ASSESSMENT OF MEDICATION ADHERENCE, KNOWLEDGE, AND HEALTH-RELATED QUALITY OF LIFE AMONG ATRIAL FIBRILLATION PATIENTS USING WARFARIN IN PENANG, MALAYSIA

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By

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for the degree of
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To

My parents…

My husband…

My children: Mahmoud, Lujain, Ibrahim & Juman

To them I dedicate my thesis.

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In the name of Allah, the Most Gracious and the Most Merciful

”وَمَا تَوْفِيقِيٓ إِلَّا بِٱللَّهِ ۚ عَلَيْهِ تَوَكَّلْتُ وَإِلَيْهِ أُنِيبُ“ (هود -88)

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Laila M. Matalqah
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AF	Atrial Fibrillation
ACEI	Angiotensin Converting Enzyme Inhibitors
ACCF/AHA	American College of Cardiology Foundation/ American Heart
/HRS	Association/ Heart Rhythm Society
AKA	Anticoagulant Knowledge Assessment
ARB	Angiotensin-Receptor Blocker
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CHADS2	Score for stratification of stroke risk based on: Congestive heart failure (C), high blood pressure (H), age 75 or older (A), and diabetes (D), and a previous stroke (S2) or transient ischemic attack (2 points)
CHF	Congestive heart failure
CI	Confidence Interval
CRC	Clinical Research Centre
DASS	Duke Anticoagulant satisfaction Scale
DDD	Daily Defined Dose
ECG	Electrocardiogram
EQ-5D	Euro-QoL with 5 Domains
EQ-5D-3L	The EQ-5D-three level version
HPP	Hospital Pulau Pinang
HRQoL	Health-Related Quality of Life
ICH	Intracranial Haemorrhage
INR	International Normalized Ratio
ISI	International Sensitivity Index
LAA	Left Atrium Appendage
LVD	Left Ventricular Dysfunction
MEMS	Medication Events Monitoring System
MI	Myocardial Infarction
MMAS-8	Morisky Medication Adherence Scale with 8 items
MMAS-BM	Morisky Medication Adherence Scale – Bahasa Malay
MRA	Medication Refill Adherence
MREC	Medical Research Ethics Committee

MSC	Mental Summary Score
n	Sample size
NMRR	The National Medical Research Register
OAK	Oral Anticoagulant Knowledge
OAC	Oral Anticoagulant
OR	Odd Ratio
P value	Level of Significance
PT	Prothrombin Time
QoL	Quality of Life
r	Correlation coefficient
P (Rho)	Reliability coefficient
PSC	Physical Summary Score
RR	Relative Risk
SD	Standard Deviation
SF-36	Medical Outcomes Survey 36-item Short Form
SJH	Seberang Jaya Hospital
SRQ	Self-Reported Questionnaire
TE	Thrombo-embolism
TIA	Transit Ischemic Attack
TTR	Time in Therapeutic Range
VAS	Visual Analogue Scale
WHO	World Health Organization

PENILAIAN KEPATUHAN PENGUBATAN, PENGETAHUAN DAN KUALITI KEHIDUPAN YANG BERKAITAN KESIHATAN DALAM KALANGAN PESAKIT FIBRILASI ATRIUM YANG MENGGUNAKAN WARFARIN DI PULAU PINANG, MALAYSIA

ABSTRAK

Penggunaan terapi antikoagulan oral (OAC) merupakan suatu amalan klinikal yang standard untuk mencegah strok pada pesakit fibrilasi atrium. Di Malaysia, tidak banyak kajian dijalankan tentang penilaian pengetahuan, ketidakpatuhan dan kualiti hidup dalam kalangan pesakit dengan penggunaan warfarin yang kronik dan perkaitan dengan kawalan antikoagulan.

Projek PhD ini bertujuan mengkaji pengetahuan serta kepatuhan pesakit fibrilasi atrium di Pulau Pinang terhadap ubatan antikoagulan oral, menilai corak kualiti hidup berkaitan kesihatan (HRQoL), serta mengkaji perkaitan antara variabel atau kajian terdahulu dengan kawalan antikoagulan sebagaimana yang diukur melalui INR (International Normalized Ratio). Kajian ini turut mengkaji faktor peramal lain, yang berpotensi menjelaskan tentang variasi nilai INR. Suatu model baru dibangunkan bagi menjelaskan peramal daripada nilai INR terkawal.

Kajian rentas-silang ini dijalankan di Klinik Kardiologi di Hospital Pulau Pinang dan Hospital Seberang Jaya, di Pulau Pinang. Ujian Pengetahuan Antikoagulan Oral (OAK) digunakan untuk mengukur pengetahuan tentang antikoagulan, Sebaliknya, untuk mengukur HRQoL, dua instrumen digunakan iaitu, Skala Kepuasan Antikoagulan Duke (DASS) dan EuroQoL yang berdimensi-lima dan bertahap-tiga (EQ-5D-3L). Kedua-dua OAK dan DASS diterjemah ke dalam bahasa Melayu dan diuji sifat psikometriknya. Bagi penilaian kepatuhan, Skala Kepatuhan Ubatan Morisky beritem-lapan (MMAS-8) dan versi Bahasa Melayu MMAS-BM telah digunakan. Satu soal selidik yang terdiri daripada sosiodemografi

dan ciri-ciri penyakit disediakan dalam dwibahasa (Bahasa Inggeris dan Bahasa Melayu)

Bagi penilaian kawalan INR pesakit, dua kaedah digunakan. Pertama, kaedah masa dalam julat terapeutik (TTR), yang dikenali juga sebagai kaedah Rosendaal. Kedua, kaedah kestabilan INR yang melibatkan bilangan lawatan, dan bacaan INR adalah julat dibahagikan dengan jumlah lawatan (INR%).

Daripada sampel seramai 382 pesakit AF yang memenuhi kriteria penyelidikan, 339 pesakit telah melengkapkan soal selidik DASS, EQ-5D dan MMAS-8. Namun demikian, hanya 328 pesakit melengkapkan ujian OAK dan memasuki analisis akhir. Dalam kalangan semua peserta kajian, min umur ± SD adalah 60.4±14.5 tahun. Secara amnya, pengetahuan peserta kajian tentang warfarin adalah lemah, iaitu dengan min skor OAK 0.47±0.18, dan hanya 9.5% pesakit mencapai kadar lulus 75%. Mereka kurang–tahu tentang aspek asas warfarin (penyesuaian diet, herba, drug dan interaksi alkohol dengan warfarin, pengurusan dos dan keberlakuannya, dan interpretasi keputusan INR). Kajian ini menunjukkan suatu perkaitan yang positif di antara pengetahuan tentang warfarin dan kawalan antikoagulan (TTR dan INR%) (P<0.05).

Dalam kajian ini, hanya 48.4% (n=164) pesakit dilaporkan mempunyai kepatuhan yang tinggi terhadap pengambilan ubatan. Ketidakpatuhan yang tinggi dilaporkan oleh pesakit yang lebih muda, mempunyai tahap pendidikan yang rendah, skor pengetahuan yang rendah, menjalani tempoh terapi warfarin yang lebih lama, dan mengambil ubatan yang kurang. Namun demikian, hanya umur, skor pengetahuan ubatan, dan AF dengan komorbiditi merupakan peramal kepatuhan

dalam analisis multivariat. Dalam kajian ini, terdapat korelasi yang lemah di antara kepatuhan pesakit dan kawalan antikoagulan (TTR atau INR%).

Penilaian QoL pesakit AF menunjukkan suatu persepsi QoL positif dengan purata skor DASS adalah 70.8 (±19.8), dan purata skor EQ-5D adalah 79.8% (±26.3), menunjukkan satu penilaian yang lemah dalam domain mobiliti dan sakit. Kajian ini menonjolkan perkaitan yang signifikan di antara tahap kawalan antikoagulan dan impaknya terhadap QoL (P<0.05).

Daripada semua faktor yang dikaji, analisis multivariat menunjukkan bahawa hanya tempoh penggunaan warfarin (2-5 tahun) yang lebih panjang dan pengetahuan yang tinggi tentang warfarin (skor OAK ≥75%) telah dikenal pasti sebagai statistik peramal bagi kawalan antikoagulan yang baik. Kajian ini menjelaskan bahawa pengetahuan pesakit tentang warfarin amat penting, bukan hanya dalam meningkatkan kawalan INR, malahan juga dalam usaha meningkatkan QoL pesakit. Intervensi pendidikan yang berterusan adalah disarankan.

ASSESSMENT OF MEDICATION ADHERENCE, KNOWLEDGE, AND HEALTH-RELATED QUALITY OF LIFE AMONG ATRIAL FIBRILLATION PATIENTS USING WARFARIN IN PENANG, MALAYSIA

ABSTRACT

The use of oral anticoagulant therapy (OAC) has been a standard clinical practice to prevent stroke in patients with atrial fibrillation. In Malaysia, studies evaluating knowledge, non-adherence and quality of life among patients with chronic use of warfarin and their relationship with their anticoagulation control, are still recent and scarce.

This PhD study aims to gain insight into the knowledge and adherence of atrial fibrillation patients in Penang state towards oral anticoagulant medication, to assess their pattern of health-related quality of life (HRQoL) as well as to investigate the relationship of the former studied variables with the anticoagulation control as measured by the International Normalized Ratio. This study also aims to explore other predictive factors that could potentially explain variations in INR values. A novel model described predictors of controlled INR values was developed.

This cross-sectional study was conducted at the Cardiology Clinics at both Hospital Pulau Pinang and Seberang Jaya Hospital, in Penang state. To measure anticoagulation knowledge, the Oral Anticoagulation Knowledge (OAK) test was used. For HRQoL measure, a specific instrument; the Duke Anticoagulant Satisfaction Scale (DASS) and a generic instrument; EuroQoL with five-dimension-three level (EQ-5D-3L) were used. Both OAK and DASS were translated to Malay language and tested for their psychometric properties. For adherence assessment, the original eight-item Morisky Medication Adherence Scale (MMAS-8) and the translated MMAS-BM in Malay language were used. A questionnaire comprised of

the socio-demographic and disease characteristics of the participants was also delivered in two languages (English and Malay). For patients' INR control assessment, two methods were used; the time in therapeutic range (TTR method) and INR stability method.

Out of a sample of 382 AF patients that met the research criteria, 339 patients have completed DASS, EQ-5D and MMAS-8 questionnaires, but only 328 of them completed OAK test and entered the final analysis. Among all study participants, the mean age ± SD was 60.4±14.5 years.

The knowledge of the study participants is generally poor with a mean OAK score of only 47%±18% with only 9.5% of patients achieved the passing rate of 75%. Their deficiency knowledge was mostly about the basic aspect of warfarin (Dietary modification, herbal, drug and alcohol interactions with warfarin, missing dose management and its consequence, and the interpretation of INR results). The present study revealed a positive association between the patients' warfarin knowledge and the anticoagulation control (INR% and TTR%) ($P<0.05$).

Only 48.4% (n=164) of patients reported high medication adherence in the present study. Non-adherence was highly reported by younger patients, lower education level, patients with lower knowledge score, longer duration on warfarin therapy and taking a less number of medications. However, only age, medication knowledge scores, and AF with comorbidities were predictors of adherence in the multivariate analysis. However, there is no significant association between patients' adherence and the anticoagulation control (TTR or INR%).

The evaluation of AF patients' QoL showed a positive perception with an average DASS score of 70.8 (±19.8) and the EQ-5D average score of 79.8% (±26.3), presented a worse evaluation in Mobility and Pain domains. This study highlighted

the significant association between the level of anticoagulation control and its impacts on the QoL ($P<0.05$).

From all factors that had been studied, the multivariate analysis showed that only longer duration of using warfarin (2-5 years) and higher warfarin knowledge (OAK score ≥ 75%) were identified as statistical predictors of good anticoagulation control. Thus promoting warfarin's knowledge to patients may be helpful not only in improving the INR control but also in improving patients' QoL. Repeated educational intervention is highly recommended.

CHAPTER 1

INTRODUCTION

1.1 Overview and Background of Atrial Fibrillation

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia (irregular heart beat) (The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology, 2010). AF is defined as "an atrial tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function described by the absence of consistent P waves on the electrocardiogram (ECG)" (Bellet, 1971) (Figures 1.1, 1.2 and 1.3).

Approximately 90% of AF patients have nonvalvular AF with different risk of strokes (Ang *et al*., 1998). People with nonvalvular AF generally present with palpitations, dyspnoea, chest pain, fatigue, dizziness, presyncope and syncope (fainting), or in extreme cases loss of consciousness, although approximately 10–30% of cases may occur asymptomatically (The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology, 2010).

AF is classified based on various classification systems such as; the ECG pattern, epicardial or endocavitary recordings, mapping of atrial electrical activity or clinical feature (ACCF/AHA/HRS Guidelines, 2011). Levy *et al*. (2003) classified AF based on the temporal pattern of the arrhythmia. When a patient had two episodes or more, AF is considered as *recurrent*. These episodes may be *paroxysmal* if they terminated spontaneously in fewer than 7 days, or *persistent* if the arrhythmia requires electrical or pharmacological cardioversion for termination and lasted longer than 7 days. Successful termination of AF does not alter the classification of persistent AF in these patients.

The third type of AF is the long-standing non-self terminating arrhythmia that fails to be terminated by cardioversion, or be preceded by recurrent self-terminating episodes, this is classified as *permanent*.

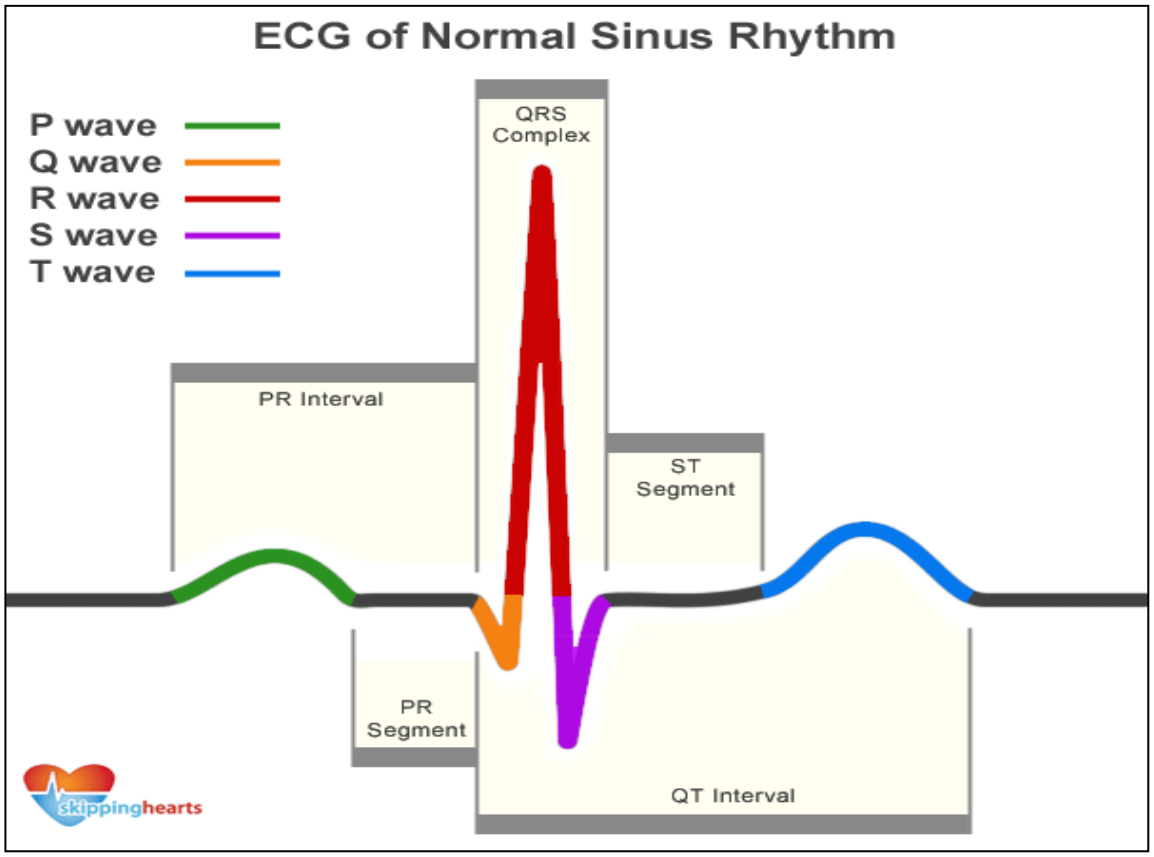

Figure 1.1 Schematic diagram of normal sinus rhythm of a human heart as seen on the ECG (Goldberger, 2012).

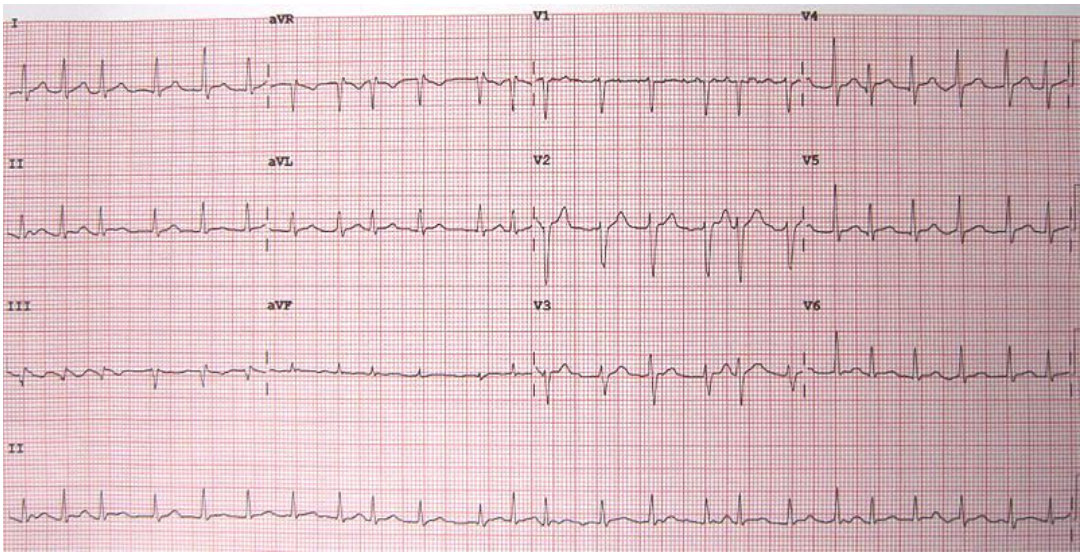

Figure 1.2 ECG of atrial fibrillation at a rate of 150 (Goldberger, 2012)

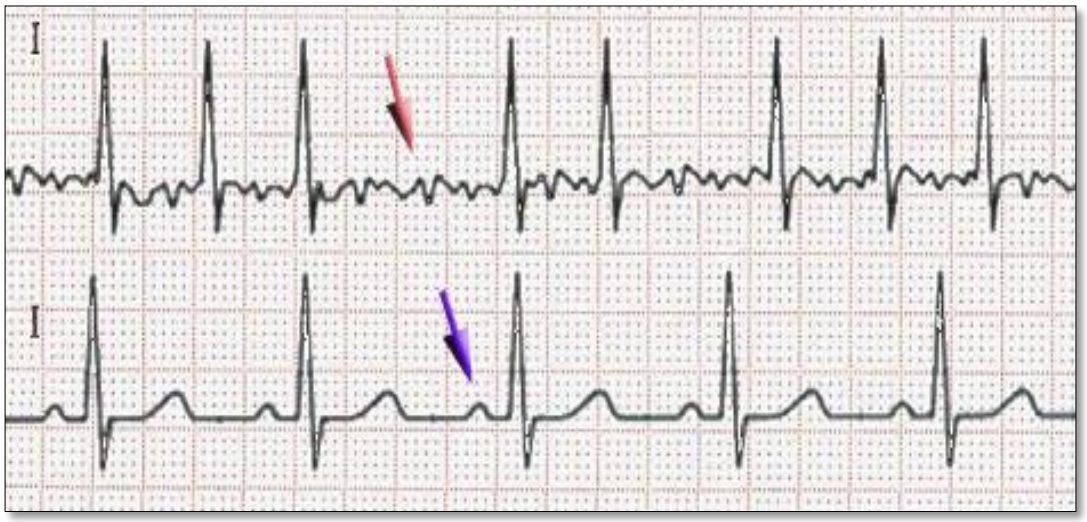

Figure 1.3 ECG of atrial fibrillation (top) and normal sinus rhythm (bottom). The purple arrow indicates a P wave, which is lost in atrial fibrillation (Goldberger, 2012)

1.2 Prevalence of Atrial Fibrillation

Atrial fibrillation is the most common sustained cardiac arrhythmia and currently affects 1–2% of the United States population (Go *et al*., 2001; Stewart *et al*., 2001). Nearly three million people in the United States are diagnosed with AF (Naccarelli *et al*., 2009). The rate of AF increases with age, from less than 1% among persons aged younger than 60 years, to 5-15% in 80 years (Naccarelli *et al*., 2009;

Heeringa *et al*., 2006; Miyasaka et a., 2006; Go *et al*., 2001; Stewart *et al*., 2001; Ryder & Benjamin, 1999; Feinberg *et al*., 1995; Wolf, Abbott, & Kannel, 1991). The median age of patients with nonvalvular AF is 75 years and 84% of patients with nonvalvular AF are over 65 years old (Feinberg *et al*., 1995). With a growing geriatric population in the United States, the prevalence of AF is expected to increase by 2.5 fold over the next 50 years (Go *et al*., 2001; Stewart *et al*., 2001).

In Malaysia, heart diseases are the leading cause of death in 2011 accounting for 25.64 percent of those who died in Ministry of Health (MOH) hospitals in 2010 (Ministry of Health, 2011). However, information on prevalence of AF in Malaysia is scarce. Data from The Asian Cardiovascular Market Outlook to 2014 (2009) estimated the prevalence of AF by 0.4% of the population in the Asia-Pacific with the most prevalent in South Korea, Philippines, Malaysia and Indonesia, affecting 0.7% of the populations. In a Malaysian cohort study conducted in Kuala Lumpur, Malaysia, the prevalence of AF was estimated by 2.8% (Freestone *et al*., 2003). Sivanandam and Lim, (2004) estimated the prevalence of AF based on the fact that the incidence of AF increases with age and 2.5% of the population of Malaysia are above 70 years of age (Rugayah, 1997), therefore approximately 0.25% of the population having AF (known that 10 % of the population above 70 years of age are in AF).

1.3 Risk Factors of Atrial Fibrillation

There are many risk factors for developing AF. Conditions associated with AF are also markers of cardiovascular risk and/or cardiac damage rather than simply causative factors.

1.3.1 Ageing

The prevalence and incidence of AF increased by increasing age, possibly through age-dependent loss and isolation of atrial myocardium and associated conduction disturbances (ACCF/AHA/HRS Guidelines, 2011). In the Framingham study, the development of AF becomes more likely by increasing age with an odds ratio (ORs) of 2.1 for men and 2.2 for women, (P <0.0001) (Benjamin *et al*., 1994).

1.3.2 Hypertension

Hypertension is a risk factor for the first incident AF and for AF-related complications such as stroke and systemic thromboembolism. Hypertension increases the risk of having AF by odds ratio 1.5 for men and 1.4 for women (Benjamin *et al*., 1994).

1.3.3 Heart Failure

Thirty percent (30%) of AF patients have heart failure with New York Heart Association (NYHA) classes II–IV (Nabauer *et al*., 2009; Nieuwallat *et al*., 2005) and 30–40% of heart failure patients are having AF. Heart failure can be a cause of the arrhythmia due to increased atrial pressure and volume overload, secondary valvular dysfunction, or chronic neurohumoral stimulation (Fuster *et al*., 2006).

1.3.4 Valvular Heart Disease

Valvular heart diseases (e.g., mitral valve stenosis and rheumatic valve disease) are found in about 30% of AF patients (Nabauer *et al*., 2009; Nieuwallat *et al*., 2005). AF caused by left atrial (LA) distension is an early manifestation of mitral stenosis and/or regurgitation. AF occurs in later stages of aortic valve disease. In the

Framingham study valvualr disease associated with increase AF risk with an odds ratio of 1.8 for men and 3.4 for women (Benjamin *et al*., 1994).

1.3.5 Diabetes Mellitus

Diabetes mellitus is found in 20% of AF patients, and may contribute to arterial damage with an odds ratio 1.4 for men and 1.6 for women (Benjamin *et al*., 1994). The relative risks (RRs) for stroke mortality and morbidity associated with diabetes were 1.8 in men and 2.2 in women after adjusting for the effect of other risk factors including age, blood pressure, and excluding persons with personal history of heart attack, heart failure, or stroke (Barrett-Connor & Khaw, 1988).

1.3.6 Coronary Artery Disease (CAD)

Coronary artery disease (CAD) is also known as coronary heart disease (CHD) is common among those with atrial fibrillation. CAD is present in ≥ 20% of the AF population (Nabauer *et al*., 2009; Nieuwallat *et al*., 2005). In CAD plaque is built up inside the coronary arteries that supply the cardiac muscle with blood that is rich in oxygen. If the flow of oxygen-rich blood to the heart muscle is reduced or blocked over time, CAD can weaken the heart muscle and lead to heart failure and arrhythmias.

1.3.7 Dietary and Lifestyle Factors

Excessive alcohol or caffeine consumption and emotional or physical stress are among the most important lifestyle factors that have been associated with AF. As a consequence of an excessive intake of alcohol over a relatively short period, AF may develop a so-called ‘holiday heart syndrome’ (Ettinger *et al.,* 1978). The

proposed mechanism for alcohol-induced AF is that acute consumption of alcohol affects catecholamine release, metabolic acidosis, electrolyte disturbances, and increased oxidative distress. In the long term, this resulted in cardiomyopathy, structural heart disease, metabolic disturbances, and increased sympathetic tone. The combination of these effects contributed to the increase in atrial arrhythmias (Balbão, de Paola, & Fenelon, 2009). Among a series of younger patients (aged < 65 years) with new onset AF, 63% of cases are caused or contributed by alcohol (Lowenstein *et al*., 1983).

Besides all factors listed above, obesity, thyroid dysfunction (hyperthyroidism), cardiomyopathy, myocarditis, pulmonary embolism and chronic renal disease may increase the risk of AF. AF is also common after surgery, especially cardiothoracic operations such as thoracotomy and coronary artery bypass graft (Fuster *et al*., 2006).

1.4 Prognosis of Atrial Fibrillation

AF is associated with increased rates of death, hospitalizations, stroke, left ventricular dysfunction (LVD) and reduced quality of life and exercise capacity.

1.4.1 Death

The rate of death is doubled by AF, independently of other known predictors of mortality (Kirchhof *et al*., 2007; Stewart *et al*., 2002, Wolf *et al*., 1998). The odds ratios for death from AF were estimated at 1.5 for men and 1.9 in women, which does not vary by age (Benjamin *et al*., 1994).

1.4.2 Hospitalizations

AF accounts for one-third of all admissions for cardiac arrhythmias. It is expected that the number of hospitalizations associated with AF continues to increase, following an already observed 14.4% increase from 1985 to 1999 among adults aged 35 years or older (Wattigney, Mensah, & Croft, 2003).

1.4.3 Stroke

AF patients are with an approximately fivefold greater risk for stroke than that of people without AF (Gattellari *et al*., 2011; Wolf *et al*., 1998; Wolf *et al*., 1991). The incidence of strokes attributable to AF increases from 1.5% at age 50–59 years to 23.5% at age 80–89 years (Wolf *et al*., 1991). Stroke in AF has been often severe and results in long-term disability or death. Paroxysmal AF carries the same stroke risk as permanent or persistent AF.

1.4.4 Left Ventricular Dysfunction (LVD)

AF is associated with haemodynamic instability with an atrial filling fraction less than 40%, this is related to the irregular, fast ventricular rate and increased end-diastolic LV filling pressure which results in a reduction in cardiac output of up to 10–20% (Tischler *et al*., 1990). An uncontrolled AF rate may even precipitate critical cardiac ischemia.

1.4.5 Quality of Life and Exercise Capacity

AF adversely impacts quality of life and overall well-being and it results in reduced exercise tolerance. It was found that patients with AF had significantly

worse quality of life compared with control subjects with significantly lower total functional capacity and global life satisfaction (Sanoski, 2009; Thrall *et al*., 2006).

1.5 Pathophysiology of Thrombus Formation (Stroke)

Thrombus associated with AF arises most frequently in the left atrium appendage (LAA) which is a muscular pouch connected to the left atrium (LA) of the heart. LAA flow velocities are reduced because of loss of organized mechanical contraction during AF (Manning *et al*., 1989). This substrate of decreased flow within the LA/LAA has been associated with spontaneous echo contrast, thrombus formation, and embolic events (Mitusch *et al*., 1995).

1.6 Stroke Risk Stratification

Strokes in patients with AF are more severe than other types of ischaemic stroke, and result in greater morbidity and mortality (Gattellari *et al*., 2011; Béjot *et al*., 2009). The magnitude of the increase in stroke risk in patients with AF depends on the presence of other risk factors. Approximately 90% of AF patients have at least one or more additional risk factors for stroke (Nieuwlaat *et al*., 2006). These additional risk factors can be used to stratify patients into categories of stroke risk; using risk scales such as the **CHADS2** score.

CHADS2 is an acronym derived from the initial letters of **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, and **S**troke (doubled) (Gage *et al*., 2001). **CHADS2** is a marker for stroke risk factors and their scoring. **CHADS2** is calculated by adding 1 point each for any of the following: recent congestive heart failure (CHF), hypertension, age 75 years or older, and diabetes mellitus (DM); and 2 points for a history of **s**troke or transient ischemic attack (TIA) (Gage *et al*., 2001).

For example, a 78-year-old (+1) patient who had diabetes mellitus (+1) and a prior stroke (+2) would have a CHADS2 score of 4. The higher a patient's CHADS2 score indicates a greater risk of stroke (Table 1.1).

Antithrombotic therapy is highly recommended for patients with AF to prevent stroke and transit ischemic attack. Choosing antithrombotic therapy (warfarin *vs*. Aspirin) depends on patients' CHADS2 score (Fuster *et al*., 2006).

Table 1.1 Risk of stroke in National Registry of Atrial Fibrillation (NRAF) participants, stratified by CHADS2 Score (Adapted with modification from Lip *et al*., 2010; The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology, 2010; Gage *et al*., 2001).

CHADS2 Score	Adjusted stroke rate (%/year)	95% CI (95% confidence interval)
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

1.7 Management of Atrial Fibrillation

The aims of AF treatment are to reduce its symptoms and to prevent severe complications associated with AF. These therapeutic goals need to be pursued in parallel, especially in the newly detected cases of AF (The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology, 2010). For a comprehensive management of AF, it is highly recommended to identify and treat the predisposing factors and concomitant disorders (such as hypertension and hypercholesterolemia), which increase a patient's risk of stroke and other cardiovascular conditions (Lip, Fat Tse, & Lane, 2012).

Thus, the use of antihypertensive including angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs), and cholesterol-lowering therapies such as statins, is highly recommended (Fuster *et al*., 2006). In addition, overall management of AF may involve consideration of three components, depending on the subtype of a patient's AF and/or the severity of their AF-related symptoms (Fuster *et al*., 2006; Lip *et al*., 2012).

- Controlling the heart rate: using non-dihydropyridine calcium channel blocker (verapamil and diltiazem), beta-blocker (metoprolol, propranolol and esmolol) and digoxin.
- Controlling the heart rhythm using antiarrythmatic agent class Ia (quinidine and procainamide), class Ic (propafenone and flecainide) and class III (amiodarone, dofetilide, sotalol and ibutilide).
- Stroke prevention using anticoagulant drug (e.g., warfarin) or antiplatelet drugs (e.g., aspirin).

A management cascade for patients with AF is shown in Figure 1.4.

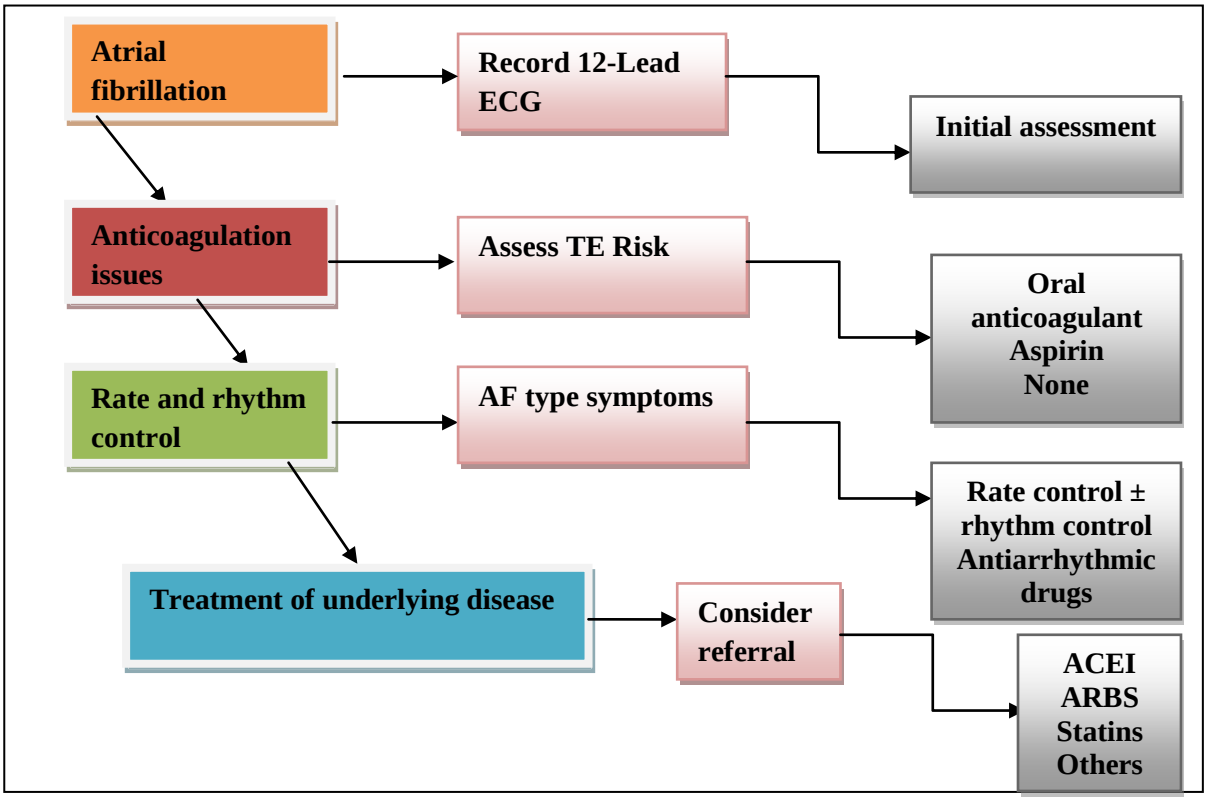

Figure 1.4 Management cascade for patients with atrial fibrillation (AF). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; TE: thrombo-embolism (Adapted with modification from Lip *et al*., 2012).

1.7.1 Anticoagulation Therapy

The use of oral anticoagulant (OAC) therapy has been a standard clinical practice to prevent stroke in patients with atrial fibrillation (Ezekowitz *et al*., 1992; Connolly *et al*., 1991). Coumarins have been used clinically since the 1950s and are likely the most widely studied medicines currently in clinical use (Roche-Nagle *et al*., 2003; Link, 1959). The Malaysian statistics on medicine showed that the use of warfarin increased in Malaysia, it was used by 0.3946 per 1000 population in 2007 (Defined Daily Dose (DDD)/1000 inhabitants/day) (Faridah *et al*., 2010), however, in 2008 its usage increased to 0.4753 per 1000 population every day in a year (or a DDD/1000 inhabitants/day of 0.4753) (Lian *et al*., 2013).

Warfarin is highly effective in reducing the incidence of stroke in patients with AF. A meta-analysis demonstrates that adjusted-dose warfarin reduces stroke

risk by 64% when compared to placebo, which is corresponding to an absolute annual risk reduction in all strokes of 2.7%, while antiplatelet agents reduce stroke risk by 22% (Hart, Pearce, & Aguilar, 2007). In the ACTIVE W trial, anticoagulation therapy had a relative risk (RR) reduction of 40% when compared to the combination of clopidogrel plus aspirin (Connolly *et al*., 2006).

Currently, new anticoagulants have been developed include; direct thrombin inhibitors (dabigatran etexilate) and factor Xa inhibitors (rivaroxaban and apixaban) (Schulman & Majeed, 2012). High cost of dabigatran precludes its use for stroke prevention in AF patients in the government hospitals of Malaysia. However, many studies found dabigatran was generally cost-effective when assuming the costs associated with intracranial haemorrhage, as well as the costs of warfarin monitoring and disability following bleeding events (Pharmaceutical Benefits Advisory Committee, 2011; Scottish Medicines Consortium, 2011)

1.7.1.1 Warfarin Mechanism of Action

Warfarin is a drug derived from 4-hydroxycoumarin group; acts by inhibiting vitamin K epoxide reductase an enzyme which recycles vitamin K into it reduced form (Figure 1.5). Reduced vitamin K is responsible for the carboxylation of the specific blood clotting factors II (prothrombin), VII, IX, X as well as anticoagulant factor protein C and protein S (Ansell *et al*., 2008; Malhotra, Nesheim & Mann, 1985; Friedman *et al*., 1977). Thus warfarin is not a direct antagonist of vitamin K, but rather acts by depletion of reduced vitamin K in tissues which results in a reduction in the conversion of fibrinogen to fibrin which in turn reduces clot formation (Figure 1.6).

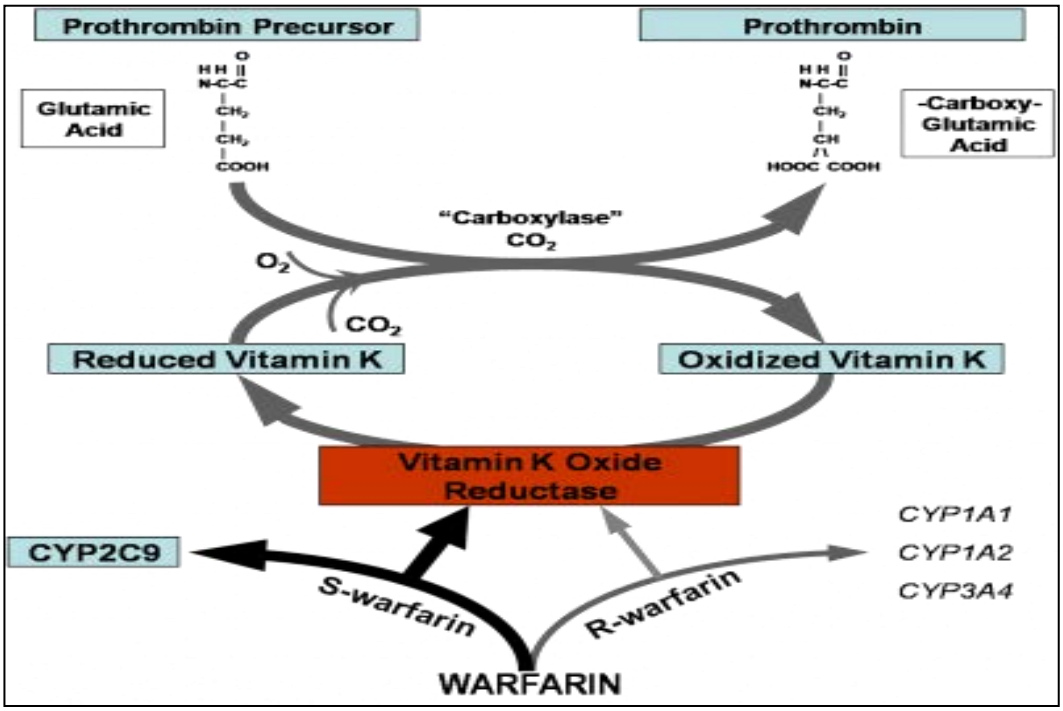

Figure 1.5 Mechanism of action of warfarin (Pharmaceutical Information, 2013).

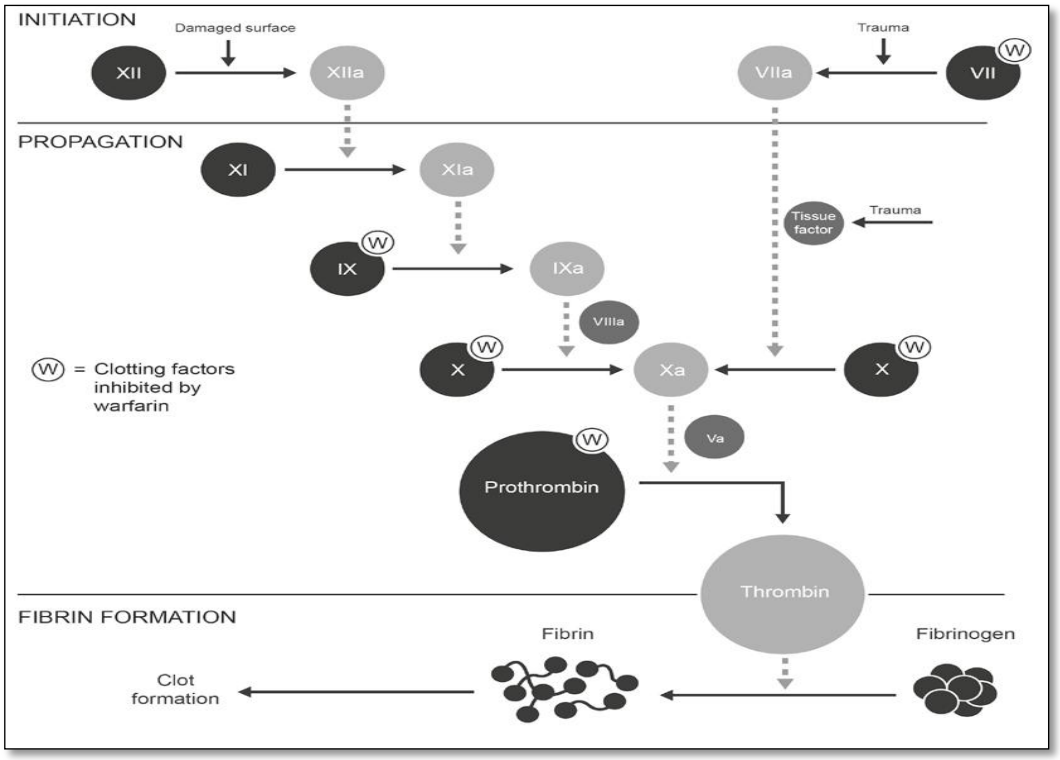

Figure 1.6 Warfarin's effects on the clotting cascade (Best Practice Journal, 2011).

1.7.1.2 Warfarin Pharmacokinetics and Pharmacodynamics

Warfarin is a racemic mixture of two optically active isomers, the R and S enantiomers (Ansell *et al*., 2008). Warfarin is highly water soluble, rapidly absorbed from the gastrointestinal tract, has high bioavailability (Breckenridge, 1978; O'Reilly, 1976), and reaches maximal blood concentrations about 1.5 hours after oral administration (Kelly & O'Malley, 1979; Breckenridge, 1978). The plasma half life of racemic warfarin mixture is 36 to 42 hours (O'Reilly, 1986), this means it takes 5−7 days to reach steady state since warfarin is started or when the dosage is adjusted.

The antithrombotic effect of vitamin-K anticoagulant has conventionally been attributed to their anticoagulant effect, which in turn is mediated by the reduction of the four vitamin K-dependent coagulation factors. The vitamin K-dependent clotting factors have varying half-lives; 6 hours for factor VII, 24 hours for factor IX, 36 hours for factor X and 60-72 hours for factor II (prothrombin). Thus, the anticoagulant effect develops in two days, whereas an antithrombotic effect of warfarin requires six days of treatment (Zivelin, Rao, & Rapaport, 1993).

Numerous environmental factors such as drugs, diet, and various disease states were identified to affect warfarin by altering its kinetics and dynamics (Holbrook *et al.,* 2005). For example, drugs such as cholestyramine can reduce the absorption of warfarin thus reducing its anticoagulant effect. R-warfarin is metabolized primarily by CYP1A2 and CYP3A4, while S-warfarin is metabolized primarily by CYP2C9 (Kaminsky & Zhang, 1997). Hence, other potential warfarin-drug interactions could occur with a concomitant administration of medicines that are metabolized by these CYP450s and as a consequence, a number of metabolic

medicine interactions have been reported for warfarin. For example, drugs such as cimetidine, amiodarone and omeprazole (inhibitors of CYP450); potentiate the anticoagulant effect of warfarin by inhibiting its metabolism whereas some drugs like barbiturates, rifampin, azathioprine, and carbamazepine (inducers of CYP450); inhibit the anticoagulant effect by enhancing its clearance (Orme & Breckenridge, 1976). In addition, long-term alcohol consumption has a similar potential to increase the clearance of warfarin (O'Reilly, 1981).

Furthermore, aspirin (Dale, Myhre, & Loew, 1980) and non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of warfarin-associated bleeding by inhibiting platelet function (Battistella, *et al*., 2005).

1.7.1.3 Dietary Vitamin K

As the action of warfarin is modified by vitamin K, a variable dietary intake of vitamin K may alter the extent of the anticoagulation effect. An increased intake of dietary vitamin K (e.g., certain green vegetables or vitamin K-containing supplements) will increase the production of vitamin K-dependent coagulation factors which is sufficient to reduce the anticoagulant response to warfarin (O'Reilly & Rytand, 1980). Furthermore, patients with poor dietary intake of vitamin K often have less stable control of anticoagulation (Sconce *et al*., 2005). It has been suggested to provide these unstable anticoagulated patients with oral vitamin K supplementation. However, unrecognized intake of such can lead to warfarin resistance (O'Reilly & Rytand, 1980).

Another consideration should be taken to grapefruit juice. It was found that grapefruit juice can enhance the plasma concentration (C_{max}) of orally concomitantly

administered drugs. This interaction has been reported with 40 pharmaceutical products, including the vitamin K antagonist (Saito *et al*., 2005).

1.7.1.4 Warfarin Monitoring

The relation between blood clotting and coumarin derivatives was established by Dam and Doisy who shared the Nobel Prize in 1943 for their work (MacCorquodale *et al*., 1939; Dam, 1935). Warfarin has a narrow therapeutic index (Katzung, Masters, & Trevor, 2012), which effectiveness and safety is a tight balance between stroke risk and bleeding risk, hence a careful dose titration and monitoring is required.

The Prothrombin Time (PT) test is the most common test used to monitor vitamin K-anticoagulant therapy (Quick, 1935). The normal prothrombin time is 12-14 seconds (Hoffbrand, 2002). Since PT monitoring of warfarin treatment is not standardized when expressed in seconds, a calibration model which was adopted in 1982, is now used to standardize PT reporting by converting the PT ratio measured with the local thromboplastin into an international normalized ratio (INR) (Kirkwood, 1983). INR is calculated by raising the prothrombin time ratio (the patient's prothrombin time divided by a reference normal prothrombin time) to the power of the International Sensitivity Index (ISI) as follow [Equation 1.1] (Dzung *et al*., 1994).

$$INR = \left(\frac{\textbf{Patient PT}}{\textbf{Mean normal PT}}\right)^{\textbf{ISI}}$$

Where ISI relates the sensitivity of a given thromboplastin (a tissue factor used as a reagent in PT test) to the sensitivity of the World Health Organization's first primary international reference preparation of thromboplastin, which was

assigned an ISI of 1.0 (Dzung *et al*., 1994). Each manufacturer assigns an ISI value for any tissue factor they manufacture which is usually between 1.0 and 2.0.

Instead of a specific value of the INR target, a therapeutic window is utilized as the recommended target range for specific diagnosis; e.g. in atrial fibrillation the clinical benefits of warfarin are highly dependent on maintaining the INR within the therapeutic range of between two and three, while mechanical heart valve replacement often requires a slightly higher target range of INR (2.5-4.0) (Oake *et al*., 2008; Odén, Fahlén, & Hart, 2006; Hirsh *et al*., 2001; Hylek *et al*., 1996). As shown in Figure 1.7, INRs below this range increase the risk of stroke, while INR values above three or four are associated with increased bleeding rate (Fuster *et al*., 2006).

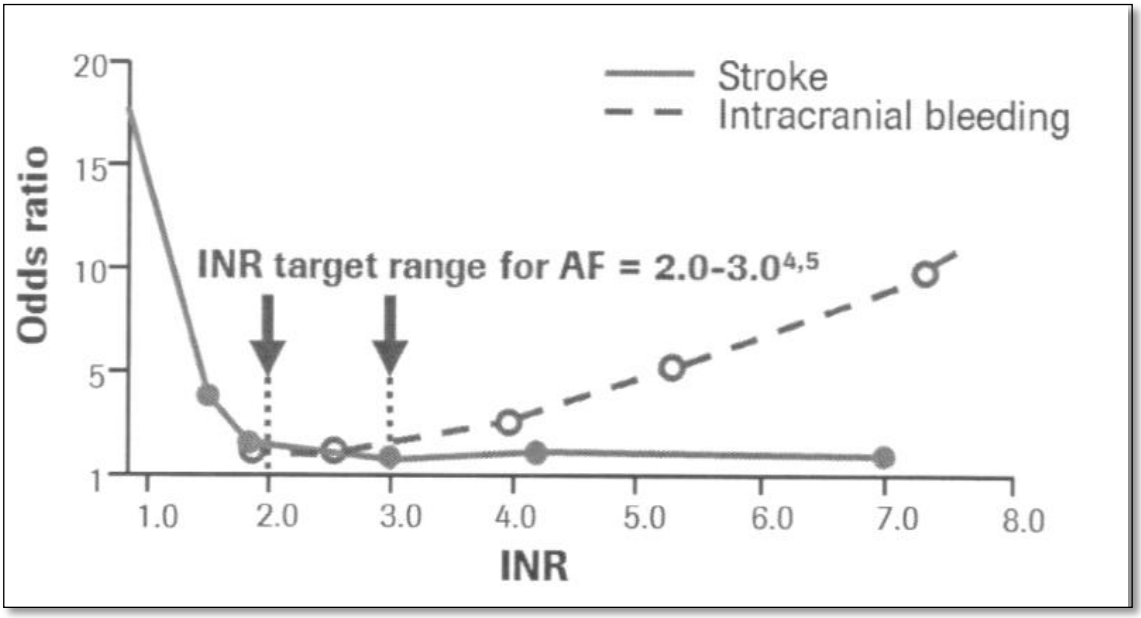

Figure 1.7 Maintaining INR in the therapeutic range is crucial to prevent strokes and avoid bleeding (Fuster *et al*., 2006).

Further quality assessment of the treatment involves calculation of Time spent in the Therapeutic Range (TTR) (Rosendaal *et al*., 1993). In Rosendaal method, the difference between 2 consecutive INR readings,

which was within the target range, was divided by the total difference between them (for more details about Rosendaal method refer to Chapter 3).

1.7.1.5 Warfarin Related-adverse Drug Events

The most common side-effect from over-anticoagulation is bleeding from any anatomical site. There are many risk factors that increase the risk of hemorrhage in patients on oral anticoagulant therapy, such as increasing age (≥ 60 years), previous stroke, diabetes mellitus, recent myocardial infarction, anemia (defined as haematocrit < 30%), presence of malignancy, concomitant antiplatelet usage, uncontrolled hypertension, liver/renal failure and previous gastrointestinal bleeding (Tay, Lane, & Lip, 2008).

The most feared hemorrhagic complication of anticoagulants is the intracranial hemorrhage (ICH) which accounts for approximately 90% of deaths from warfarin associated hemorrhage and for the majority of disability among survivors (Fang *et al*., 2007). Nonetheless, ICH rates in clinical trials conducted in AF patients on oral anticoagulant therapy are small, reported to be between 0.3% and 0.6% per year (Hart, Tonarelli, & Pearce, 2005), and the absolute increase in major extracranial hemorrhages is even smaller, at ≤ 0.3% per year (Lip & Lim, 2007). The risk of ICH associated with warfarin use was twice that of aspirin but the absolute risk was small at 0.2% per year (Hart *et al*., 2007).

Other than hemorrhage, other important side effects of warfarin are acute thrombotic complications, such as dermal vascular necrosis and limb gangrene (Weinberget *et al*., 1983; Verhagen, 1954).

1.8 Medication Knowledge

Patient's knowledge of medication use is of vital importance in the prevention of drug related problems and for treatment success as it offers an opportunity for one to attain a full health potential. The provision of information required by patients relating to their disease and the medication they are to use is not only a necessary factor in treatment success but also a right (Brown & Bussell, 2011). Otherwise, treatment outcomes will not be achieved if such information is not given in a simple clear format that can be understood by the patient.

Currently, only two valid and reliable anticoagulation knowledge questionnaires are available; the Oral Anticoagulation Knowledge (OAK) test, created and validated by Zeolla *et al.* (2006), and the Anticoagulation Knowledge Assessment (AKA) questionnaire, designed and validated by Briggs *et al*. (2005). Both have been validated for content validity, construct validity, and reliability.

1.9 Health-Related Quality of Life (HRQoL)

Quality of life (QoL) is a ubiquitous concept that has different philosophical, political and health-related definitions; it includes the physical, functional, emotional and social aspects of health. The concept quality of life (QoL) and, more specifically health-related quality of life (HRQoL) emerged in the literature in 1920 (Wood-Dauphinee, 1999) and since then various definitions have been proposed. Cella and Nowinski (2002) defined HRQoL as the extent to which one's physical, emotional and social well being are affected by a medical condition or its treatment.

HRQoL is a subjective construct based on patient-reported outcome from their perspective, usually measured with carefully designed and validated instruments such as questionnaires or semi-structured interview schedules. It is also multidimensional that composed of broad domains to provide both an overall

indicator of a person's HRQoL as well as separate indicators for each domain (Taylor, Gibson, & Franck, 2008).

In relation to specific domains, physical aspect refers to bodily functions that may be influenced by disease symptoms and treatment side-effects (e.g., pain, nausea, fatigue). Functional well-being represents the ability of the persons to perform his/her usual daily activities (e.g., work, study, housework, family leisure activities). Social well-being includes social relationships, interaction and support. Finally, emotional well-being is ranging from stress and anxiety to a ppositive sense of well-being (Cella & Nowinski, 2002). In another word, HRQoL is the assessment of physical, functional, emotional and social dimensions of health that are influenced by an individual's perception of his/her health status, the disease and its treatment.

1.9.1 Measurement of HRQoL

By evolving HRQoL researches, there has been a proliferation of HRQoL instruments which can be either generic or disease-specific measures (Solans *et al*., 2008). Generic scales assess constructs that are common to a wide range of population and patients (e.g., physical function, physical role, bodily pain, general health, vitality, social function, emotional role, and mental health). In contrast to generic scales, condition specific scales are intended to be much more narrowly focused toward those aspects of HRQoL that are of the greatest salience of the specific condition (Solans *et al*., 2008). For example, an arthritis specific scale might include questions about joint pain, the number of joints that are swollen or tender, and so forth.

The following are example of generic instrument:

- Medical Outcome Study Short Form 36 (SF-36)

- EuroQol (EQ-5D)
- Sickness Impact Profile (SIP)
- Nottingham Health Profile (NHP)

Disease -specific instruments such as:

- Functional Assessment Of Cancer Therapy-General (FACT-B)
- European Organization Of The Research And Treatment Of Cancer Quality Of Life Questionnaire Core 30-item (EORTC QLQ-C30)

The most consistently used generic QoL scales in AF studies include the SF-36, the Short Form-12 (SF-12), and the EuroQOL/EQ-5D. It has been extensively validated, has a long track record of use in a variety of medical conditions, and has the additional advantage of having a well-accepted method (the EQ-5D) for transforming raw scores to preference-based utility weights (Rabin & de Charro, 2001)

Strengths of the generic tools for measuring QoL in AF studies include their extensive validation, generalizability, and the wealth of data already collected on AF patients. The greatest weakness of the generic measures is that, by design, they reflect general health and functioning, and, therefore, scores among AF patients are strongly influenced by patient demographics and comorbid conditions (Reynolds *et al*., 2006a). This makes the generic measures potentially less sensitive to change in the many older AF patients who have multiple health problems

1.10 Adherence to Medication

Medication adherence is defined as "the extent to which a patient take medication as prescribed by their health care providers" (Osterberg & Blaschke, 2005). According to the World Health Organization (2003), adherence is defined as

"the extent to which a person's behavior - taking medication, following a diet and/or executing lifestyle changes - corresponds with agreed recommendations from the health care provider". Nonadherence includes not only a cessation of medication therapy but also taking the medication other than as prescribed (e.g., under adherence, over adherence, or not taking the dose at the prescribed time).

Most studies report the rate of medication adherence as a percentage of doses actually taken out of those prescribed medications over a specific period of time (Osterberg & Blaschke, 2005; Winkler *et al*., 2002). Patients with acute conditions reported higher adherence rates as compared to those with chronic conditions, whose adherence dropped most dramatically after the first six months of therapy (Cramer *et al*., 2003; Haynes, McDonald, & Garg, 2002). It was cited that adherence rates to long-term therapy was approximately 50%, regardless of the illness, regimen or measurement criteria (DiMatteo, 2004). Other literatures reported that adherence rate among patients receiving treatment for chronic conditions, ranged from 43% to 78% (Cramer *et al*., 2003; Claxton, Cramer, & Pierce, 2001). In another systemic review, the non-adherence to medication is estimated to affect approximately 30-50% of patients with chronic conditions (Haynes *et al*., 2008). However, there is no consensual standard for what constitutes adequate adherence, some trials consider rates of greater than 80% to be acceptable, whereas others consider rates of greater than 95% to be mandatory for adequate adherence (Osterberg & Blaschke, 2005).

Nonadherence may be intentional (for example patients decide not to take the medication) or unintentional (patients forget or are unable to take their medication) (Unni & Farris, 2011). The consequences of non-adherence include a treatment failure, poor health outcomes and increased healthcare costs. For example, non-adherence is responsible for 48% of asthma deaths, an 80% increased risk of death in

diabetes and a 3.8-fold increased risk of death in the year following a heart attack (Elliot, 2009). In the United Kingdom (UK) the cost of unused or unwanted medicines was estimated to exceed £300 million annually (Trueman *et al*., 2010).

Two methods often used to evaluate and assess patients' adherence to medication are medication event monitoring systems (MEMS) and self-reported questionnaires (SRQs) (Farmer, 1999). The MEMS is a medication vial cap that electronically records the date and time of bottle opening. It is also known as the "imperfect gold standard," due to its recording effectiveness in the measurement of patient adherence (Claxton *et al*., 2001). This method has many disadvantages such as; it could be time consuming, expensive and may not be suitable for all medications or formulations.

Another method is the self-reported questionnaires (SRQs) which has been considered the method of choice for measuring non-adherence in clinical practice (National Collaborating Centre for Primary Care, 2009). SRQs have frequently been used because they are low in both cost and time expenditure, relatively unobtrusive, can be used on all types of medicines and are able to distinguish between intentional and unintentional non-adherence (Garfield *et al*., 2011). Other research suggested that self-reported method may provide a reasonably accurate estimate of adherence (Grymonpre *et al*., 1998; Craig, 1985).

On the other hand, earlier studies found that the self-reported method was underestimating non-adherence when compared with pill counts or biological assays (Gordis, Markowitz, & Lilienfeld, 1969; Park & Lipman, 1964). Furthermore, another limitation of SRQs use, that they are subjected to measurement bias such as social desirability, recall bias, and response bias (Cook *et al*., 2005; Garber *et al*., 2004).