotic clinic
AV	Atrioventricular
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
$CHADS_2$	Congestive heart failure, Hypertension, Age, Diabetes, Stroke
CHF	Congestive Heart Failure
CI	Confidence Interval
CONSENSUS	Cooperative North Scandinavian Enalapril Survival
DCM	Dilated (hypertrophic) Cardiomyopathy
DM	Diabetes Mellitus
DTI	Direct Thrombine Inhibitor
DVT	Deep Vein Thrombosis

DXI	Direct Xa Inhibitors
EAFT	The European Atrial Fibrillation Trial
ECG	Electrocardiogram
ED	Emergency Department
ERP	Effective Refractory Period
FDA	Food Drug Administration
FFP	Fresh Frozen Plasma
FHS	Framingham Heart Study
GI	Gastrointestinal
GFR	Glomerular Filtration Rate
BAFTA	The Birmingham Atrial Fibrillation Treatment of the Aged study
HF	Heart Failure
HPT	Hypertension
ICH	Intracranial Hemmorrhage
INR	International Normalized Ratio
ISCOAT	The Italian Study On Complications Of Oral Anticoagulant Therapy
LA	Left Atrium
LV	Left Ventricle
MI	Myocardial Infarction
NMRR	National Malaysia Research Registry
MOH	Ministry of Heath Malaysia
MREC	Malaysian Registry Ethic Committee
MTAC	Medication Therapy Adherence Clinic
NSAIDs	Non-Steroid Anti Inflamatory Drugs

NSR	Normal Sinus Rhythm
NVAF	Non-Valvular Atrial Fibrillation
NYHA	New York Heart Association
OAC	Oral Anti Coagulation
PAD	Peripheral Artery Disease
PE	Pulmonary Embolism
QALY	Quality of Life Adjusted Year
QoA	Quality of Anticoagulation
QoL	Quality of Life
RA	Right Atrium
RV	Right Ventricular
SPAF	Stroke Prevention in Atrial Fibrillation
SPINAF	Stroke Prevention in Nonrheumatic Atrial Fibrillation
SPORTIF	Stroke Prevention using an Oral Direct Thrombin Inhibitor In Patients with Atrial Fibrillation
TIA	Transient Ischemic Attack
TTR	Time In Target Range
VKA	Vitamin K Antagonist
VKORC1	Vitamin K epoxide reductase complex subunit1

PENILAIAN HASIL KLINIKAL PADA PESAKIT PEMFIBRILAN ATRIUM YANG MENERIMA WARFARIN UNTUK PENCEGAHAN STROK SEKUNDER DI KLINIK KEPATUHAN TERAPI UBAT-UBATAN DI HOSPITAL SERDANG DAN HOSPITAL SEREMBAN

ABSTRAK

Di Klinik Kepatuhan Terapi Ubat-ubatan (Warfarin-MTAC), ahli farmasi perlu memainkan peranan dalam pasukan kesihatan pelbagai disiplin untuk meningkatkan kepatuhan pesakit bagi mencapai matlamat terapi warfarin. Matlamat utama kajian ini adalah untuk menilai keberkesanan perundingan ahli farmasi dalam mencapai kualiti yang lebih baik dalam kawalan antikoagulasi. Ia juga bertujuan untuk mengenal pasti faktor-faktor yang menyumbang kepada kegagalan atau kejayaan untuk mencapai INR terapeutik. Suatu kajian prospektif telah dibuat di Warfarin-MTAC yang beroperasi di Unit Jantung di Hospital Serdang dan Hospital Tuanku Ja'afar Seremban pada tahun 2011. Seramai tiga ratus lima puluh dua pesakit yang didiagnosis dengan pemfibrilan atrium memenuhi kriteria kelayakan dan dipilih menggunakan teknik persampelan rawak. Pesakit terdiri daripada kaum Melayu, Cina dan India dengan purata umur 64.2 dan 64.6 tahun memiliki risiko strok kategori sederhana (skor $CHADS_2$: 2.3±1.2 dan 2.7±1.3) untuk pesakit di Hospital Serdang dan Hospital Seremban. Kepatuhan pesakit terhadap terapi warfarin seperti yang dinasihatkan oleh ahli farmasi didapati menjadi faktor penyumbang kepada pencapaian kualiti yang baik dalam kawalan antikoagulasi (nisbah kebarangkalian: 53.3 dan 52.0, $p < 0.05$; CI = 95%) bagi pesakit di Hospital Serdang dan Seremban. Kawalan didapati mencapai prestasi yang baik dengan %TTR sebanyak (81.1$\pm$21.1) % dan (77.9$\pm$12.6) % untuk kedua-dua hospital. Kesimpulannya, untuk mengelakkan strok dan pengambilan warfarin yang berlebihan, serta memastikan perundingan yang berkesan dengan ahli farmasi, ahli farmasi perlulah memberi nasihat yang menyeluruh kepada pesakit pemfibrilan atrium yang menerima rawatan warfarin di Klinik Terapi Antikoagulasi dan menekankan keutamaan untuk terapi warfarin.

THE CLINICAL OUTCOME EVALUATION ON THE ATRIAL FIBRILLATION PATIENTS RECEIVING WARFARIN FOR SECONDARY STROKE PREVENTION IN THE MEDICATION THERAPY ADHERENCE CLINIC IN SERDANG AND SEREMBAN HOSPITALS

ABSTRACT

In the Warfarin-Medication Therapy Adherence Clinic (Warfarin-MTAC), pharmacists should play their role in the multidisciplinary health team to improve patients' adherence in achieving the goal of warfarin therapy. The primary aim of this study is to evaluate the effectiveness of pharmacists' consultation in order for atrial fibrillation (AF) patients receiving warfarin to achieve better quality of anticoagulation control. It also aims to identify the factors contributing to the failure or success of reaching the therapeutic INR. A prospective study was carried out in the Warfarin-MTAC that operated in the Cardiac Unit of Serdang and Seremban Hospitals in 2011. Three hundred and fifty-two AF-diagnosed patients were represented in the inclusion criteria, selected using the convenience sampling technique. The patients consist of Malay, Chinese and Indian with the mean age of 64.2 and 64.6 years old, and had the $CHADS_2$ score of 2.3±1.2 and 2.7±1.3 for patients in Serdang and Seremban Hospitals, respectively. Patients' adherence to warfarin therapy as had been guided by Pharmacist was found to be a factor that contributed to the achievement of good quality of anticoagulation control (Odds ratio: 53.3 and 52.0 at $p < 0.05$ and CI = 95% for those in Serdang and Seremban Hospitals respectively). The anticoagulation control achieved is 'good' with %TTR of (81.1 $\pm$21.1)% and (77.9$\pm$12.6)% for both hospitals. As a conclusion, to prevent stroke and avoid overwarfarinization, and to ensure effective consultation with pharmacists, the pharmacists should provide comprehensive advice to patients with atrial fibrillation who are receiving warfarin treatment at the Anticoagulation Therapy Clinic and emphasize on the prioritized characteristics for the warfarin therapy.

CHAPTER 1

INTRODUCTION

1.1 Research Background.

1.1.1 The significance of anticoagulation therapy using warfarin with the involvement of pharmacists in collaborative multidiscipline health care practices.

Warfarin therapy for patients with atrial fibrillation has been done to resonate with the consideration that warfarin is effective and inexpensive for secondary prevention against stroke. A care system for patients had been improved with the implementation of integrated and multidisciplinary services to control warfarin anticoagulation. Practically, there are many other aspects that have been constrained in the monitoring of warfarin treatment. In evaluating the effectiveness of warfarin therapy, the social characteristics of the patients cannot simply be ignored. Even though it resulted in the lack of clarity of the causal answer, the extent of the socioeconomic status of the patients had influenced the risk of haemorrhage and other adverse outcomes (Cressman *et al.*, 2015).

Extra stringent monitoring is very much needed to be done in warfarin therapy for patients with atrial fibrillation because it may be able to prevent stroke without increasing the risk of bleeding. That outcome would be impossible to be achieved if the pre-existing risk factors are obeyed, regardless of the factors such as young age, those with less co-disorder, and those having low-risk factor to get stroke (Chishaki *et al.*, 2015).

The practice of pharmacy has been improved including ambulatory care services. There is a global concern for pharmacists to build a model that aims to minimize side effects and optimize anticoagulation control (Louis *et al*., 2010).

In Malaysia, the Medication Therapy Adherence Clinic (MTAC), a multidiscipline ambulatory care system for atrial fibrillation patients with warfarin therapy has been established since 2004.

In Malaysia, all patients treated with warfarin anticoagulation have been integrally relocated in phases, in the MTAC clinic which is organized by the General Hospital in each state. All atrial fibrillation diagnosed patients who received warfarin treatment was referred to the clinic.

At the beginning of this research, several surveys were conducted in a number of existing government health clinics around the hospital where warfarin MTAC are located. There was no patient receiving warfarin therapy there because all of them had been referred to the hospital, and it is also due to the fact that services such as warfarin MTAC had not been established yet.

There have been widely published papers or reports on warfarin therapy but the study on the evaluation of care management is irrefutably scarce. Most of the researchers were interested to focus their study on the effect of care management to control the anticoagulation therapy. However, the evaluation of the effectiveness of warfarin in patients with atrial fibrillation is supposed to be examined from several clinical and management aspects. A very complex set-up through multidisciplinary care may become an important consideration for the improvement of the

effectiveness of warfarin anticoagulation service. This is certainly in accordance with the implication of the existing guidelines (Alpert, 2010).

The existing guideline is lengthy for the doctors, hence time-consuming for them to understand. It is also difficult for them to use and the approach used is less comfortable for the patients. The rigid guidelines and frequent monitoring therapy were not favoured by both the physician and patient. Even doctors sometimes require specific guidelines which include patients with specific criteria (Alpert, 2010).

How pharmacists should play their role is also included in the evaluation. In real practice, an evaluation of the human factors that include the pharmacists' involvement in the service should be determined as the variables or indicators that may affect the outcome of the therapy. In this study, those factors will be investigated as variables in achieving clinical outcomes in the prevention of stroke in patients receiving warfarin therapy.

1.1.2 The challenge for pharmacists in achieving the therapeutic goal of warfarin therapy in patients with atrial fibrillation.

The therapeutic goals of warfarin therapy in patients with atrial fibrillation are to minimize the symptoms and to prevent thromboembolic events such as death, stroke, and hospitalizations. It also aims to increase the quality of life and exercise capacity, and to reduce the left ventricular dysfunction. The pharmacologic treatment for atrial fibrillation with antithrombotic agent includes anticoagulation therapy with vitamin K antagonist, antiplatelet therapy, vitamin K antagonist combined with anti platelet and/or other antithrombotic drug regimens (Camm *et al*., 2010).

To achieve a better outcome, a number of anticoagulation managed care had been arranged by pharmacist in collaboration with other health professionals. In fact, a lot of publications have revealed that patients with atrial fibrillation had been found to be undertreated in warfarin therapy for stroke prophylaxis. It was proven that patients who are at high risk of stroke were significantly associated with the suboptimal warfarin treatment (Nieuwlaat *et al.*, 2010).

The administration of warfarin should be controlled in order to individualize dose regimen, and this may result in the appropriate therapeutic effect of anticoagulation. Underutilization of warfarin prescribed to young and elderly patients may cause the international normalized ratio (INR) to not be able to reach the target range. For those patients, having non-therapeutic INR was strongly associated with stroke risk, arterial thromboembolism and intracranial bleeding (Walker & Bennett, 2008).

The investigation on the decision-making between physicians and patients that resulted in a dichotomous opinion was reported by Xuereb *et al*. (2012). In the situation where intensive communication between physicians and patients should exist, "patient education" became critical to be achieved. Through this communication, educational intervention can meet the needs and concerns to achieve better patient outcome as expected.

Pharmacists involved in a healthcare team should play an intensive role in providing information as suggested by McCabe *et al*. (2008). New trends in antithrombotic therapy should not allow patients to self-manage the therapy. The booklet given by health providers to patients does not guarantee complete guidance

because patients might be unable to understand the efficacy and safety of warfarin. Furthermore, if patients could not identify warfarin-related ADR, it is highly not recommended for them to perform self-management and monitoring.

Although patients have received warfarin booklets, they may still require educational intervention to improve their knowledge and perceptions on the treatment of atrial fibrillation with anticoagulation. They should improve their knowledge on the risks of using warfarin (Lane *et al.*, 2006).

Pharmacists' involvement in anticoagulation clinics to encourage the application of evidence-based therapy is important. Pharmacists need to share their knowledge regarding correct warfarin regimen. If the prescribed dose results in lower than minimum response of anticoagulation, it may cause thromboembolism, while excessive dose will probably cause bleeding. Thus, this means that the spread of knowledge to patients receiving warfarin must be encouraged. To gain this knowledge, patients should get help from pharmacists and other healthcare professionals. From the pharmacist, patients may get help to improve compliance, and from the physician, patients need help to achieve the goal therapy. Therefore, the pharmacists involved should share the knowledge on appropriate dose management with the physicians. In this interrelationship, Kakkar and Kaur (2004) suggested that good patients' adherence to warfarin guidelines is compulsory.

The significant gaps in stroke-related health literacy existing among high risk patients taking warfarin are likely to represent the mismatches of ways in which clinicians educate patients on what they must learn. This gap resists the improvement

of health communication about stroke-related knowledge between patients and health clinicians (Fang *et al.*, 2009).

Interactive patients' education model by means of audiovisual communication between physicians and patients has been tested, where it gave different results in warfarin-related knowledge, and belief in the importance of INR testing. Mazor *et al.* (2007) concluded the investigation by stating that patients with oral anticoagulant therapy would benefit from educational efforts periodically to reinforce the importance of information about drug safety, both during and after the education continuously takes place.

Warfarin is effective for stroke prophylaction in patients with atrial fibrillation, as measured proportionally to the predictor, which is the time in target range (TTR). However, warfarin practice managed by primary care physicians is more often based on their own experiences. Evidence-based methods for warfarin maintenance dose are underused by primary care physicians (Nieuwlaat *et al.*, 2010).

Characteristics of atrial fibrillation patients aged more than 80 years old include having problems in attending outpatient anticoagulant monitoring service and in self-managing their own warfarin dose, being unable to identify bleeding signs and symptoms, bruising, falling, taking concomitantly interacting medication, showing erratic INR readings, necessitating emergency department assessment for vitamin K-reversal, having the difficulty to make or even missed appointments. There is a need to increase the resources for monitoring in the community setting, for instance home visits, portable INR monitoring devices and dose adjustments (Tan *et al.*, 2012).

There are some herbs and supplements that have been reported to interact with warfarin as *Cinnamomum sp*, Ginko, *Allium sp*, *Zingiber sp*, green tea, St. John's wort, *Curcuma sp*, saw palmetto, *Valeriana officinalis*, milk thistle and *Echinacea*. These findings help healthcare practitioners to monitor consumption of herbs and supplements for the safety of patients receiving warfarin (Colalto, 2010).

Pharmacists should be concerned about the medications or herbal medicines taken by the patients' own initiative that might not accurately reflect its contents as mentioned on the label. The renal toxic agent contained in pharmaceuticals product, non-steroid anti inflammatory drugs (NSAIDs), laxatives, corticosteroids and highly heavy metal contaminations and some other herbs that may interfere with the platelet functions should become part of the information that needs to be conveyed to patients (Fugh-Berman, 2000).

1.1.3 The growing population of patients with atrial fibrillation.

The number of patient with atrial fibrillation (AF) is seemingly increasing and spreading rapidly. Atrial fibrillation is a type of disease that disrupts the rate and heart rhythm. The disruption of the rate and rhythm of the heart, known as arrhythmia, may be investigated by electrocardiogram (ECG). The abnormalities of rate and heart rhythm in atrial fibrillation patients are due to impaired mechanical function of the atrium termed supraventricular tachycardia (Fuster *et al*., 2006a).

The population of patients with atrial fibrillation has increased, along with the increasing underlying risk factors and its severities. The risk factors of atrial fibrillation include older age, male, high blood pressure, ischemic heart disease,

valvular heart disease, diabetes mellitus, and history of thromboembolic event, obesity, hyperthyroidism, alcoholism and cigarette smoking (Nguyen *et al.*, 2013). The increased population of patients with atrial fibrillation is likely due to other risk factors that include problem of respiratory system, dyslipidemia, renal insufficiency and coagulopathy, dementia, and history of gastrointestinal bleeding. According to Walker & Bennett (2008), cardiovascular disease is most likely the co-morbidity factor that contributes to the prevalence of atrial fibrillation.

The population of atrial fibrillation patients increased with the rise of the number of patients that may be subjected to heart failure. Heart failure will exacerbate the atrial fibrillation, or vice versa. In patients with heart failure, the left ventricular function will be impaired, hence the left ventricle ejection fraction (LVEF) will be reduced. Maisel and Stevenson (2003) had reviewed the association between the reduction of LVEF with the prognosis of atrial fibrillation. The prevalence of patients having the symptoms of severe heart failure associated with atrial fibrillation increased twofolds, compared to patients with moderate heart failure.

The prevalence of atrial fibrillation increases with age of patients. Among the elderly, congestive heart failure is associated with the history of myocardial infection. An equal prevalence of atrial fibrillation was found between the elderly with or without the preserved left ventricular function. Hospital admission is an indication of atrial fibrillation prevalence. Maisel and Stevenson (2003) revealed that hospital admission of atrial fibrillation patients with left ventricle ejection fraction less than 40% was higher compared to that of patients aged more than 70 years old.

Freestone *et al.* (2003) reported that the prevalence of atrial fibrillation patients in 2003 recorded in Kuala Lumpur General Hospital in Malaysia was 2.8%. This report indicates that the rise of atrial fibrillation is newly diagnosed. This information is almost similar to the previous report from the investigation done by Choy *et al*. (1993) showing that the atrial fibrillation population in Malaysia increase with the number of cardiovascular patients, especially those suffering from hypertension and ischemic heart disease.

Regionally, Asia contributes to the increment in prevalence of atrial fibrillation patients as reported by Chiang *et al.* (2012). In 2045, the number of patients with atrial fibrillation in China is projected to increase dramatically from 10 million to 25 million patients (Ma & Qi, 2009).

Stroke prevalence is said to increase the mortality rate of patients with atrial fibrillation. It was recorded that patients with atrial fibrillation who experienced thromboembolic event constituted the top leading cause of death in Asian countries. The death rates approximately ranged from 11.9 per 100,000 in Malaysia, 10.9 per 100,000 in Thailand and up to 54.2 per 100,000 in Singapore as reported by Merican *et al*. in 2006. In several countries in Asia such as China, Japan, Singapore, Malaysia and Taiwan, the prevalence of stroke related to atrial fibrillation is found to be varied with the range of 13.0%–15.4% (Guo *et al.*, 2012).

Some efforts to reduce the prevalence rate of stroke that complicate patients with atrial fibrillation have been conducted. A total of 40,000 patients with atrial fibrillation in Taiwan who visited the hospital and three clinics during the two-year

period had been investigated by Lin *et al*. (2008). Patients were recommended to be prescribed with anticoagulants but it was proven that as much as 75% of them were not treated with antithrombotic therapy appropriately.

The growing number of patients with atrial fibrillation in Asian countries will rise as predicted by Ryder and Benjamin (1999) due to the change of age composition in which the number of elderly people increases. The prevalence of atrial fibrillation in Hong Kong is 1.3% for patients in the age group of 60–94 years.

In 2012, Suarez *et al.* reported that hospital admission of heart failure patients with atrial fibrillation in the Asia Pacific region and Latin America countries had increased. These countries include Mexico, Australia, Hong Kong, Indonesia, Malaysia, Philipines, Singapore, Taiwan, Thailand and Brazil. Additionally, previous study conducted by Omar *et al.* (2011) supported that the prevalence of atrial fibrillation in Asia is said to be parallel with increasing morbidity rate and the number of patients who are at risk of cardiovascular events.

Factors contributing to atrial fibrillation were assessed in the Framingham Heart Study based on age, gender and racial background. The prevalence of atrial fibrillation in men was threefold in three decades from 3.2% to 9.1% and was almost doubled in women. The incidence of atrial fibrillation increases sharply with age. The prevalence of atrial fibrillation was also contributed by race. In Blacks and Afro-Caribbean, atrial fibrillations increase as patients' hypertension increases; in South Asian population, atrial fibrillations increase with ischemic heart disease; and in Ethiopia it increases with rheumatic heart disease (Ryder & Benjamin, 1999).

In the United States over the past three decades, the number of adults who have atrial fibrillations increased by 50% more than the number of the elderly (more than 80 years old). It is estimated that the overall prevalence of atrial fibrillation is 3 in 1000 persons per year in men and 2 in 1000 persons per year in women aged 55–64 years old (Hersi & Wyse., 2005).

1.1.4 The pathophysiology, clinical significance and treatment option of atrial fibrillation.

.

1.1.4(a) The pathophysiology of atrial fibrillation.

Atrial fibrillation is defined as a deterioration of atrial mechanical function caused by uncoordinated atrial function characterized as supraventricular tachyarrhythmia. Clinically, atrial fibrillation is presented as newly diagnosed atrial fibrillation that is considered to have been presented for the first time and pre-existing atrial fibrillation that is presented on the follow-up encounter (Fuster *et al.,* 2006a).

The morphology of heart is changed in atrial fibrillation patients. The inner layers of atrial myocardium are altered. It may be caused either by heart disease (coronary heart disease, high blood pressure or aortic stenosis) or aging process (such as fibrosis). The morphologic change may lead to abnormal electrophysiological properties of the heart. This abnormality is responsible for the exacerbation of atrial fibrillation and extends to the severe state of atrial fibrillation, or commonly referred as a concept of “atrial fibrillation begets atrial fibrillation” (Lee & Chen, 2008).

Although heart disease may cause atrial fibrillation, this mechanism is unclear, even though the predisposition of heart failure is suggested as a condition that is responsible for the change of the heart, especially the atrial. The morphologic change occurs concomitantly along with the functional change of heart in atrial fibrillation, which may be described as below:

a. The change in neurohormonal activation due to the stimulation of the renin-angiotensin-aldosterone system.
b. The change in the electrophysiological activity that is basically referred as the change in the parameter of the heart function, and it is called the atrial refractory period. In atrial fibrillation, the atrial refractory period is reduced as the mechanical function decreases. The decrease in the atrial effective refractory period (ERP) will cause irregular atrial repolarisation response. This change will then deteriorate the morphology (remodelling) of the heart and in turn, the rate and rhythm of the heart will interfere.
c. The change of the hemodynamic properties such as the pressure and volume of blood that may be due to the change of neurohormonal stimulation, or vice versa (Maisel & Stevenson, 2003).

The change in the heart for patients with heart failure is markedly influenced by the progressions of atrial fibrillation or the mechanism might occur in opposite to exacerbate the failure. The mechanism is proposed by Maisel and Stevenson (2003) where it is termed as “heart failure begets atrial fibrillation”, or vice versa.

Atrial fibrillation is said to be a structural heart disease that is often associated with the diseases that interfere with the function of the heart (Hersi & Wyse, 2005).

It is caused by the presence of both atrial electrical remodelling – contractile or structural – which will be clearly visible when the period of atrial fibrillation effect is long term. Electrical remodelling is characterized by a shortening of the atrial refractory period. Thorough clinical evaluation of patients who are presented with the risk factors that include hypertension, congestive heart failure, ischemic cardiomyopathy, valvular (rheumatic) heart disease, diabetes mellitus, hyperthyroidism, obesity, and obstructive sleep apnoea can facilitate early diagnosis of atrial fibrillation (Eagle *et al*., 2011).

The onset of atrial fibrillation may be classified based on the mechanism and its duration. European Heart Rhythm has classified it as paroxysmal, persistent or permanent atrial fibrillation. Paroxysmal atrial fibrillation episodes generally last for less than 24 hours but sometimes up to seven days, intermittently, repetitively and that it self-subsides (Fuster *et al.,* 2006b). Paroxysmal atrial fibrillation constitutes 35% to 65% of all cases of atrial fibrillation. It is more common in men and in younger patients than is chronic atrial fibrillation (Masoudi & Goldschlager, 1997). Persistent atrial fibrillation episode lasts more than seven days and requires its termination, either pharmacologically or electrically, or self-termination, but it can be effectively cardioverted to sinus rhythm. Sustained for a period of time, physical and molecular changes in the electrical and structural properties of the atria ("remodelling") occur and facilitate the conversion from transient to persistent atrial fibrillation (Peters *et al.*, 2002). Permanent atrial fibrillation has long-standing, continuous episodes, and it cannot be terminated by cardioversion. It can be terminated only for brief intervals, and it may lasts longer than a year without the cardioversion. Acute episode of atrial fibrillation lasts with its onset usually within

48 hours. Chronic atrial fibrillation requires a continuous clinical course similar to persistent and permanent atrial fibrillation (Peters *et al.*, 2002).

Recurrent atrial fibrillation is a term used to describe that at least twice of paroxysmal or persistent episodes can occur. The episodes of recurrence last more than 30 seconds. Reversible causes such as cardiac surgery, myocardiac infarction, pulmonary embolism, myocarditis or thyroid disease are excluded. If the reversible causes exist, the treatment of these underlying causes simultaneously with atrial fibrillation episodes will eliminate the arrhythmia, and the rhythm management will take longer duration (Hersi & Wyse, 2005).

In the absence of the predisposing factors, "lone atrial fibrillation" is used to describe younger patients (less than 60 years old) who have atrial fibrillation. The baseline ECG does not experience or recognize any symptoms. The term should be used to describe those patients with atrial fibrillation who do not have other co-existing valvular or structural heart disease and diabetes (Masoudi & Goldschlager, 1997).

1.1.4(b) The clinical significance of atrial fibrillation.

The symptom of atrial fibrillation may be presented with the onset of palpitations, chest pain, dyspnoea, fatigue, dizziness, light-headedness, syncope, and polyuria. Loss of normal atrial contractility is the sign that affects the synchronization of ventricle at the atrioventricular (AV) node. Heartbeat rate irregularity and rapid ventricular response are typical signs found in atrial fibrillation. Each sign may contribute to variable degrees of atrial fibrillation

manifestation (Peters *et al.*, 2002). Atrial fibrillation patients are called asymptomatic if they do not present any of the symptoms.

The diagnosis of atrial fibrillation is supported by evidence of oscillation or fibrillatory wave in the electrocardiogram, which seems to be regularly inconsistent in shape, amplitude and time interval (Fuster *et al*., 2006a).

Atrial fibrillation is commonly presented with underlying co-morbidities such as cardiovascular disease. In the circumstances, atrial fibrillation will aggravate the risk of presenting thromboembolic event or ischemic stroke, as revealed by The Reduction of Atherothrombosis for Continued Health (REACH) Registry (Ohman *et al.*, 2006).

As defined by Malaysian Guideline, stroke is "a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with onset lasting more than 24 hours or leading to death, without apparent cause other than that of vascular origin" (Merican *et.al.*, 2006).

Stroke is a condition that has higher mortality and morbidity especially in those with atrial fibrillation risk factors such as rheumatic heart disease. Atrial fibrillation in an individual who has rheumatic heart disease of the mitral valve or history of valve replacement is referred as non-valvular atrial fibrillation or NVAF (Fang *et al.*, 2007).

1.1.4(c) Treatment options for atrial fibrillation.

The treatment options for atrial fibrillation aim to solve two major problems:

a. To treat the primary problems related to structural and functional abnormalities of the heart. It is focused on restoring the heart function to the normal sinus rhythm and to control the rate of the heartbeat.
b. To protect the heart which extends to precipitating the worst onset caused by the factors that result in an abnormal condition that is called thromboembolism or stroke. Some of the researchers used the term 'secondary stroke prevention' as the treatment of this atrial fibrillation does not seek to resolve the condition caused by the primary problems. Hirsh *et al.* (2003) revealed that in the European Atrial Fibrillation Trial (EAFT), anticoagulation therapy is recommended as a treatment for secondary stroke unless otherwise contraindicated.

The paradigm of atrial fibrillation treatment is shifting, from the conventional focus of achieving heart rate control or rhythm restoration, to the use of the safest agents that potentially reduce patients' symptoms and improve their quality of life and cardiovascular outcomes. No new anti atrial fibrillation drugs have been introduced for decades. The existing pharmacotherapeutic modalities have potentially resulted in serious side effects as well as suboptimal efficacy in converting and maintaining normal sinus rhythm and preventing the recurrence (Omar *et al.*, 2011).

Digoxin in combination with β-blockers or calcium channel blockers is recommended as the first-line therapy in elderly patients with atrial fibrillation, because of its effectiveness in controlling ventricular rates and avoiding the toxicity

of digoxin single therapy (Lee & Chen, 2008). Olshansky *et al.* (2004) also reported in their investigation that an adequate rate control can be achieved either alone with the β-blocker only, calcium channel blocker, digoxin or each combination with digoxin. Among these combinations with digoxin, β-blocker is stronger in controlling the ventricular rate compared to calcium channel blocker.

Direct current cardioversion by means of the administration of antiarrhythmic drug is beneficial for patients with chronic atrial fibrillation in order to reduce, to make less frequent and to shorten the duration of the antiarrhythmia. Antiarrhythmic drug administration may be selected based on the Vaughan Williams class IA, *e.g*. disopyramide and procainamide, class IC (flecainide, propafenone), and class III such as sotalol, amiodarone, ibutilide, and dofetilide (Slavik's *et al*., 2001).

Pharmacologic treatment of ventricular rate control is recommended for asymptomatic atrial fibrillation patients who have been experiencing the urgency to restore sinus rhythm, for those with persistent atrial fibrillation in which it is not possible for antiarrhythmia drug to restore sinus rhythm or for patients who have worse symptoms with antiarrhythmic drug. The maintenance of sinus rhythm is recommended if these conditions do not exist (Prystowsky *et al*., 2000).

The pharmacologic treatment for prevention for patients with atrial fibrillation may be performed by the maintenance of the sinus rhythm. Dronedarone or amiodarone are recommended for the conversion to sinus rhythm, thereby reducing the recurrence period. Amiodarone is more likely efficacious than dronedarone. Dronedarone administration is contraindicated with the use of CYP3A4 inhibitors

such as macrolide antibiotics and diltiazem due to the potentiation of dronedarone's response (Wann *et al.*, 2011).

The AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) recommended amiodarone as an antiarrhythmic drug for elderly patients with atrial fibrillation. Amiodarone is safe in preventing attacks (recurrent) and it facilitates electrical cardioversion in elderly patients with paroxysmal atrial fibrillation (Sellers & Newby, 2011).

The management of atrial fibrillation specially prioritized the prevention of thromboembolism and the control of heart rate and rhythm. Pharmacological rate control has been shown to produce similar results compared with pharmacological restoration of sinus rhythm. The therapy of atrial fibrillation should be initiated for elderly patients. The priority in the pharmacologic treatment of atrial fibrillation is to prevent thromboembolism and control heart rate and rhythm, including for elderly patients. However, the administration of anticoagulants is still given for secondary prevention against stroke in elderly patients. Therefore, elderly patients are particularly at risk of bleeding and experiencing cognitive dysfunction, and functional disorders as well as highly at risk of fall, hence close monitoring needs to be performed (Fang *et al*., 2007).

Men were more likely to have ischemic heart disease than women. The prevalence of morbidity related to atrial fibrillation is higher in women; therefore women are more likely to experience symptomatic attacks than men. Atrial fibrillation therapy with antiarrhythmic drug, amiodarone, increased the risk of

bradyarrhythmia more in women than in men. Hormonal fluctuations should be considered in selecting antiarrhythmic drugs for premenopausal women. The risk of morbidity related to atrial fibrillation is significantly higher in women than in men. Women who experienced longer symptomatic episodes and frequent recurrences were more likely to have lower Quality of Life (QoL). Therefore women were more likely to withhold oral anticoagulation despite being at risk. This evidence suggests that anticoagulation is underutilized in women aged more than 75 years, a subgroup that has particularly high thromboembolic risk (Volgman *et al.*, 2009).

Rate control is more reasonable for the initial treatment of older patients to minimize the symptoms and to avoid tachycardia-induced cardiomyopathy rather than rhythm maintenance as the elderly tend to have higher mortality. Antiarrhythmic drugs are beneficial to maintain sinus rhythm in the subgroup that remains symptomatic even though the rate control is effective. In elderly patients who have reduced renal and hepatic clearance, the risk for proarrhythmia and drug interactions increase when using antiarrhythmic drugs, and there is the highest likelihood of increase in polypharmacy (Eagle *et al*., 2011).

1.1.5 The pharmacologic treatment for stroke prevention.

The pharmacologic treatment for stroke prevention focused on antithrombotic that are anticoagulant and antiplatelet. In the AFASAK study investigated by Peterson *et al.* (1989), warfarin was recommended as an anticoagulant because it is more effective to prevent stroke/TIA and thromboembolic events in patients with non-rheumatoid chronic atrial fibrillation than low-dose aspirin as antiplatelet or placebo.

Various studies had indicated an association between atrial fibrillation with the risk of stroke. Although it is known that haemorrhage is a complication of anticoagulation use, overcoming the incidence of stroke remains a major goal (Sa *et al.*, 2011).

Now being developed is the research on the affectivity of the direct thrombin inhibitor as an alternative. However, it will involve the age risk factor in the subpopulation of atrial fibrillation patients who are at risk of stroke, especially with liver insufficiency. That is due to the fact that direct thrombin inhibitors would be metabolized in the liver (Donnan *et al*., 2004).

Warfarin has been shown to be highly effective in preventing stroke in the elderly with atrial fibrillation. However, the therapeutic index of warfarin is narrow. Bleeding complication may make the anticoagulation therapy difficult. In SPORTIF III and V trials, ximelagatran was reported as not inferior to warfarin, but it is recently declined in the market as it is found to contribute to higher rate of liver toxicity (Sellers & Newby, 2011).

Individualized and closed monitoring should be performed in warfarin therapy to achieve the minimum therapeutic level. The rate of warfarin-related major bleeding is significantly higher in patients aged 75 years old and older than in younger patients. Intracranial haemorrhage is especially common in female patients over the age of 85 years. Therefore loading and maintenance need to be smaller than for the male (Sellers & Newby, 2011).

Atrial fibrillation significantly increases with age. Cardiac and/or non-cardiac (alcoholic, hyperthyroidism or pulmonary disease) co-morbidity are commonly associated with atrial fibrillation in the elderly. Warfarin management in elderly patients with atrial fibrillation should be prioritized first that involves the identification and correction of any precipitating and/or worsening factors for atrial fibrillation (Lee & Chen, 2008).

The risk stratification needs to be confirmed for atrial fibrillation patients undergoing the anticoagulation therapy to ensure minimal risk of warfarin-related adverse effects such as thromboembolism and hemorrhagic complications. Optimal anticoagulation intensity needs to be controlled, and it is indexed using the INR. The INR value should fall within the therapeutic range. The value that is outside of the INR range will cause warfarin-related adverse reaction, which is either stroke or bleeding. This means that the warfarin dose should exceed the minimum effect limit and that it should be maintained, not over the adverse effect limit (Peterson *et al.*, 1989).

The stroke risk in patients with atrial fibrillation may be identified by using the risk stratification scheme. Various studies have been conducted to predict thromboembolism that is generally measured to predict stroke risk. Fang *et al*. (2007) revealed that these stratification schemes are the $CHADS_2$ which functioned to score the factors of congestive heart failure, hypertension (high blood pressure), patient aged more than 75 years old, diabetes mellitus, stroke history and the SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in Atrial Fibrillation) III and V trials.

Further investigation that supports the use of $CHADS_2$ scheme has been done by Garcia *et al*. (2012), and it is suggested that the $CHADS_2$ is applicable for stroke risk prediction. The $CHADS_2$ scheme is also useful for recommending whether the antiplatelet or anticoagulation is better for stroke prevention in patients with atrial fibrillation. The $CHADS_2$ scheme categorizes patients' stroke risk as low, moderate and high risks. However, based on the $CHADS_2$ scores in their investigation on the use of oral anticoagulation used to prevent stroke, it was found that there is still a large percentage or specifically 50% of atrial fibrillation patients receiving oral anticoagulation in United States who failed to reach the desired outcome and in France 13% patients were even admitted due to the complications related to oral anticoagulation (Durham *et al.*, 2010).

The inability to adhere to the intensive INR monitoring according to the guideline in older patients with supratherapeutic INR level will prolong the time of the outside therapeutic range. The supratherapeutic level of INR is common in older patients who received too high loading and maintenance warfarin dose, and it will delay return to the therapeutic range. For elderly patients, they usually have accommodation problems aside from transportation difficulty when they need to perform blood test to monitor the INR at the clinic. It is also difficult to contact some of them (Fang *et al.*, 2007).

The most common stroke occurred to patients who were admitted to hospital was due to untreated atrial fibrillation. Fortunately, stroke can be prevented, even for those who are at high risk (Panchal & Hussain, 2009). Increasing age, prior stroke, gastrointestinal bleeding (GI), hypertension, concurrent NSAID use, anaemia, renal impairment, neuropsychiatric disorder, and malignancy are related to the increase of

the risk of warfarin-associated adverse effect and hospitalization rates for intracranial and extra cranial bleeding. Polypharmacy and poor knowledge about anticoagulation have also been linked to haemorrhage (Fang *et al*., 2007).

In 2006, Oden *et al.* recommended that high intensity anticoagulation associated with INR variability following initial warfarin administration and a moderate INR's intensity between 2.0–2.5 appear to provide optimal stroke prophylaxis and death in patients with atrial fibrillation.

The incidence of stroke in patients with atrial fibrillation can be estimated by identifying the age factor. It was found that increasing age will also increase the risk of stroke. The research done by Wolf *et al.* (1991) has shown that atrial fibrillation is the only independent factor significantly associated with stroke; not hypertension, heart failure and coronary heart disease.

1. 2 Problem Statement.

In view of the effectiveness of warfarin as antithrombotic agent for patients with atrial fibrillations who are at high risk of stroke, the health professionals including pharmacists should be concerned about achieving better outcome of anticoagulation therapy.

To achieve the goal, monitoring is absolutely needed to maintain the dose as warfarin has a narrow therapeutic index. An anticoagulation control has been performed but it was not systematically evaluated. To carry out their role,

pharmacists should really be concerned with the risk-benefit of warfarin therapy. The risk-benefit should be considered as a primary factor to determine the appropriate as well as the desired, therapeutic outcomes.

The most important issue discussed in this study focuses on how the evaluation of the pharmacists' role in the multidisciplinary anticoagulation has been done. Will the role of the pharmacist who focuses only on issues related to monitoring of warfarin able to improve the outcome of therapy and would it be more appropriate than expected? Factors such as the characteristics of patients' response that are related to the therapy should also be considered.

Another important focus is to examine how patients respond to pharmacists' advices. Patients who are receiving warfarin are expected to comply with the pharmacist's instructions about dosage and consumption of food, herbs, supplements, and other drugs.

The Medication Therapy Adherence Clinic (Warfarin MTAC) is established in which pharmacists can play their important roles in the multidisciplinary team. It should be a great opportunity for the pharmacists to give contribution to obtain better outcome in patients' care. It is also to ensure that patients may get the benefit from the pharmacists' education on their medication therapy. Therefore, pharmacists should think and act appropriately in order to help the patients to improve better clinical endpoints. Pharmacists at the Warfarin MTAC play their roles to monitor warfarin medication and educate patients in order to reduce warfarin-related adverse effect.