COST-EFFECTIVENESS OF WARFARIN MEDICATION THERAPY ADHERENCE CLINIC VERSUS USUAL MEDICAL CLINIC AT KUALA LUMPUR HOSPITAL

by

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LIST OF ABBREVIATIONS

AF	Atrial fibrillations
AMO	Assistant Medical Officers
AMS	Anticoagulation Management Services
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CER	Cost Effectiveness Ratio
$CHADS_2$	Stroke Risk Scoring System in Atrial Fibrillation
CI	Confidence Interval
CUA	Cost Utility Analysis
DSA	Deterministic Sensitivity Analysis
DVT	Deep Vein Thrombosis
FHER	Fatal Haemorrhagic Events
FTE	Fatal Thromboembolism
HK$	Hong Kong Dollars
ICER	Incremental Cost Effectiveness Ratio
Int. $	International Dollars
INR	International Normalized Ratio
ISI	International Sensitivity Index
IV	Intra Venous
KLH	Kuala Lumpur Hospital
LTHER	Life Threatening Haemorrhagic Events
LTTE	Life Threatening Thromboembolism
MHV	Mechanical Heart Valve
MO	Medical Officers

MOH	Ministry of Health
MYR	Malaysian Ringgit
NMRR	National Medical Research Registry
PE	Pulmonary Embolism
PSA	Probabilistic Sensitivity Analysis
PSM	Patient Self-Monitoring
POCT	Point of Care Testing
PT	Prothrombin Time
QALY	Quality Adjusted Life Years
RCT	Randomized Control Trial
RR	Relative Risk
SD	Standard Deviations
STE	Serious Thromboembolism
SHER	Serious Haemorrhagic Events
TE	Thromboembolism
TTR	Time in Therapeutic Range
UMC	Usual Medical Clinic
USD	United States Dollars
VKA	Vitamin K Antagonists
VTE	Venous Thromboembolism
WHO	World Health Organization
WMTAC	Warfarin Medication Therapy Adherence Clinic
WTP	Willingness To Pay

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KEBERKESANAN KOS KLINIK KEPATUHAN TERAPI WARFARIN BERBANDING KLINIK PERUBATAN BIASA DI HOSPITAL KUALA LUMPUR

ABSTRAK

Rawatan antikoagulasi secara sistematik disyorkan dalam pengurusan pesakit yang menggunakan rawatan warfarin secara kronik. Perkhidmatan seperti ini baru diperkenalkan di Malaysia dan dikenali sebagai Klinik Kepatuhan Terapi Warfarin (WMTAC) dimana ia dikendalikan oleh ahli farmasi dengan nasihat pakar perubatan. Objektif kajian ini ialah untuk menilai keberkesanan kos rawatan antikoagulasi sistematik berbanding klinik perubatan sedia ada (UMC) yang dikendalikan oleh pegawai perubatan di Hospital Kuala Lumpur (KLH), hospital kerajaan bagi rujukan rawatan tertiari. Satu kajian kohort retrospektif selama enam bulan dilakukan untuk membandingkan kedua-dua jenis model rawatan ini. Satu pesampelan rawak digunakan untuk mengenalpasti 92 pesakit dari setiap klinik. Min peratusan masa di dalam julat terapeutik (TTR) bagi International Normalized Ratio (INR) bagi pesakit yang disyorkan dalam Garispanduan Praktis Klinikal di Malaysia bagi pencegahan dan rawatan *Venous Thromboembolism* bagi tahun 2013 digunakan untuk menilai keberkesanan klinik. Kos min rawatan setiap klinik merangkumi empat aktiviti kos, iaitu kos pemantauan, masa perundingan klinik dan pendispensan, ubat dan peristiwa mudarat. Kos dianggarkan mengunakan kajian masa-pergerakan bagi INR di dalam dan di luar julat terapeutik. Satu model Markov yang berkitaran enam bulan dari perspektif penyedia perkhidmatan digunakan untuk mensimulasikan keberkesanan kos seumur hayat. Kes asas model berbatasan masa selama 20 tahun dengan keberkesanan kos yang berandaian kohort pesakit dengan AF berumur 57 tahun

dengan penyakit komorbid. Kebarangkalian peralihan untuk hasil klinik diperolehi dari carian jurnal. Andaian model yang digunakan ialah kebarangkalian kesan yang sama antara klinik dan antara kitaran. Kos dan keberkesanan masa hadapan menggunakan diskaun 3% untuk ditukarkan ke nilai semasa. Semua kos berdasarkan Ringgit Malaysia (MYR) tahun 2007. Peratusan masa dalam julat terapeutik (TTR) lebih tinggi secara signifikan di WMTAC berbanding UMC (66.1% berbanding, 48.3%; $p < 0.001$). Perbezaaan kos min enam bulan juga signifikan ($p < 0.001$), dimana kos UMC dan WMTAC ialah MYR 537.38 (SD = 352.39) dan MYR 352.62 (SD = 180.21) masing-masing. Keputusan model jangkamasa 20 tahun menunjukan kos min WMTAC ialah MYR 5864.10, manakala kos min UMC ialah MYR 6550.96 bagi jangkamasa hayat selama 6.15 dan 6.17 tahun bagi UMC dan WMTAC. UMC didominasi oleh WMTAC bagi kedua-dua jangkamasa analisa, enam bulan dan seumur hayat. Analisa kepekaan model menunjukkan bahawa kos klinik mempengaruhi keberkesanan kos. Sekiranya kos WMTAC meningkat melebihi 50% atau kos UMC menurun melebihi 25%, WMTAC tidak menjadi intervensi yang dominan. Secara kesimpulannya, perkhidmatan WMTAC lebih kos-efektif berbanding UMC di KLH. WMTAC lebih kos efektif, kerana dapat meningkatkan peratusan jangkamasa dalam julat terapeutik dan mengurangkan kekerapan lawatan klinik dan kemasukan ke wad. Pengekalan peratusan jangkamasa dalam julat terapeutik melebihi 70%, iaitu masa piawai adalah penting untuk memastikan keberkesanan kosnya.

COST-EFFECTIVENESS OF WARFARIN MEDICATION THERAPY ADHERENCE CLINIC VERSUS USUAL MEDICAL CLINIC AT KUALA LUMPUR HOSPITAL

ABSTRACT

Systematic anticoagulation management clinic is now recommended to manage atrial fibrillation (AF) patients on chronic warfarin therapy. In Malaysia, the service is recently introduced as pharmacist managed Warfarin Medication Therapy Adherence Clinic (WMTAC) which is managed by the pharmacist with a physician advisory. The objective of the present study was to assess the cost effectiveness of anticoagulation clinic in comparison to usual medical clinic (UMC) which is managed by medical officers in Kuala Lumpur Hospital (KLH), a tertiary referral hospital in Malaysia. A six month retrospective cohort study comparing the two anticoagulation management models was conducted. Systematic random sampling was used to sample a total of 92 patients from each clinic. The mean percentages of time within therapeutic range (TTR) for the patients which is recommended in the 2013 Malaysian Clinical Practice Guidelines on the Prevention and Treatment of Venous Thromboembolism were used as effectiveness. The mean total cost of each clinic included four cost activities such as the cost of monitoring, clinic consultation and dispensing, drug and adverse event. The costs were estimated using the time-motion study for the INR within and outside the therapeutic range. A six monthly cycle Markov model from the provider perspective was used to simulate life time cost effectiveness. The base case analysis assumed a cohort of patients with AF, 57 years of age with comorbid illnesses. The transition probabilities of these clinics outcomes were obtained from a literature search. The model assumptions were that the outcomes probabilities were similar for both the clinics and between the

cycles. Future costs and effectiveness were discounted 3% to convert to present values. All costs were in Malaysian Ringgit (MYR) based on year 2007. Percentage of time in therapeutic range (TTR) was also significantly higher in WMTAC than those in UMC (66.1% vs. 48.3%; $p < 0.001$). Mean six months treatment cost was MYR 537.38 (SD = 352.39) for UMC and MYR 352.62 (SD = 180.21) for WMTAC, which was significantly higher ($p < 0.001$). Results of a 20-year period model showed that the mean cost of the WMTAC was MYR 5864.10 whereas the UMC cost was MYR 6550.96 and the life-years to be 6.15 and 6.17 years for UMC and WMTAC respectively. UMC was found to be dominated by the WMTAC for both intermediate and lifetime analysis. The sensitivity analysis showed that clinic treatment costs had a major impact on the cost-effectiveness analysis. If the cost of WMTAC increased by 50% or if the UMC cost dropped more than 25% of the current cost, the WMTAC would not be a dominant intervention. In conclusion, WMTAC is a more cost effective option than UMC in KLH. The WMTAC is cost-effective, as it is able to improve the percentage of time within therapeutic range and reduce the frequency of clinics visits and ward admissions. Maintaining the TTR above the gold standard of 70%, is important to ensure its' effectiveness.

CHAPTER 1: INTRODUCTION

The incidence of Venous Thromboembolism Embolism (VTE) is increasing globally. The worldwide incidence exceeds 1 per 1000 (Ministry of Health Malaysia, 2003b, Nordstrom et al., 1992). VTE is a general term used to describe the blockage of a blood vessel by a blood clot. VTE is often a silent disease and the first appearance can be fatal. Diagnosing and treating VTE patients in the United States with anticoagulants costs United States Dollars (USD) 3.2 to 15.5 billion per year (Cundiff, 2004), whereas in Europe, the total direct costs of all VTE events were estimated at USD 3.99 billion each year (Coalition to Prevent VTE, 2012). Vitamin K antagonist (VKA) is the commonly prescribed anticoagulant, as it is effective in preventing and treating arterial and venous thrombosis (Geerts et al., 2001, Hyers et al., 2001, Albers et al., 2001, Stein et al., 2001, Cairns et al., 2001). Successful anticoagulant management requires careful monitoring of the International Normalized Ratio (INR), patient education and good communication between patients and their caregivers. Many of the patients on warfarin are elderly and require assistance from family or friends or caregivers to manage the monitoring and medication administration (Schulman et al., 2010). Communication with care givers are important, as 30% of the patients are accompanied by a family member for clinic based testing (Lafata et al., 2000). Careful monitoring of INR is important as it is affected by many factors such as genetics, drugs and environmental factors. In addition to this, dietary vitamin K intake, physical activity and adherence to therapy are also known to affect the stability of INR (Ageno et al., 2012). Quality of anticoagulant therapy has proven to influence the risk of undesirable outcomes among these patients (Wilson et al., 2003). A strong relationship between percentage of Time in Therapeutic Range (TTR) for the INR and the rates of bleeding or thromboembolic events has been observed across studies with

different patient populations, target ranges, scales for measuring intensity of anticoagulation, methods of measuring TTR and different models of dose management (Ageno et al., 2012).

Studies have indicated that anticoagulation management and outcomes across different health care systems in different countries, showed an array of management styles and outcomes related to the model of anticoagulation care (Ansell et al., 2007a). The primary models of anticoagulant care are usual medical clinic, nurse, pharmacist or physician-managed oral anticoagulation clinic and patient self-management (Wilson et al., 2003). Poor quality of dose management in routine clinical practice or usual medical clinic is an obstacle to the safety and effectiveness of warfarin therapy (Ageno et al., 2012). Evidence suggests that the rigorous provision of follow-up care by anticoagulation clinic models are more likely to attain the desired patient outcomes and reduce costs per person-year of follow-up than usual medical care (Wilson et al., 2003, Chamberlain et al., 2001). Despite evidence that the introduction of organized anticoagulation clinics may prevent complications, the introduction of such clinics has been relatively slow and the cost effectiveness of the different monitoring alternatives remains unknown (Lafata et al., 2000). The systematic pharmacist managed anticoagulation clinic model was introduced as Warfarin Medication Therapy Adherence Clinic (WMTAC) in Malaysia in 2005. However systematic anticoagulation model or WMTAC is not the primary treatment model in Malaysia.

1.1 Thromboembolism

Thromboembolism (TE) is a major health problem, where it is the third most common cardiovascular disease after myocardial infarction and stroke (Naess et al., 2007). The Global Burden of Diseases, Injuries, and Risk Factors Study 2010 clearly document the major impact of arterial thrombosis on the global disease burden, because it is the pathologic mechanism of most underlying cases of ischemic heart disease and ischemic stroke. A systematic review of global burden of disease attributable to VTE identified the incidence as 0.75 to 2.69 per thousand individual in the population. Though the annual incidence rates in the Asian populations are reported to be lower, studies have demonstrated that the disease burden is not low due to population aging and increased life expectancy. Recent studies have demonstrated that the rates of VTE after major surgery and in hospitalized medical patients are approaching western population rates (Raskob et al., 2014). In Malaysia, obstetric VTE is now the leading cause of maternal death (Ministry of Health Malaysia, 2013a). Initially perceived as rare in Asia, the VTE incidences approach values close to incidences in western countries. About 10% would die within the first month of diagnosis. Thus VTE is considered a worldwide health crisis (Naess et al., 2007, Ministry of Health Malaysia, 2013a) .

1.1.1 Venous Thromboembolism (VTE)

VTE is an important cause of death in hospitals. Treatment of VTE and its' related long term morbidities are associated with considerable health service cost. VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Three major pathophysiologic determinants of VTE are venous stasis, endothelial injury and hypercoagulability. All risk factors for VTE influence at least one of these three

mechanisms (Nicolaides et al., 1971, Kakkar et al., 1969, Kumar et al., 2010). Complications of VTE include post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension. Adjusted-dose VKAs are historically the primary agent used to effectively reduce VTE and its' consequences (Geerts et al., 2004, National Institute for Health and Clinical Excellence, 2012). There is substantial evidence that venous thromboembolism after stroke is also a significant problem in Asia with prevalence ranging from 0.5 – 45 % (Tan et al., 2008). Without treatment, 50% of patients with symptomatic proximal DVT or PE are likely to have recurrent thrombosis within the first three months of diagnosis (Ribeiro et al., 1999, Dalen et al., 1997). Ten percent of symptomatic PE is fatal within one hour of onset of symptoms (Paraskos et al., 1973, Laporte et al., 2008). As for PE, 50% resolution occurs after two to four weeks of treatment (Dalen et al., 1997), whereas complete resolution of PE occurs in about two thirds of patients (Paraskos et al., 1973, Riedel et al., 1982, Torbicki et al., 2008). Resolution of proximal DVT is slow and less than half have complete lysis after six months of anticoagulation (Holmstrom et al., 1997). The risk of recurrence upon cessation of anticoagulation is similar following proximal DVT and PE (Douketis et al., 1998, Heit et al., 2000). However, the risk of mortality is two to three folds higher with recurrent PE. The risk of recurrent VTE is higher in unprovoked VTE or with persisting risk factors for thrombosis compared to patients with transient risk factors (e.g. recent surgery) (Prandoni et al., 1996, Research Committee of the British Thoracic Society, 1992, Levine et al., 2002, Kearon, 2004, Galioto et al., 2011). Mechanical prophylaxis is used for patients who are ineligible for pharmacologic therapy but is less efficacious than pharmacologic methods when used alone (Sachdeva et al., 2010, Agu et al., 1999, Kearon and O'Donnell, 2010). Pharmacological prophylaxis includes low molecular weight heparin (LMWH), pentasaccharide sodium (fondaparinux),

unfractionated heparin (UFH) and the newer anticoagulants (dabigatran, rivaroxaban, apixaban) (Geerts et al., 2004, Kahn et al., 2012). Maintenance treatment of VTE with anticoagulation is recommended, following initial heparinisation or fondaprinux treatment in patients with VTE (Ministry of Health Malaysia, 2013a).

1.1.2 Atrial fibrillation (AF)

Vascular diseases has been found to increase the risk of AF and AF has likewise been shown to be a major risk factor for vascular disease and cardiovascular death. Both VTE and AF share a number of risk factors such as increasing age, obesity, diabetes, heart failure and hypertension (Olesen et al., 2012).

Atrial fibrillation is an atrial tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function (Ministry of Health Malaysia, 2012a). The five types of recognized AF are initial event, paroxysmal, persistent, long standing persistent and permanent (Camm et al., 2010). AF is a naturally progressive disease except for a small proportion of patients who are free of AF promoting conditions, who may remain in paroxysmal AF over several decades (Jahangir et al., 2007). AF is the most common sustained cardiac arrhythmia, though local data is scarce. Data from western populations estimated the prevalence of AF as 0.4 to 1% in the general populations. The prevalence of AF doubles with each decade of age, whereas the mortality rate is about double of patients in sinus rhythm (Ministry of Health Malaysia, 2012a).

AF is associated with a pro-thrombotic state, intra-atrial stasis, structural heart disease or blood vessel abnormalities and abnormal platelets haemostasis, which predisposes patients to thrombus formation. This condition leads to stroke and thromboembolism. Antithrombotic therapy has proven to be the only method to

reduce AF-related mortality (Hylek et al., 2003). The $CHADS_2$ (Congestive heart failure, hypertension, age = 75 years, diabetes mellitus, stroke) risk stratification scheme is used to assess stroke risk, where oral anticoagulation therapy is initiated if the score is ≥ 2. A meta-analysis showed that adjusted-dose oral anticoagulation therapy lead to a significant 64% risk reduction of stroke and 26% reduction of all-cause mortality in patients with non-valvular AF (Hart et al., 2007). In addition to the cost for treatment per admission of MYR 9,000 in tertiary Malaysian education hospital, acute major stroke also lead to at least 10 to 15 clinic visits in the first six months for rehabilitation (Aznida et al., 2012). AF increases the risk of stroke, which is a leading cause of death and disability worldwide. The appropriate use of oral anticoagulation in this moderate to high risk of stroke population, improves health outcomes (Steinberg and Piccini, 2014).

1.2 Anticoagulation Therapy - Vitamin K Antagonists

Warfarin remains the predominant anticoagulant used in Malaysia (Omar et al., 2011). However, there are other available VKAs worldwide such as acenocoumarol, phenprocoumon and fluindione. VKAs have been consistently shown to be highly effective in many settings and are now used by millions of patients' worldwide. VKAs produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its' epoxide. This leads to the reduction of four vitamin K dependant coagulation factors (Ageno et al., 2012).

Warfarin has become the most widely used oral anticoagulant since its introduction in 1954. The most common indications for warfarin anticoagulation are atrial fibrillation (AF), mechanical heart valve (MHV) and venous thromboembolism (Ministry of Health Malaysia, 2013a). Due to its pharmacokinetic and pharmacodynamics complexities, the management of warfarin therapy to

obtain an optimal outcome is a great challenge (Garabedian-Ruffalo et al., 1985, Wilson et al., 2003). Multiple factors have been shown to affect anticoagulation control, such as warfarin dosage, warfarin dosage preparation, drug or food interactions, patient compliance, patient knowledge, the setting of anticoagulation services (Saokaew et al., 2010) and the genetic and environmental factors (Ageno et al., 2012). Higher doses are needed in warfarin resistant patients, who have genetic mutations in the gene coding (Ageno et al., 2012). Warfarin is also highly susceptible to drug- drug interactions, where it is known to interact with more than 200 agents (Coumadin Package Insert, 2007). Nutritional supplements and herbal products are particularly known to be problematic, which patients often fail to inform physician and the physicians rarely ask (Wittkowsky et al., 2007). A number of medical conditions are also known to influence anticoagulation with warfarin (Ageno et al., 2012). Congestive heart failure and diabetes are associated to the instability of the INR. Though a predictive model has predicted, age more than 65 years, myocardial infarction and diabetes to have an increased bleeding risk. However impact of age on bleeding risk remains controversial (Ageno et al., 2012). Inadequate doses lead to thromboembolic events, while patients that receive excessive anticoagulation are at risk of bleeding (Pirmohamed, 2006, Wysowski et al., 2007). It is known to be safe and effective when it is maintained within a narrow therapeutic window (Garabedian-Ruffalo et al., 1985, Wilson et al., 2003). The effective management of warfarin therapy requires a considerable amount of clinician time and resources because of the need for frequent INR laboratory tests and dosing adjustments (Sullivan et al., 2006, Verret et al., 2012). A study on the cost of adverse event showed that the mean 12 months healthcare costs for patients on warfarin were USD 22,507 if they had no bleeding, USD 22,824 if minor gastrointestinal

bleeding occurred, USD 36,571 if major gastrointestinal bleeding occurred and USD 42,574 if intra cranial bleeding occurred (Ghate et al., 2011).

1.2.1 Monitoring Anticoagulant Intensity

The Prothrombin Test (PT) is the most common test used to monitor VKA therapy. The PT responds to a reduction of three of the four vitamin K dependent pro-coagulant clotting factors that are reduced by warfarin at a rate proportional to their respective half-lives (Quick, 1935, van den Besselaar, 1991, Poller, 2004). PT monitoring of VKA treatment is not standardized when expressed in seconds, or as a simple ratio of the patient plasma value to that of plasma from a healthy control subject, or as a percentage of diluted normal plasma. A calibration model, which was adopted in 1982 (Kirkwood, 1983, Marlar and Gausman, 2011), is now used to standardize reporting by converting PT ratio measured with the local thromboplastin into an INR, calculated as follows:

$$INR = (\text{patient PT} / \text{mean normal PT})^{ISI} \text{ or } \log INR = ISI \ (\log \text{observed PT ratio})$$

Where ISI denotes the International Sensitivity Index (ISI) of the thromboplastin used at the local laboratory to perform PT measurement. Though not validated, INR is more reliable than the unconverted PT ratio (World Health Organization Expert Committee on Biological Standardization, 1983) and its use is thus recommended during both the initiation and maintenance of VKAs. An obstacle to the safety and effectiveness of warfarin therapy is the poor quality of dose management in routine clinical practice, as it necessitates regular and diligent monitoring, which can be toilsome for patients and physicians (Melamed et al., 2011, Ageno et al., 2012). Patient education, an essential component in anticoagulation management, is often neglected as is time consuming for clinicians

and overwhelming for patients (Wofford et al., 2008). Adequate anticoagulant care with VKAs requires a system of patient education and careful data management to record and track INR values and to ensure patients are treated with anticoagulants for an appropriate period of time (Ageno et al., 2012). Thus, various approaches have been recommended to improve anticoagulant care. These approaches which include anticoagulation management services, point-of-care testing, computer decision support systems, patient self-testing and patient self-management (Ansell et al., 2001, Testa et al., 2012) is shown in Table 1.1.

Table 1.1 Recommended Methods of Improving Anticoagulation Care

Care Model	Operated by	Operations method
Anticoagulation management service	Physicians or; Nurses/ pharmacists with physician advisory	Systematically organized follow-up, structured education programme and specifically trained health personnel
Point of care testing	Nurses or; Pharmacists	Point of care testing (POCT) method is used as 1st alternative for blood testing in the healthcare facility; venous blood sampling only conducted when INR is beyond the POCT sensitivity.
Patient self-testing	Patients	POCT is carried out at home by patients to monitor their INR.
Computer decision support systems	General practitioners or; Nurses or; Pharmacists	A computer based dosing algorithm and protocol is used to manage the patients warfarin dosing.
Patient self-management	Patient with physician/ pharmacist	Selected patients are trained to self-monitor INR using POCT, interpret the result and making their own dosing decision.

1.3 Anticoagulation Management Models

Various models of care have been identified for the management of anticoagulation therapy (Ansell et al., 2001, Wilson et al., 2003). The primary models of anticoagulation therapy management are the usual medical care (UMC), the systematically organized anticoagulation clinic or anticoagulation management service (AMS) (managed individually or collaboratively by physicians, pharmacists or nurses) and patient self-management (PSM) (Ansell et al., 2008b, Rudd and Dier, 2010). Usual medical care usually consists of venepuncture blood draw for INR and supply of warfarin with no organized anticoagulation management method (Lafata et al., 2000). The patient self-testing management method usually warrants a home monitoring, which requires the patients to communicate their results to a clinic for advice on their warfarin dosing (Lafata et al., 2000). Whereas, anticoagulation clinics are designated to coordinate and optimize the delivery of therapy, manage warfarin dosing and provide continuous monitoring of patients' INR results, dietary factors, concomitant medication and interfering diseases (Wilson et al., 2003).

1.3.1 Anticoagulation Management in Malaysia

The Malaysian health care system consists of tax-funded and government-run universal services and fast growing private sector. Public health facilities provide about 82% of in-patient care and 35% of ambulatory care (Jaafar et al., 2013). The usual medical clinic (UMC) service that is used for the management of patients on warfarin in Malaysian government health facilities is a clinic which is run by rotational medical officers and physicians. Patients are seen on an appointment basis for their follow-up.

In order to provide comprehensive and focused patient care, the Pharmaceutical Service Division of the Ministry of Health Malaysia introduced the Medication Therapy Adherence Clinic (MTAC) as part of their ambulatory pharmacy services in 2004. The pharmacist-managed anticoagulation clinic or the Warfarin MTAC (WMTAC) initiated in the same year, but incorporated differently in different facilities. It is operated by pharmacists who provide drug therapy monitoring and education to patients. It aimed to improve patients' ability to successfully manage their disease condition and prevent debilitating symptoms together with reducing likelihood of medication errors (Ministry of Health Malaysia, 2010).

1.4 Problem Statement

In Malaysia, circulatory system diseases accounted for a total of 170, 933 or 7.55 % of the admissions in Malaysia in 2011, where it was within the top 10 principal reasons for admissions to Ministry of Health (MoH) hospitals (Abdul Rahman et al., 2012). Diseases of the circulatory system are one of the highest causes of mortality in 2011, 25.64 % in MoH hospitals. Latest data in a number of hospital -based studies indicate that VTE incidence is showing an increasing trend (Liew et al., 2012). Patients with VTE also had an increased risk of subsequent AF (Hald et al., 2014).

Prevalence of AF itself is increased by the natural history of progression with age and cardiovascular co-morbidities. The associated morbidity and mortality necessitate continued research into AF pathophysiology, pharmacologic and invasive therapies, and disease management strategies to achieve and sustain improvements in global AF burden (Kim, 2012). One of the goals of AF management is to prevent stroke with antithrombotic therapy (Camm et al., 2010) as thromboembolic stroke is one of the most feared complications associated with AF (Olesen et al., 2012).

The use of oral anticoagulants such as warfarin has been shown in clinical trials to reduce the risk of stroke by 64%; thus, warfarin therapy is widely accepted in patients with AF (Hart et al., 2007, Singer et al., 2008). In order to achieve maximal protection against stroke and to minimize bleeding complications, warfarin therapy must be tightly controlled and maintained within a narrow therapeutic index of International Normalized Ratio (INR) (Melamed et al., 2011). It is estimated that optimal anticoagulation could prevent 28,000 cases of stroke in the United States annually (Caro, 2004). The Pew Health Professions Commission of the United States of America reported that the systematic clinical management of patients on anticoagulation exclusively conducted by a pharmacist or implemented in collaboration with physicians or nurses has shown marked improvement (Santschi et al., 2011). Though available literature acknowledged the superior outcomes of anticoagulation management services over usual medical care in terms of anticoagulation control (Ansell et al., 2007b, Baker et al., 2009), caution is required due to the difference in the healthcare system, prescribing pattern and anticoagulation clinic model (Jowett et al., 2011). However anticoagulation management often is in the physicians' domain, where the choice of the management model is at the physicians discretion (Ansell et al., 2007b, Baker et al., 2009). With the rising number of patients needing anticoagulation therapy in Malaysia, effective anticoagulant management is critical for achieving good clinical outcomes. Therefore there is need to identify efficient models of anticoagulation care from the available practices in Malaysia.

World Health Organization (WHO) Programme on Cardiovascular Disease has included development of standards of care and cost-effective case management for cardiovascular diseases and global action to enhance capacity of countries to

meet the health care needs of effectively controlling the cardiovascular risks (WHO Programme on Cardiovascular Disease, 2014). Identifying a cost effective management method is affected by the variation in the population, the reference cost and events used, which may also vary across different countries (Jowett et al., 2011). Thus a cost analysis is needed to identify the cost of different models of anticoagulation care available in Malaysia and the cost to healthcare service provider on whole. Consequently a cost effectiveness analysis is needed to compare the available models of anticoagulation care in terms of the maximum gain in patients' health outcomes per unit of expenditure of the individual model. This would allow identifying the most cost effective system for the anticoagulation management and the control of cardiovascular risk factors in a Malaysian hospital.

1.5 Study Objective

The study aimed to compare the cost and efficiency of the warfarin mediation therapy adherence clinic (WMTAC) with usual medical clinic (UMC) in the management of chronic warfarin (more than six months) therapy patients in an ambulatory care setting in Kuala Lumpur Hospital (KLH). The efficiency is measured in terms of how the clinic converted its' resources into outcomes which is the anticoagulation control.

The specific objectives of the study are:

i) To compare the quality, anticoagulation control between the clinics in terms of mean percentage of time in international normalized ratio (INR) therapeutic range (TTR), calculated using the Rosendaal method

ii) To compare the costs of managing patients both in the WMTAC and UMC

iii) To compare the cost-effectiveness of anticoagulation management between the WMTAC and UMC

CHAPTER 2: LITERATURE REVIEW

2.1 Evaluation of Health Services

Health services include all services dealing with the diagnosis and treatment of disease, or the promotion, maintenance and restoration of health. They include personal and non-personal health services. Health services are the most visible functions of any health system, both to users and the general public. Service provision refers to the way inputs such as money, staff, equipment and drugs are combined to allow the delivery of health interventions. Improving access, coverage and quality of services depends on these key resources being available; on the way services are organized and managed, and on incentives influencing providers and users (World Health Organization, 2014). The Malaysian Patient Safety Goals stressed on clinical governance, where organizations are accountable in continually improving the quality of the health services (Ministry Of Health Malaysia, 2013b). Thus, monitoring patients on anticoagulation, a form of health service, needs quality assessment and constant improvement on how the services are organized or managed. In spite of the many advances in the treatment available to chronically ill patients, these patients do not always receive optimal care (Nolte and McKee, 2008, Norris et al., 2003, Renders et al., 2001). Most of this is because, healthcare delivery focuses on acute problems and rapid short term solutions, without effective treatment or the active involvement of the patients (Lenfant, 2003). In addition, system design has been identified as a fundamental barrier to quality improvement in the care delivery for the chronically ill patients (Cramm et al., 2014). The model by Wagner et al. (2001) on chronic care recommends quality improvement in chronic care delivery by providing examples of how health-care practices can shift fundamentally from acute and reactive care to care that is organized, structured, planned, patient

centred and proactive through a combination of effective multidisciplinary team care and planned interactions with patients (Cramm and Nieboer, 2013, Wagner et al., 2001).

Health intervention is a programme or strategy designed to produce behaviour changes or improve health status among individuals or an entire population. Interventions may include educational programmes, new or stronger policies, improvements in the environment, or a health promotion campaign. Interventions that include multiple strategies are typically the most effective in producing desired and lasting change (Missouri Department of Health and Senior Services, 2014). Evidence suggests that multi component interventions are required to change the processes and outcomes of chronic care delivery (Nolte and McKee 2008, Wagner, Austin 1996a, 1996b). As such, multiple strategies are now employed in a disease management programme (DMP) to ensure patients benefits from the effort taken by the healthcare provider. These programmes typically are multidisciplinary efforts to improve the quality and cost effectiveness of care for defined patient populations with chronic illness so that the results seen in one setting can be replicated in other settings. Disease management has emerged as potential strategy to enhance the quality of care received by patients suffering from one or more chronic conditions and cardiovascular diseases are the focus of many such ongoing and potential efforts. The term disease management programme refers to multidisciplinary efforts to improve the quality and cost-effectiveness of care for select patients with chronic illness. Economic pressures and the desire to provide better-quality care have compelled health care providers to examine and increasingly to employ disease management techniques (Faxon et al., 2004, Mosadeghrad, 2014).

Monitoring and evaluation of any programme or intervention is vital to determine whether it works, to help refine programme delivery and to provide evidence for continuing support of the programme (Global Road Safety Partnership, 2007). Types of evaluation include process evaluation, impact assessment and outcome evaluation. As for impact and outcome evaluations, a quantitative method would be appropriate; however it would depend on the aim and available budget (Global Road Safety Partnership, 2007).

In an era of fundamental concerns about the way that health care is provided to individuals and populations, there is a need for outcomes research to bridge the capabilities of the medical profession in the best interests of patients and society. Assumptions about what is achieved by the healthcare system should be tested by evidence of what actually results from the efforts (Krumholz, 2008). The themes of health outcomes research should be based on safety, effectiveness, equity, efficiency, timeliness, and patient-centeredness as key properties of high-quality health systems (Richardson et al., 2001).

Innovative strategies, once found to improve patient outcomes and reduce cost should be appropriately adopted. Outcomes research also addresses the gap between the research to reduce cost; and improve outcomes and the policies that exist to facilitate their adoption (Krumholz, 2008). Effectiveness research is at the core of outcomes research. The basic research questions addresses the gap between what can be achieved through an intervention or policy and what is actually accomplished. Seemingly brilliant interventions may fall short of their promise for many reasons. Characterizing and addressing these gaps is an important focus of effectiveness research. In view of the nature of the inquiry, much of this work is best performed in observational studies, witnessing the experience of patients in actual practice (Krumholz, 2008).

There are specific difficulties in defining, developing, documenting and reproducing complex interventions that are subject to variations (Campbell et al., 2000a), such as the anticoagulation clinics as it involves various health professionals, their skill mix, dosing algorithm and drug related problems. In order to evaluate health interventions, a review of previous studies which may have provided some empirical evidence for example, an intervention may have been found effective for a closely related condition or in another country with a different organisation of health care would be useful. Upon review, the information would be used to identify the type of interventions, study design where there is a need to assess the feasibility of the study and parameters measured. Trials of complex interventions are of increasing importance because of the drive to provide the most cost effective health care. Although these trials pose substantial challenges to investigators, the use of an iterative phased approach that harnesses qualitative and quantitative methods should lead to improved study design, execution, and generalizability of results. Iterative phase is when research is conducted in a non-sequential phase, where an exploratory research can be carried out before or after an observational study (Campbell et al., 2000a). In addition to evaluating the performance of the indicators, government funding agencies may require additional information for further roll out of a programme. An economic evaluation is able to demonstrate "value for money" and possible cost savings for the funding organization (Global Road Safety Partnership, 2007).

WMTAC is an anticoagulation management programme initiated by the Pharmaceutical Services Division, Ministry of Health as part their role in improving pharmaceutical care delivery. Disease management programme is identified as means of improving quality and efficiency of care for patients with chronic illness. Only limited number of published trials has documented the effectiveness of disease management, thus its

cost effectiveness is yet to be determined (Weingarten et al., 2002). The disease management programmes for anticoagulation such as the AMS in University of Mississippi Medical Centre has proven to have fewer subsequent hospitalizations and emergency department visits (Peden and Hood, 2002).

2.2 Effectiveness of vitamin K antagonist

AF is associated with a 1.5 to 1.9 fold higher risk of death, which is part due to strong association between AF and thromboembolic events (Wolf et al., 1991, Steinberg et al., 2015). In a meta-analysis, the relative risk reduction with VKA was highly significant and amounted to 64%, corresponding to an absolute annual risk reduction in all strokes of 2.7%. This reduction was similar for both primary and secondary prevention and for both disabling and non-disabling strokes. Many strokes occur when patients were not taking therapy or were sub-therapeutically anticoagulated. All-cause mortality was significantly reduced (26%) by adjusted-dose VKA versus control (placebo) (Camm et al., 2010).

Anticoagulation effectiveness usually are measured by i) clinical outcomes - clinical event rates (thromboembolic and haemorrhagic events) and ii) surrogate outcomes - proportion of INR values within target range or percent time in therapeutic range (TTR) (van Walraven et al., 2009, Samsa and Matchar, 2000). The event rates defined as number of thromboembolism and major bleeding events per patient year patient per year of follow-up are not operationalized in the same way in many studies. This is simple to calculate, but biased as it depends on the tendency of the physicians to perform repeated tests soon after an out of range INR (Samsa and Matchar, 2000). Though ultimately event rates are the outcomes of interest in comparison to the intermediate outcomes of TTR or the proportions of in-range test, even in high risk

populations, significant clinical events are relatively uncommon (Disertori et al., 2013, Samsa and Matchar, 2000). Sample size using event rates as the primary outcome need a much larger sample size than the sample size for a study using the TTR (Samsa and Matchar, 2000). Strong relationship between TTR and event rates are not only consistent with the pharmacokinetics of warfarin and consensus statements (Hirsh et al., 1998), but observed in large number of studies with different patient populations, target ranges and intensity measurement scales (Samsa and Matchar, 2000, Wan et al., 2008). As clinical outcomes need larger sample sizes and are not easily observed in trials, since it is highly coherent with TTRs, TTR should be used as the primary outcome while recording the clinical events as secondary outcomes (Holbrook et al., 2012).

In order to achieve maximal protection against stroke and to minimize bleeding complications, warfarin therapy must be tightly controlled and maintained within a narrow therapeutic index of INR values (Melamed et al., 2011). TTR is a standard quality measure of the use of warfarin (Samsa et al., 2000, Piccini et al., 2014). Therapeutic INR ranges for anticoagulation are 2.0 to 3.0 for prophylaxis and treatment of uncomplicated disease and 2.5 to 3.5 for patients with mechanical heart valves or failure with previous warfarin treatment, respectively, in accordance with the recommendations of the American College of Chest Physicians Consensus Conference on Antithrombotic Therapy (Hirsh et al., 2001b). Thus high anticoagulation control, expressed as the time spent within the therapeutic range (TTR), has a paramount effect on patient outcomes, reducing stroke events which lead to a USD 2.5 billion cost reduction (Melamed et al., 2011) and reducing mortality rates (Reynolds et al., 2004, Morgan et al., 2009). Stable INRs are defined based on consistent results for at least 3 months (Holbrook et al., 2012). Therapeutic INR range can be expressed in terms of

percentage of time spent by individuals in the range where INR value within target/ therapeutic INR range can be used to assess the thromboembolic or bleeding risk (Fitzmaurice et al., 2003). The expanded therapeutic INR range is defined as the therapeutic range ± 0.2 INR units (Wilson et al., 2003, JHS You, 2008) and is not considered clinically important and would not necessarily require a dosage adjustment (Wilson et al., 2003). As described by Rosendaal et al.(1993) , the percentage of patient-time spent in the TTR and expanded therapeutic INR range is estimated using linear interpolation between measured INR values (Rosendaal et al., 1993). This method allows the determination of the optimal effects of anticoagulation (Rosendaal et al., 1993) and takes into account actual days in target range and allows one to calculate INR specific incidence rates of adverse events (Schmitt et al., 2003). A TTR of more than 60% is a generally accepted threshold above which warfarin confers significant benefit compared with antiplatelet therapy (Connolly et al., 2008). The association between TTR and clinical outcomes was confirmed in a multi-level multivariable model, whereas in a separate model, a 10% increase in TTR independently predicted a 20% lower rate ($p < 0.001$) of the composite clinical outcome (e.g. stroke) among patients on warfarin (Van Spall et al., 2012, Apostolakis et al., 2012). Occurrence of adverse events, both thromboembolic and haemorrhagic events are used as a secondary outcomes measure (Lalonde et al., 2008).

2.3 Effectiveness of Anticoagulation Management Services (AMS)

Systematic outpatient anticoagulation services are systems of care designed to coordinate and optimize the delivery of anticoagulation therapy by evaluating patient-specific risks and benefits to determine the appropriateness of therapy; facilitating the management of anticoagulation dosages and prescription pick up or

delivery; providing ongoing education of the patient and other caregivers about warfarin providing ongoing education of the patient and other caregivers about warfarin and the importance of self-care behaviour leading to optimal outcomes; providing continuous systematic monitoring of patients, international normalized ratio results, diet, concomitant drug therapy, and disease states; and communicating with other healthcare practitioners involved in the care of the patient (Ansell et al., 1997, Chiquette et al., 1998, Bungard et al., 2009).

Meta-analysis evaluating the service settings on anticoagulation control demonstrated that the AMS is associated with somewhat better outcomes than those with usual care (van Walraven et al., 2006, Cios et al., 2009, Baker et al., 2009). Patients in AMS were spending 64 % of their treatment time in therapeutic range versus 51 % in usual care (Cios et al., 2009). A meta regression of six studies compared usual care patients to AMS, where usual care patients were spending 11% (95%CI = 2 - 20%) less time in therapeutic INR range (Baker et al., 2009). Many non-randomized studies have reported better outcomes in patients when anticoagulant therapy is managed by an AMS than UMC. UMC reported major haemorrhagic rates ranging from 2.8 to 8.1% per patient year of therapy, whereas AMS reported rates ranging from 1.4 to 3.3% (Ansell et al., 2008a).

A meta-analysis of 24 studies, consisting of randomized control trials (RCTs), non-RCTs and cohort studies, a pharmacist managed AMS in comparison to clinics managed by other healthcare personnel, showed improved care, in terms of anticoagulation control, and reduced thromboembolic and haemorrhagic events. In a random-effect meta-analysis of randomized controlled trials, the group that received pharmacist-supported warfarin therapy had statistically significant improvements in the prevention of total bleeding [RR, 0.51; 95% confidence interval (CI) 0.28 - 0.94].

However, the effects on major bleeding [RR, 0.64; 95% CI, 0.18-2.36], thromboembolic events [RR, 0.79; 95% CI, 0.33-1.93], mortality from all causes [RR, 0.93; 95% CI, 0.41-2.13] and mortality from warfarin-related causes [RR, 0.65; 95% CI, 0.18-2.42] were not significant (Saokaew et al., 2010). Studies have shown that pharmacist administered anticoagulation management service is an effective methods for the management of anticoagulation, in terms of greater control of INR, reduced thromboembolic complications and decreased length of hospital stay in comparison to UMC (Bungard et al., 2009, Donovan et al., 2006). However, studies followed -up for less than 6 month had a tendency to observe higher bleeding events and lower thromboembolic events. The study design of future trials were recommended to be 6 months or more to capture all dimensions of effects on clinical outcomes (Saokaew et al., 2010).

The anticoagulant control was significantly greater during AMS care compared with UMC; patients were in the target INR range 66.5% versus 48.8% of the time, respectively [95% confidence interval [CI] 13.4%–22.0%; $p < 0.0001$]. The relative risk of a thromboembolic event in UMC care was 17.6 [95% CI 6.0–51.9; $p < 0.0001$], while the relative risk of a haemorrhagic event before AMS care was 1.6 [95% CI 0.7–3.7; $p = 0.25$] (Bungard et al., 2009). Another meta-analysis identified that specialty pharmacy clinic patients spent 71% of their treatment time in therapeutic range (Baker et al., 2009). A study comparing usual medical care, nurse managed clinic and pharmacist managed clinic identified the pharmacist managed AMS yielded the lowest rates of hospitalization and emergency department visits, with hospitalizations reduced by 56% versus nurse-managed service and 61% versus usual care ($p < 0.01$). In addition, the pharmacist-managed service incurred a lower of cost United States Dollars (USD) 141, 277.34 in hospitalization costs and USD 10, 183.76 in emergency department visit

costs versus the nurse-managed service and USD 95, 579.08 in hospitalization costs and USD 5, 511.21 in emergency department costs compared with the usual care model (Rudd and Dier, 2010). The anticoagulation management service varied in terms of the health personnel managing the patients and their level of involvement and the management model and its' cost (Nutescu et al., 2013).

2.4 Cost of Anticoagulation Management Services

Costs are important attributes in economic evaluations, thus appropriate costs and benefits must be considered. To be of maximum value, economic evaluations must be flexible enough to take into account local variations in resource costs and the estimation of cost has to be a comprehensive approach (Haycox and Walley, 1997). Cost definitions in the current review were from various currencies of various years. First, costs expressed in various currencies and base years were converted to USD in year 2010 using the purchasing power parity. Second, all the relevant costs were then converted to International Dollars (Int. $) of the same year. A summary of clinical outcomes and cost of anticoagulation therapy management is shown in Table 2.2.

An earlier study of the cost of anticoagulation management compared the AMS and UMC in terms of adverse events noted that the savings in terms of prevention of subsequent morbidity was USD 211, 776 per year for all patients receiving warfarin in the AMS (Garabedian-Ruffalo et al., 1985), whereas another study noted that AMS in comparison to UMC produced a savings of USD 132, 086 annually in expenses for warfarin related hospitalizations and emergency department visits (Chiquette et al., 1998). Though the costs of AMS are available based on adverse events and consultation cost, little available evidence identifies the details of the costing method (Aziz et al., 2011, Bjorholt et al., 2007, Menzin et al., 2005, Anderson, 2004, Schulman et al., 2010,

Chan et al., 2006). One study costed only the anticoagulant medications and its' dispensing fee, INR test and the laboratory fee and clinical pharmacy specialist for the analysis (Anderson, 2004). Another study in the USA identified only the monitoring cost as the cost of anticoagulation clinic (Menzin et al., 2005). A Swedish study conducted a detailed analysis of the monitoring costs, however the cost of complication was excluded (Bjorholt et al., 2007). Another Canadian study identified the professional time spent by each healthcare personnel and also provided both provider and patient perspective costs, but this study avoided the costing of adverse events too (Schulman et al., 2010). A study in the Asian region found that the cost per patient per month in the pharmacist-managed group (USD 76 (SD = 95)) was lower than in the physician-managed group (USD 98 (SD = 158)) ($p < 0.001$). The limitation in this study was the assumption of the major component of the cost, the clinic cost, that the pharmacy managed clinic costs 50 % lower than the usual medical clinic (Chan et al., 2006). Another study in the United States of America detailed the anticoagulation clinic cost analysis using the top down method and concluded that the hospitalization cost per patient per six months in the AMS was USD 401 in comparison to UMC which costs USD 1, 929 (Aziz et al., 2011). A newer study found that the mean 12 month costs of managing 136 patients were USD 18, 248 (SD = 24, 184) (Hulvershorn, 2014). Variations in the costing method and the type of resources used were noted in all the studies. Some used actual treatment cost, some used estimates of treatment and adverse event costs and some used only adverse event costs, whereas others used the cost of all the resources used for the clinic (Chan et al., 2006, Garabedian-Ruffalo et al., 1985, Chiquette et al., 1998, Aziz et al., 2011). A time-motion analysis would be necessary to validate the time estimates in a study (Anderson, 2004).