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Mai Alhazami

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**COST EFFECTIVENESS OF WARFARIN IN ANTICOAGULANT CLINIC AFTER
INTRODUCTION OF DABIGATRAN FOR STROKE PREVENTION IN ATRIAL
FIBRILLATION PATIENTS IN THE UNITED STATES**

A thesis submitted in partial fulfillment of the requirements for the degree of Masters Science in
Pharmaceutical Sciences at Virginia Commonwealth University.

By

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March 2015

Dedication

I dedicate this work to my beloved Mom, to my dearest husband, and my family; I couldn't have done this without your great support.

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List of Abbreviations

AAWP:	Average Average Wholesale Price
ACA:	American College of Cardiology
AF:	Atrial Fibrillation
AHA:	American Heart Association
ARISTOTLE:	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
AWP:	Average Wholesale Price
CAD:	Coronary Artery Disease
CDC:	Centers of Disease Control
CHEERS:	Consolidated Health Economic Evaluation Reporting Standards
CI:	Confident Interval
CrCl:	Creatinine Clearance
DRG:	Diagnosis-Related Group
DVT:	Deep Vein Thromboembolism
ECH:	Extracranial Hemorrhage
ER:	Emergency Room
GI:	Gastrointestinal
GPPC:	Generic Product Packing Code
HCUP:	Healthcare Cost and Utilization Project

HRS:	Heart Rhythm Society
ICD-9:	International Classification of Diseases Ninth Revision
ICER:	Incremental Cost Effectiveness Ratio
ICH:	Intracranial Hemorrhage
INR:	International Normalized Ratio
IS:	Ischemic Stroke
LL:	Lower Limit
LVEF:	Left Ventricular Ejection Fraction
MI:	Myocardial Infraction
MPR:	Medication Possession Ratio
NB:	Net Benefit
NMB:	Net Monetary Benefits
NOACs:	New Oral Anticoagulants
NYHA:	New York Heart Association
PE:	Pulmonary Embolism
QALYs:	Quality Adjusted Life Years
RELY:	Long-Term Anticoagulation Therapy
ROCKET-AF:	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RRR:	Relative Risk Reduction

SD:	Standard Deviation
SE:	Systematic Embolism
SE:	Standard Error
SPORTIF:	Stroke Prevention using Oral Thrombin Inhibitor in atrial Fibrillation
TIA:	Transient Ischemic Attack
UL:	Upper Limit
UPMC:	University of Pittsburgh Medical Center
VKA:	Vitamin K Antagonist
WTP:	Willingness To Pay

Abstract

COST EFFECTIVENESS OF WARFARIN IN ANTICOAGULANT CLINIC AFTER INTRODUCTION OF DABIGATRAN FOR STROKE PREVENTION IN ATRIAL FIBRILLATION PATIENTS IN THE UNITED STATES

By **Mai S. Alhazami, BS.**

A thesis submitted in partial fulfillment of the requirements for the degree of Masters Science in Pharmaceutical Sciences at Virginia Commonwealth University.

Virginia Commonwealth University, 2015.

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OBJECTIVES: To assess cost effectiveness of anticoagulant clinics after FDA approval of New Oral Anticoagulants (NOACs) for preventing ischemic stroke in Atrial Fibrillation (AF) patients in the United States. **METHODS:** A decision tree was built to compare cost and effectiveness of 150mg dabigatran twice a day to adjusted dose of warfarin within anticoagulation clinic. The analysis was for one year using a societal perspective. The population in this analysis was a cohort of AF patients, ≥ 65 years old, with a CHADS₂ score >2 , and no contraindication to anticoagulation. **RESULTS:** The base case analysis showed that changing from warfarin with anticoagulant clinic to dabigatran without monitoring resulted in an additional \$82,793 per QALY saved. Sensitivity analyses found that the model was sensitive to utilities of patients on warfarin. **CONCLUSION:** This study showed that substituting dabigatran for warfarin in this population was not within acceptable willingness to pay values for new therapy.

Chapter I: Introduction

Section 1.1: Background

Atrial Fibrillation (AF):

Atrial fibrillation (AF) is considered one of the most common sustained cardiac arrhythmias in clinical practice. Statistics show that it affects more than 2.2 million Americans.¹ One of the most common complications of AF is Ischemic Stroke (IS). Approximately 15 percent of strokes are a result of AF.² Independently, AF increases the risk of IS 5 fold among all ages.³

Risk of IS increases in AF patients with advancing age, hypertension, heart failure, diabetes mellitus, history of previous stroke or Transit Ischemic Attack (TIA),vascular disease, and female sex.³ According to the latest report of Heart Disease and Stroke Statistics, the percentage of strokes related to AF increases from 1.5% at 50 to 59 years of age to 23.5% at 80 to 89 years of age.³ Previous stroke or TIA is considered a strong independent predictor of stroke among AF patients with a relative risk of 1.9 to 3.7.⁴ AF patients with hypertension and diabetes mellitus have a relative risk of stroke of 1.7 compared to non- hypertension and non-diabetics patients.⁴ AF patients with cardiac failure have relative risk of 1.4 for stroke.⁴

There are several indexes that help to estimate stroke risk in patients with AF. The most commonly used index is CHADS₂ score which is a validated scheme for stratifying stroke risk in AF patients.^{1,5} The CHADS₂ score is a number from 0 to 6, where 0 is lowest risk and 6 is

highest risk. Stroke risk is calculated depending on the following risk factors: congestive heart failure history, hypertension history, age ≥ 75 , diabetes mellitus, and history of stroke or TIA symptoms. Presentation of each risk factor adds 1 point to the total CHADS₂ score with the exception of history of a previous stroke which adds 2 points.⁶

AF patients who have experienced a stroke have higher mortality rates.¹ Moreover; stroke can affect a patient's quality of life as it may cause different types of disabilities, such as vision impairment, inability to walk without assistance, cognitive deficits, and depression. Stroke complications are associated with socioeconomic burden on both individuals and the healthcare system. In the United States, the mean lifetime cost per patient with an IS has been estimated at \$140,048.¹ Inpatient care is considered the main cost driver, accounting for 70% of costs in the first year after a stroke.¹ After the first year of survival, costs of lost productivity and rehabilitation can be significant. According to the U.S. Centers of Disease Control (CDC), the estimated direct and indirect cost associated with stroke in the US 2010 was \$53.9 billion dollars.⁷

Warfarin

Warfarin has long been the most common treatment for preventing stroke in AF patients at higher risk for stroke (i.e., CHADS₂ score ≥ 1). Warfarin is a Vitamin K Antagonist (VKA). The synthesis of clotting factors II, VII, IX, and X and the anticoagulant proteins C and S depend on vitamin K, and warfarin acts as an anticoagulant by antagonizing vitamin K and thus inhibits synthesis of these clotting factors.⁸ Warfarin has been used since the 1940's.⁹ Studies have shown it to be effective in preventing stroke in AF patients and relatively inexpensive.⁸ However, warfarin is under-utilized in the general practice. It is estimated that almost one third to one half

of all eligible AF patients do not receive warfarin.⁹ According to the Agency of Health Care Policy and Research, underuse of warfarin in AF patients results in 40,000 preventable strokes in the US each year at a cost of \$600 million annually.¹⁰

A major reason for the sub optimal use of warfarin is its narrow therapeutic range and potential for negative side effects. Effective treatment with warfarin requires patients to be maintained within a narrow International Normalized Ratio (INR) range of 2 to 3. Maintenance of that range requires continuous monitoring and potential dosing changes due to pharmacokinetic properties of warfarin. The difficulty of warfarin dosing and monitoring is complicated by many drug and food interactions. For example, anticoagulation effects of warfarin may decrease when taken with food rich in vitamin K such as broccoli, asparagus, or cabbage. Also, warfarin metabolism involves CYP450 isozymes, so concomitant administration of any CYP450 inducers like phenytoin or cigarette smoking may decrease the effect of warfarin. Inhibitors like acyclovir may increase effect of warfarin. These drug and food interactions may influence the pharmacokinetics of the drug in the body, or they may worry patients and reduce their adherence behavior.¹¹ Inadequate dosing of warfarin can increase the potential for stroke, while overdosing increases risk of bleeding.

Anticoagulation Clinics

In 1996, Rosendaal reported that extensive monitoring of oral anticoagulation therapy by individuals in specialized anticoagulation clinics improves the effectiveness and reduces complications associated with oral anticoagulation therapy.¹⁰ The American College of Chest

Physicians emphasized on the important role of anticoagulant clinics in improving quality of care of patients on warfarin treatment.¹⁰

The anticoagulant clinic offers various services in order to enhance health outcomes of patients on anticoagulant treatment. It involves conducting necessary laboratory tests, continuous follow up for patients on anticoagulant treatment, and patient's education.¹² These activities may differ between one clinic to another depending on the setting used and clinical standards. The anticoagulant clinics are usually delivered by pharmacists or nurses and considered the most common service offered by outpatient pharmacists.¹³ In the United States most of the anticoagulant clinics are run by pharmacists. It has been estimated that approximately 60% of anticoagulant clinics in US are managed by pharmacists.¹⁴

Studies have shown that the pharmacist-managed anticoagulant clinics are cost effective compared to usual care. Elaine Chiquette et al. concluded that anticoagulation control is improved by the pharmacist run anticoagulant clinics and saved \$162,058 per 100 patients annually.¹⁰ Despite the effectiveness of these clinics, most warfarin patients are not followed by anticoagulant clinics.¹⁵ Only 30-40% of AF patients on warfarin attend the anticoagulant clinic.¹⁴

New Oral Anticoagulation Medications

In recent years, novel anticoagulant agents have entered the US market with the potential to dramatically impact anticoagulation clinics and other anticoagulation services. These medications are Dabigatran, Rivaroxaban, and Apixaban.

Dabigatran was the first new oral anticoagulation agent approved by FDA in 2010. While warfarin works by inhibiting of first step in the coagulation cascade, dabigatran works by inhibiting a second step (figure 1.1). Dabigatran etexilate is a reversible direct thrombin inhibitor. It inhibits coagulation by preventing thrombin-mediated effects including cleavage of fibrinogen to fibrin monomers, activation of factors V, VIII, XI, XIII and inhibition of thrombin-induced platelet aggregation.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial investigated the efficacy and safety of dabigatran (110mg twice daily, 150mg twice daily) compared to an adjusted dose of warfarin in 18,113 AF patients for a period of 2 years.¹⁶ Based on this study, dabigatran 150mg was found to be better in preventing strokes compared to warfarin ($P < 0.001$), while the 110mg dose was similar to warfarin ($P < 0.35$). However regarding the safety profile dabigatran 150 mg had higher risk for Gastrointestinal (GI) bleeding ($P < 0.001$) compared to warfarin, while 110mg was similar to warfarin ($P = 0.43$). Both doses showed significantly lower Intracranial Hemorrhage (ICH) compared to warfarin ($P < 0.001$). For the risk of developing Myocardial infarction (MI), dabigatran 150 mg showed higher risk compared to warfarin ($P = 0.048$), while 110 mg had similar risk as warfarin ($P = 0.07$).

Based on these results, only the 150 mg dose was approved by FDA. In this study dabigatran has not been studied in patients with severe renal impairment, as patients with a Creatinine Clearance (CrCl) less than 30 mL/min were excluded from RE-LY. FDA approved a dose of 75 mg of dabigatran for patients with renal impairment. Dabigatran is approved for stroke prevention in

AF patients, treatment and prevention for deep vein thrombosis (DVT) and pulmonary embolism.

Recently on May 2014, FDA had reported the results of a study conducted by them on more than 134,000 Medicare patients.¹⁷ In this study they measured the safety and effectiveness profile of dabigatran compared to warfarin in almost similar population as the RELY trial. Their findings were consistent with the RELY trial, except for probabilities of developing MI with dabigatran 150 mg and warfarin. In contrast to RELY trial, this study had reported that there is no significant difference in the probabilities of developing MI between two treatment options.

Following dabigatran, FDA approved rivaroxaban in 2011 as a treatment to prevent stroke in AF patients. Rivaroxaban is a factor Xa inhibitor, and it prevents stroke by inhibiting platelet activation and fibrin clot formation via direct, selective and reversible inhibition of factor Xa.

The efficacy and safety of rivaroxaban were evaluated in Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial.¹⁸ It compared rivaroxaban 20 mg once a day (reduced to 15 mg a day for patients with a CrCl of 30 to 49 mL/min) to an adjusted dose of warfarin in 14,269 patients with AF for an average period of 1.6 years. Rivaroxaban was shown to be similar to warfarin in preventing stroke ($P = 0.12$) and MI ($P = 0.12$). It was found to have superior effect in reducing ICH compared to warfarin ($P = 0.02$). However, for GI bleeding, rivaroxaban had significantly higher risk compared to adjusted dose of warfarin ($P < 0.001$).

A once daily dose of 20mg of rivaroxaban was approved by FDA for patients with CrCl >50 mL/min and a 15mg once daily dose for patients with a CrCl between 15–50 mL/min to prevent stroke in AF patients. Moreover, FDA approved rivaroxaban for preventing stroke for post-operative thrombophylaxis Deep Vein Thromboembolism (DVT), and Pulmonary Embolism (PE).

Apixaban is a factor Xa inhibitor approved by FDA in 2013 for stroke prevention in AF patients. It prevents stroke with a similar mechanism of action to rivaroxaban.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, the efficacy and safety of apixaban was assessed.¹⁹ Apixaban was found to be superior to warfarin for preventing stroke ($P = 0.01$). GI bleeding and MI was similar to warfarin ($P= 0.37$ for both events). Risk of ICH was significantly lower in apixaban patients compared to warfarin ($P<0.001$). Apixaban 5mg twice daily was approved by FDA to prevent stroke in patient with AF, treatment and prevention for DVT and pulmonary embolism.

A 2012 study looking at the potential for switching warfarin to new oral anticoagulants (NOACs) found that more than 60% of patients in Johns Hopkins anticoagulation clinics could do so.²⁰

Despite the effectiveness and safety of NOACs compared to warfarin, they face challenges to replace warfarin. NOACs are considered to have higher acquisition cost compared to warfarin. NOACs are also mainly excreted by kidney and may not be appropriate in renal impairment

unlike patients treated with warfarin. Apixaban may be a relatively safer option with renal impairment as it is excreted via multiple pathways. Furthermore, there is little evidence of the long term effect of NOACs, and there is no antidote to reverse effect of these drugs, unlike warfarin. So adoption and usage for NOACs may depend heavily on its perceived economic value.

Section 1.2: Objectives

1. Calculate costs and Quality Adjusted Life Years (QALYs) associated with treatment of AF patient with dabigatran 150mg BID and adjusted dose of warfarin within pharmacist-managed anticoagulant clinic.
2. Build a decision tree model with the 2 therapeutic approaches and map out associated outcomes.
3. Evaluate the cost effectiveness of dabigatran 150mg BID compared to adjusted dose of warfarin within pharmacist-managed anticoagulant clinics.

Section 1.3: Rationale

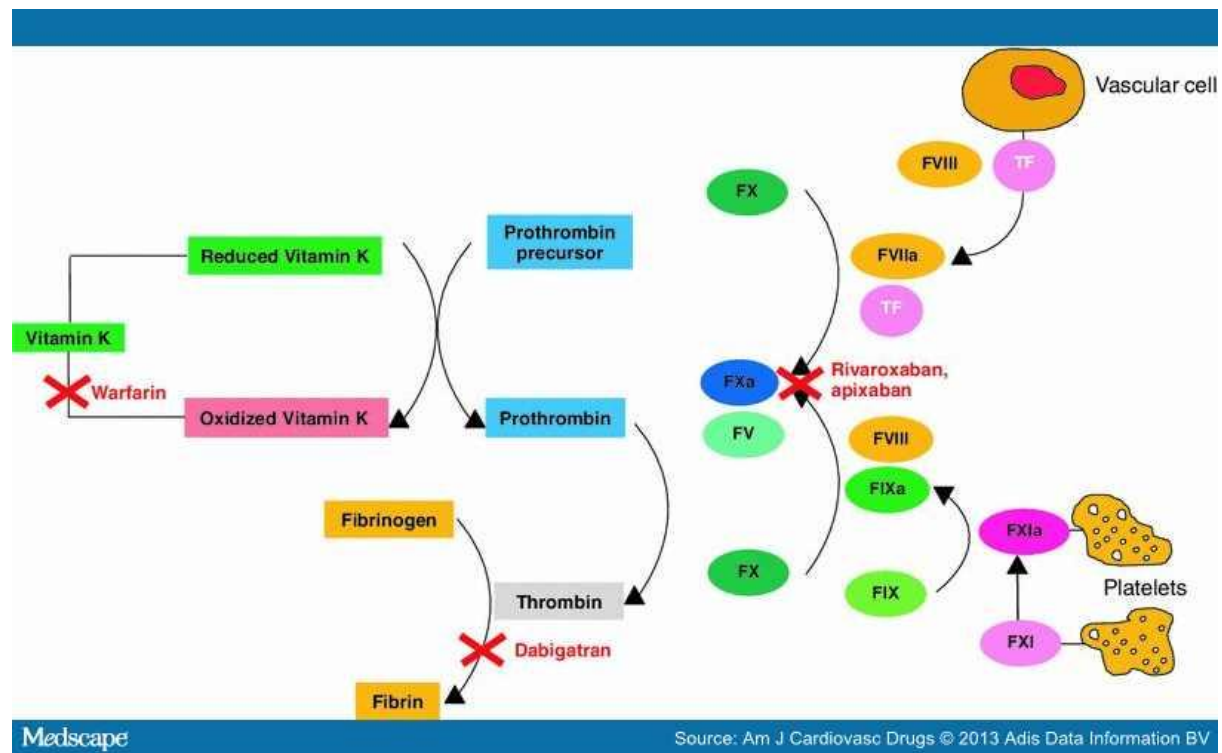
Studies addressing the cost effectiveness of NOACs compared to warfarin have used similar models and outcome measurements. Most of the previous studies built Markov model with almost similar health states and time horizons. Moreover, they only used single source as a reference for their probabilities.

Furthermore, there were limited studies that account for INR control level in their cost effectiveness analysis. There is lack of studies that directly assessed cost effectiveness of NOACs to warfarin treatment within anticoagulant clinic settings.

Because the dabigatran was the first NOACs introduced into the US market and so it is assumed to be well utilized, it was chosen in the present analysis to represent NOACs. Moreover there are more available data regarding dabigatran compared to other NOACs.

Based on the available literature, this is the first study that compared directly between dabigatran and warfarin treatment within pharmacist-managed anticoagulant clinic. This study will enable us to answer the question about the future of these clinics after introduction of NOACs into the market, especially as they do not require monitoring like warfarin. Finally in this study, we tried to obtain probabilities data from a secondary source and test it in the sensitivity analysis.

Figure 1.1: Mechanism of action of oral anticoagulants²¹



Chapter II: Literature review and discussion of decision analysis

Section 2.1: Literature review

In order to assess cost effectiveness of NOACs compared to warfarin in usual care setting and anticoagulant clinic, we need to evaluate what is there in the literature. This was done in two steps. First, studies that looked at the effectiveness and cost effectiveness of warfarin in usual care versus anticoagulant clinic were evaluated. Based on the literature, we hypothesized that anticoagulant clinic is more cost effective compared to usual care.

Then, the effectiveness and cost effectiveness of NOACs versus warfarin in anticoagulant clinic were assessed. This part was done under the assumption that patients treated with NOACs do not need a follow up in an anticoagulant clinic. According to study done by Lee, et al. that looked at adherence rate and clinical outcomes of dabigatran in anticoagulant clinic versus usual care, they concluded that neither the adherence rate nor the therapeutics outcomes differed between patients in the two groups.²² So this study can support the assumption that NOACs do not required monitoring by anticoagulant clinic in order to improve patient outcomes.

Section 2.2: Systematic literature review on the effectiveness and cost effectiveness of pharmacist-managed anticoagulant clinic compared to usual care

A systematic literature review was conducted on October 2014 using PubMed/MEDLINE, CINAHL, ECONLIT and IPA. The search terms were combinations of: ("Warfarin" AND "Anticoagulant clinic") AND ("Cost" OR "Costs"), ("Anticoagulant clinic" AND "pharmacy"), ("pharmacist managed Anticoagulant clinic"), ("pharmacist managed Anticoagulant service"). Titles and abstracts from search result articles were screened for using the following inclusion criteria and exclusion criteria:

Inclusion criteria:

1. Assess cost-effectiveness of pharmacist-managed anticoagulant clinic.
2. Assess effectiveness of pharmacist-managed anticoagulant clinic.
3. Published in English.
4. Addressed patient with Atrial Fibrillation (AF).
5. Abstract is available.

Exclusion criteria:

1. Studies not conducted in the United States.
2. Studies compared aspirin or heparin to warfarin.

The search of the databases revealed a total of 1,293 articles. After eliminating duplicates and applying inclusion and exclusion criteria, 57 research articles remained.²³⁻⁷⁹ Out of these 57 articles, 6 articles were chosen to be discussed as they were the most recent studies, and had more updated information. Moreover, these chosen articles were the most relevant to the

inclusion criteria, while the other articles were either focusing only on the cost of anticoagulant clinic compared to usual care or did not include a comparison group.^{29,31,40,54,61,72}

Literature Summary

Most articles revealed by the literature review looked at the effectiveness of an anticoagulant clinic compared to usual care for patients receiving warfarin therapy. Most did not indicate a specific diagnosis for treated patients; including patients with AF and other indication who are on warfarin.

Five articles compared the effectiveness of anticoagulant clinics compared to usual care, and 1 article was a cost-effectiveness analysis of an anticoagulant clinic compared to usual care (Tables 2.1 and 2.3).

One of the 5 effectiveness articles, by Nichol et al. (2008), specified AF patients.⁶¹ The study was a retrospective observational cohort that used claim data of a physician group practice. Using International Classification of Diseases Ninth Revision code (ICD-9), they identified AF patients on warfarin and having more than 1 INR test between March 2001 to March 2004. Patients were excluded if they had more than a one year gap between 2 INR tests.

Usual care in this study consisted of patients treated by a care team which included primary care physicians and nurses but which had no standardized protocol of care. Patients treated in the anticoagulant clinic were managed by similar care team guided by a standardized warfarin management protocol. Any patients treated with warfarin were eligible to be referred to an anticoagulant clinic. Patients included in this study were either treated with usual care or attended an anticoagulant clinic, with no crossover between two groups.

The outcome measures used to assess quality were time spent in therapeutic range (INR 2-3) and time to first occurrence of major bleeding or stroke. A t-test compared time spent in therapeutic range between the 2 groups, and a Kaplan Meier survival analysis compared rates of bleeding or stroke.

The study found that the 351 patients in the anticoagulant clinic spent significantly more time in therapeutic range compared to the 756 patients in the usual care group. Rates of major bleeding and stroke were lower, but not statistically so, in the anticoagulant clinic group compared to usual care.

Some studies in the literature have assessed the effectiveness of anticoagulant clinics managed by pharmacists compared to usual care; but are not specific to AF patients (i.e. several indications of warfarin). Chiquette E, et al. compared 142 newly treated anticoagulant patients in usual care to 176 newly treated patients in an anticoagulant clinic.³¹ The outcome measures were anticoagulant control (time within therapeutic range), bleeding, thromboembolism events, and cost of hospitalization and emergency room (ER) visit. Based on the results of this study, patients treated in an anticoagulant clinic had lower rates of significant bleeding, major to fatal bleeding, thromboembolism events, and significantly lower annual rates of hospitalization and ER visits related to warfarin treatment.

A recent article by Hall, et al. in 2011 evaluated differences in health care expenditures and the clinical outcomes between usual care and a pharmacist-managed anticoagulant clinic.⁴⁰ Using

data from the University of Pittsburg Medical Center (UPMC), they reviewed 175 patients in each group of which 60% were AF patients. They looked at cost, medical outcomes, and patient compliance. Direct, overall medical and operational costs were included when measuring costs. The therapeutic outcomes were adverse events, percentage of INR within therapeutic range, time spent within therapeutic range, and ER visits. Patient compliance was measured by calculating the Medication Possession Ratio (MPR). Similar to Chiquette E, et al., authors reported that patients in the anticoagulant clinic had significantly higher therapeutic INR rates and spent longer time in this range compared to usual care. Anticoagulant clinic patients experienced fewer adverse events and ER visits.

Locke, et al. (2005) explored the difference in adverse events related to warfarin treatment in pharmacist-managed anticoagulant clinics and usual care.⁵⁴ Using a before and after research design, 420 patients in a community hospital outpatient anticoagulant clinic were discontinued from an anticoagulation clinic program and assigned to usual care. Authors found that patients discontinued from the clinic experienced significantly more adverse events related to warfarin treatment compared to those treated with pharmacist-managed anticoagulant clinic.

One study was less compelling for the benefits of an anticoagulation clinic in managing warfarin therapy. It compared patient outcomes in pharmacist managed anticoagulant clinic (n=41) to usual care (n=75).²⁹ In contrast to previous studies, no statistical significant difference was detected in the rate of adverse events or ER visits between two groups, although the percentage of anticoagulant clinic patients within therapeutic ranges was significantly higher. The absent of statistical significant can be due to the small sample size in each groups.

A study by Sullivan et al. evaluated the cost-effectiveness of a pharmacist-managed anticoagulant clinic compared to usual care for AF patients with high risk of stroke.⁷² The analysis used a semi-Markov model to compare usual care and clinic services using a societal perspective. A cohort of AF patients similar to the SPORTIF (Stroke Prevention using Oral Thrombin Inhibitor in atrial Fibrillation) III and V trials was used.

They found that anticoagulation monitoring services improved effectiveness by 0.057 QALYs and cost \$US2100 less, and therefore dominated usual care. Their sensitivity analysis found that the results were sensitive to the risk of all strokes and systemic embolic events associated with usual care, but were robust with other input variables. Moreover, a Monto Carlo simulation showed robust results in favor of anticoagulation management services dominating usual care in 91% of possible circumstances.

In summary, the literature suggests that AF patients receiving warfarin and managed in anticoagulation clinics have better therapeutic control over their INRs, less adverse events, fewer health care visits for warfarin related causes, and lower costs of care.

Section 2.3: Systematic literature review on the effectiveness and cost effectiveness of NOACs compared to warfarin in pharmacist-managed anticoagulant clinic

Systematic literature review was conducted on October 2014. PubMed/MEDLINE, CINAHL, ECONLIT and IPA were used for literature search with combination of the search terms:

("Warfarin") AND ("Anticoagulant" OR "Anticoagulants") AND ("Cost" OR "Costs"),

("Warfarin") AND ("Apixaban" OR "Dabigatran" OR "rivaroxaban") AND ("Cost" OR "Costs"),

("Anticoagulant clinic") AND ("NOACs" OR "Apixaban" OR "Dabigatran" OR "rivaroxaban").

Titles and abstracts were first screened for inclusion criteria and exclusion criteria. The inclusion and exclusion criteria that were applied are defined as the following:

Inclusion criteria:

1. Assess effectiveness of NOACs compared to warfarin.
2. Assess cost-effectiveness of NOACs compared to warfarin.
3. Published in English.
4. Addressed patient with AF.
5. Abstract is available.

Exclusion criteria:

1. Studies not conducted in the United States.
2. Studies compared NOACs with aspirin or heparin.

A search of the 4 databases revealed a total of 2,989 articles. After eliminating duplicates and applying inclusion and exclusion criteria, a total of 21 research articles were found.^{22,80-99} Out of 21 articles 13 articles were chosen to be discussed, as they were most relevant to the search criteria, and available.^{80,83,84,87,88,90-96,98}

Literature Summary

Thirteen articles were identified as relevant to this research. Five compared effectiveness and safety of NOACs to warfarin (Table 2.2).^{80,87,90,96,98} The 8 remaining articles assessed cost effectiveness of NOACs compared to warfarin.^{83,84,88,91-95,97}

One of the 5 effectiveness studies compared all three NOACs to warfarin.⁹⁸ In this study, the authors searched a clinical trials database and found 3 large clinical trials comparing NOACs to warfarin (ARISTOTLE for apixaban, RELY for dabigatran, and ROCKET-AF for rivaroxaban).⁹⁸ Almost similar inclusion/exclusion criteria were used for all three trials. Efficacy was determined by rates of developing stroke or Systemic Embolism (SE). Safety was measured in the RELY and ARISTOTLE studies by major bleeding events, while the ROCKET-AF trial measured major and non-major bleeding. The analysis indicated that there were no significant differences in efficacy between the 3 NOACs. Regarding safety profile, apixaban showed a significantly lower rate of major bleeding compared to dabigatran and rivaroxaban. No significant difference between the 3 NOACs was found in all-cause mortality. Overall, the 3 NOACs produced almost similar effects in reducing stroke in AF patients with higher risk of stroke, however, the apixaban was the safest.

The remaining 4 studies compared the effectiveness of apixaban to warfarin by using the data from the ARISTOTLE trial. Amin et al. estimated the real world rate of stroke and bleeding of apixaban in AF patients.⁸⁰ Authors used a Medco claims database to identify AF patients with CHADS₂ score ≥ 1 and treated with warfarin. They calculated rate of stroke and bleeding associated with warfarin. By using the Relative Risk Reduction (RRR) from ARISTOTLE trial,

they estimated events that can be avoided if apixaban was used instead of warfarin in the real world. The analysis showed that event rates associated with warfarin were higher in the real world compared to ARISTOTLE trial, and the clinical benefit of apixaban might be greater in the real world compared to a clinical trial. However, this is an extrapolation of results from the clinical trial and so may not reflect the true apixaban effect in the real world practice. Further studies using real world data are needed.

In addition to these articles, the literature review revealed 8 studies that evaluated cost-effectiveness of NOACs compared to warfarin (Table 2.3).^{83,84,88,91-95,97} There were a lot of similarity in the method and model building in the 8 studies. They all used Markov models with almost similar health states: well, ICH, Extracranial Hemorrhage (ECH), IS, MI, minor bleeding, and death. Cost/QALY was the outcome measure in all of the 8 studies. The analysis was either done from societal perspective^{83,88,91-93} or US payer/Medicare perspective^{84,94,95,97}. The input transition probabilities were obtained mainly from the three major clinical trials (ARISTOTLE, RELY, ROCKET-AF). The populations of all the 8 studies were chosen to be similar to clinical trials.

Overall, there were 2 studies that assessed cost effectiveness of all the 3 NOACs compared to warfarin in one model.^{83,91} The literature mostly suggested that NOACs are more cost effective compared to warfarin. Harrington, et al. found that all the 3 NOACs produced a greater QALY compared to warfarin.⁹¹ At willingness to pay threshold of \$50,000 per QALY gained, all the 3 NOACs are cost effective compared to warfarin. However, a study done by Canestaro, et al. found that at a willingness to pay of \$100,000 only the apixaban is cost effective compared to

warfarin, although all of the 3 NOACs may produce higher efficacy relative to warfarin.⁸³

Despite that these 2 studies were using similar models, the Harrington model did not account for ECH as health state and that can explain why the result was favorable to all of the 3 NOACs.

The literature review revealed two studies that evaluated specifically cost effectiveness of apixaban compared to warfarin. Both studies found that apixaban is a cost effective strategy relative to warfarin.^{92,94} The cost data of apixaban were different in the two studies as the apixaban was not yet approved in the US market at the time of the analyses. One study used the UK price of apixaban⁹², while the other study assumed it had a similar cost as dabigatran.⁹⁴ Rivaroxaban cost effectiveness was compared to warfarin in a study by Lee et al.⁹⁵ The authors reported that rivaroxaban has a higher cost and higher QALY. The base case analysis revealed that rivaroxaban is cost effective compared to warfarin from Medicare perspective with an ICER value lower than willingness to pay of \$50,000 per QALY gained.

Three studies evaluated cost effectiveness of dabigatran versus warfarin.^{84,88,93,97} Kamel, et al. found that dabigatran is cost effective, unless the INR is well control with warfarin treatment.⁹³ A study by Freeman, et al. was done before dabigatran was approved in US market, so they used the UK price of the dabigatran in their analysis.⁸⁸ The base case analysis revealed that dabigatran is cost effective compared to warfarin; however this result was sensitive to the cost of dabigatran.⁸⁸ Clemens, et al. looked at cost effectiveness of dabigatran in different age groups (patients <75 years old, ≥75 years old, and all patients). The authors found that dabigatran is cost effective regardless age group.⁸⁴

In summary, the literature indicates that NOACs are more effective and more costly compared to warfarin, and that the cost effectiveness of NOACs depends on level of INR control with warfarin treatment.

Section 2.4: Gaps in Literature

This literature review found that it is not clear whether anticoagulation clinics are needed any longer after introduction of NOACs. In general, warfarin is less cost effective using clinical trial data but it is not clear if similar results will be seen in regular practice settings. It is also not clear whether anticoagulation clinics or similar intensity services were used in clinical trials. In addition, the costs of providing anticoagulation services were not adequately described in the studies. Moreover, all the studies had used one source to obtain the probabilities for each event.

Finally, no study clearly investigates how patients might benefit from an anticoagulant clinic if they receive NOACs. So this study is the first study that looked at cost effectiveness of NOACs compared to warfarin in anticoagulant clinic.

Section 2.5: Discussion of decision analysis

Based on the literature review, the treatment with warfarin appears to be more cost effective in anticoagulant clinics than usual care. The value of these clinics with the availability of NOACs is not clear, so an economic model is needed to compare between patients treated with warfarin in anticoagulant clinic versus NOACs. Dabigatran was chosen in this analysis to represent NOACs, as it was the first one introduced into the US market and so assumed to be well utilized in the healthcare facilities.

A decision tree model will enable us to evaluate the cost effectiveness of warfarin within anticoagulant clinics compared to 150 mg BID of dabigatran within time period of 1 year. The decision tree was chosen to model the present analysis due to simplicity and lack of data regarding long term safety and efficacy profile of dabigatran. The tree will assess most common outcomes associated with each treatment strategy which are: well, IS, ICH, MI, GI bleeding, dyspepsia, and death. The probabilities of each event will be mainly obtained from RELY clinical trial or published literature.

In any cost effectiveness analysis, it is very important to clearly define the base case population. In this study the population of interest is AF patients, age >65, with CHADS₂ score ≥ 2 , and no contraindication to anticoagulation. Patients with creatinine clearance of < 30 ml per minute or with active liver disease will be excluded from the study population.

It is crucial to state the perspective that the study will take, as it can affect types of costs included in evaluation. In this study the cost effectiveness of dabigatran compared to warfarin within

anticoagulant clinic was assessed from a societal perspective. The decision tree will help to map up all the resource utilized by each outcome (figure 2.1). The resources utilized were physician visits, hospital admissions, INR monitoring and anticoagulant clinic visits with warfarin treatment.

Various sensitivity analyses were carried out due to parameter and input uncertainty. Examples of parameter uncertainty include probabilities of safety of each treatment strategy and cost of anticoagulant clinic.

Figure 2.1: Schematic representation of the decision model

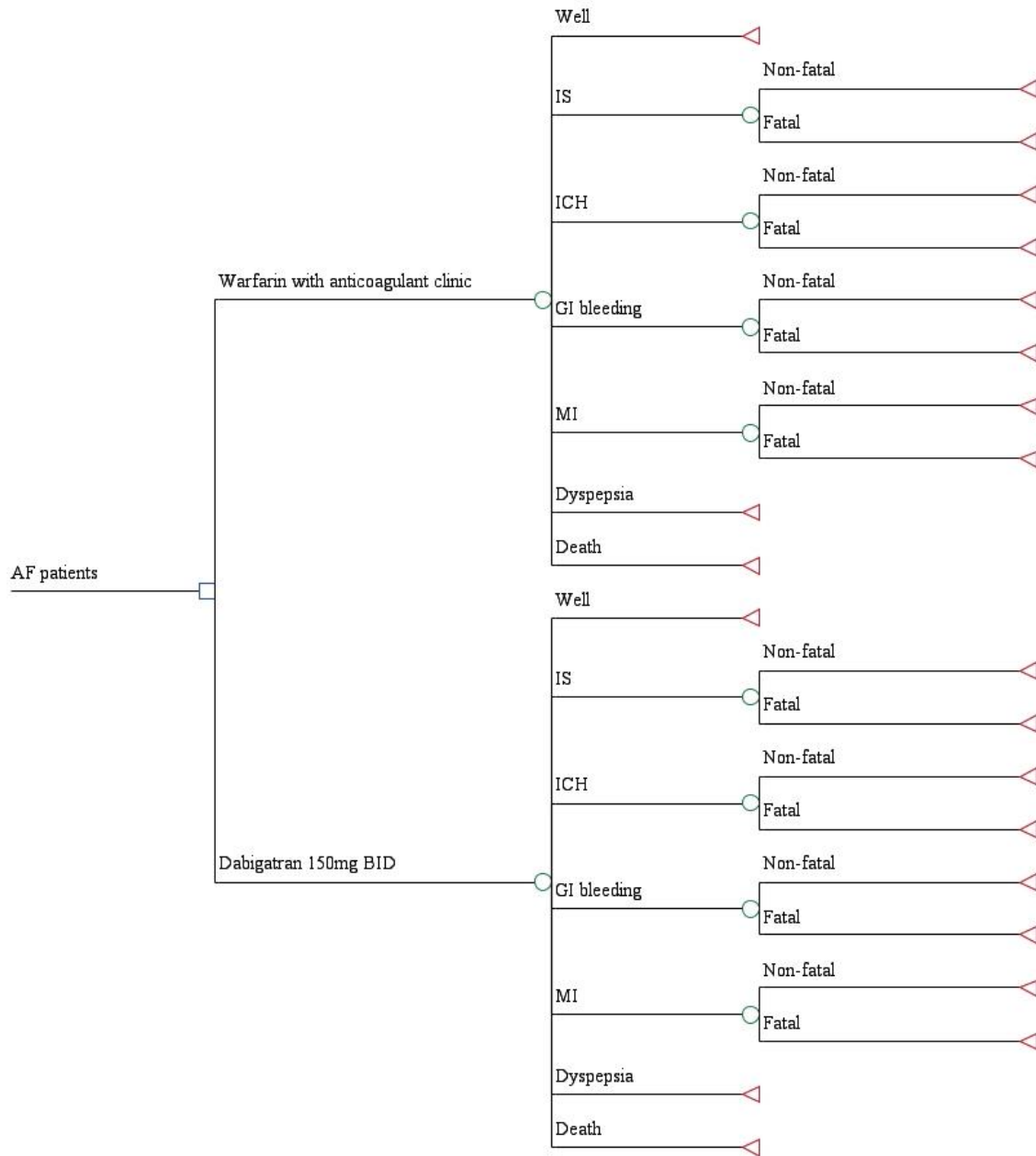


Table 2.1: Included articles from summary of literature comparing effectiveness of anticoagulant clinic to usual care

Authors/Year	Primary measures	Patient characteristics	Data source	Author's conclusion
Nichol et al. ⁶¹ (2008)	-Time in therapeutic range - Time to first bleeding event or stroke	AF patients	Medical and pharmaceutical claims data from Sharp Rees-Stealy (SRS) physician group	Anticoagulant clinic had positive impact on anticoagulation management.
Chiquette et al. ³¹ (1998)	-Anticoagulation control -Development of bleeding or stroke -Cost of hospitalization and ER visits	All patients treated with warfarin	University healthcare system	Pharmacist run anticoagulant clinic improved anticoagulation control, reduced rate of bleeding and stroke, and reduced hospitalization and ER visit costs.
Hall et al. ⁴⁰ (2011)	-Health care expenditure -Therapeutic outcomes	All patients treated with warfarin	University of Pittsburgh Medical Center	Pharmacist run anticoagulant clinic reduced health care expenditure and improved therapeutics outcomes.
Locke et al. ⁵⁴ (2005)	Number of adverse events related to anticoagulation treatment	All patients treated with warfarin	St. Joseph's Medical Center	Pharmacist managed anticoagulant clinic reduced adverse events related to warfarin.
Chamberlain et al. ²⁹ (2001)	-Anticoagulation control - ER visit and inpatients admission related to stroke or bleeding	All patients treated with warfarin	Family Medicine of Southwest Washington	Patients treated in anticoagulant clinic had better anticoagulation control, however, there are no statistical significant different in rate of adverse events

Table 2.2: Included articles from summary of literature of effectiveness of NOACs

Authors/Year	Primary measures	Population characteristics	Source data	Author's conclusion
Apixaban				
Amin et al. ⁸⁰ (2013)	Real world rate of stroke and major bleeding associated with apixaban	AF patients with CHADS ₂ score ≥ 1	U.S. commercial and Medicare health plans (Medco claims database)	Apixaban might have a better impact in real world relative to warfarin
Easton et al. ⁸⁷ (2012)	Efficacy (stroke or SE) and safety (major bleeding) profiles	AF patients with and without previous stroke or TIA	ARISTOTLE trial	Absolute benefit of apixaban is higher in patients with previous stroke compared to warfarin
Granger et al. ⁹⁰ (2011)	Efficacy (stroke or SE) and safety (major bleeding and death from any cause) profiles	AF patients with at least one additional risk factor for stroke	ARISTOTLE trial	Apixaban had lower stroke, SE, major bleeding, and mortality compared to warfarin
Lopes et al. ⁹⁶ (2012)	Efficacy (stroke or SE) and safety (major bleeding) profiles according to patients' CHADS ₂ , CHA ₂ DS ₂ VASc*, and HAS-BLED scores**	AF patients with CHADS ₂ score ≥ 1	ARISTOTLE trial	Apixaban had better safety and efficacy profiles compared to warfarin regardless stroke risk index
All NOACs				
Schneeweiss et al. ⁹⁸ (2012)	Efficacy (stroke or SE) and safety (major bleeding) profiles	AF patients with a CHADS ₂ score ≥ 3	RELY, ROCKET-AF, ARISTOTLE trials	There are non-significant differences in efficacy measures between 3 NOACs, but apixaban had lower bleeding risk

* CHA₂DS₂VASc: score scale for AF patients with stroke risk

** HAS-BLED scores: score scale to estimates major bleeding risk for patients on anticoagulant

Table 2.3: Included articles from summary of literature of cost effectiveness analysis

Authors/Year	Primary comparisons	Population characteristics	Model	Time horizon	Perspective	Model results	Author's conclusion
Anticoagulant clinic							
Sullivan et al. ⁷² (2006)	Usual care vs. pharmacist-managed anticoagulation monitoring service	Cohort of 70 years old AF patients with higher risk of stroke	Semi-Markov model	10 years	Society	Anticoagulation services enhanced effectiveness by 0.057 QALYs and cost \$US2,100 less	Anticoagulation management service is cost-effective compared to usual care
Dabigatran							
Kamel et al. ⁹³ (2012)	Dabigatran 150 mg twice-daily vs. adjusted dose warfarin (INR range 2-3)	Cohort of AF patients aged ≥ 70 years history of stroke or TIA, and no contraindication to anticoagulation	Markov model	20 years	Society	Dabigatran provided additional 0.36 QALYs with cost of \$9,000 (ICER of \$25,000)	Dabigatran is cost effective compared to warfarin for stroke prevention in AF patients with history of stroke or TIA
Freeman et al. ⁸⁸ (2011)	Dabigatran 110 mg twice, daily vs. dabigatran 150 mg twice, daily vs. adjusted dose warfarin	Cohort of AF patients ≥ 65 years with CHADS ₂ score ≥ 1 , and no contraindications to anticoagulation	Markov model	Lifetime	Society	ICER of 150 mg dabigatran was \$45,372 per QALY, and \$51,229 per QALY for 110mg dabigatran.	Dabigatran 150mg is cost-effective compared to warfarin

Authors/Year	Primary comparisons	Population characteristics	Model	Time horizon	Perspective	Model results	Authors conclusion
Dabigatran							
Clemens et al. ⁸⁴ (2014)	Dabigatran 150 mg twice daily vs. warfarin	AF patients at age <75 and at age ≥75	Markov	Lifetime	US Medicare payer	ICER was \$52,773, \$65,946, and \$56,131 for cohorts <75, ≥75, and All respectively	Dabigatran is cost-effective compared to warfarin regardless age group
Rivaroxaban							
Lee et al. ⁹⁵ (2012)	Rivaroxaban 20 mg/day vs. adjusted dose warfarin	Cohort of AF patients ≥65years old, CHADS ₂ score of 3, no contraindications to anticoagulation	Markov	Lifetime	US Medicare payer	The ICER of rivaroxaban was \$27,498 per QALY	Rivaroxaban is cost-effective compared to warfarin for stroke prevention in AF patients
Apixaban							
Lee et al. ⁹⁴ (2012)	Apixaban 5mg twice daily vs. adjusted dose warfarin	Cohort of AF patients ≥65years old, CHADS ₂ score of 2.1, no contraindications to anticoagulation	Markov	Lifetime	Medicare	Apixaban provided additional 0.34 QALYs and cost \$2,633 less than warfarin	Apixaban is cost-effective alternative to warfarin
Kamel et al. ⁹² (2012)	Apixaban 5mg twice daily vs. adjusted dose warfarin	Cohort of AF patients of 70 years old, with history of stroke, and no contraindications to anticoagulation	Markov	20 years	Society	The ICER for apixaban was \$11,400 per QALY	Apixaban is cost-effective compared to warfarin

Authors/Year	Primary comparisons	Population characteristics	Model	Time horizon	Perspective	Model results	Authors conclusion
NOACs							
Harrington et al. ⁹¹ (2013)	Apixaban 5 mg vs. dabigatran 150 mg vs. rivaroxaban 20 mg vs. adjusted dose warfarin	Cohort of AF patients age 70 year old, with CHADS2 ≥ 1 , renal CrCl ≥ 50 mL/min, and no contraindications to anticoagulation	Markov	Lifetime	Society	Compared with warfarin, apixaban resulted in an additional 0.5 QALYs at a cost of \$7,513, and ICER of \$15,026 per QALY	NOACs are all cost-effective compared to warfarin
Canestaro et al. ⁸³ (2013)	Apixaban 5 mg vs. dabigatran 150 mg vs. rivaroxaban 20 mg vs. adjusted dose warfarin	Cohort of AF patients of 70 years old, with mean CHADS2 of 2, and no contraindications to anticoagulation	Markov	Lifetime	Society	ICER compared with warfarin, for dabigatran, rivaroxaban, and apixaban are \$140,557, \$111,465, and \$93,062 per QALY gained, respectively	At willingness to pay value of \$100,00, apixaban is the cost effective strategy compared to warfarin and other NOACs

Chapter III: Method

Economic evaluation of warfarin in anticoagulant clinic versus dabigatran was done by following the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) guideline.¹⁰⁰

Section 3.1: Model

In order to evaluate cost effectiveness of warfarin in anticoagulant clinic to dabigatran, a decision tree model was built. Figure 3.1 illustrates the model. There are 2 possible alternatives that a patient with AF might be treated with: adjusted warfarin dose with INR 2-3 in a pharmacist-managed anticoagulant clinic or 150mg BID of Dabigatran. Each treatment option might result in one of the following health states: well (with no complication), IS, ICH, GI bleeding, MI, dyspepsia, or death from any cause. These health states were chosen in this model as they were the most common complications reported in the RELY clinical trial and highly expensive to treat.¹⁶ Each complication can either be treated or lead to patient death except for dyspepsia.

The analysis was conducted from the societal perspective as it is consider appropriate for our outcome measure (QALY). The reason behind conducting such analysis was to assist decision makers to choose best anticoagulant strategy for AF patients. The target population of this analysis was similar to the RELY trial population, which was cohort of AF patients, ≥ 65 years old, with mean CHADS₂ 2.1, and no contraindication to anticoagulation. Patients with CrCl <30 mL/min and active liver disease were excluded from study population.

The time horizon of the analysis was 1 year as probabilities reported in the RELY trial were annual and because the period was sufficient to assess effectiveness and identify complications.

Outcome measures included in this study were reported in 2014 \$US costs, QALYs, Incremental Cost Effectiveness Ratios (ICERs), and Net Monetary Benefit (NMB). The primary measure for treatment effectiveness was QALYs saved. QALY is common measure of effectiveness that takes into account the quantity of years lived adjusted to its quality.¹⁰¹ It has been recommended by the panel on cost-effectiveness in Health and Medicine as the preferred outcome measure.¹⁰¹ To calculate QALY, we multiply years lived by coefficient (between 0-1) which corresponds to quality of life, such as utilities. For example, the QALY for 1 year equals utility of health state of patient multiply by 1. The most common utility measures are time trade off (TTO), standard gamble (SG), rating scale (RS), and health state classifications system such as EQ-5D.^{102,103} in our analysis, utility of patients can be affected by the health state and type of anticoagulant therapy. All analyses were done using TreeAge Pro 2014 software (Appendix A).

Several assumptions were made in the model:

1. Patients were assumed to be similar to those in the RELY clinical trial.¹⁶ The population in this study were assumed to be AF patients with at least one of the following conditions:
 - a. Previous stroke, TIA, or SE.
 - b. Age ≥ 65 years with diabetes mellitus, Coronary Artery Disease (CAD), or hypertension.
 - c. Left Ventricular Ejection Fraction (LVEF) $< 40\%$.
 - d. Age ≥ 75 years.

- e. Patients with symptomatic heart failure, New York Heart Association (NYHA) Class ≥ 2 within at last 6 months.
2. Population of the study assumed to have mean CHADS₂ score of 2.1, similar to the RELY trial.
3. Probabilities of events for patients treated with warfarin and attending anticoagulant clinic were assumed to be similar to patients treated with warfarin in RELY clinical trial. This assumption was made as the patients in the RELY were monitored continuously almost similar to the anticoagulant clinic setting.¹⁶
4. The dose of warfarin was assumed to be 5mg once daily for the cost calculation.
5. Generic warfarin was used.
6. Patients on warfarin were assumed to have 1 INR test monthly.
7. Cost of fatal IS, ICH, GI bleeding was assumed to be similar to the cost of death, due to the lack of ICD 9 or DRG code.
8. Patients develop the event once through the study period.
9. Patients treated with dabigatran and who develop major bleeding (GI bleeding or ICH) were assumed to discontinue treatment, and replace it with rivaroxaban 20 mg once daily. This assumption was made according to different bleeding and anticoagulation management guidelines. They stated that when the patient develops bleeding with dabigatran then it should be discontinued immediately and substituted it with another anticoagulant. Rivaroxaban was chosen as it has advantage of once daily dose.⁵

10. If patients experience any adverse events requiring discontinuation, the cost of dabigatran would be for only six months and then rivaroxaban for the following six months of the study period.
11. Patients on both treatment options were assumed to have only 1 physician visit throughout the study period. In the physician visit the patients either get the referral to anticoagulant clinic for patients on warfarin, or to get annual prescriptions of dabigatran.
12. Utility of patients treated with dabigatran was assumed to be similar to utility of those treated with ximelagatran, an older direct thrombin inhibitor due to the lack information about utility of patients on dabigatran.
13. Adherence rates for both treatment alternatives were assumed to be similar due to insufficient data about adherence rate in patients on dabigatran.
14. Willingness to pay (WTP) was set to be \$50,000 as it is the most common value used in the economic analysis.

Section 3.2: Outcome data

The outcomes of this analysis were mainly obtained from the RELY clinical trial and supplemented by other literature (Table 3.1, 3.2). The probabilities of adverse events were based on data from the RELY clinical trial.¹⁶ Probabilities of MI for both treatment alternatives were obtained from an updated report of the RELY trial.¹⁰⁴ Probability of being on the treatment with no change in the health state (well state) was calculated by subtracting sum of all the events probabilities in the tree from 1. Mortality rates of IS, ICH, GI bleeding, and MI were estimated from previous literature.⁸³

Patient's quality of life or utility may be affected by the type of anticoagulation therapy. Dabigatran has advantages over warfarin as the patients do not require continuous monitoring, or food restriction and have fewer drug-drug interactions. The patients then may be less worried and concerned about treatment.¹¹ On the other hand, warfarin is less expensive than dabigatran and had well established safety and efficacy profile.¹¹ These factors may affect patients' preferences toward one medication over another.

Patient utilities for the different health states in the model were obtained from the published literature. Utility of AF patients treated with warfarin was based on a study that estimated the utility of AF patients treated with warfarin or aspirin.¹⁰⁵ The time tradeoff and standard gamble methods were used to calculate utilities of 83 AF patients. In our study the mean utility for patients on warfarin therapy was used in the model. Due to lack of direct data regarding the utility of patients on dabigatran, it was estimated to be similar to utilities of those treated with ximelagatran, an older direct thrombin inhibitor, as seen in previous analysis.¹⁰⁶ The utility of dabigatran patients was greater than patients on warfarin as the dabigatran does not require routine monitoring. By definition, utility of dead patients is zero. Utilities of patients experiencing IS, GI bleeding, ICH, MI, or dyspepsia were obtained from previous literature.^{93,107}

Section 3.3: Cost data

In this analysis all direct medical costs associated with both treatment branches were added in the calculation (Table 3.3). The prices of the medicines (warfarin, dabigatran, and rivaroxaban) were obtained from Virginia Commonwealth University hospital database. The prices used were 340B cost of the drugs. The 340B cost is drug discount program applied to certain eligible

health care organizations and covered entities participating in the public health services such as Medicare/ Medicaid allow them to get the outpatients drugs at reduced prices from Manufacturers.¹⁰⁸ The 340B cost was chosen in our model as they are considered a better estimate of drug cost for our targeted population (age >65 years old) who are eligible to Medicare.¹⁰⁹

According to American College of Cardiology (ACA)/American Heart Association (AHA) and the Heart Rhythm Society (HRS) guidelines for management of AF patients, the anticoagulation drug should be discontinued immediately and the patient carefully monitored if bleeding occurs.⁵ In our study, if bleeding develops for the patients on warfarin therapy, then warfarin would be immediately withdrawn and resumed after the bleeding is resolved, as the patients would still be at risk of developing stroke. For patients on dabigatran, it is recommended that when bleeding occurs that anticoagulation therapy discontinue and a new agent replace dabigatran.¹¹⁰ In our study, we assumed that rivaroxaban would replace dabigatran after treating the bleeding. Rivaroxaban was chosen because it has a good safety and efficacy profile and it is taken once daily.

The cost of an anticoagulant clinic was derived from a study that estimated the quality and costs associated with 3 different anticoagulant clinics: pharmacist-managed, nurse-managed, and both pharmacist and nurse-managed anticoagulant clinics.¹¹¹ In this study costs were broken into 3 parts: labor expense, lab expense, and overhead cost. In our analysis we used estimates from pharmacist-managed anticoagulant clinics as we are more interested in the pharmacist role in these clinics. The annual cost per patient associated with pharmacist managed anticoagulant

clinic, adjusted to 2014, was \$423. The majority of the cost was related to laboratory tests. The cost of a physician visit was obtained from blue book (physician office visit level 3) for both treatments.¹¹² It was assumed patients in both branches have only 1 physician visit at the beginning of the treatment for either referral to anticoagulant clinic or an annual prescription for dabigatran.

The cost of treating each event was obtained from Healthcare Cost and Utilization Project (HCUP) by using relevant Diagnosis-Related Group codes (DRG) (Table 3.4).¹¹³ The cost of fatal MI was based from HCUP by using the associated DRG code of fatal MI (DRG 283). Due to lack of DRG and ICD-9 codes for fatal IS, ICH, and GI bleeding, it was assumed that the cost of death associated with these events is similar to cost of death from any cause which was estimated from Shah SV, et al study.⁹⁷ In that study, the researchers assumed that the cost of death from any cause was equal to \$10,000. Because this number is considered reasonable when comparing it to cost of fatal MI, it was used in our analysis as cost of death from any cause, fatal IS, fatal ICH, or fatal GI bleeding.

All the costs, from different years, were inflated to 2014 \$US by using the US Healthcare inflation rate from Bureau of Labor Statistics.¹¹⁴ Because the time horizon of this study is assumed to be 1 year, there was no need for discounting costs and outcomes.¹⁰⁰

Section 3.4: Sensitivity analysis

Due to the uncertainty of the input values in the model, several sensitivity analyses were performed. Sensitivity analysis allows us to test the impact of uncertainty of the estimate values and model assumptions and how it affects the result of the analysis. The more similar the results of sensitivity analysis to the base case results, the greater the confidence we will have in our analysis.

One way sensitivity analysis was performed on all the probability, utility and cost variables over plausible ranges presented in Table (3.1, 3.2, and 3.3). The values of ranges were obtained from previous literature by using 95% CI if available, or by calculating a range of 20% in each direction.

The 95% confidence interval (CI) of anticoagulant clinic cost was calculated by using Standard Deviation (SD) of the mean cost that was reported by the Menzin study and applying it to equation 3.1.¹¹¹ The calculated range was used then in the sensitivity analysis. Ranges of the cost of death were derived from Shah, et al.⁹⁷ Standard Errors (SE) of mean cost for each event (MI, fatal MI, GI bleeding, ICH, and IS) were used to calculate 95% CI by applying equation 3.1. The Healthcare inflation rate was also applied to SD, SE, and estimated range of death to convert them to 2014 \$US.

$$95\%CI = \text{mean} \pm SE(1.96) \quad \text{Equation 3.1}$$

Depending on the severity of dyspepsia, sometime patient will only be managed by anti-ulcer on an outpatient basis without the need of admission. For this reason the lower limit of the range

used in the sensitivity analysis for dyspepsia was set to be \$10. The upper limit of dyspepsia range was calculated by using the SE of mean cost reported by HCUP.

Due to the different findings regarding probabilities of developing MI in both treatment strategies between RELY trial and FDA study , probabilities from the FDA study were used as the upper limit in our sensitivity analysis, while the lower limit was estimated to be 20% below the base case value.

For the remaining variables, ranges were calculated by varying estimates by $\pm 20\%$, due to lack of reporting 95% CI.

In addition two way sensitivity analysis was performed between cost of warfarin and cost of dabigatran. Two way sensitivity analysis allow us to demonstrate impact of the two variables when changing their values simultaneously within given ranges.

Moreover, Monte-Carlo probabilistic sensitivity analysis was performed, specifically second order simulation (parameter level), to simultaneously address uncertainty in all the variables in the model. Monte-Carlo allows us to calculate means of the cost, effectiveness and net monetary benefits of each treatment option. In this study, 10,000 simulations were conducted on all the variables. Each variable was defined based on certain distribution functions and a specific value of its mean and SD. The beta distribution was used for events probabilities and utilities as it ranged between 0-1. Gamma distribution was used for all cost variables. Mean of distribution for each variable was assumed to equal the base case input value in the model. SD for distribution of

each estimate in the model was equal to standard error (SE) that was calculated using following equation:

$$SE = \frac{UL - LL}{2 \times 1.96} \quad \text{Equation 3.2}$$

This equation used upper limit (UL) and lower limit (LL) based on range values used in the sensitivity analysis. ¹¹⁵

Figure 3.1: Schematic representation of the model

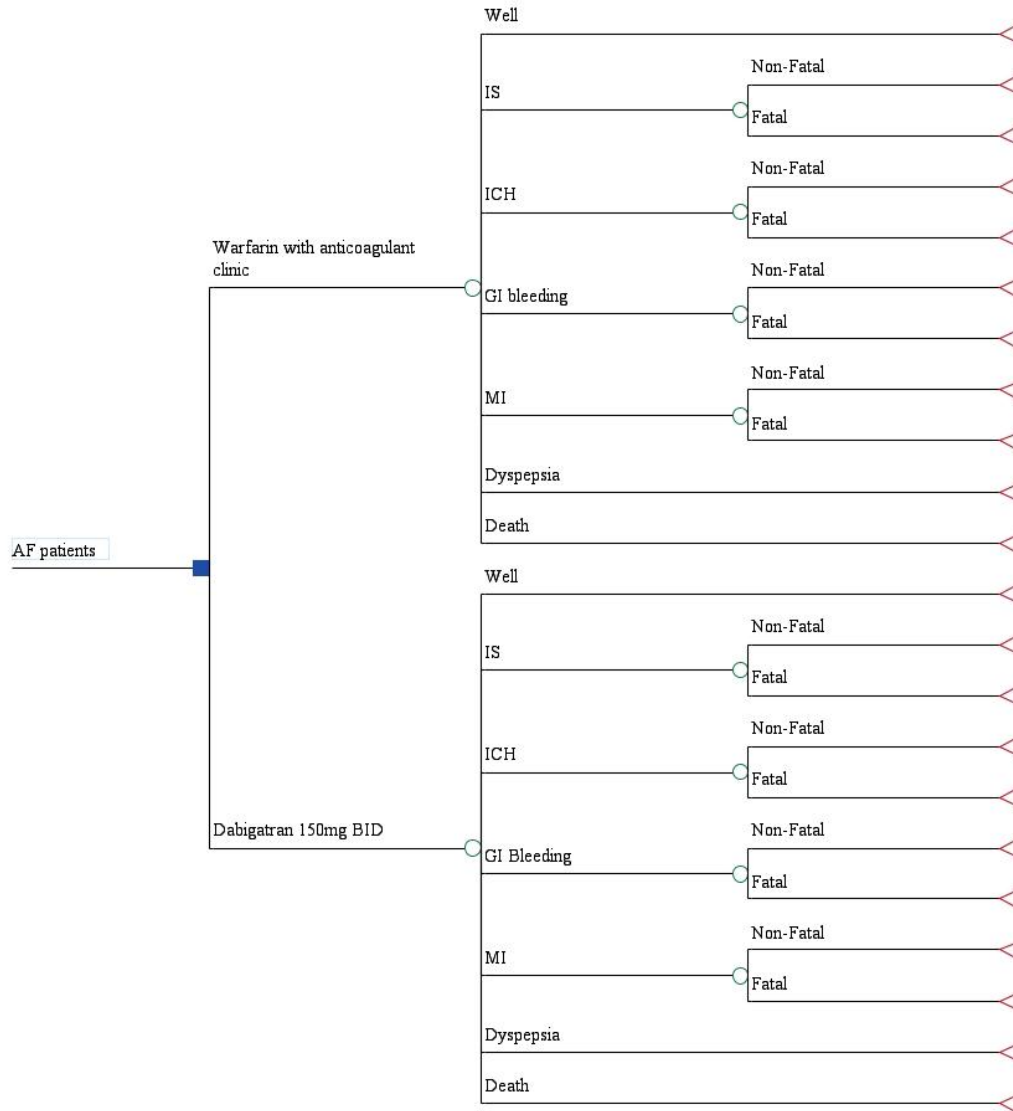


Table 3.1: Base-case probabilities values and ranges used in sensitivity analyses

Variable	Base case	Probabilities ranges used in the sensitivity analysis		Reference No.
		Minimum	Maximum	
Dabigatran:				
Dyspepsia	0.113	0.0904	0.1356	16
GI bleeding	0.0151	0.01208	0.01812	16
ICH	0.003	0.0024	0.0036	16
IS	0.0092	0.00736	0.01104	16
MI	0.0081	0.00648	0.0157	16,104
Death	0.0364	0.02912	0.04368	16
Warfarin:				
Dyspepsia	0.058	0.0464	0.0696	16
GI bleeding	0.0102	0.00816	0.01224	16
ICH	0.0074	0.00592	0.00888	16
IS	0.012	0.0096	0.0144	16
MI	0.0064	0.00512	0.0169	16,104
Death	0.0413	0.03304	0.04956	16
Mortality:				
GI bleeding	0.072	0.0576	0.0864	83
ICH	0.179	0.1432	0.2148	83
IS	0.082	0.0656	0.0984	83
MI	0.166	0.1328	0.1992	83

Table 3.2: Base-case utilities values and ranges used in sensitivity analyses

Variable	Base case	Utilities ranges used in the sensitivity analysis		Reference No.
		Minimum	Maximum	
AF patient on warfarin	0.987	0.7896	1	105
AF patient on Dabigatran	0.994	0.7952	1	106
Dyspepsia	0.996	0.7968	1	107
Non-fatal IS	0.61	0.488	0.732	107
Non-fatal MI	0.87	0.696	1	107
Non-fatal ICH	0.39	0.312	0.468	93
Non-fatal GI	0.94	0.752	1	107
Death	0	0	0	By definition

Table 3.3: Base-case cost values and ranges used in sensitivity analyses

Variable	Base case (\$)	Cost ranges used in the sensitivity analysis		Reference No.
		Minimum (\$)	Maximum (\$)	
Warfarin(per year)	11	9	14	VCU hospital
Dabigatran (per year)	1,162	930	1,394	VCU hospital
Rivaroxaban (per 6 months)	780	624	936	VCU hospital
Anticoagulant clinic	423	148	698	111
Physician visit	139	111	167	112
Dyspepsia (DRG 391)	9,737	9,495	9,978	113
Non-fatal GI (DRG 377)	14,169	13,862	14,477	113
Non-fatal IS (DRG 61)	25,435	24,457	26,413	113
Non-fatal ICH (DRG 64)	15,628	15,246	16,009	113
Non-fatal MI (DRG 280)	13,997	13,683	14,310	113
Fatal MI (DRG 283)	15,222	14,634	15,810	113
Death	10,908	0	21,815	97

Table 3.4: DRG codes and corresponding definitions

DRG code	Definition
DRG 391	Esophagitis, gastrointestinal & misc. digest disorders w mcc*
DRG 377	GI hemorrhage w mcc*
DRG 61	Acute ischemic stroke w use of thrombolytic agent w mcc*
DRG 64	Intracranial hemorrhage or cerebral infarction w mcc*
DRG 280	Acute myocardial infarction, discharged alive w mcc*
DRG 283	Acute myocardial infarction, expired w mcc*

*w mcc: with major comorbidity\complication

Chapter IV: Results

Section 4.1: Base case analysis

In the base case analysis warfarin therapy in an anticoagulant clinic resulted in lower QALYs with a value of 0.934, while 150 mg BID dabigatran resulted in 0.948 QALYs (Table 4.1). Total costs were \$2,222 for warfarin therapy supported by anticoagulation clinic management, and \$3,394 for dabigatran provided according to standard of care. Therefore, dabigatran resulted in a gain of 0.014 QALYs at an additional cost of \$1,172. The ICERs for dabigatran compared with warfarin therapy was \$82,793 per QALY saved (Note: $1,172/0.014$ will not equal 82,793 due to rounding issue).

Based on willingness to pay threshold of \$50,000 per QALY saved, the ICER for dabigatran is not considered to be cost effective, so warfarin treatment provided as part of pharmacist-managed anticoagulant clinic is considered more cost effective.

In addition to ICER, the Net Monetary Benefit (NMB) is another method that can be used to determine the cost effective strategy. The value of NMB enables us to choose the most cost effective strategy based on the combination of cost, effectiveness and willingness to pay. The NMB is the difference between the monetary value of effectiveness measure (expected QALYs multiplied by the WTP value) and total expected costs (equation 4.1).¹¹⁶ The advantage of NMB is that it enables us to quantify the net benefit (in term of money) for each strategy.¹¹⁷

It is calculated by converting the effectiveness (in our case QALYs) into monetary value by multiplying it by WTP, and then subtracted from cost associated with the strategy (equation 4.1).¹¹⁸ The strategy with the higher NMB is the most cost effective one. Based on our analysis warfarin therapy with an anticoagulant clinic is cost effective compare to dabigatran as it has higher NMB value compared to dabigatran (\$44,471 for warfarin vs. \$44,006 for dabigatran). The NMB is considered a better method, compared to ICER, to determine cost effectiveness strategy when there are small differences in effectiveness (as in our analysis Δ QALYs=0.014).¹¹⁸ Another advantage of NMB over ICER is that it helps us to rank strategy from most cost effective to least.¹¹⁹

$$\text{NMB} = (E \times \text{WTP}) - C \text{ (Equation 4.1)}$$

(Where E = effectiveness; WTP = willingness-to-pay threshold; C = cost)

$$\text{NMB (for warfarin within anticoagulant clinic)} = (0.934 \times \$50,000) - \$2,222 = \$44,471$$

$$\text{NMB (for dabigatran 150mg BID)} = (0.948 \times \$50,000) - \$3,394 = \$44,006$$

Section 4.2: One-way and two-way sensitivity analyses

A tornado diagram (figure 4.3) is a bar chart of the results of a series of one-way sensitivity analyses which illustrate the variables with the most impact on the results of the model. The most influential cost variables were cost of death, cost of dyspepsia and cost of anticoagulant clinic. Important outcomes in the model were the probability of death associated with warfarin and utility values of AF patients on warfarin and utilities for dyspepsia.

Based on the tornado diagram, one way sensitivity analyses were done for the most influential variables with the higher impact on the model over plausible ranges. Varying the utilities of AF patients on warfarin had an impact on ICER value. If the value for utility of patients on warfarin was 0.947 or lower, the ICER value for dabigatran will be lower than WTP, and so the results will be favored toward dabigatran (Table 4.2). Net Benefit (NB) graph enable us to identify exactly threshold in which below it the result will change. The NB graph demonstrates the one way sensitivity analysis, in term of NMB. The NB graph is combination of effectiveness, cost and the willingness to pay (presented as NMB on y axis). In this graph the net monetary benefit (NMB) is being analyzed as a variable, while the values of utility of warfarin patient being change over the plausible range. The strategy with the higher net benefits is the more cost effective. When running the sensitivity analysis, the model will be recalculate five times over the plausible range of utility of warfarin patient (4 intervals) (Table 4.3).¹²⁰ The values in the table (4.3) is then plotted to give us NB graph. NB Graph (Figure 4.4) tells us that if the utility of AF patients on warfarin is 0.976 or lower then it is a better to choose dabigatran therapy, and vice versa. For the utility of dyspepsia, changing the inputs values over the plausible range did not differ from the base case results.

A one way sensitivity analysis was also conducted on cost of death and the results were almost similar to the base case analysis. Moreover, varying values of cost of anticoagulant clinic over their 95% CI did not influence the ICER values of dabigatran compared to warfarin therapy from the base case analysis. On the other hand, changing the values of cost of dyspepsia over plausible ranges had an impact on the ICER value (Table 4.4). NB graph for one way sensitivity analysis of cost of dyspepsia shows that if the cost for treating dyspepsia was \$1,294 or less then

dabigatran will be more cost effective strategy compared to warfarin within anticoagulant clinic (Figure 4.5).

Another one way sensitivity analysis was performed for the probability of death associated with warfarin therapy over $\pm 20\%$ range, and result indicates that it did have an impact over ICER value (Table 4.5). When the probability of death associated with warfarin reaches 0.049 or higher, then the results will be favored to dabigatran to be cost effective compared to warfarin (Figure 4.6)

Finally, due to the differences between RELY trial and FDA study regarding probabilities of developing MI on both strategies, a one way sensitivity analysis was conducted by varying values of probability of MI for dabigatran and then for warfarin over plausible ranges to include the same probability value from FDA study. Both sensitivity analyses were similar to base case analysis.

The two-way sensitivity analysis for the cost of warfarin and the cost of dabigatran indicated that warfarin treatment within pharmacist-managed anticoagulant clinic is dominated over dabigatran 150mg BID over their plausible ranges.

Section 4.3: Probabilistic sensitivity analysis

The mean cost, effectiveness, and NMB of each strategy derived from Monte Carlo simulation were almost similar to the base case analysis (Table 4.6). Using a WTP threshold of \$50,000 per QALY gained, almost 86.75% of calculations prefer treatment with the warfarin in anticoagulant

clinics compared to 13.25% of the simulation to dabigatran 150mg (figure 4.7). These percentages agree with our base case analysis. Moreover, we can be more confident by looking at the cost effectiveness acceptability curve and by setting a range of WTP between 0 to \$100,000. This graph tells us the percentage of iterations that prefer each strategy based on different values of WTP. Looking at acceptability curve (figure 4.8), even when WTP set to \$100,000 still treatment of warfarin in anticoagulant clinic is preferred compared to Dabigatran therapy.

Figure 4.1: Schematic representation of model with base case results

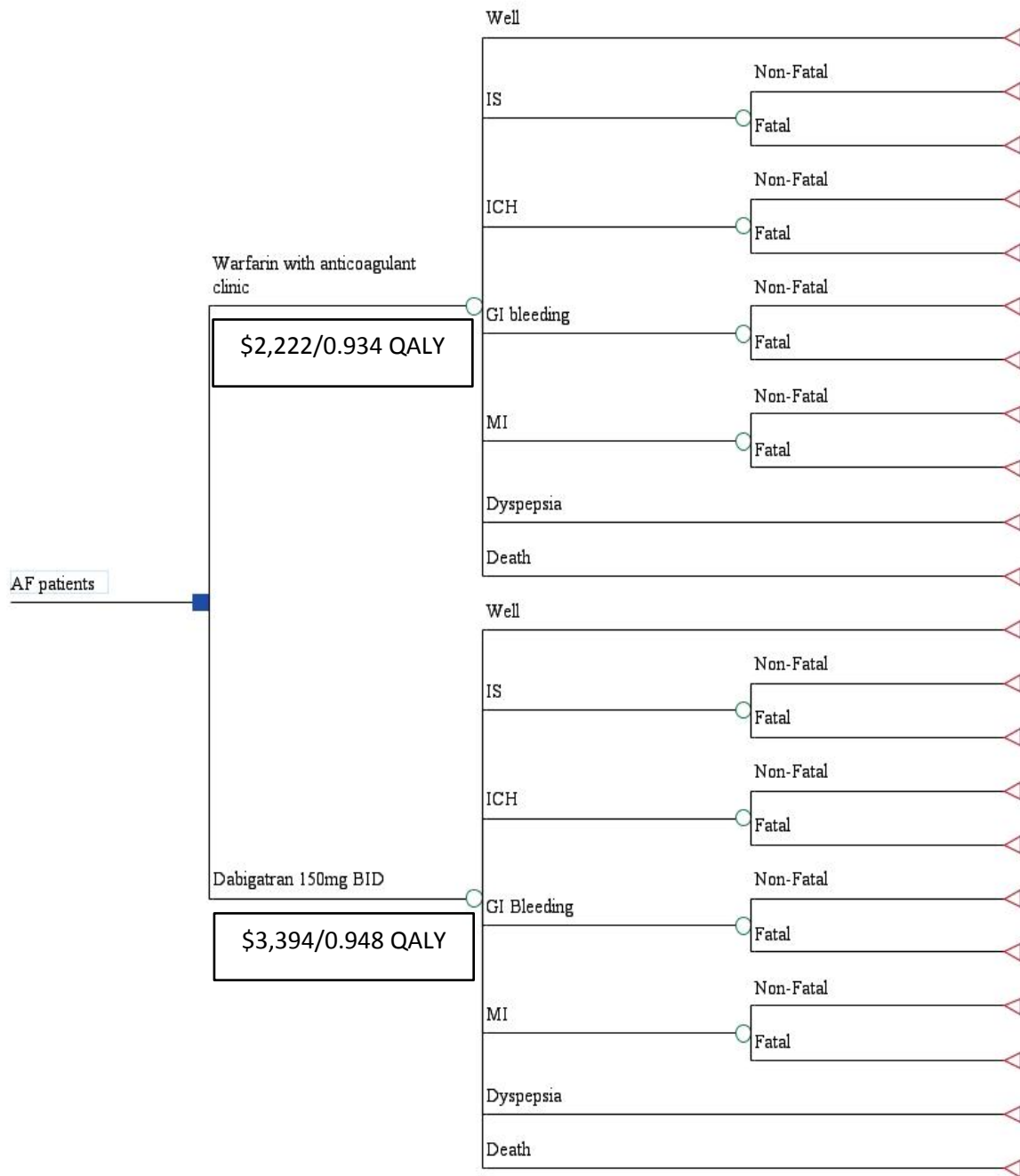


Table 4.1: Base case results

Strategy	Cost (\$)	Incremental cost (\$)	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost/effectiveness	ICER* (\$/QALY)	NMB** (\$)
Warfarin in anticoagulant clinic	2,222		0.934		2,379		44,471
Dabigatran 150mg BID	3,394	1,172	0.948	0.014	3,581	82,793***	44,006

*ICER: Incremental cost effectiveness ratio

**NMB: Net Monetary Benefit

***Note: 1,172/0.014 will not equal 82,793 due to rounding issue

Table 4.2: One way sensitivity analysis results for utility of AF patients on warfarin

Utility of AF patients on warfarin	Strategy	Cost (\$)	Incremental cost (\$)	Effectiveness (QALY)	Incremental effectiveness (QALY)	ICER* (\$/QALY)	NMB** (\$)
0.7896	Warfarin in anticoagulant clinic	2,222	0.00	0.763	0.00	0.00	35,936
	Dabigatran 150mg BID	3,394	1,172	0.948	0.185	6,342	44,006
0.8422	Warfarin in anticoagulant clinic	2,222	0.00	0.809	0.000	0.000	38,210
	Dabigatran 150mg BID	3,394	1,172	0.948	0.139	8,412	44,006
0.8948	Warfarin in anticoagulant clinic	2,222	0.00	0.854	0.000	0.000	40,484
	Dabigatran 150mg BID	3,394	1,172	0.948	0.094	12,488	44,006
0.9474	Warfarin in anticoagulant clinic	2,222	0.00	0.900	0.000	0.000	42,759
	Dabigatran 150mg BID	3,394	1,172	0.948	0.048	24,222	44,006
1.0	Warfarin in anticoagulant clinic	2,222	0.00	0.945	0.000	0.000	45,033
	Dabigatran 150mg BID	3,394	1,172	0.948	0.003	401,533	44,006

Table 4.3: Net Benefit table for sensitivity analysis of utility of warfarin patients

Value of utility of warfarin patient	Net Monetary Benefit (NMB) (\$)	
	Warfarin within anticoagulant clinic	Dabigatran 150 mg BD
0.790	35,936	44,006
0.842	38,210	44,006
0.895	40,484	44,006
0.947	42,759	44,006
1.000	45,033	44,006

Table 4.4: Net Benefit table for sensitivity analysis of cost of dyspepsia

Cost of dyspepsia (\$)	Strategy	Cost (\$)	Incremental cost (\$)	Effectiveness (QALY)	Incremental effectiveness (QALY)	ICER* (\$/QALY)	NMB** (\$)
10	Warfarin in anticoagulant clinic	1,658	0.00	0.934	0.00	0.00	45,035
	Dabigatran 150mg BID	2,295	637	0.948	0.014	45,014	45,105
2,502	Warfarin in anticoagulant clinic	1,802	0.00	0.934	0.000	0.000	44,891
	Dabigatran 150mg BID	2,577	774	0.948	0.014	54,693	44,824
4,994	Warfarin in anticoagulant clinic	1,947	0.00	0.934	0.000	0.000	44,746
	Dabigatran 150mg BID	2,859	912	0.948	0.014	64,372	44,542
7,486	Warfarin in anticoagulant clinic	2,091	0.00	0.934	0.000	0.000	44,601
	Dabigatran 150mg BID	3,140	1,049	0.948	0.014	74,051	44,261
9,978	Warfarin in anticoagulant clinic	2,236	0.00	0.934	0.000	0.000	44,457
	Dabigatran 150mg BID	3,422	1,186	0.948	0.014	83,730	43,979

Table 4.5: One way sensitivity analysis results for probability of death associated with warfarin therapy

probability of death associated with warfarin therapy	Strategy	Cost (\$)	Incremental cost (\$)	Effectiveness (QALY)	Incremental effectiveness (QALY)	ICER* (\$/QALY)	NMB** (\$)
0.033	Warfarin in anticoagulant clinic	2,132	0.00	0.942	0.00	0.00	44,968
	Dabigatran 150mg BID	3,394	1,262	0.948	0.006	210,128	44,006
0.037	Warfarin in anticoagulant clinic	2,177	0.00	0.938	0.000	0.000	44,719
	Dabigatran 150mg BID	3,394	1,217	0.948	0.01	120,725	44,006
0.041	Warfarin in anticoagulant clinic	2,222	0.00	0.934	0.000	0.000	44,471
	Dabigatran 150mg BID	3,394	1,172	0.948	0.014	82,793	44,006
0.045	Warfarin in anticoagulant clinic	2,267	0.00	0.93	0.000	0.000	44,222
	Dabigatran 150mg BID	3,394	1,127	0.948	0.018	61,817	44,006
0.049	Warfarin in anticoagulant clinic	2,312	0.00	0.926	0.000	0.000	43,973
	Dabigatran 150mg BID	3,394	1,082	0.948	0.022	48,505	44,006

Table 4.6: Results of Monte Carlo probabilistic sensitivity analysis

Attribute	Statistics	Warfarin with anticoagulant clinic	Dabigatran 150mg BID
Cost	Mean	2224	3,421
	SD*	297.58	276.6
Effectiveness	Mean	0.934	0.948
	SD*	0.047	0.041
NMB**	Mean	44,480	43,987
	SD*	2,350.83	2,093.77

*SD: Standard deviation

**NMB: Net Monetary Benefit

Figure 4.2: Base case cost effectiveness graph

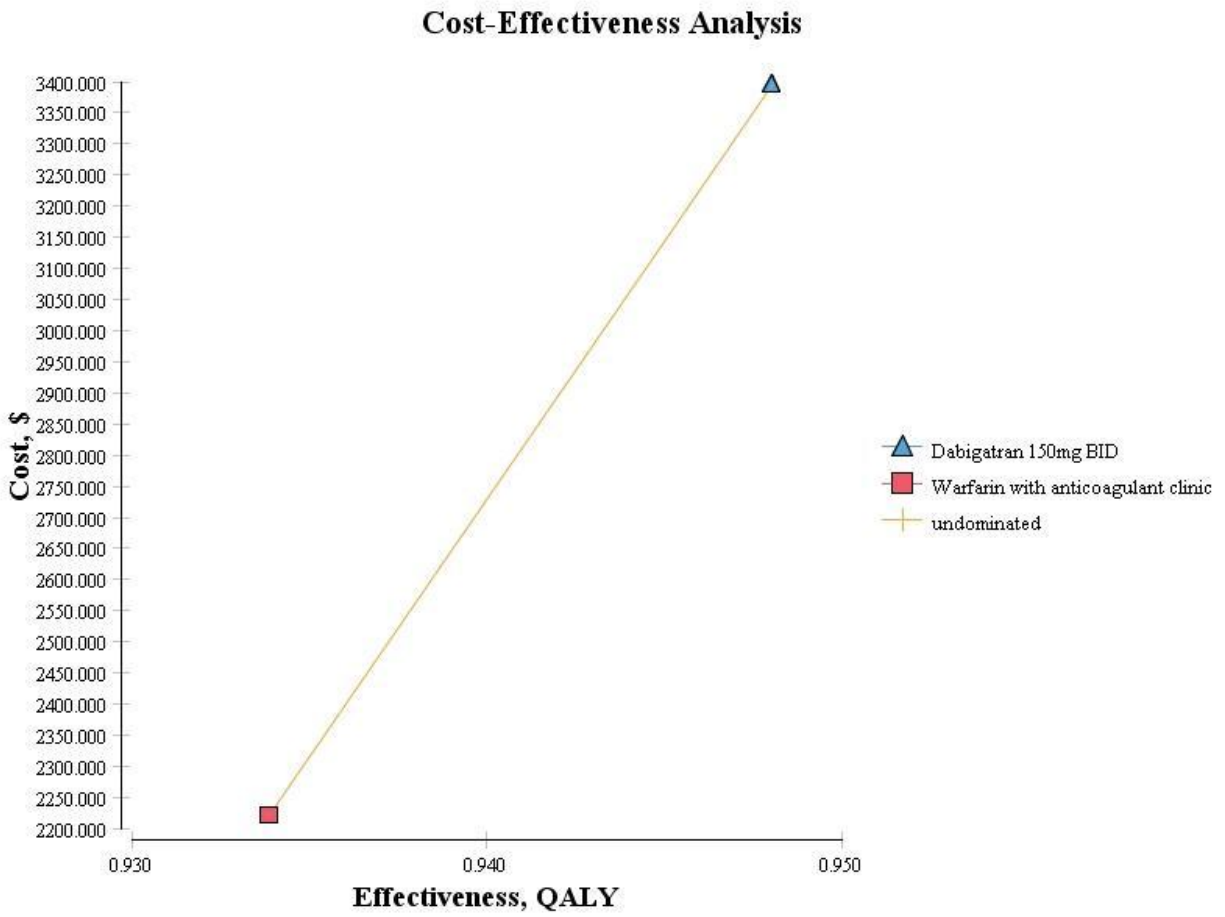


Figure 4.1: Tornado Diagram demonstrate influence of each variable on the base case results

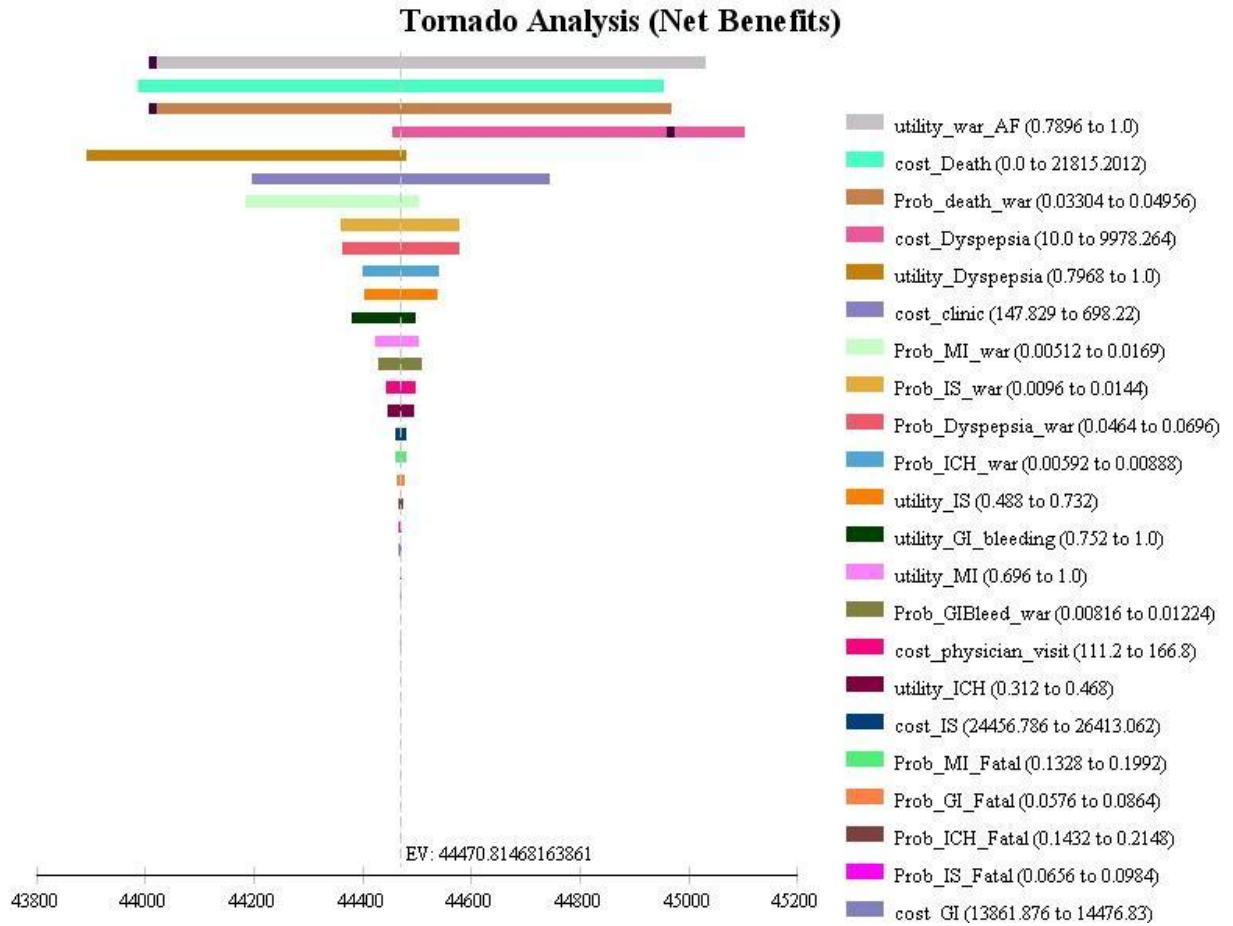


Figure 4.4: Net benefit graph for one way sensitivity analysis for utility of AF patients on warfarin

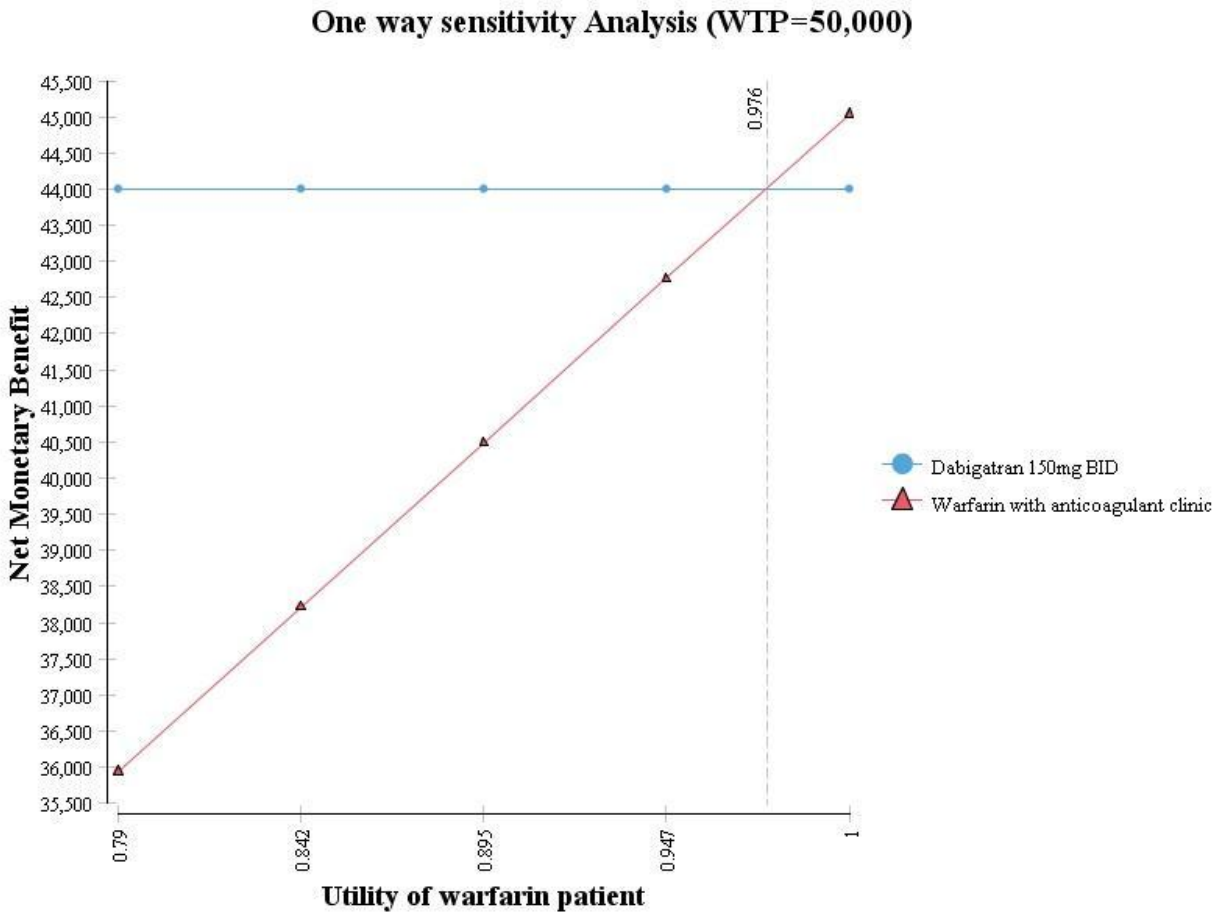


Figure 4.5: Net benefit graph for one way sensitivity analysis for cost of dyspepsia

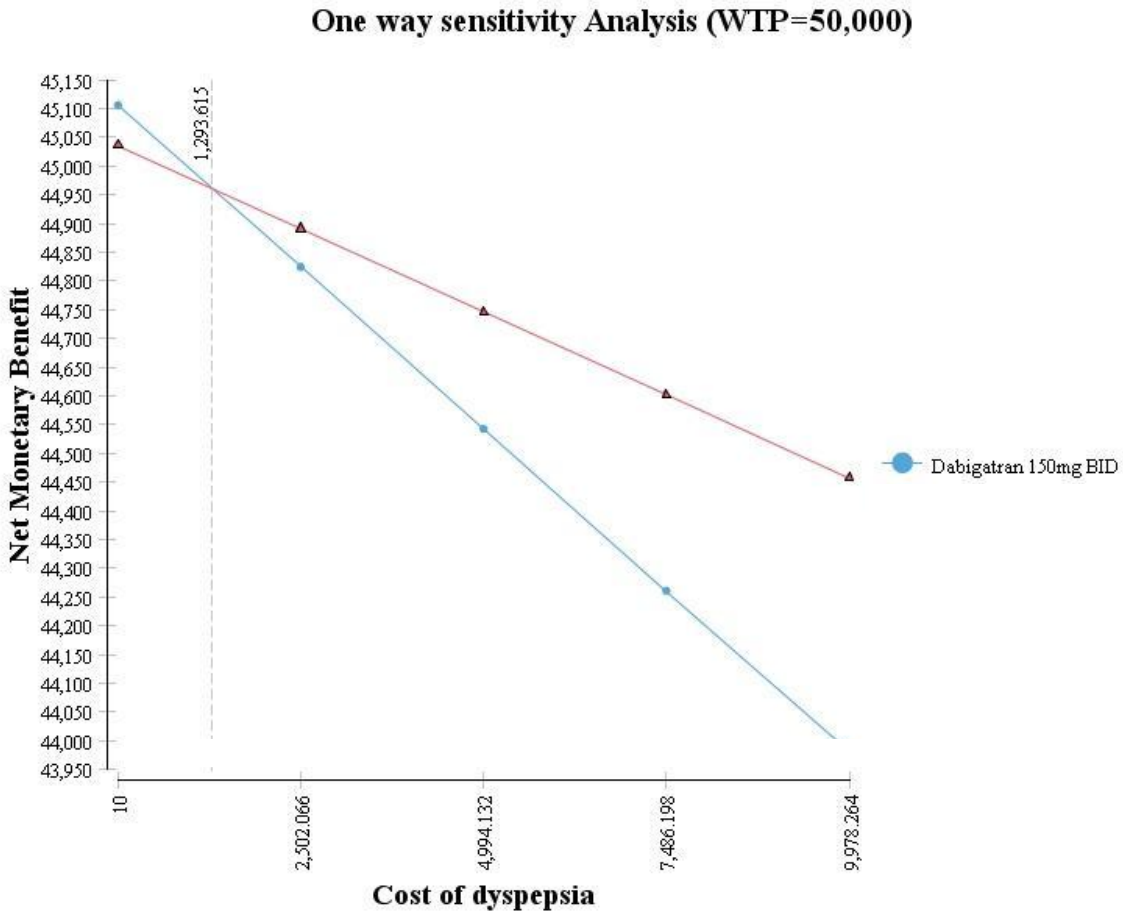


Figure 4.6: Net benefit graph for one way sensitivity analysis for probability of death associated with warfarin therapy

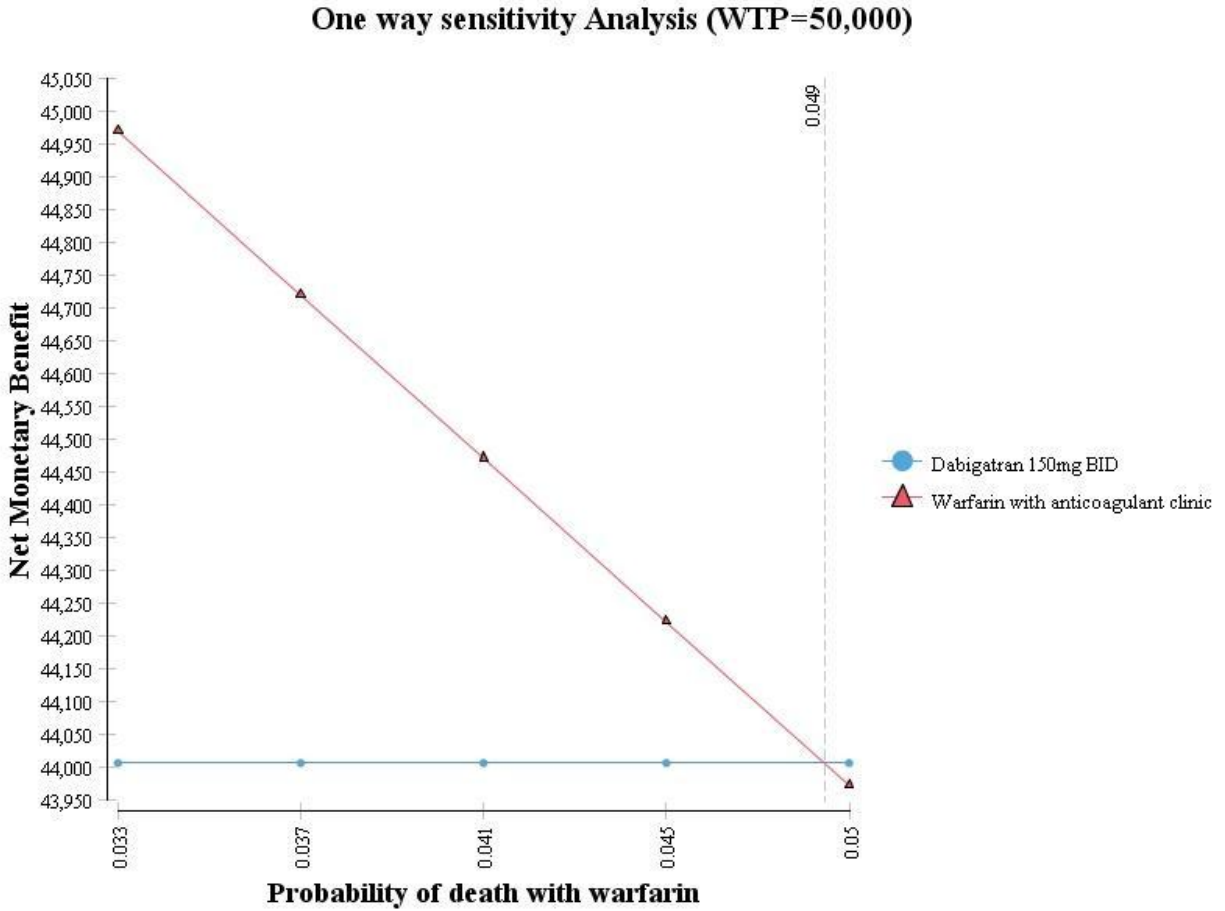


Figure 4.7: Strategy selection chart demonstrate percentage of iterations that prefer each strategy

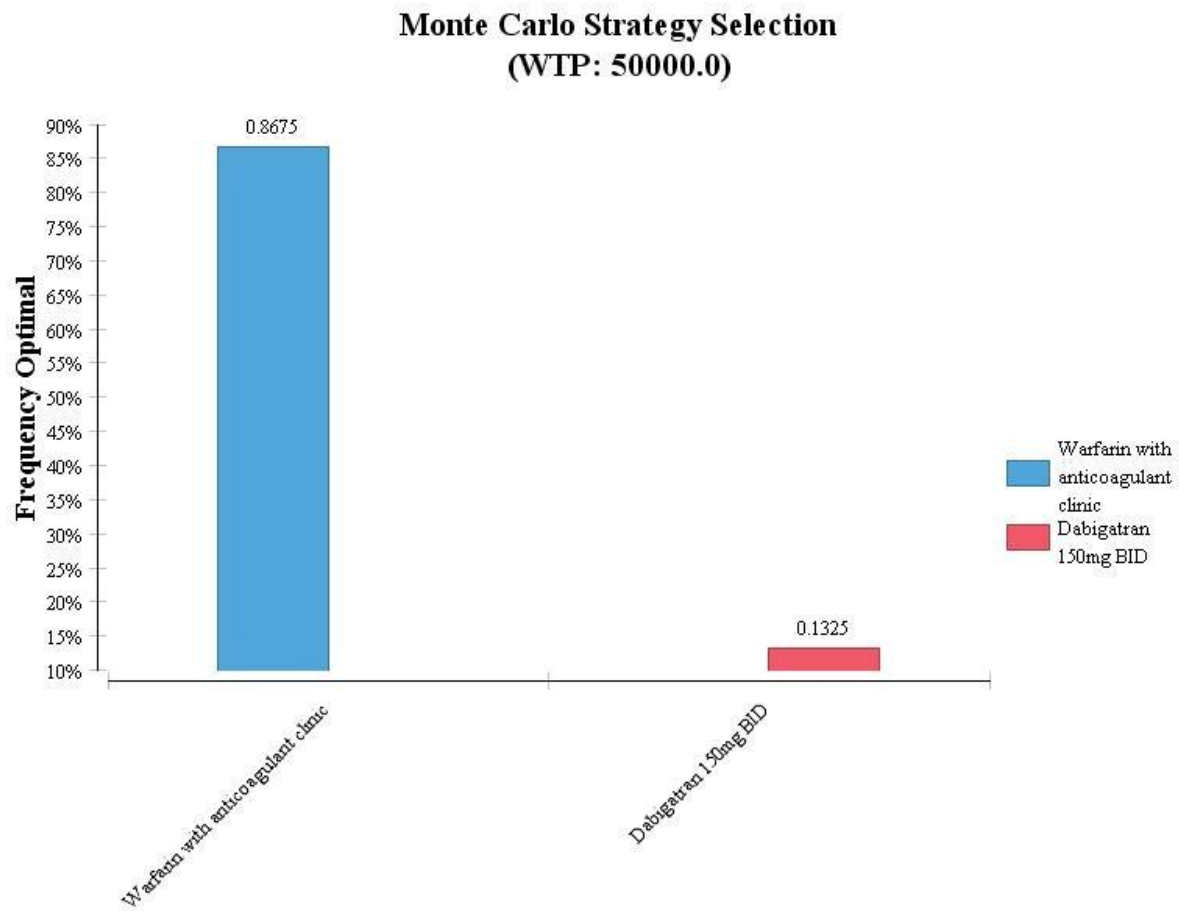
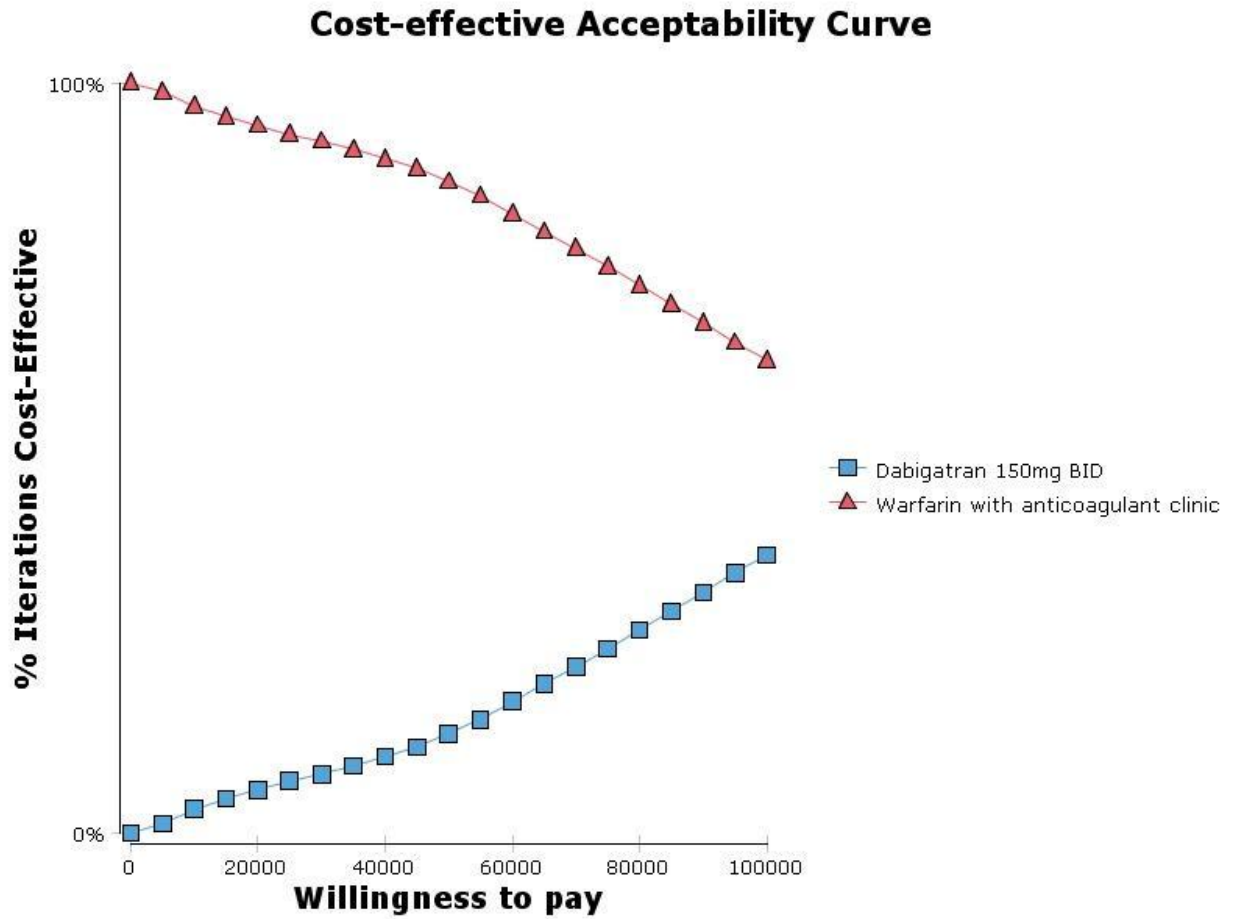


Figure 4.8: Cost effectiveness acceptability curves representing percentage of iterations that prefer each strategy according to different values of WTP



Chapter V: Discussion

In this study we assessed cost effectiveness of Dabigatran 150mg BID compared to adjusted dose of warfarin within pharmacist-managed anticoagulant clinics. Dabigatran was chosen to represent NOACs, as it is the most studied NOAC and the first one introduced into the US market. According to this study, for AF patient age ≥ 65 years old with higher risk of stroke (CHADS₂ score >2), it is more cost effective to treat them with warfarin within an anticoagulant clinic rather than dabigatran. The base case analysis showed that neither treatment was dominant. However, the ICER for dabigatran was over \$82,000 per QALY saved exceeded the established WTP threshold of \$50,000, making warfarin treatment at anticoagulant clinics a more cost effective option. Moreover, warfarin treatment resulted in higher net monetary benefits (NMB) compared to dabigatran therapy. The base case analysis revealed that for every 100 patients treated by dabigatran, there is almost a 1.4 QALY gained compared to those treated with warfarin and attending anticoagulant clinic. On the other hand, treatment with dabigatran cost approximately an extra \$1,172 per patient compared to warfarin in anticoagulant clinic. This analysis was found to be sensitive to utility of patients on warfarin, which determined by control of INR levels and time spent within therapeutic INR ranges. It suggested that if the utility of warfarin patient dropped lower than 0.947, then the results will change and be to favor dabigatran compare to warfarin.

Also the sensitivity analysis indicates that cost of treating dyspepsia and probability of death associated with warfarin therapy have an impact on the ICER value.

Moreover, the analysis revealed that the cost of anticoagulant clinic did not have an impact on the overall findings. Varying cost of anticoagulant clinic over plausible ranges did not decrease the ICER associated with dabigatran below WTP threshold (\$50,000/QALY). This is considered interesting finding, as it addressed a crucial component of our research. In this analysis, we were trying to assess importance of anticoagulant clinic after introduction of NOACs. Based on this result, despite the fact that NOACs provide a greater QALYs compared to warfarin, they may not represent an acceptable economic value. In other words, the relative advantage of NOACs over the warfarin depends mainly on quality of control of warfarin therapy and how well it is managed. Basically, the important factor that can affect the preferred treatment option is not the cost of anticoagulant clinic associated with warfarin therapy, but the level of INR control and the impact on quality of patients' life.

In most previous studies, cost effectiveness analyses have concluded that dabigatran is more cost effective compared to warfarin. Freeman et al. reported that dabigatran may be cost effective compared to warfarin within ICER value of \$45,372 per QALY gained with dabigatran.⁸⁸ A model by Kamal et al. yielded a similar conclusion with an ICER estimate of \$25,000 per QALY gained for dabigatran.⁹³ Shah et al. estimated an ICER of \$86,000 per QALY gained for dabigatran compared to warfarin.⁹⁷

The primary difference between the conclusions in this analysis and similar published economic studies resulted from assumptions about the patient population being treated. They all concluded that dabigatran is only cost effective if the INR control is poor.^{93,97} In these two studies (by Shah et al. and Kamal et. Al.) they incorporated time in therapeutic range as a variable in their sensitivity analysis and found that that INR control had impact on the base case findings. This means that warfarin might be more economical if the INR control is excellent, which may be the case with most of anticoagulant clinics.^{10,121}

There are other reasons why our results differed in finding that warfarin treatment with anticoagulant clinic is preferred over dabigatran for AF patients with higher risk of stroke. One reason is that our analysis used a decision tree with a time period of one year, while other studies used Markov models assessing lifetime outcomes and costs. The cost calculation and the probabilities of developing any adverse event can be affected by the time horizon of the study. Also the type of economic model used to analyze data can have an impact over the result due to the differences in the underlined assumptions and model design.

Another reason is that in our study we assumed that patients treated with warfarin would be within therapeutic range and have excellent INR control for all the study period. Most of the previously discussed studies reported that their results will only be applicable if the INR control was poor. This is because the efficacy and the safety of warfarin therapy depend mainly on the level of INR control and the time spent within therapeutic ranges.

Previous to the appearance of NOACs, studies of anticoagulant clinics showed them to be significantly better at controlling anticoagulation than usual care.^{29,31,40,54,61,72} For example, Nichol et al. showed that time spent in therapeutic ranges was significantly longer for the patients attending pharmacist-managed anticoagulant clinics compared to usual care (68.14% vs. 42.07%, $p < 0.001$).⁶¹ Therefore, NOACs are likely to be economically superior if warfarin is not monitored in anticoagulation clinics or some other similar program.

In addition to the findings of this study, there are other reasons to limit its use in replacing warfarin in real world practice. One is that most evidence for its use comes from specific populations of AF patients ≥ 65 years old with no renal failure disorder; while in the real world most of the AF patients are 75 and older with renal disorder and other complications.¹²² Some clinicians still hesitate of prescribing dabigatran in those patients without clinic evidence of effectiveness and safety.¹²³ Moreover, most AF patients are elderly with chronic conditions and are maintained on warfarin, which make it difficult to replace with new drug like dabigatran. In practice, NOACs are dispensed more often for deep vein thrombosis (DVT) patients as they are relatively younger and do not usually need chronic use of medications.

There is a crucial need for real world data treatments for AF patients. Each AF patient in real practice is unique and choice of the appropriate drug depends on numerous factors: patient's clinical conditions, clinician and patient's preference, and cost.⁵ There are several guidelines for selecting appropriate anticoagulant agents such as AHA/ACC/HRS Guideline for the management of patients with AF. However, there is scarce clinical information for appropriate management of major bleeding specially with NOACs. Moreover there is no clear guideline of

when to switch to another agent and what type of agent. This is can be due to complexity of AF patients, and that each scenario could be treated with different way.

In this study we were able to show that anticoagulant clinics are still economically viable after the introduction of NOACs. Anticoagulant clinics are still needed to monitor warfarin treatments for AF patients who may not benefit from NOACs.

There are several limitations of our study that need to be addressed. First, all of the event probabilities were derived from a single clinical trial. This is because the RELY trial is the only published clinical trial that directly compared warfarin and dabigatran. We tried to test this limitation by using some data in our sensitivity analyses from an FDA study report that looked at adverse events probabilities between dabigatran and warfarin. Second, we assumed that pharmacist-managed anticoagulant clinics were able to keep INR for all warfarin patients within therapeutic ranges similar to those in the RELY study. In the real world the percentage of INR control and time spent in the therapeutic range varies. Estimates of anticoagulant clinic patients within therapeutic ranges vary from 50.2-68.14%, while the patients in the RELY clinical trial (64%).^{16,29,40,61} This can have an impact on our results as we might overestimate effectiveness of patients in anticoagulant clinic. Third, we assumed that all patients in both treatment options had the same medication adherence rates. This might differ from the real world, because each option differed in dosage regimen, safety profile, and monitoring. This assumption was made because there was insufficient data regarding level of adherence of NOACs in real world. This is can be due to the fact that NOACs are still considered new and there are smaller numbers of patients treated with them compared to those treated with warfarin. One point that we can add here is

that because dabigatran patients were not followed in anticoagulants services, they may have lower adherence rate compare to those on warfarin and attend anticoagulant clinic. This can impact on our results as we might overestimate effectiveness of dabigatran in real world.

Another limitation of the study is that we assumed that rivaroxaban would replace dabigatran in case of developing major bleeding. This assumption was made due to limited clinical information for appropriate management of major bleeding specially with NOACs. Moreover, although this study was done from societal perspective, we only captured direct medical cost associated with each treatment option. In this analysis, the long term effect of both treatments was not addressed as our time horizon was only for one year. This is due to the lack of data regarding long term effect of the NOACs. Finally, as the case with most of this type of analysis, data were driven from different sources; however we tried to answer this by running multiple sensitivity tests.

In conclusion, warfarin treatment associated with pharmacist-managed anticoagulant clinic is an economically viable strategy for AF patients age ≥ 65 years old and with higher risk of stroke (CHADS₂ score ≥ 2). This result is highly affected by patient utility preferences for warfarin treatment, which determined by control of INR levels and time spent within therapeutic INR ranges. Based on the results, there is a need to focus on improving the role of pharmacist in these clinics and try to recruit more of AF patient to attend the anticoagulant clinic in order to enhance therapeutics outcomes and reduce complications associated with warfarin treatment. Because this model is built upon clinical trial data, future studies may be needed to assess effectiveness and safety of NOACs compared to warfarin within anticoagulant clinic in real world settings.

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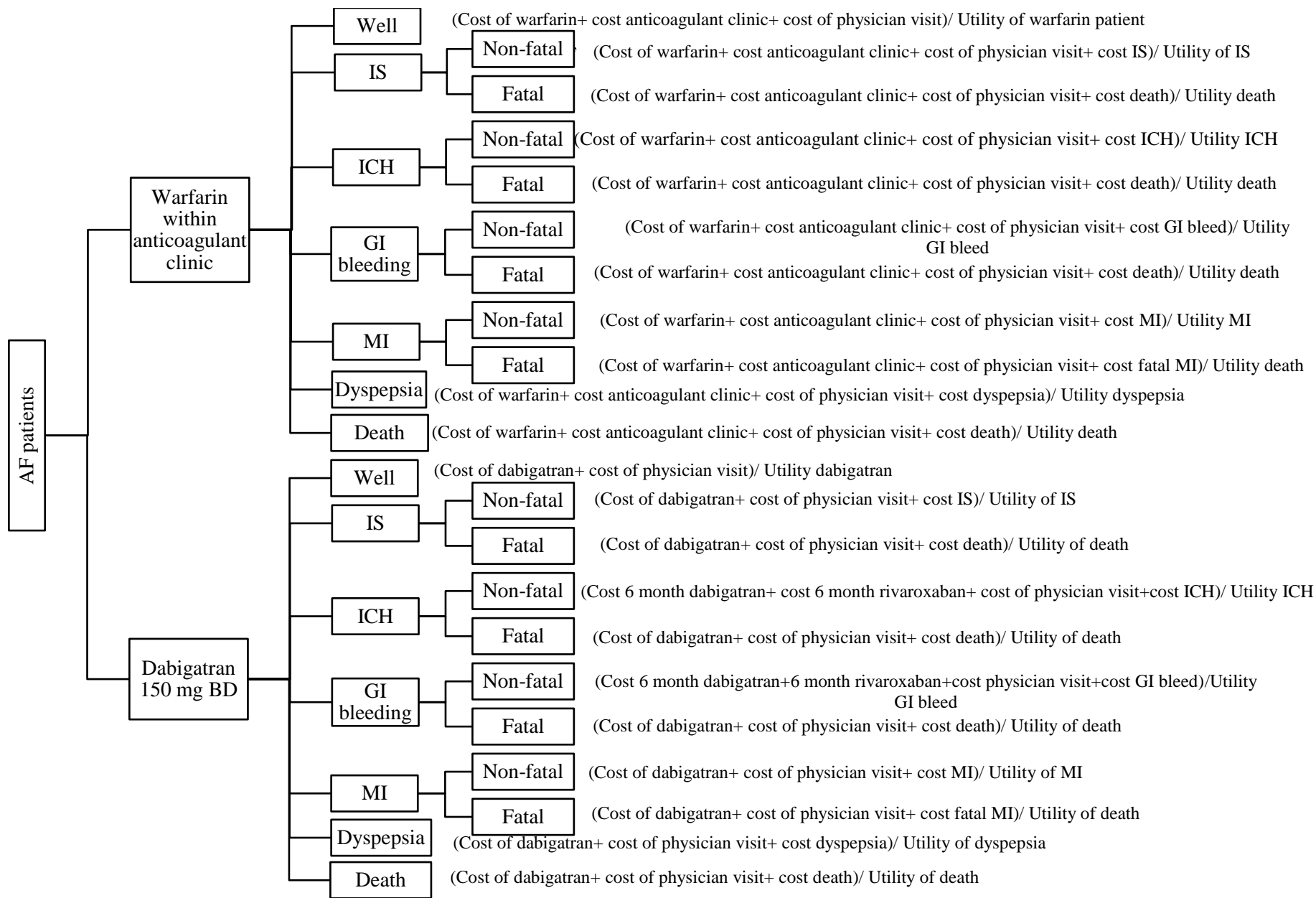
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Appendix A

Figure A.1: Schematic representation of model with payoffs



Appendix B

Table B.1: Resource utilized and cost associated with each branch in the descion tree for warfarin patients within pharmacist-managulant clinic

Path of each branch in the tree	Cost of warfarin (per year) (\$)	Cost of 1 physician visit (\$)	Cost of anticoagulant clinic (\$)	Cost of treating adverse event (\$)	Total cost (\$)
Well state	11	139	423	-	573
Non-fatal IS	11	139	423	25,435	26,008
Fatal IS	11	139	423	10,908	11,481
Non-fatal ICH	11	139	423	15,628	16,201
Fatal ICH	11	139	423	10,908	11,481
Non-fatal GI bleeding	11	139	423	14,169	14,742
Fatal GI bleeding	11	139	423	10,908	11,481
Non-fatal MI	11	139	423	13,997	14,570
Fatal MI	11	139	423	15,222	15,795
Dyspepsia	11	139	423	9,737	10,310
Death from any cause	11	139	423	10,908	11,481

Table B.2: Resource utilized and cost associated with each branch in the decision tree for dabigatran patients

Path of each branch in the tree	Cost of dabigatran (per year) (\$)	Cost of dabigatran (6 months) (\$)	Cost of rivaroxaban (6 months) (\$)	Cost of 1 physician visit (\$)	Cost of treating adverse event (\$)	Total cost (\$)
Well state	1,162	-	-	139	-	1,301
Non-fatal IS	1,162	-	-	139	25,435	26,736
Fatal IS	1,162	-	-	139	10,908	12,209
Non-fatal ICH	-	581	780	139	15,628	17,128
Fatal ICH	1,162	-	-	139	10,908	12,209
Non-fatal GI bleeding	-	581	780	139	14,169	15,669
Fatal GI bleeding	1,162	-	-	139	10,908	12,209
Non-fatal MI	1,162	-	-	139	13,997	15,298
Fatal MI	1,162	-	-	139	15,222	16,523
Dyspepsia	1,162	-	-	139	9,737	11,038
Death from any cause	1,162	-	-	139	10,908	12,209